Chapter 1

Introduction to Ischemic Heart Disease

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Additional information is available at the end of the chapter

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1. Introduction

"The heart has its reasons which reason knows not." Blaise Pascal (1623-1662)

The heart is the vital organ that tirelessly pumps oxygenated blood from the lungs to the organs and peripheral tissues via the circulatory system. In return, deoxygenated blood is returned via the heart and the pulmonary circulation to the lungs to expel waste carbon dioxide (figure 1). The average human heart beats approximately 72 beats per minute totalling around 2.5 billion beats in a 66-year lifespan. The human heart weighs 250-300g in females and 300-350g in males. The heart is located in the mediastinum of the thorax, anterior to the vertebrae and posterior to the sternum. *Archosaurs* (crocodilians and birds) as well as *Mammalia* species show complete separation of the heart into two pumping units comprised of four distinct chambers. The myogenic musculature of the heart is supplied by the coronary arteries and the entire organ is held within the pericardial sac.

1.1. Development and anatomy of the coronary arteries

As with any organ, the heart requires its own supply of blood for continued functioning. The supply of blood to the myocardium occurs via the coronary artery circuit (figure 2). Their name is derived from the Latin 'Corona', meaning crown as the main vessels encircle the interventricular and atrioventricular grooves.

The arterial tree has two main compartments; firstly, the main arteries (table 1) and ramifications on the surface of the myocardium, known as the extramural coronary system. Secondly, the branches of the surface vessels which penetrate deep into the myocardial tissues are known as the intramural coronary system.

The extramural coronary system is formed from two main arteries. The left coronary artery (LCA) and the right coronary artery (RCA). A third vessel exists in up to 50% of the population and is known as the conus artery. The diameters of the vessels are given in table 1. The intramural coronary system is a complex vascular network containing the main intramural branches which have region specific distribution patterns. The ventricular branches arise at right angles from the subepicardial arteries taking an endocardial route. An important component of the intramural system is the collateral or anastomotic arterial system. These vessels have a characteristic corkscrew appearance. They are present at birth and do not differ in distribution by age or gender. In the normal heart they are 20-350 μm in diameter.

