

Ministry of Defence

Synopsis of Causation

Atherosclerosis

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Atherosclerosis is a disease of large and medium-sized muscular arteries characterised by inflammation and dysfunction of the lining of the involved blood vessels and the build up of cholesterol, lipids and cellular debris. This results in the formation of a plaque, obstruction of blood flow and diminished oxygen supply to target organs.¹

2. Clinical Features

- 2.1. The symptoms of atherosclerosis are variable. Clinical features often do not correlate with the extent of pathological changes (severe signs and symptoms may be associated with mild anatomical disease and vice versa).
- 2.2. Complicated atheromatous lesions(plaque) account for the major morbidity and mortality associated with atherosclerosis. Changes that may occur include:
 - **Calcification** (deposition of calcium) – causing brittleness and narrowing
 - **Ulceration and rupture** – spreads cholesterol-rich fragments of tissue to organs
 - **Superimposed thrombosis** – causing obstruction to blood flow
 - **Haemorrhage into the plaque** – the resultant blood clot may remain localised to the blood vessel wall or may rupture into the lumen of the vessel. In small vessels, this may cause significant and sudden obstruction to blood flow
 - **Aneurysmal dilation** – due to pressure atrophy weakening the underlying blood vessel wall
- 2.3. **Heart** Coronary heart disease (CHD)
 - 2.3.1 **Angina pectoris** is typically retrosternal chest pain which radiates to the left arm and may be associated with shortness of breath. It is relieved by rest and treatment by nitrates and worsened by exertion. As it progresses, it may lead to increasing intensity and frequency of pain, which may occur even at rest (unstable angina).
 - 2.3.2 **Myocardial infarction** (heart attack) usually occurs due to rupture of a plaque or clot formation or both, which may partly or completely occlude one or more blood vessels supplying the heart.²

The topic is explored in more detail in the Synopsis *Coronary Heart Disease*

- 2.4 **Central Nervous System** Impaired blood supply to the brain results in manifestations varying from transient ischaemic attack (TIA) leading to complete recovery, to a stroke which may leave permanent neurological damage (paralysis of arms and legs or impairment of speech, vision, swallowing, bowel or bladder function).
- 2.5 **Peripheral Vascular disease** This may lead to:
 - **Intermittent claudication** Pain in the legs (calf, thigh or buttocks) which comes on with walking or exercise and is relieved by rest. Abnormal sensations (paraesthesiae) may accompany the pain
 - **Infections of the extremities** with non-healing ulcers. Poor blood supply to the toes may lead to digital necrosis (tissue death)

- **Impotence** This is due to reduced blood flow in the penis or ischaemia of the neurological control system
- **Amputation** Atherosclerosis is responsible for about 50% of the amputations resulting from dysvascular causes.³ Also, compared with older counterparts, amputees with premature atherosclerosis have a higher number of failed bypasses before undergoing amputation, and die at a younger age⁴

2.6 Gastrointestinal system and abdomen

- There may be central abdominal pain following a meal (post-prandial mesenteric angina). This may be associated with haematemesis, melaena, diarrhoea, deficiency of essential nutrients and weight loss⁵
- Abdominal aortic aneurysms may remain asymptomatic, come to light as a pulsatile abdominal mass or may rupture, with a high mortality rate

2.7 Physical signs These depend on the system and organs involved but may include:

- Decreased or absent pulses in arms and legs, discolouration of limbs, ulceration or gangrene
- High blood pressure, abnormal heart sounds, increased heart rate. Carotid artery bruits, focal neurological deficits
- Tendon xanthomas are a sign of hyperlipidaemia. Premature xanthelasma may be a sign of hyperlipidaemia

3 Aetiology

- 3.1 Risk factors for the development of atherosclerosis have been extensively studied and may be divided into unmodifiable, modifiable and newer novel risk factors.

Unmodifiable

- 3.2 **Age** The process of atherosclerosis begins in childhood with the development of fatty streaks. They can be found with increasing frequency in adult life but the specific clinical features usually begin after the fifth decade of life.
- 3.3 **Sex** Atherosclerosis is commoner in men than women. However, the protective effect of the female sex hormones is lost after menopause.
- 3.4 **Family history** Having close relatives who had heart disease or a stroke at a relatively young age.

