UNIT NO. 1

EPIDEMIOLOGY OF ATHEROTHROMBOSIS AND EVIDENCE FOR THE RISK FACTORS

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ABSTRACT

Atherothrombosis is the major cause of cardiovascular morbidity and mortality. Atherosclerosis is a diffuse disease affecting multiple vascular territories. Coronary artery disease, stroke and peripheral arterial disease should thus be considered as a single pathologic disorder. Cardiovascular risk factors have been shown to be associated with atherothrombosis. They are now used to stratify cardiovascular risk and are also targets for intervention to reduce risk of atherothrombosis. Recent studies have shown that circulating tissue factors and cells may have important roles in increasing blood thrombogenicity and contribute to atherothrombosis.

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INTRODUCTION

Atherothrombosis[1] is defined as disruption of atherosclerotic plaque with superimposed thrombosis, the common pathophysiologic pathway of cardiovascular diseases (CVD). The major clinical manifestations of atherothrombosis include coronary artery disease (CAD) (e.g. myocardial infarction (MI), angina pectoris, sudden cardiac death); stroke (e.g. ischaemic stroke, transient ischaemic stroke) and peripheral arterial disease (PAD) (e.g. intermittent claudication, critical limb ischaemia).

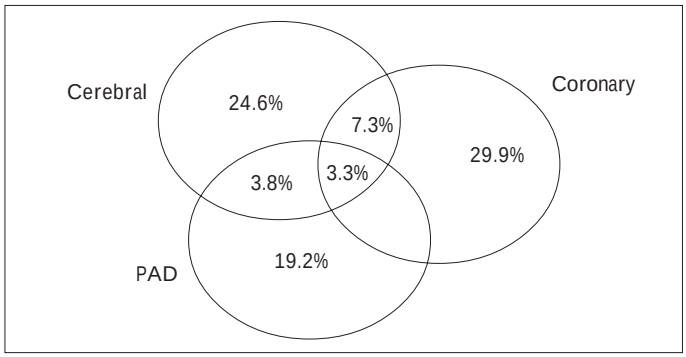
Atherosclerosis is responsible for almost all cases of CVD. It begins as a fatty streak seen in adolescence and progresses into fibrofatty plaques in early adulthood. It culminates in atherothrombosis with thrombotic occlusions causing acute ischaemic vascular events in middle age (usually man) and later life. CVD, especially CAD, is a very important health problem. In Singapore, CAD is second only to cancer as a leading cause of mortality.

Atherosclerosis and atherothrombosis shared common cardiovascular risk factors. There are also many emerging new risk factors for atherothrombosis. Most of the evidence comes from studies in patients with CAD.

EPIDEMIOLOGY OF ATHEROTHROMBOSIS

CAD, stroke, and PAD are all manifestations of atherosclerosis. It is therefore not surprising that all three conditions commonly occur together. The presence of co-existing vascular diseases depends on the sensitivity of the methods used. Co-existing vascular diseases are often underestimated in epidemiologic studies which are often based on clinical symptoms or simple screening tests. Generally, the prevalence of CAD in patients with intermittent claudication (IC) is between 40-60%, but may be as high as 90% or more if coronary angiograms are performed. Similarly, the relative risk (RR) of IC in patients with CAD is between 3.9 and 7.2. Figure 1 shows the significant overlap between CAD, stroke and PAD in the CAPRIE study[2].

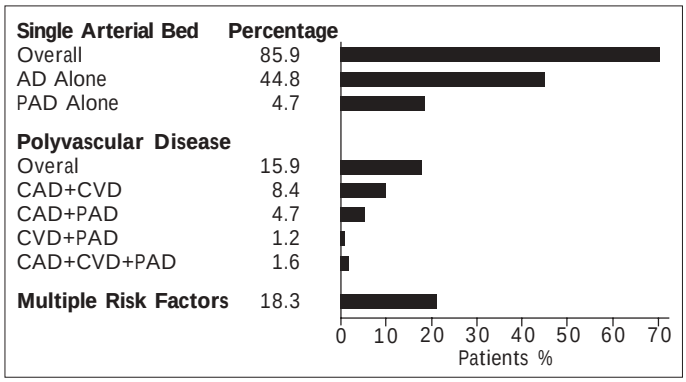
Figure 1. Overlap between CAD, stroke, and PAD in CAPRIE study