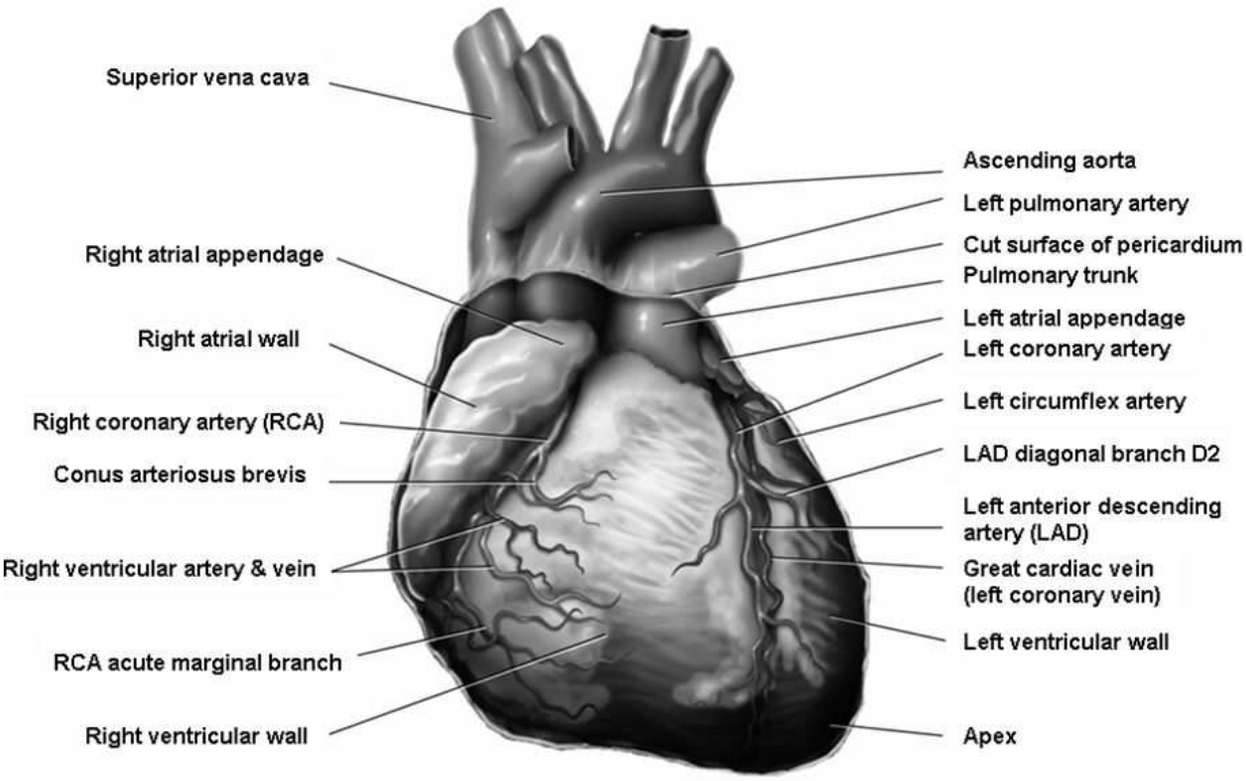

Figure 1. Anterior view of the human heart with blood vessels identified

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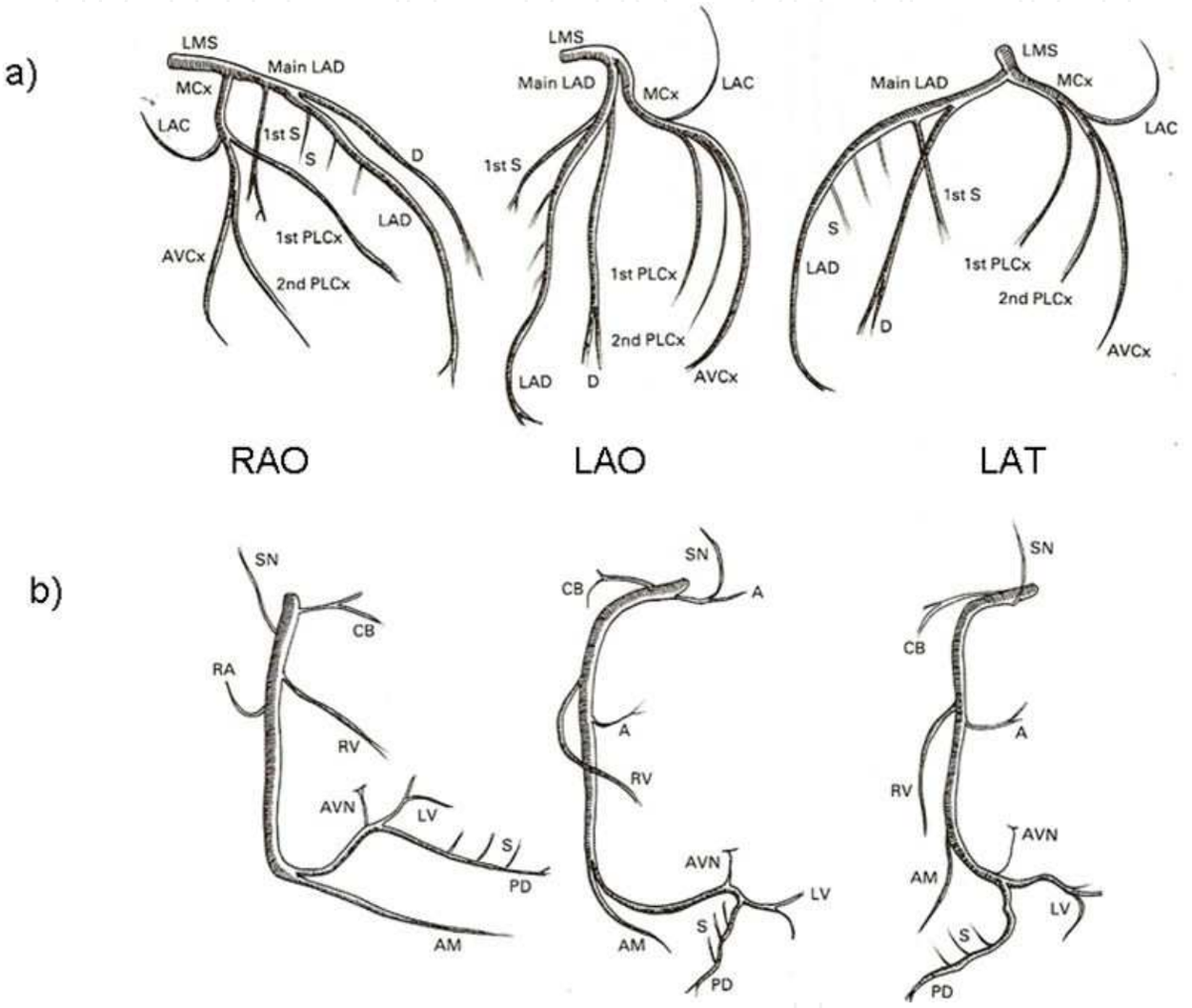

