Chapter from the book Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment
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1. Introduction

Epidemiology involves the study of the frequency, distribution, and impact of diseases within a community in order to address potential prevention or treatment of these conditions. Accordingly, evaluating the epidemiology of coronary artery disease (CAD) constitutes a particularly wide spectrum that cannot be comprehensively covered in a solitary book chapter. Consequently this first section will provide an introductory broad overview of CAD including pathophysiological concepts, clinical manifestations, geographic variations and its impact on patient health. After defining the broader context of this large field, the specific scope of chapter will be outlined.

1.1 Defining coronary artery disease

The coronary circulation consists of coronary arteries, the microcirculation and the coronary veins. Its function is to supply oxygen and nutrients to the myocardium and remove carbon dioxide and waste products. The importance of this function is exemplified by the fact that a 50% or more reduction in this blood supply to the myocardium is incompatible with life. Thus, not surprisingly, dysfunction of the coronary circulation may result in significant morbidity and mortality.

Although beyond the scope of this chapter, it should be noted that disturbances of the coronary circulation may involve dysfunction within the microcirculation as well as the coronary arteries. Thus the all-encompassing term ‘coronary heart disease’ includes both CAD and microvascular dysfunction. The later may mimic the clinical manifestations of CAD and indeed may co-exist with CAD. However, defining the epidemiology of microvascular dysfunction is especially difficult since specialised investigations are required to confirm its presence, as it may occur in the absence of associated structural microvascular disease.

In contrast, CAD is more readily identifiable and the most common underlying pathophysiological process is coronary atherosclerotic disease. This may be identified by imaging techniques such as coronary angiography, or unequivocally at post-mortem autopsy. Accordingly, detailing the epidemiology of CAD is more readily achievable and the focus of this chapter.

1.2 Atherosclerotic coronary syndromes

Coronary atherosclerotic disease involves the epicardial coronary arteries and may manifest as an acute or chronic coronary syndrome. Acute coronary syndromes (ACS) typically arise
from atherosclerotic plaque rupture with subsequent coronary thrombosis and/or spasm. The resulting coronary artery occlusion gives rise to intense myocardial ischaemia or even myocardial necrosis thereby manifesting as unstable angina or myocardial infarction. On occasions, the ischaemia/infarction may manifest as sudden cardiac death from malignant arrhythmias or acute pulmonary oedema in the compromised left ventricle. Hence ACS may have a spectrum of clinical manifestations ranging from unstable angina, acute myocardial infarction, acute pulmonary oedema or even sudden death, all arising from the same underlying pathophysiological process.

Chronic coronary syndromes (CCS) may also arise from coronary atherosclerotic disease. This typically manifests as exertional angina arising from a coronary atherosclerotic lesion that has progressed to the extent that it compromises coronary blood flow to the myocardium during the increased oxygen demand associated with exercise. As this obstructive lesion is non-occlusive, adequate oxygen supply is restored once the excess myocardial oxygen demand is removed with the cessation of exercise and thus the resolution of the ischaemic chest pain. Hence the principal manifestation of CCS is angina pectoris, which can be monitored in epidemiologic studies.

1.3 Geographic variations in coronary artery disease

The global prevalence of these CAD-related clinical manifestations is increasing although there are regional variations that are influenced by the extent of economic development and social organisation. With industrialisation, there is a shift from nutritional and infectious disorders to the chronic diseases such as CAD. This ‘epidemiologic transition’ has been described as involving 4 stages (Omran, 1971), as detailed in Table 1, (Yusuf et al, 2001). In developing countries, infectious disease and nutritional deficiency are responsible for most deaths (Stage 1) and cardiovascular disease plays only a minor role. The cardiovascular disorders (CVD) that are prevalent in these communities include infectious disease such as rheumatic heart disease or nutritional disorders such as beriberi. With improvements in public health and nutrition, these conditions become less prevalent and disorders related to uncontrolled hypertension become more common (Stage 2). With further industrialisation, lifestyle diseases become more evident. Thus smoking, high fat diets and obesity result in the rapid development of atherosclerosis so that CAD mortality is a major cause of death in middle-aged individuals (Stage 3). With further improvements in public health measures to address these lifestyle risk factors and advances in medical care, atherosclerotic disease associated mortality is delayed so that it is a condition of the elderly (Stage 4). Progression through each of these transition stages is associated with a greater life expectancy. Moreover as shown in Table 1, cardiovascular disease (and especially CAD) contributes proportionally more to the total population mortality.