The recent REACH Registry[3] collected data on atherosclerotic risk factors and treatment in 67,888 patients aged 45 years or older from 44 countries. Risk factors in patients with CAD, stroke, or PAD were remarkably consistent across geographic regions. A high proportion of atherothrombotic patients had hypertension (81.8%), hypercholesterolemia (72.4%), and diabetes mellitus (DM) (44.3%). The prevalence of overweight (39.8%), obesity (26.6%), and morbid obesity (3.6%) were also significant and similar in most geographic locales although it was noted to be highest in North America. Current tobacco use in patients with established vascular disease was also substantial (14.4%).

In symptomatic atherothrombotic patients, a significant proportion (15.9%) had symptomatic polyvascular disease. One of six patients with CAD, stroke, or PAD had symptomatic involvement of one or two other arterial beds. This finding confirms the diffuse nature of atherothrombosis (see Figure 2).

Figure 2. Prevalence of polyvascular disease in the REACH registry



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CLASSICAL RISK FACTORS FOR ATHEROTHROMBOSIS

Non-Modifiable	Modifiable
o Increasing age (Men > 55 years; Women > 65 years)	o Dyslipidaemia
o Male gender	o Hypertension
o Family history of premature cardiovascular disease (Men < 55 years; Women < 65 years)	o Diabetes mellitus
o Indian ethnicity	o Cigarette smoking
	o Obesity
	o Sedentary lifestyle
	o Stress

NON-MODIFIABLE ATHEROTHROMBOTIC RISK FACTORS

1. Age and Gender

Increasing age is probably the most vital risk factor for CVD[4]. The incidence of CVD is approximately three to four times higher in men compared to pre-menopausal women[4]. However, after menopause, the risk of women developing CVD increases rapidly. DM, low HDL-C and smoking seem to have greater effect in women than man.

2. Family History of Premature CVD

A positive family history of premature CVD is a vital independent risk factor for atherothrombosis[5], particularly among younger individuals. A RR of CVD of 1.85 in men and 2.05 was found in women with parental history of MI. Paternal MI at age <60 or any maternal history are associated with a greater risk of CVD.

It is estimated that a positive family history independent of conventional risk factors could account for 15% of MI.

3. Ethnicity

Indians are at an increased risk, partly because of a higher prevalence of DM, dyslipidaemia and other reasons which are, at present, not entirely clear[6].

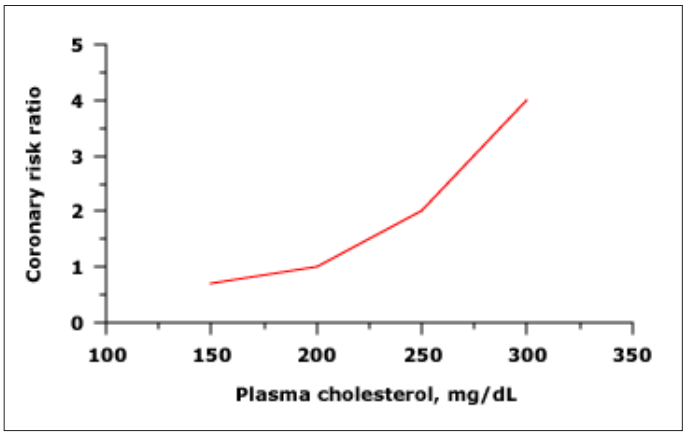
MODIFIABLE ATHEROTHROMBOTIC RISK FACTORS

1. Dyslipidaemia

a. Hypercholesterolaemia and Raised Low Density Lipoprotein Cholesterol (LDL-C)

The serum total cholesterol (TC) concentration is a clear risk factor for CAD with the risk increasing progressively with higher serum TC. The relationship between CAD and TC levels is continuous and curvilinear (see Figure 3). Clinically relevant risk of CAD begins with a TC level of around 3.9 mmol/L (150 mg/dL) and escalates sharply when the TC exceeds 5.2 mmol/L (200 mg/dL)[7].