Figure 2. Coronary artery anatomy. a) Left coronary artery and b) Right coronary artery. A, atrial branch; AM, acute marginal artery; AVCx, atrioventricular groove branch of circumflex; AVN, atrioventricular node artery; CB, conus branch; D, diagonal branch of LAD; LAC, left atrial circumflex; LAD, left anterior descending; LAO 30° left anterior oblique projection; LAT, left lateral projection; LMS, left main stem; LV, left ventricular branches; MCx, main circumflex; PD, posterior descending; PLCx, posterior circumflex branch (obtuse marginal); RA, right atrial branch; RAO, 30o right anterior oblique projection; RV, right ventricular branch; S, septal perforating arteries; SN, sinus node artery.

Vessel	Median Diameter (range) in mm
LEFT CORONARY ARTERY (LCA)	4 (2.5-5.5)
Left anterior descending	3.6 (2-5)
DG diagonal	2 (0.5-2.5)
LCX circumflex	3 (1.5-5)
LMG marginal	2.2 (1-3)
RIGHT CORONARY ARTERY (RCA)	3.2 (1.5-5.5)
RMG marginal	1.7 (1-2.5)
PD posterior descending	2.1 (1-3)
THIRD CORONARY ARTERY 'conus artery'	1.1 (0.7-2)
Septal branches anterior from LCX	1 (0.5-2.5)
Septal branches posterior from PD	0.7 (0.3-0.9)
From ascending LAD	0.4 (0.3-0.7)

Table 1. The major coronary arteries.

The primitive embryonic heart is nourished via lacunar or intertrabeclar spaces, forming a net-like structure separating bundles of muscle fibres. Further evolutionary development results in endothelial budding. Originally this was thought to derive from the coronary sinus and aorta, forming superficial veins and arteries which penetrate into the myocardial tissue joining the lacunar spaces. It was then demonstrated in chick-quail chimaeras that the vessels were derived from the proepicardium structure common to the embryo and undergo a transition from epithelial to mesenchymal tissue. Mouse studies refute this, suggesting that the proepicardium gives rise to myocardial stroma and vascular smooth muscle but not coronary artery endothelial cells. Using clonal and histological analysis in the mouse, Red-Horse and colleagues (Red-Horse et al. 2010) demonstrate that coronary arteries are formed by developmental reprogramming of venous cells, arising from angiogenic sprouts of the sinus venosus which returns blood to the embryonic heart. The understanding of angiogenesis in the myocardium may in future lead to more natural methods to stimulate vascular growth and engineering coronary bypass grafts rather than transplanting veins to revascularize damaged myocardium.

2. Cardiovascular disease

A variety of diseases affect the primary functioning of the heart. Cardiovascular disease (CVD) is the collective name for diseases of the heart and blood vessels of the circulatory system. An atlas of types of cardiovascular diseases in the heart and in the circulation are given in table 2.

International efforts have been implemented to classify and code the different types of ischemic heart diseases. A number of notable indexing databases such as the International Classification of Diseases database, Disease Database eMedicine and MeSH databases have produced indexing codes. These are given in table 3.

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Cardiovascular Disease	
Diseases of the Heart	**Diseases of the Circulation**
Angina Pectoris	Aortic aneurysm
Stable Angina	
Unstable Angina	Aortitis
Variant (Prinzmetal's) Angina	
	Arteriosclerosis
Arrhythmia	
Heart block (first-degree and second-degree and complete AV block)	Atherosclerosis
Premature atrial complex	
Atrial flutter	Aortic dissection
Paroxysmal supraventricular tachycardia	
Wolff-Parkinson-White syndrome	Hypertension
Premature ventricular complex	Essential (primary) hypertension
Ventricular tachycardia	Secondary hypertension
Ventricaular fibrillation	Malignant hypertension
Long QT syndrome	
	Stroke (Cerebrovascular accident)
Cardiomyopathy	
Dilated Cardiomyopathy	Transient ischemic attack
Hypertropic Cardiomyopathy	
Restrictive Cardiomyopathy	Arterial disease
	Arterial embolus
Congestive heart failure	Acute arterial occlusion
	Raynaud's phenomenon
Congenital heart disease	Arteriovenous fistula
Atrial septal defect	Vasculitis
Ventricular septal defect	Thoracic outlet syndrome
Patent ductus arteriosus	