As evident from Table 1, CAD is present across the globe although its frequency varies with geographic region. Consequently there is a wide spectrum in the prevalence of CAD in developing and industrialised countries; thus discussions relevant to one country may not be necessarily be pertinent to others. Hence it is important to report on the context of the findings when describing the epidemiology of CAD.
### Table 1. The Epidemiologic Transition of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>% Deaths*</th>
<th>Cardiovascular Conditions</th>
<th>Countries</th>
</tr>
</thead>
</table>
| 1. Infections & Nutritional Deficiency | 5-10% | • Rheumatic Heart Disease  
• Nutritional Cardiomyopathy | • Sub-Saharan Africa  
• Rural South America  
• Rural Southern Asia |
| 2. Hypertensive Diseases | 10-35% | • Haemorrhagic Stroke  
• Hypertensive Heart Disease | • China  
• Urban Southern Asia |
| 3. Atherosclerotic CVD in the Middle-aged | 35-65% | • CAD  
• Atherothrombotic Stroke | • Urban India  
• Latin America  
• Former USSR |
| 4. Atherosclerotic CVD in the Elderly | < 50% | • CAD  
• Atherothrombotic Stroke  
• Heart Failure | • Western Europe  
• North America  
• Australia, New Zealand |


*%Deaths from CVD, in relation to total deaths. CVD = Cardiovascular Disease.*

1.4 Health status in coronary artery disease

Epidemiology not only involves monitoring diseases within the community but also their impact on health. Thus the focus should not only be on the disease manifestations of CAD (such as acute and chronic coronary syndromes) but also the patient’s perception of the impact of these disorders on their health. The term ‘health status’ (see Figure 1) is used to define the patient’s perception (rather than the clinician’s perception) of the disease process on their lifestyle. This incorporates the symptoms experienced (e.g. angina), the functional limitation from the symptom (e.g. reduced exercise tolerance) and quality of life (i.e. the

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### Figure 1. Summary of Patient-centred Health Status


Fig. 1. Summary of Patient-centred Health Status.
discrepancy between actual and desired function) (Rumsfeld, 2002). Thus congruous with our evolving patient-centred health care, this chapter will not only focus on CAD in relation to the prevalence and incidence of disease processes but will also detail the impact of CAD on health status.

1.5 Scope of the chapter

Considering the wide spectrum encompassing CAD epidemiology, it is necessary to limit the topics covered in this chapter. Thus the chapter will evaluate overall CAD mortality, myocardial infarction as an example of an ACS and chronic stable angina as the example of a CCS. Within each of these areas, the discussion will focus on (1) the difficulty and limitations in defining the condition and thus its impact in interpreting the data, (2) the prevalence of the condition, (3) the incidence of the condition, where relevant, (4) and the impact of the condition on health status, when appropriate. This comprehensive approach will provide a detailed evaluation of the epidemiology of CAD.

Since the prevalence of CAD varies with geographic location, the discussion in this chapter will be largely focus on industrialised countries (i.e. Stage 4 countries, Table 1). Data from these countries are readily available, generally reliable and the prevalence of disease similar, although there are small differences even within these countries. Thus although the data presented in this chapter is comprehensive in relation to the industrialised countries, it is acknowledged that it is not globally inclusive.