Modifiable

- 3.5 **Hyperlipidaemia** is a major risk factor. The Scandinavian Simvastatin Survival Study (4S)⁶ and the West of Scotland Coronary Prevention Study (WOSCOPS)⁷ have demonstrated a 30-40% decrease in mortality from coronary heart disease following lowering of total serum cholesterol.
- 3.6 **Hypertension** plays a very important role in the development of atherosclerotic cardiovascular disease and stroke. Untreated high blood pressure results in damage to the lining of the blood vessels, which along with other risk factors, such as hyperlipidaemia and diabetes results in the formation of atheromatous plaques.
- 3.7 **Diabetes mellitus** is intimately linked to atherosclerosis, hypertension, hyperlipidaemia, dysfunction of the blood vessels and abnormalities of blood coagulation. Better diabetes control along with control of hypertension and hyperlipidaemia is associated with reduced cardiovascular and overall mortality.
- 3.8 **Cigarette smoking** is a major modifiable risk factor; smoking damages the blood vessel wall lining and causes an increased tendency for blood to clot.
- 3.9 **Metabolic syndrome**⁸ is a relatively new concept which links together all of the above mentioned modifiable risk factors with obesity, and is a practical way for the clinicians to treat the overall risk of developing cardiovascular disease rather than just laying emphasis on individual factors.
- 3.10 **Lifestyle** Inactivity/obesity/lack of exercise is linked to Type 2 diabetes, hypertension and hyperlipidaemia.
- 3.11 The effect of the **oral contraceptive pill** on atherosclerosis is not completely clear. Although it increases the tendency to form blood clots in the veins of the legs, the oestrogenic component probably confers some protection from cardiovascular disease.^{9,10} The “pill” may be contra-indicated if other risk factors for atherosclerosis are present.¹⁰
- 3.12 **Alcohol.** Moderate amounts of alcohol (1-2 drinks/day), especially red wine, has been postulated to have a beneficial cardiovascular effect attributable to the flavonoids present in red wine and the increase in high density lipoprotein (HDL)-cholesterol (the “good” cholesterol) in blood.¹¹ However, excess alcohol is

detrimental to cardiovascular health. It favours hyperlipidaemia and liver disease, worsens diabetes and predisposes to hypertension.

3.13 **Psychosocial risk factors ("stress")**

- 3.3.9 Stress is an imprecise term with different meaning to the general public and different study groups. An expert working group of the National Heart Foundation of Australia¹² examined different components of "stress" which included a) depression, anxiety and panic disorders b) social isolation and lack of quality social support c) acute and chronic life events d) psychosocial work characteristics e) Type A behaviour, hostility. (Type A behaviour pattern refers to a number of personality trait characteristics, including rushed, ambitious and competitive behaviour, impatience, hostility, and intolerance). The researchers conducted a review of systematic reviews and concluded firstly that there was strong and consistent evidence of an independent causal association between depression, social isolation and lack of quality social support, and the causes and prognosis of CHD; and secondly that there was no strong or consistent evidence for a causal association between chronic life events, work-related stressors (job control, demands and strain), Type A behaviour patterns, hostility, anxiety disorders or panic disorders and CHD¹².
- 3.3.10 Pathophysiological mechanisms can be divided into behavioural mechanisms, whereby psychosocial conditions contribute to a higher frequency of adverse health behaviour, such as poor diet and smoking, and direct pathophysiological mechanisms, such as neuroendocrine and platelet activation. These lead to exacerbation of coronary artery atherosclerosis as well as endothelial dysfunction. Acute stress triggers myocardial ischaemia and arrhythmias, stimulates platelet function and increases blood viscosity through haemoconcentration. In the presence of underlying atherosclerosis, acute stress can cause coronary vasoconstriction. The endothelial injury induced by acute stress is also associated with increased responsiveness of the sympathetic nervous system among some individuals, reflected by increased heart rate and blood pressure. Psychosocial stress also disturbs endocrine regulation in women leading to accelerated atherosclerosis.¹³
- 3.3.11 However, there is an ongoing debate regarding the causative role of psycho-social factors in chronic disease in general and cardiovascular diseases specifically. One of the best proponents is the Whitehall study,¹⁴ which demonstrated a correlation between higher mortality and lower professional status/social class even after adjustment for age, smoking, systolic blood pressure, plasma cholesterol concentration, height and blood sugar. This social gradient is a dynamic phenomenon and can change over time. Also, there is an interplay between various risk factors e.g. social class can determine the plasma cholesterol level. Various other studies support this hypothesis.^{15,16,17}
- 3.3.12 However, the above discussion is by no means conclusive. It has been eminently argued that bias and confounding can generate spurious findings and associations, especially in observational studies and that the evidence is not strong to support a causative role of psychosocial factors in CHD.^{18,19} In one study, on active-duty U.S. army personnel without known coronary artery disease, there was a lack of correlation between