Cardiovascular Disease	
Diseases of the Heart	**Diseases of the Circulation**
Pulmonary stenosis	Venous disease
Congential aortic stenosis	Venous thrombosis
Teratology of Fallot	Deep vein thrombosis
Tricuspid atresia	Varicose veins
Truncus arteriosus	Spider veins
Ebstein's abnormality of the tricuspid valve	
Great vessel transposition	Lymphedema
Coronary artery disease	
Ischemic heart disease	
Acute myocardial infarction	
Cor pulmonale	
Heart valve disease	
Mitral stenosis	
Mitral valve regurgitation	
Mitral valve prolapse	
Aortic stenosis	
Aortic regurgitation	
Tricuspid stenosis	
Tricuspid regurgitation	
Myocarditis	
Rheumatic disease	
Pericarditis	
Sudden cardiac death	
Syncope	
Cardiac tumours	
Myxoma	

Table 2. Atlas of cardiovascular diseases of the heart and circulatory system.

Classification system	Code	
International Classification of Diseases (ICD-9) World Health Organisation, Geneva, Switzerland	410	Acute Myocardial infarction (AMI)
	411	Other acute and subsequent forms of Ischemic Heart Disease
	412	Old Myocardial Infarction
	413	Angina Pectoris
	414	Other forms of chronic ischemic heart disease
International Classification of Diseases (ICD-10) World Health Organisation, Geneva, Switzerland	120	Angina Pectoris
	121	Acute Myocardial Infarction (AMI)
	122	Subsequent Myocardial Infarction
	123	Certain current complications following AMI
	124	Other acute ischemic heart diseases
	125	Chronic ischemic heart disease
Diseases Database (DiseaseDB) Medical Object Oriented Software Enterprises Ltd London UK	8695 - Ischemic or Ischaemic Heart disease, Myocardial Ischaemia, Steoncardia, Angina Pectoris, Coronary Artery Arteriosclerosis, IHD	
eMedicine (WebMD) New York, USA	Med/1568 – Angina Pectoris	
Medical Subject headings (MeSH) Unites States National Library of Medicine Bethesda, Maryland, USA	D017202 – Myocardial Ischemia	

Table 3. Classification codes of Ischemic Heart Disease

3. Pathobiology of ischemic heart disease

Hypoxia refers to the physiological or pathological state in which oxygen supply is reduced despite adequate perfusion of the tissue. Anoxia is the absence of oxygen from the tissue, despite being adequately perfused. These are clearly distinguishable from ischemia where oxygen supply is restricted as a direct result of suboptimal tissue perfusion. Ischemic tissue also accumulates toxic metabolites due to the inadequate removal through the capillary and venous blood systems.

The atherosclerotic process responsible for restriction of blood flow in the coronary arteries is a multifactorial process and is initiated by damage to the endothelium. Cholesterol rich low density lipoprotein (LDL) particles enter the intimal layer via the LDL receptor protein (Brown and Goldstein 1979), a mosaic cell surface protein that recognizes apolipoprotein B100 embedded in the LDL particle. It also recognizes apolipoprotein E found in chylomicrons and very low density lipoprotein remnants, or intermediate density lipoprotein. Macrophage cells accumulate oxidized lipid independently of the LDL receptor by endocytosis. This results in formation of juvenile raised fatty streaks within the endothelium. The macrophage release their lipid content and cytokines into the intima. Cytokines stimulate intimal thickening by

smooth muscle cell proliferation, which then secrete collagen, causing fibrosis (figure 3). The lesion appears raised and yellow.