2. Coronary artery disease mortality

2.1 Defining coronary artery disease mortality

Detailing mortality data may seem straightforward since the presence/absence of death is seldom a contentious issue, however whether the death can be attributed or indeed is associated with CAD is more problematic. Many epidemiologic studies derive mortality data from administrative death registries. In most of these registries, the cause of death is obtained from the death certificate completed by the treating doctor, who ascribes the cause of death based upon clinical impression. This contrasts to the more objective assignment of a cause of death from formally conducted autopsy studies. Since non-forensic national autopsy rates are about 5% in most industrialised countries, the cause of death derived from these registries may be unreliable and this should be considered when interpreting the mortality data detailed below.

2.2 Prevalence of coronary artery disease mortality

CVD encompasses not only CAD but also cerebrovascular disease, peripheral arterial disease as well as other cardiac disorders, and is currently the leading cause of death in the world, particularly amongst women. The World Health Organisation (WHO) estimates that such diseases caused almost 32% of all deaths in women and 27% in men in 2004 (World Health Organisation [WHO], 2008). CAD is the most common cause of CVD deaths (45% of all CVD deaths) accounting for 7.2 million deaths/year, or 12% of all deaths worldwide (Figure 2).

In many developed countries, CAD is the single leading cause of death. In the United Kingdom (UK) in 2008, CAD was responsible for about one in five male deaths and one in eight female deaths; a total of 88,000 CAD deaths (15% of total deaths) (British Heart
Similarly in the United States in 2005, CAD was responsible for one of every five deaths, accounting for 445,687 deaths (18% of total deaths) (Lloyd-Jones et al, 2009). In Australia in 2006, CAD accounted for 22,983 deaths (17% of all deaths) and once more was the most common condition responsible for Australian deaths (Australian Institute of Health and Welfare [AIHW], 2010).

2.3 Temporal changes in coronary artery disease mortality

The ‘epidemiologic transition’ described above (Table 1), not only accounts for geographic variations in CAD but also temporal changes. Over the past 30 years, two epidemiological trends have been observed in relation to CAD mortality. In many developed countries there has been an initial rise followed by a fall, while in developing countries there has mainly been a rise in CAD mortality.

In developed countries, there was a peak in CAD mortality in the 1950’s with a progressive decline since the 1960’s. The WHO Multinational MONItoring of trends and determinants in CARdiovascular disease (MONICA) project identified an annual 4% decline in CAD mortality rate trends over 10 years from the 1980’s across 21 countries (Tunstall-Pedoe et al, 2000). For example, in 1996 Australia reported 29,637 deaths (23% of all deaths) due to CAD, and in 2006, the equivalent figure was 22,983 (17% of all deaths). This decline in CAD deaths rates over the past 2 decades has been the most remarkable in Denmark, Australia, Sweden, the Netherlands and Canada, with the rate of CAD death falling by more than 60% (Figure 3). These trends are consistent with an ‘epidemiologic transition’ from Stage 3 to Stage 4 in these countries and reflect an increased life expectancy with the onset of CAD manifestations at an older age.

*Source World Health Organisation, Global Burden of Disease 2004 Update
Figure 3 also highlights the heterogeneity between the countries in the improved CAD mortality. Thus while many Western European countries have shown substantial improvements in CAD mortality as described above, the Eastern European countries (such as Hungary) generally showed less improvement. These trends typically parallel socio-economic differences with the decline in CAD mortality being sharper in countries with a more favoured socio-economic status.

In contrast, some developing countries have an increasing rate of CAD mortality. Indeed, the WHO estimates that 60% of the global burden of CAD occurs in developing countries. Although mortality estimates are difficult to obtain in some of these countries, broad assessments of overall CVD epidemiology report rising CVD mortality in urban China, Malaysia, Korea and Taiwan. In China, CVD mortality increased as a proportion of total deaths from 12.8% in 1957 to 35.8% in 1990 (Khor, 2001). Like many developing countries, it has experienced rapid urbanisation, socioeconomic and health changes, together with an increase in life expectancy - features consistent with stage 2 of the epidemiologic transition.