Figure 3. Relationship between CAD risk and TC levels



The fraction of cholesterol that has been shown to be the most important is the LDL-C. Intervention trials in the last decade have shown unequivocal benefits when TC and LDL-C levels are reduced by statins in patients, with and without pre-existing CAD (primary and secondary prevention). The higher the risk, the greater the benefit. A 10% reduction in plasma TC is followed by a 25% reduction in incidence of CAD after five years, and a reduction of LDL-C of 1 mmol/L (40 mg/dL) is accompanied by a 20% reduction in CAD events[8]. Stroke risk is also reduced when LDL-C is lowered. However, the results are less impressive in PAD risk.

In the worldwide INTERHEART study of patients from 52 countries, dyslipidemia accounted for 49% of the population attributable risk of a first MI.

b. Low High Density Lipoprotein Cholesterol (HDL-C)

HDL-C and TC-to-HDL-C ratio have a powerful protective effect against CAD. A low HDL-C is a vital independent risk factor for CAD. HDL-C is decreased with obesity, cigarette smoking and a sedentary lifestyle, and is increased with exercise and alcohol intake. A recent trial has shown the benefit of raising HDL-C in CAD patients with a normal LDL-C level and a low HDL-C level[9].

c. High Triglyceride (TG)

Hypertriglyceridaemia is associated with an increased risk of CVD. The association between TG and CAD is not as strong as for LDL-C and HDL-C. Nevertheless, hypertriglyceridaemia is important in patients with DM, with pre-existing CAD and whose TC/HDL-C ratio is <5. Recent studies showed the combined adjusted odds ratio for CAD was 1.7, comparing individuals in the top third of serum TG levels with those in the bottom third[10].

d. Epidemiology

The Singapore 2004 National Health Survey (NHS) found that the mean TC level of our adult population aged 18-69 years was 5.3 mmol/L (205 mg/dL). The prevalence of high blood cholesterol level, defined as a TC of ≥6.2 mmol/L (240 mg/dL) was 18.7%. Malays had the highest prevalence

(22.8%), followed by Chinese (18.2%) and Indians (16.9%). More males (19.8%) than females (17.5%) had high TC. The prevalence of low HDL-C, defined as a level <1.0 mmol/L (40 mg/dL) was 5.5%. Indians had the highest prevalence of low HDL-C (19.1%), compared to Malays (7.3%) and Chinese (3.9%).

e. Other Lipid Abnormalities

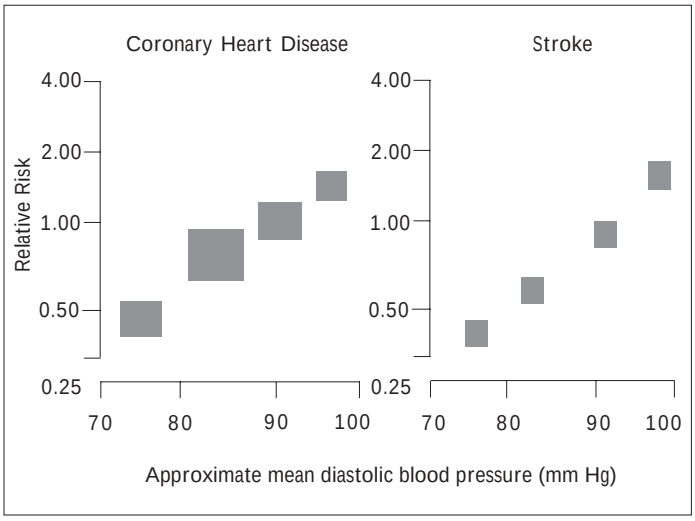
The following lipid abnormalities are also associated with increased CAD risk:

- Increased Lp(a)
- Increased non-HDL-cholesterol
- Increased apolipoprotein B (apo B; found primarily in LDL)
- Decreased apolipoprotein A-I (apo A-1; found in HDL)
- Small, dense LDL particles, oxidized LDL
- apoE epsilon 4 allele

2. Hypertension

Blood Pressure (BP) levels are continuously related to the risk of CVD as shown in Figure 4[11]. The definition of hypertension or raised BP is therefore arbitrary. Even within the normotensive range, people with the lowest levels of BP have the lowest rates of CVD. Longitudinal data from the Framingham Heart Study indicated that BP values in the 130–139/85–89 mmHg range are associated with a two-fold increase in RR of CVD compared with those with BP levels <120/80 mmHg.