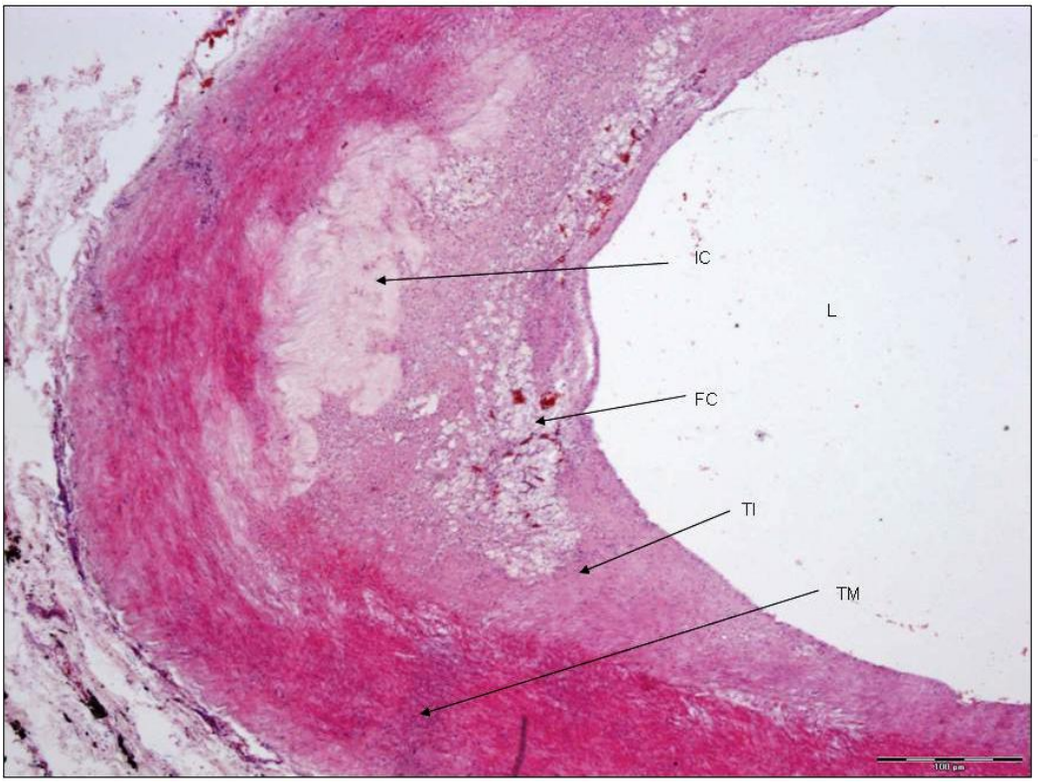

Figure 3. Medium powered H&E histological micrograph of an intimal lesion (x200). FC, foam cell infiltrate; IC, intimal calcification; L, lumen; TI, tunica intima; TM, tunica media.

As the lesion develops, the medial layer of the vessel wall atrophies and the elastic lamina becomes disrupted. Collagen forms a fibrous cap over the lesion that appears hard and white (known as a fibrolipid plaque). The plaque contains macrophage laden with lipid (foam cells) as well as extracellular or 'free' lipid within the lesion. The endothelium is now in a fragile state. Ulceration of the cap occurs at weak points such as the shoulder region, near the endothelial lining. Rupture to the cap can cause turbulent blood flow in the lumen. The exposed lipid core causes aggregation of platelets and development of a thrombosis. This lesion grows due to further platelet aggregation and is responsible for narrowing of the lumen of the artery resulting in localized ischemia. Distal embolization of a piece of such thrombus may travel downstream and can completely occlude smaller arteries.

The symptomatic part of the continuum is known as the acute coronary syndrome (ACS) which is due to the rupture/erosion of the plaque. This produces, depending on the plaque size, vascular anatomy and presence of collateral vessels, a mismatch between the supply and demand for oxygen. A net reduction in supply compared to the demand results in ischemia. Tissue hypoxia proceeds resulting in inadequate blood/oxygen perfusion. If blood flow is not re-established, cardiac cell necrosis will occur. Post AMI survival results in remodelling processes in the myocardium and the development of cardiac failure.

4. Epidemiology of ischemic heart disease

According to the World Health Organisation, chronic diseases of which heart disease is the single largest contributing category; are responsible for 63% of all global deaths (United Nations High-Level Meeting on Noncommunicable Disease Prevention and Control 2012). Non communicable diseases kill 9 million people under the age of 60 every year which has a profound socio-economic impact.