2.4 Factors influencing coronary artery disease mortality

The landmark Framingham Heart Study was established in 1948 by the US Public Health Service to investigate the epidemiology of atherosclerotic CVD and hypertension. Its contribution to this field was huge as it precipitated a paradigm shift in the approach to CVD. This study transformed the popular belief at the time, which regarded atherosclerotic coronary artery disease as a normal aging process, to the ground-breaking concept of ‘risk factors’ thereby proposing that lifestyle modification could prevent CVD. This iconic longitudinal study demonstrated that advancing age, smoking, hypercholesterolaemia, hypertension and obesity increased the risk of CVD. Subsequently, these investigators developed the ‘Framingham Risk Score’, which predicts the 10 year risk of developing CAD based upon age, cholesterol profile, blood pressure level, diabetic and smoking status. They conclude that at the age of 40 years, the lifetime risk of CAD is 50% for men and 33% for women. Further insights into CAD continue to evolve from the study including the role of gender, depression, and socioeconomic status.

2.4.1 Age

Ageing is an unmodifiable risk factor for CAD, with males clinically manifesting this condition at 50-65 years of age and females about 10 years later, following menopause (Lerner & Kannel, 1986). The WHO reports that the principal cause of death of people over 65 years is CAD, and as age increases, a substantial proportion of deaths are among females. In many developed countries, the number and proportion of older people (i.e over 65 years) is increasing, which is largely explained by declines in fertility and mortality. The ageing population of many countries has accelerated the contribution of CAD to total disease burden. It is predicted that the global ageing population will maintain CAD as a predominant cause of death worldwide (Mensah, 2004).

Among countries with high but declining CAD mortality, it is suggested that these trends are changing with respect to younger age subgroups (O’Flaherty et al, 2009). A slowing or
levelling of the decline in CAD mortality in young adults has now been reported in England and Wales, the US, France, Australia, and New Zealand. These findings are cause for concern, indicating that decades of progress in reducing deaths from CAD appear to be stalling. Changes in lifestyle factors in the young (increasing obesity and sedentary lifestyles) may account for this reduced improvement.


Source Organisation for Economic Co-operation and Development (OECD), 2009
Fig. 3. Age Standardised CAD Death Rates in Developed Countries in 1980 and 2004
2.4.2 Gender

CAD is the leading cause of mortality for both adult males and females alike worldwide. Although the initial manifestation of CAD is delayed in females by about ten years compared to males, there is not an abrupt increase in CAD mortality rates for females immediately following menopause but a progressive increase over subsequent years. Thus more elderly post-menopausal females succumb to CAD then men and have done so since 1984 (Castelli, 1988). Nonetheless, CAD is not solely a disease of elderly women.

In the US, among men aged 35 to 54, the average annual mortality rate from CAD fell by 6.2% in the 1980’s, and levelled off between 2000 and 2002, with an annual decline of just 0.5%. Among women in the same age group, the annual rate of death from CAD dropped by 5.4% in the 1980’s. Between 2000 and 2002, CAD mortality actually increased for females by an average of 1.5%. Furthermore, even in younger females (35 to 44 years), the CAD mortality increased by an average of 1.3% annually between 1997 and 2002. Overall within the transitional trends, the percentage decline in mortality rates has been far greater for men than women, particularly in the US, the UK, Australia and Sweden. The age-standardised mortality rate for males and females since 1978 for the UK is depicted in Figure 4. More alarming is the higher mortality rate observed for young females following myocardial infarction. Younger women, but not older women, have higher rates of death during hospitalisation for myocardial infarction than men of the same age (see Myocardial Infarction section below).

![Age-standardised CAD Mortality in the United Kingdom for Males and Females from 1978 to 2008](source: British Heart Foundation, Coronary Heart Disease Statistics, 2010)

Source British Heart Foundation, Coronary Heart Disease Statistics, 2010.