Figure 4. Relation between CVD risk and BP levels



Systolic BP is at least as powerful a cardiovascular risk factor as diastolic BP, particularly in older patients, and isolated systolic hypertension is now established as a major risk for CAD and stroke. There is also evidence that the pulse pressure, which is determined primarily by large artery stiffness, is an independent predictor of cardiovascular risk.

In the INTERHEART study, hypertension accounted for 18% attributable risk of a first MI.

The 2004 NHS showed that the prevalence of hypertension (defined as a blood pressure of ≥140/90 mmHg) in adults aged 30 to 69 years was 24.9%. Chinese had the highest prevalence, followed by the Malays and Indians. Hypertension was more common among males (29.5%) than females (20.4%). The age-specific prevalence for hypertension rises markedly from age 40 years onwards. The age-specific prevalence of hypertension amongst those aged 60 to 69 years was 56.1%, as compared to 8.8% in those aged 30 to 39 years.

Randomised trials have shown clear evidence of a lower incidence of major CVD events after BP was lowered with antihypertensive drugs. Each reduction of 10-14 mmHg in systolic BP and 5-6 mmHg in diastolic BP confers about two-fifths reduction in stroke, one-sixth reduction in CAD and one-third reduction in major cardiovascular events[12].

The estimated absolute treatment benefits range from less than five events prevented per thousand patient-years of treatment (low risk) to more than 17 events (very high risk) (see Figure 5). These estimates of benefits are based on trials of about five years duration. Longer term treatment may produce an even greater risk reduction[13].

Figure 5. BP treatment effects

Patient group	Absolute risk of CVD events over 10 years	Absolute treatment effects (CVD events prevented per 1000 patient-years)	
		10/5 mmHg	20/10 mmHg
Low risk patients	<15%	<5	<9
Medium risk patients	15-20%	5-7	8-11
High risk patients	20-30%	7-10	11-17
Very high risk patients	>30%	>10	>17

3. Diabetes Mellitus (DM)

Insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic CVD. The RR of MI, stroke and death is increased two to three fold in those with type 2 DM independent of other CVD risk factors. In the INTERHEART study, DM accounted for 10% attributable risk of a first MI.

In Singapore, almost 60% of subjects with DM die from CVD. In the 2004 NHS, DM was found to affect 8.2% of our population and is associated with a three-fold increase in mortality, most of which is related to CVD.

Studies in type 2 diabetes had shown that a 1% increase in HbA1c was associated with a pooled RR for cardiovascular events (CAD and stroke) of 1.18 and for all-cause mortality of 1.24 in men and 1.28 in women.

The Diabetes Control and Complications Trial (DCCT) confirmed the risk of microvascular complications with elevated blood glucose levels in patients with type 1 DM[14]. Tight glucose control lowered the risk of a CVD event by 42% and the risk of a serious event (MI or stroke) by 58%. The UK Prospective Diabetes Study (UKPDS) showed that intensive blood glucose

control by drugs substantially decreased the risk of microvascular disease in patients with type 2 DM[15]. A 1% decrease in HbA1c value correlates to a 35-60% reduction in risk for microvascular complications.

4. Smoking

Cigarette smoking is an important and reversible risk factor and approximately doubles the risk of CVD, which is directly related to the number of cigarettes smoked[16]. The incidence of an MI is increased six-fold in women and three-fold in men who smoke at least 20 cigarettes per day. In the INTERHEART study, smoking accounted for 36% attributable risk of a first MI.

In a study of smokers, the risk of recurrent infarction was reduced by 50% within one year of smoking cessation and normalised to that of nonsmokers within two years. The benefits of smoking cessation are seen regardless of how long or how much the patient has previously smoked[17].