The incidence of Ischemic heart disease (IHD) is higher than for any cancer or other non-CVD condition. Cardiovascular diseases (CVD) are the leading cause of death in the Western World and are dramatically increasing within developing countries. The Age-standardized estimate of mortality by cardiovascular diseases and diabetes per 100,000 people is given in figure 4. 17.1 million people die as a direct result of CVD per year and 82% of these deaths occur in the developing word

It is predicted that by 2030 23 million people will die from a CVD. Data from the USA suggests that CVD was responsible for 34% of deaths in 2006 and over 151,000 Americans who died were <65 years old. The incidence of CVD is declining in the Western World even though rates of lifestyle associated risk factors such as obesity, smoking and type II diabetes mellitus are increasing. The decline is in part due to advances in therapeutic and invasive intervention. In creating better outcomes for those with acute cardiac conditions, patients develop heart failure which requires longer term treatment and monitoring and may in fact be a greater health burden than the acute events themselves.

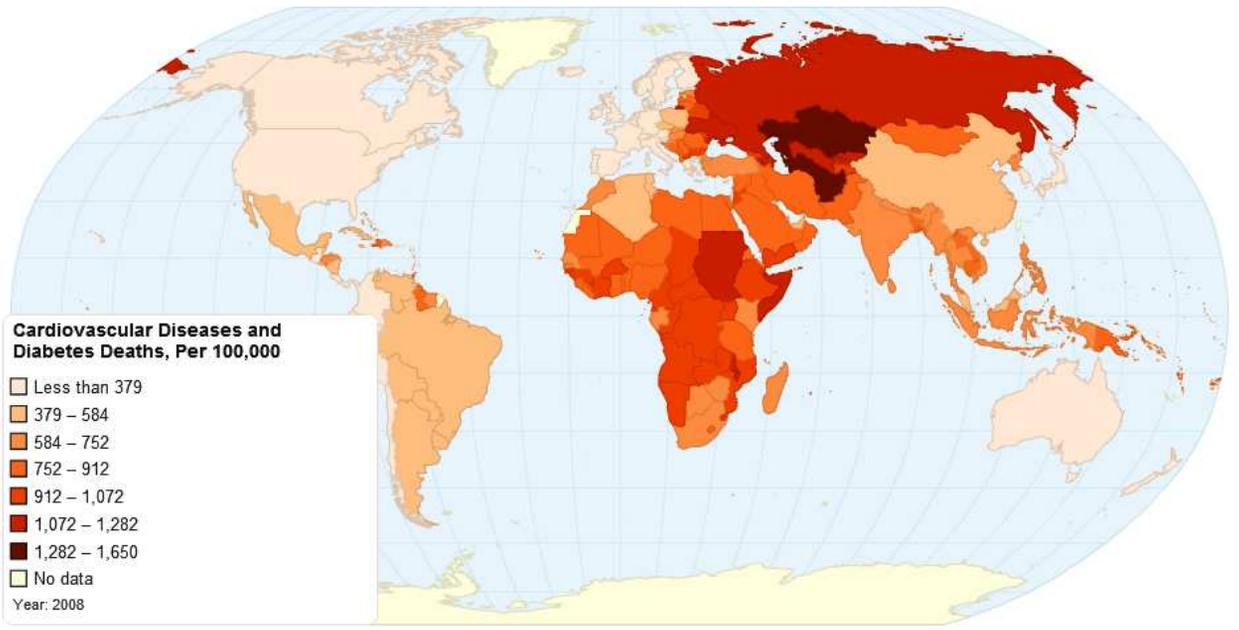

Figure 4. Age-standardized estimate of mortality by cardiovascular diseases and diabetes per 100,000 people. Source: Global Health Observatory Data Repository, World Health Organisation.

5. Risk factors

There is no single causative risk factor for the development of IHD. A number of genetic and environmental risk factors have been established as causative in the development of the atherosclerotic lesion. Smoking and obesity cause 36% and 20% of IHD respectively. A large European meta-analysis of 197,473 participants reported an small association between job stress and the development of coronary artery disease (Kivimaki et al. 2012). There has been extensive research linking a sedentary lifestyle and a lack of exercise with a risk of IHD. The major risk factors for the development of IHD are given in table 4.

Constant risk factors	Modifiable risk factors
Age	Hypercholesterolaemia/dyslipidaemia
Gender	Hypertension
Family history of IHD	Obesity (particularly central abdominal obesity)
Personal history of early IHD	Tobacco and passive tobacco Smoking
Diabetes Mellitus type I	Excessive alcohol consumption
Elevated homocysteine	Diabetes Mellitus type II
Elevated haemostatic factors	Sedentary lifestyle
Baldness & hair greying	Low antioxidant levels
Earlobe crease (Frank's sign)	Infection
	Air pollution (CO, NO_2, SO_2)
	Combined oral contraceptive pill

Table 4. Risk factors for the development of Ischaemic Heart Disease.