Fig. 4. Age-standardised CAD Mortality in the United Kingdom for Males and Females from 1978 to 2008
2.4.3 Geographic differences

It is common to categorise CAD epidemiology by geographic region, however the natural history of CAD epidemics varies substantially between countries. For example, in Europe, the changes in CAD mortality in France and Southern European countries were smaller than that observed in the UK and Finland. The differences in industrialised nations are clearly evident in Figure 3. In Asia, CAD mortality is similar in Hong Kong and China, but it is different to trends in Thailand and South Korea, which report lower CAD mortality rates. These differences may be attributed to a low prevalence of CVD risk factors in the South-east Asian countries. Favourable trends observed in the US, Australia, Argentina, Chile and Cuba, who rates of CAD death are traditionally and substantially lower than in most other areas of the world, may in part be explained by improved control of hypertension, as well as better management of patients with CAD. In Eastern European countries, including Bulgaria, Croatia, Romania, and especially the Russian Federation, there is a persisting upward trend in mortality from CAD. Russian CAD mortality rates in the late 1990's were higher than those of Finland, the USA, or Australia three decades earlier.

Regional variation in Britain has been consistently reported for 25 years. In Scotland and Northern England, CAD death rates are the highest, Southern England the lowest and intermediate rates in Wales and Northern Ireland. The rate of sudden death for males in Scotland is 63% higher and for females it is 100% higher compared to the rates observed in South Western England. Furthermore, the highest mortality rates are concentrated in urban areas.

2.4.4 Socio-economic status

Socioeconomic status (SES) indicators, including education, income and occupation, are associated with CAD risk factors, morbidity, and mortality. Early studies beginning in the 1930’s generally showed increased CAD prevalence with industrialisation and affluence in developed nations. However, contemporary data demonstrate that low SES, i.e. less education, lower income, and blue-collar occupations are associated with increased rates of CAD and increased risk of CAD mortality. Correspondingly, lower SES groups also have the least favourable lifestyle characteristics, including obesity, smoking, high cholesterol, hypertension, and lack of physical activity. It is suggested by some that these SES-related differences are increasing even as age-adjusted CAD mortality declines.

The British Heart Foundation reports a clear gradient in CAD mortality across low to high SES group. The inequality is more striking in females than males, with the CAD death rate being five times higher in female blue-collar workers compared to females in professional occupations.

2.4.5 Depression

Additional risk factors are continually being evaluated in order to identify their contribution to CAD mortality and thus potentially develop further targeted therapies. Research has consistently shown that depression is a risk factor contributing to both the development and complications of CAD. Depressive symptoms, regardless of a formal clinical diagnosis have an unfavourable impact on mortality in CAD patients. Both major depression and elevated depressive symptoms are associated with at least a doubling in risk of subsequent death in
CAD patients. The negative prognostic effect also remains in the long-term and after adjustment for other risk factors.

2.5 Summary comments

Epidemiologic data on CAD mortality is limited by the data source since most are derived from administrative registries where the cause of death is obtained from subjectively completed medical certificates rather than objectively performed autopsies. Considering this limitation, CAD is reported as the world’s leading cause of mortality for men and women, being responsible for more than 7 million deaths each year. Although in developed nations CAD is the most common cause of death, globally over 60% of fatalities now occur in developing countries. It is clear that a wide spectrum in the prevalence of CAD mortality exits, and despite much effort to improve the disproportional mortality rates, a social gradient in CAD still remains. This is evident by the higher CAD death rates in lower SES areas within regions and even within countries, and also an apparent gender bias, particularly amongst younger women. With a slowing down of age-adjusted mortality, it is likely that social differences will increase. By 2030, it is projected that the number of CAD deaths will rise by up to 137% in developing nations, and by up to 48% in areas where CAD is in decline, as such CAD will remain the leading cause of death worldwide.

3. Myocardial infarction

3.1 Defining myocardial infarction

Acute myocardial infarction (AMI) remains a leading cause of worldwide mortality, being responsible for 12.6% of total deaths each year (Beaglehole, 2004). As described above, AMI and unstable angina constitute the CAD-related acute coronary syndromes. AMI differs to unstable angina as the former is associated with evidence of myocardial necrosis. A variety of methods are available to detect myocardial necrosis including changes on the electrocardiograph (ECG), plasma cardiac markers (creatine kinase, troponin), imaging techniques (cardiac magnetic resonance imaging, myocardial scintigraphy) and ultimately autopsy gross pathology and histology. The availability of these techniques allow for the definitive diagnosis of AMI to be made. In contrast, the diagnosis of unstable angina is more subjective relying on clinical impression and the absence of evidence of myocardial necrosis. Accordingly, investigating unstable angina epidemiologic data is less reliable and so this chapter will focus upon AMI data only.