psychological factors and subclinical coronary artery disease.²⁰ Paradoxically, in another study, stress was apparently protective, with a lower all-cause and cardiovascular mortality.²¹ The above discrepant results preclude any definitive conclusions.

- 3.3.13 **Acute life-event stress** Acute life event stressors can trigger CHD although it is difficult to quantify the effect of these factors.¹² Acute stressors include significant common events such as bereavement as well as catastrophic events such as earthquakes or terrorist attacks. It is important to differentiate between acute and chronic stress. Although the effect of the former as a CHD trigger is well documented,^{22,23} the effects of the latter remain unclear as discussed above.
- 3.3.14 **Work-related stress** This remains a controversial risk factor. Job-strain has been defined as a joint effect of job demands and job control. Although the Bunker review¹² concluded that there was no strong or consistent relationship between job-related stressors and CHD, other studies have demonstrated a relationship between job strain and increased tendency towards atherosclerosis, especially in early nonsymptomatic stages in men. Women may be protected from such effects.^{25,26} Low job control (the degree to which an employee feels they can control their work) has been associated with increased risk of coronary heart disease and coronary mortality.^{27,28} However, in some cases, poor study design may render such definitive conclusions debatable.
- 3.14 **Hormonal factors** Premature menopause or surgical removal of both ovaries, without subsequent hormone replacement therapy, considerably increases the risk of development of atherosclerosis, most probably due to loss of the protective effect of oestrogens.
- 3.15 **High altitude and cold** The effect of high altitude and cold on atherosclerosis is not clear-cut. Although people living at high altitudes have high haematocrit values, due to the low prevalence of systolic hypertension and possibly lower serum cholesterol concentrations, they have a lower incidence of ischaemic heart disease.²⁹ However, another study has shown a higher risk of stroke associated with long-term stay at high altitude in young males in the armed forces.³⁰
- 3.16 **Newer risk factors** In some individuals, clinical evidence of atherosclerosis may be present without any obvious above-mentioned risk factors. In such cases (and in certain others) it becomes important to investigate for certain “newer” risk factors, which may help in diagnosis and management.
- 3.16.1 **Elevated homocysteine concentration** Homocysteine is an amino acid present as a normal constituent of proteins. Elevated homocysteine concentration is likely to be an independent risk factor for atherosclerosis.³¹ It is postulated to cause damage to the blood vessel wall lining and increase the tendency for the blood to clot. There is ethnic diversity in “normal” homocysteine concentrations, with south Asians having relatively higher levels than Europeans. Deficiency of folic acid, Vitamin B12 and Vitamin B6 may result in abnormally high homocysteine concentrations. Certain rare inherited disorders of homocysteine metabolism may result in grossly high concentrations. Modification is possible by use of folic acid taken daily. However, proof of its efficacy in reducing atheroma is presently lacking.

- 3.16.2 **hs-CRP** (highly sensitive-C-reactive protein) is a marker of systemic inflammation which is also emerging as an independent predictor of cardiovascular disease.³² Since atherosclerosis starts with inflammation of the blood vessel lining, it is likely to become a useful test. However, the measurement of hs-CRP requires further evaluation and standardisation. There is some correlation between raised CRP and plaque instability but no definite mechanism of modification or the risk factor has yet emerged.
- 3.16.3 **Fibrinogen** may be an independent risk factor in apparently healthy people with no history of previous cardiovascular disease.
- 3.16.4 **Lipoprotein(a)** is a subclass of a type of lipoprotein (fat) present in the blood which is likely to be established as an independent risk factor for cardiovascular disease. Its concentration is genetically determined, but tests to measure it reliably need further evaluation.³³ Further, there does not appear to be effective and acceptable treatment for raised levels of lipoprotein(a) at the moment.