5. Obesity and Metabolic Syndrome

Obesity is associated with a number of risk factors for atherosclerosis, CVD, and cardiovascular mortality. These include hypertension, insulin resistance and glucose intolerance, hypertriglyceridaemia and reduced HDL-C[18]. Although the association between obesity and cardiovascular risk tends to lose significance after multivariate adjustment, body weight is still an important target for intervention as it has adverse effects on many risk factors. Recent studies have demonstrated that regional distribution of adipose tissue may be more important in determining cardiovascular risk than total body weight. Excess central (visceral abdominal) fat in particular has been shown to be strongly associated with metabolic and cardiovascular risk[19].

WHO and international guidelines recommend BMI cut-offs of 25 and 30 kg/m^2 to define overweight and obesity respectively, and waist circumference cut-offs of 102 and 88 cm to define excess risk in males and females respectively. For Asians, BMIs of 23 and 27.5 kg/m^2 and waist circumference 90 and 80 cm respectively are probably more appropriate.

Individuals with **metabolic syndrome,** a constellation of abdominal obesity, hypertension, DM and dyslipidaemia (also called the insulin resistance syndrome or syndrome X) have a markedly increased risk of CAD[20]. The diagnosis of the metabolic syndrome is of greatest importance in non-DM subjects as an indicator of an increased risk of developing type 2 DM and CVD.

6. Sedentary Lifestyle

A sedentary lifestyle doubles the risk of premature death and is associated with an increased risk of CVD. Avoiding a sedentary lifestyle may extend total life expectancy and CVD-free life expectancy by 1.3–3.5 years[21]. Exercise of even moderate degree has a protective effect against CAD, 20–25% risk reduction[22]. The beneficial effects of exercise include an elevation in serum HDL-C, a reduction in BP, less insulin resistance, and weight loss.

In the INTERHEART study, lack of regular physical activity accounted for 12% attributable risk of a first MI.

7. Psychosocial Stress

The following psychosocial risk factors increase the risk of CVD and worsen the clinical course and prognosis in patients with CVD:

- Low socio-economic status
- Stress at work and in family life
- Social isolation and lack of social support
- Negative emotions, including depression and hostility

Several psychosocial interventions have been shown to have beneficial effects on risk factors, and some studies improved CVD outcomes[23].

OTHER RISK FACTORS FOR ATHEROTHROMBOSIS[24]

1. Diet, Alcohol and Homocysteine

Fruit and vegetable consumption is inversely related to the risk of CVD and stroke. The risk of stroke is reduced by 11% for each additional daily portion of fruit. High fiber intake is also associated with a reduction in the risk of CVD and stroke, a 10 g increase in total daily dietary fiber intake is associated with a RR of 0.81 for MI. Conversely, a diet rich in calories, saturated fat, and cholesterol contributes to other risk factors that predispose to CVD.

Epidemiologic data indicates that moderate alcohol intake has a protective effect on CVD. The RR of death from cardiovascular disease in moderate drinkers compared to nondrinkers is 0.7 for men and 0.6 for women. The benefit of alcohol appears to be mediated by an elevation in serum HDL-C. Antioxidant, antithrombotic, and antiinflammatory effects have also been reported. The benefit of alcohol is not seen with alcohol abuse which is associated with hemorrhagic stroke, traumatic death or cancer.

Hyperhomocysteinaemia is associated with increased risk for CVD. It is frequently accompanied by reduced levels of folate and vitamin B12. However, trials of folate supplementation to lower serum homocysteine have not demonstrated benefit.

2. Infection

Acute infections may be associated with a transient increase in the risk of cardiovascular events. Some infections with low-grade persistent inflammatory process may play a role in the pathogenesis of atherosclerosis, e.g. Chlamydophila (formerly Chlamydia) pneumoniae, cytomegalovirus, Helicobacter pylori, hepatitis A virus and herpes simplex virus type 1 and type 2. However, large randomised trials do not support the use of antibiotic therapy to reduce coronary events.