The clinical diagnosis of AMI has evolved over the past 10-15 years with the need to make an early diagnosis so that prompt therapy can be instituted. Traditionally the diagnosis is made on the basis of chest pain symptoms, ECG changes and an abnormal plasma cardiac marker. These plasma cardiac markers are particularly pertinent as they are intracellular proteins that are released into the plasma when myocardial cell necrosis occurs. Previously the routine cardiac marker used was creatine kinase, which had limited sensitivity and specificity. The development of the more sensitive and specific troponin assay resulted in myocardial necrosis being detected in patients with a normal creatine kinase. When these troponin leaks were found to have prognostic implications, the clinical diagnosis of AMI was redefined to focus upon the troponin findings. Thus as shown on Table 2, a clinical diagnosis of AMI is primarily made on the basis of an abnormal troponin with at least one other feature; alternatively the diagnosis may be made on autopsy pathological examination (Thygesen et al, 2007).
This change in the diagnostic criteria for AMI, particularly with reference to the plasma cardiac marker, has resulted in more AMI’s being detected. Hence any longitudinal study of AMI will be confounded by the change in the criteria and needs to be considered when interpreting the epidemiologic data. This problem will be further compounded in the future with the evolution of high-sensitivity troponin assays, which may potentially detect even more AMI’s.

In addition to detecting myocardial infarction in the acute setting, a number of the above techniques may detect a previous myocardial infarct. Thus epidemiological studies may survey a population to detect the frequency of myocardial infarction by techniques mentioned in Table 2 relating to ‘healed myocardial infarction’. Each of these methods has their advantages and disadvantages in relation to availability, cost and accuracy. These need to be considered when interpreting the epidemiologic data.

Clinically, AMI has been sub-classified on the basis of the presenting electrocardiograph (ECG) as either ST-elevation myocardial infarction (STEMI) or Non-ST elevation myocardial infarction (NSTEMI). Differentiating these two forms of AMI is important as the immediate clinical management differs. In STEMI, immediate coronary reperfusion strategies (either percutaneous coronary interventions or thrombolysis) on arrival to hospital are mandated in order to reduce the risk of death. In contrast, NSTEMI does not require immediate intervention although early invasive therapy (at least within 7 days) is preferred. This nomenclature has replaced the previous classification of Q-wave and non-Q wave myocardial infarction since the later ECG findings do not occur until late in the course of AMI evolution and do not influence contemporary management strategies. However, as mentioned above, the Q wave can be used to diagnose the presence of a previous myocardial infarct.

### Criteria for acute, evolving or recent Myocardial Infarction

*Either one of the following satisfies the diagnosis for acute, evolving or recent MI:*

1. Typical rise and/or fall in cardiac biomarkers (preferably troponin) with at least one of the following:
   - Ischaemia symptoms
   - Development of pathological Q waves in the ECG
   - Electrocardiographic changes indicative of ischaemia (ST-segment elevation or depression
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2. Pathologic findings of an acute myocardial infarction

### Criteria for healing or healed Myocardial Infarction

*Any one of the following criteria satisfies the diagnosis for healing or healed myocardial infarction:*

1. Development of new pathological Q waves with or without symptoms. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause.

2. Pathological findings of a healed or healing myocardial infarction.

Adapted from Thygesen K et al. Universal definition of myocardial infarction. Eur Heart J 2007; 28: 2525. Copyright permission gained from Oxford University Press 01/08/2011

Table 2. Revised Definition of Myocardial Infarction
In the following sections, the prevalence and incidence of myocardial infarction are described. The *prevalence* of a condition refers to its frequency within a given population at a particular point in time. The *incidence* of a condition refers to the number of new cases within a given population over a specified period of time. The estimates detailed in these sections are derived from several data sources including hospital discharge data, general practice registries and patient self-report from national survey data. Accordingly, the reliability of the data is dependent on the data source.