6. Signs and symptoms of ischemic heart disease

Ischemia may manifest in many forms. Most commonly, patients present with chest pain on exertion, in cold weather or in emotional situations. This discomfort is known as angina pectoris. Patients may present with acute chest pain at rest which typically radiates down the left arm and up the left side of the neck. Patients may experience nausea, vomiting, sweating and enhanced anxiety. Symptomatically, women present with less 'textbook' symptoms and often describe their condition as weakness, indigestion and fatigue (Kosuge et al. 2006). Up to 60% of AMI are referred to as silent without any observation of chest pain or other symptoms (Valensi et al. 2011).

Angina is diagnosed by evidence of deviation of the ST segment on the electrocardiogram, reduced uptake of thallium-201 during myocardial perfusion imaging or regional or global impairment of ventricular function. In patients with stable angina often have chest pain on

exertion. Patients benefit from cardiac stress testing, echocardiography. If indicated patients should receive coronary angiography to locate anatomically any stenosis with a view to revascularisation by stenting during percutaneous coronary intervention or coronary artery bypass grafting (CABG) surgery.

7. Diagnosis of ischemic heart disease

In the primary care setting, patients may be suspected of having ischemic heart disease based on risk factor assessment and blood chemistry tests such as lipid profiling, inflammatory markers and homocysteine concentration.

Primarily the diagnosis of IHD occurs in the acute setting when patients present with symptomatic chest pain. Patients often present with a myriad of symptoms which confuse the clinical picture. Patients should receive immediate electrocardiography and pharmacological or surgical intervention in those who demonstrate ST-segment elevation in the context of ST-segment myocardial infarction (STEMI). In suspected non-ST segment elevation myocardial infarction (NSTEMI) patients should undergo serial venepuncture for cardiac biomarkers, namely the cardiac troponins which are indicative of myocyte necrosis. Patients may undergo stress testing, whereby the stress response is induced by exercise or pharmacological agents allowing comparison of the coronary circulation at rest and under stress. Patients are monitored continuously whilst exercising on a treadmill, on a ergometer bicycle or following injection of agents such as adenosine, the adenosine A2A receptor Regadenoson or the beta-agonist dobutamine. The agent of choice is dependent on drug interactions with medication or concomitant disease states.

Cardiac ultrasound or echocardiography by two-dimensional, three-dimensional or Doppler ultrasound create images of the myocardium at work. Transthoracic echocardiogram (TTE) is the commonest form and the ultrasound transducer probe is placed non-invasively on the thorax. Transoesophageal echogram (TOE) is an alternative method where the transducer tip is passed into the oesophagus, allowing imaging directly behind the heart.

8. Treatment of ischemic heart disease

Stable IHD patients can be adequately treated in the primary care setting with emphasis on both lifestyle and risk factor modifications to reduce the risk of a future adverse cardiac event. Modification of lifestyle risk factors such as smoking cessation and weight loss control have a direct impact on risk reduction. Further intervention such as treating hypertension, glycaemic control in diabetics and therapeutic intervention in hyperlipidaemia result in risk reduction. Furthermore, elective revascularisation of occluded coronary arteries may confer a reduction in mortality risk compared to conservative therapy. A meta-analysis of 13,121 patients in whom 6476 were randomised to revascularisation compared to medical treatment in the

remainder demonstrated that bypass grafting and Percutaneous coronary intervention are superior to medical therapy alone with respect to 1-10 year mortality (Jeremias et al. 2009).

Patients with symptomatic chest pain suggestive of an AMI and ST segment elevation should receive immediate revascularisation. Fibrinolytic therapy should be administered within 30 minutes and door-to-balloon PCI should occur in no more than 90 minutes from the onset of pain. For non ST segment elevation AMI patients, treatment with aspirin, glycoprotein IIb/IIIa inhibitor such as clopidogrel, low molecular weight heparin, glyceryl trinitrate and opioid therapy for persistent pain.

9. Conclusion

Ischemic heart disease is the major contributing cause of death in the Western World and the incidence is increasing in developing countries. Successful advances in surgical and therapeutic intervention are able to salvage myocardial tissue and increase prognosis if administered in the early phase following injury.

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