3. Inflammatory Markers

Plasma concentration of C-reactive protein (CRP) predicts the risk of a first MI, ischaemic stroke, or PAD. Cardiovascular risk has also been associated with a variety of other markers of inflammation, further supporting the role of inflammation in atherosclerosis:

- increased the white blood cell count
- elevated erythrocyte sedimentation rate (ESR)
- increased levels of the leukocyte enzyme myeloperoxidase
- increased plasma interleukin-6 (IL-6), IL-18 concentrations
- increased circulating serum concentrations of soluble receptors for tumor necrosis factor (TNF) alpha
- elevated serum concentrations of soluble intercellular adhesion molecule-1 (sICAM-1) and P-selectin, soluble vascular cell adhesion molecule-1 (sVCAM-1) and E-selectin
- elevated lipoprotein-associated phospholipase A2

4. Haemostasis/Thrombosis Markers

Plasma fibrinogen levels are important predictors of CVD, but it has been unclear whether plasma fibrinogen is an independent risk factor.

Other coagulation and haematological factors which may be related to increased cardiovascular risk:

- elevated levels of D-dimer, fibrinopeptide A, prothrombin fragment 1+2
- elevated plasma von Willebrand factor (vWF) concentrations
- elevated factor V, VII, VIII and IX
- low soluble thrombomodulin
- reduced plasminogen activator inhibitor 1(PAI-1), increased tissue-plasminogen activator
- raised haematocrit
- platelet-related factors: aggregation, activity, size and volume

5. Microalbuminuria and Chronic Kidney Disease

Microalbuminuria reflects vascular damage and is a marker of early arterial disease. It is an important risk factor for CVD and early cardiovascular mortality. Patients with ESRD have increased CVD and mortality. Recently, mild to moderate renal dysfunction is also recognised as an important cardiovascular risk factor.

6. Left Ventricular Hypertrophy (LVH), Heart Rate and Abnormal ECG

LVH, mostly related to hypertension, is associated with two to three times the risk of CAD.

Resting and peak exercise heart rate may be predictive of cardiovascular and CAD mortality. Resting heart rate >90 beats per minute has an adjusted RR of 2.02 compared to those <70 beats per minute for cardiovascular mortality. An increment of 35 beats per minute in the peak heart rate was also associated with a RR of 2.7 for death. A lower than expected peak heart rate during exercise (chronotropic incompetence) is also predictive of CAD and all-cause mortality.

Abnormal ECG at rest and during exercise often indicates myocardial ischaemia which increases the risk for CAD.

7. Endothelial Dysfunction, Arterial Intima-Media Thickness (IMT) and Arterial Stiffness

Endothelial dysfunction induced by dyslipidaemia, oxidative stress, and various cardiovascular risk factors indicates early arterial disease and atherosclerosis. It predicts progression of atherosclerosis and is associated with an increased incidence of cardiovascular events.

Common carotid and femoral artery IMT are evidence of early atherosclerotic process. Increased carotid IMT is associated with increased risk of future cardiovascular events. Each 0.10 mm increase in carotid IMT is associated with a RR of 1.15 for MI and 1.18 for stroke after adjusting for age and sex.

Arterial stiffness, measured as aortic pulse wave velocity between the carotid and femoral arteries, suggests arterial organ damage and appears to be an independent predictor of cardiovascular events.

8. Coronary Artery, Aortic Arch/Abdominal Aorta Calcification

Coronary artery calcification (CAC) detected by computed tomography is now used to quantify the amount of calcium present in the coronary arteries. The coronary calcium score correlates with the risk of cardiovascular events in both asymptomatic and symptomatic patients.

Like CAC, calcium deposits in extracoronary arteries, particularly the aortic arch and abdominal aorta, may be a marker for CVD and is associated with an increase risk for cardiovascular events.

9. Estrogen Deficiency

The incidence of CAD increases in women after menopause, an effect that was thought to be secondary to hypoestrogenemia. A number of observational studies suggested that hormone replacement therapy may have a cardioprotective effect. However, these findings were not confirmed in the Women's Health Initiative and the HERS trials.