### 3.2 Prevalence of myocardial infarction

Based upon self-reported myocardial infarction in a UK national survey, the prevalence of myocardial infarction was reported as approximately 4.1% of men and 1.7% of women in 2006 (BHF, 2010). This represents some 1.5 million people within the UK. As shown in Figure 5, the prevalence is age-dependent, extending from 1% of men < 45 years of age to 17% of those ≥ 75 years old. Furthermore, there is local geographic variation for all ages in the United Kingdom the highest prevalence is seen in men from Wales (9%) and women from Scotland (2.4%).

Similarly, in the USA, the prevalence of myocardial infarction was 3.6% in 2006 based upon national survey data available from the American Heart Association (Lloyd-Jones et al, 2009). The prevalence was slightly higher in African American males (5.1%) compared with Caucasian males (4.9%) but lower in African American (2.2%) females compared with their Caucasian counterparts (3%). As with the UK data, the prevalence of myocardial infarction was greater in the elderly compared with those < 50 years of age.

In contrast to these developed countries, South Asian countries (such as India, Pakistan, Bangladesh, Sri Lanka, and Nepal) the highest prevalence of myocardial infarction is seen in those younger than 40 years of age, whereas it is less marked in those older than 60 years. These observations are consistent with Stage 3 of the epidemiologic shift (Table 1) and reflect the development of risk factors at younger ages (Joshi et al, 2007).

### 3.3 Incidence of myocardial infarction

While the prevalence of myocardial infarction reflects both previous and new (acute) myocardial infarcts, the incidence of myocardial infarction only reflects the later. The incidence of AMI has decreased in a number of developed countries during the past three decades, including the UK and remains the lowest in China and Japanese populations. Age adjusted data has indicated that for men and women between the ages of 35-64 years there are only 90/100,000 new cases for AMI in China and 20/100,000 new cases in Japan (Ueshima et al, 2008).

The most recent estimates of incidence of AMI in the UK are based on national level data from associated hospital and/or mortality statistics and suggest that in Scotland the incidence of AMI has decreased by about 25% between 2000 and 2009 in both men and women. Thus considering all ages in Scotland in 2006, approximately 252/100,000 males were newly diagnosed MI cases and 118/100,000 females.

In relation to the clinical type of AMI, it has been estimated that more than 3 million suffer from STEMI and 4 million people suffer from NSTEMI worldwide each year (White & Chew,
The 6-month mortality rate following infarction has been reported as 4.8% for STEMI and 6.2% for NSTEMI in an international registry involving 14 countries (Goldberg et al, 2004). Other studies have also shown an adverse prognosis for NSTEMI compared with STEMI patients at 12 months post-infarction (Terkelsen et al, 2005; Montalescot et al, 2007).

3.4 Factors influencing myocardial infarction

The prevalence and incidence of myocardial infarction can be influenced by demographic, biological and psychosocial factors, some of which are modifiable and thus potential therapeutic targets. These factors warrant further discussion.

3.4.1 Demographic factors

Acute myocardial infarction is rare in childhood and adolescent years but increases in prevalence in the middle decades, particularly in the developing countries. In developed countries it is increasingly becoming a disease of the elderly, which has important economic implications. For example, 70% of AMI admissions in Australia are for patient’s ≥ 65 years old. These patients often have a complicated course as they have existing co-morbidities that complicate the therapy of their AMI.

Considerable interest has evolved in gender differences in CAD and is the focus of another chapter within this book. Epidemiologic data concerning AMI amongst women is now being

Adapted from the British Heart Foundation, 2010 report. Prevalence rates are weighted for non-response. Respondents were asked to recall whether they had ever been diagnosed with myocardial infarction by a doctor.