4 Prognosis

- 4.1 The incidence of atherosclerosis is difficult to determine since it is mainly an asymptomatic condition. The pathological process begins in childhood and continues throughout life.
- 4.2 In the United Kingdom, the frequency of clinical manifestations of atherosclerosis is high, especially in the West of Scotland.
- 4.3 Coronary heart disease (CHD) is a leading cause of death in the UK. One in 4 deaths in men and one in 6 deaths in women are due to CHD. There are an estimated 2.68 million people living with CHD. It is the biggest killer, causing over 117,000 deaths a year.³⁴
- 4.4 There are an estimated 268,000 heart attacks a year in the UK, which equates to one every 2 minutes.³⁴
- 4.5 Although an extensive systemic disease, it affects different organs in different patients. Symptoms arise due to impairment in blood flow to the target organs, usually once more than 50% of the lumen of the blood vessel is obstructed.
- 4.6 Failure to treat atherosclerosis results in predictable clinical events in the same or other vascular beds. For example, a patient with limb claudication can be assumed to have significant atherosclerosis in multiple vascular beds, including the blood vessels of the heart and brain.
- 4.7 The overall mortality of ruptured abdominal aortic aneurysms is about 80%. The single most important primary preventive measure is smoking cessation.³⁴ Diagnosis of abdominal aortic aneurysm by ultrasound offers a prophylactic method of treatment either by surgery or endovascular techniques.
- 4.8 The prevention and treatment of atherosclerosis and its complications involves control of the known modifiable risk factors. This includes weight loss/physical exercise, diet low in saturated fats, giving up cigarette smoking, control of hypertension, diabetes mellitus and hyperlipidaemia, and medications.
- 4.9 The mainstay of treatment of high cholesterol is the statin group of drugs (which decrease the synthesis of cholesterol by the liver) and are instrumental in reducing coronary heart disease events.^{6,7}

5 Summary

- 5.1 Atherosclerosis is a disease of large and medium-sized arteries, characterised by inflammation and dysfunction of the lining of the involved blood vessels, resulting in the obstruction of blood flow and diminished oxygen supply to target organs.
- 5.2 The process of atherosclerosis begins in childhood and progresses throughout adulthood, but the specific clinical features usually begin after the fifth decade of life.
- 5.3 The modifiable risk factors are inactive life-style, cigarette smoking, a diet rich in calories and saturated fats, high blood pressure, diabetes mellitus and hyperlipidaemia.
- 5.4 Lowering cholesterol by the use of statins, along with sensible dietary changes, can reduce the risk of stroke and heart attack.

6 Related Synopses

Diabetes Mellitus.

Hyperlipidaemia.

Coronary Heart Disease

Stroke

Hypertension

7 Glossary

aneurysm	An abnormal blood-filled dilatation of a blood vessel, especially an artery, resulting from disease of the vessel wall.
bruits	Abnormal sounds heard on auscultation over an artery.
claudication	Cramping pain and weakness in the legs and especially the calves on walking that disappears after rest and is usually associated with inadequate blood supply to the muscles.
fibrinogen	A plasma protein that is produced in the liver and is converted into fibrin during blood clot formation.
folic acid	A type of Vitamin B that is required for normal production of red blood cells.
haematemesis	The vomiting of blood.
hyperlipidaemia	The presence of excess fat or lipids in the blood.
melaena	The passage of dark tarry stools containing decomposing blood that is usually an indication of bleeding in the upper part of the gut.
mesenteric	Related to the mesentery (folds of membrane that cover and support the intestines).
paraesthesia	A sensation of pricking, tingling, or creeping on the skin having no objective cause.
post-prandial	Occurring after a meal.
pulsatile	Throbbing or beating.
retrosternal	Situated or occurring behind the sternum (the breast bone).
transient ischaemic attack (TIA)	A brief episode of decreased brain blood supply that is usually characterised by temporary blurring of vision, slurring of speech, numbness, paralysis, or syncope and that is often predictive of a serious stroke; also called a mini-stroke.

xanthoma

A fatty irregular yellow patch or nodule containing lipid-filled cells that occurs on the skin (as of the eyelids, neck, or back) or in internal tissue and is associated especially with disturbances of lipid metabolism.

xanthelasma

A xanthoma of the eyelids.

8 References

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