10. Others

- Collagen vascular disease, e.g. rheumatoid arthritis and systemic lupus erythematosus
- Hyperuricaemia, elevated serum phosphate
- Excess iron, mercury
- Increased brain natriuretic peptide (BNP) and N-terminal pro-BNP

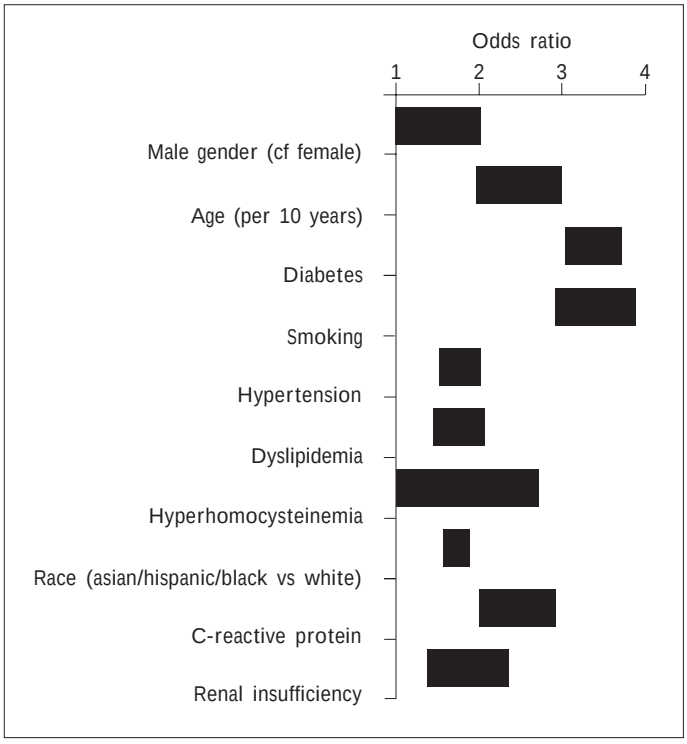
- Retinal arteriolar narrowing
- Air pollution
- Reduced circulation endothelial progenitor cells
- Elevated asymmetrical dimethylarginine (ADMA), serum amyloid A.

ATHEROTHROMBOTIC RISK FACTORS AND VASCULAR DISEASES

Although the risk factors for developing atherosclerotic diseases are similar, the influence of each of these risk factors may vary with specific vascular beds. For example, hypercholesterolaemia is strongly associated with CAD, hypertension with stroke, and smoking with PAD. In addition, specific risks such as atrial fibrillation and carotid stenosis are strongly related to stroke.

The odd ratios for risk factors for symptomatic PAD are shown in Figure 6[25].

Figure 6. Odd ratio for symptomatic PAD risk factors



Patients with vascular diseases often have multiple cardiovascular risk factors and extensive co-existing atherosclerotic diseases, which put them at markedly increased risk for further cardiovascular events. Although lowering LDL-C may not have major impact on the limb outcome in PAD patients, it significantly reduces the CAD risk and mortality in this group of patients. Therefore, whether patients have CAD, stroke, or PAD, it is crucial to reduce or control all modifiable atherothrombotic risk factors to improve overall prognosis.

CONCLUSIONS

Atherosclerosis is a diffuse disease. Aggressive treatment of cardiovascular risk factors reduces the risk of atherothrombosis. Although new emerging atherothrombotic risk factors are associated with vascular risks, their use in routine screening and risk stratification remains to be determined and have not been shown to add significant risk predictions provided by conventional risk factors.

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LEARNING POINTS

- **Atherothrombosis is the major cause of cardiovascular morbidity and mortality.**
- **Atherosclerosis is a diffuse disease affecting many vascular territories.**
- **Patients with vascular diseases often have multiple cardiovascular risk factors and extensive co-existing atherosclerotic diseases.**
- **Cardiovascular risk factors have been shown to be associated with atherothrombosis. Many of the important risk factors for cardiovascular disease are modifiable, and aggressive treatment of cardiovascular risk factors reduces the risk of atherothrombosis.**
- **In the INTERHEART study, nine potentially modifiable factors accounted for over 90% of the population attributable risk of a first MI. These included smoking, dyslipidaemia, hypertension, DM, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular moderate alcohol consumption, and regular physical activity.**
- **Although new emerging atherothrombotic risk factors are associated with vascular risks, their optimal use in routine screening and risk stratification remains to be determined.**