Fig. 5. Age specific prevalence of AMI in the United Kingdom, England, 2006
revised as early data primarily focused on middle-aged males. It is well described that men experience myocardial infarction about 10 years younger than women (Figure 5) but in the post-menopausal years, women rapidly catch up to the men. Despite this, women have a larger in-hospital mortality from their AMI until about the age of 80 years when they are similar to men (Figure 6) (Vaccarino et al, 1999). Of particular concern is that the greatest disparity in this mortality is between young women and men (Figure 6). The cause for this gender difference is not apparent and the focus of ongoing investigations.

In addition to age and gender, geographic factors influence the incidence of AMI. These have been described above and are likely to be multifactorial in origin. Factors such as ethnicity, and following social economic class, industrialisation may all contribute to apparent geographic differences.

![Fig. 6. Age & sex specific prevalence of AMI mortality](image)


3.4.2 Biological/lifestyle risk factors

The Framingham Heart Study was instrumental in establishing modifiable biological risk factors that were associated with AMI. A plethora of subsequent therapeutic studies have since demonstrated that modifying these risk factors can prevent AMI thereby confirming the importance of these risk factors and establishing the practice of preventative cardiology. These risk factors have since been incorporated into many risk scores for predicting the risk of AMI.

A potential limitation of the Framingham study is the select population studied; an east coast USA community. More recently a large multinational study has been conducted to evaluate the association between the conventional modifiable risk factors and AMI (Yusuf et al, 2004). The INTERHEART study recruited patients from 52 countries in a case-control study. They reported that the traditional risk factors described in the Framingham study
accounted for most of the risk of AMI, independent of the country (Yusuf et al, 2004). In particular, the risk of AMI increased with the following factors in descending order of their adjusted approximate odds ratio: dyslipidaemia (3.3-fold, as defined by apolipoprotein B/A1 ratio), smoking (2.9-fold), psychosocial factors (2.7-fold), diabetes (2.4-fold), hypertension (1.9-fold) and abdominal obesity (1.6-fold). Reduced exercise and daily fruit/vegetable intake also increased the risk. Figure 7 highlights the importance of these factors and in particular the exponential risks when these factors are combined.

The prevalence of these biological factors within the community varies with age and gender, as shown in Figure 8. In relation to smoking rates, the UK prevalence is around 20% with the prevalence having peaked for men and even begun to decline; however for women they continue to climb. In contrast, hypercholesterolaemia, hypertension and diabetes all remain prevalent (Figure 8). Whereas the prevalence of hypertension and diabetes increases with age, the prevalence of hypercholesterolaemia plateau’s/declines in the elderly.

3.4.3 Psychosocial factors

Both social and psychological factors are associated with AMI risk. Socioeconomic factors such as shorter education and lower income (particularly in women), and unmarried cohabitation have been shown to contribute towards the risk of AMI (Nyboe et al, 1989). In particular, socioeconomic status, work and home roles may play an important prognostic
role, particularly in young women (Lacey & Walters, 2003). Women often work outside the home, in addition to their roles within the household as wives, mothers and caregivers to elderly parents. There is also mounting evidence that age, gender, and social class affect health related quality of life (HRQoL) in the general population, with women reporting a poorer HRQoL than men, particularly following a cardiac event.

Depression is the leading cause of disability worldwide affecting more than 120 million people every year. It is known to be an independent risk factor for the onset and subsequent poor prognosis of CAD (Schrader et al, 2004; Schrader et al, 2006) and can be a precursor to AMI and even cardiac death. Following AMI, 65% of patients report experiencing symptoms of depression and major depression is present in 15-22% of these patients (Guck, 2001). Depressed patients, particularly women, are also at an increased risk of mortality, experience a greater likelihood of cardiac hospitalisation and suffer from poor HRQoL in the first year post AMI (Frasure-Smith et al, 1999).

Depression has a significant, negative impact on psychological and social functioning, as well as on work and leisure-related activities. Patients who are depressed are more likely to experience social problems over the first year of post-MI recovery, are slower in returning to work, experience more frequent episodes of angina, report more physical impairment and are less likely to attend cardiac rehabilitation than are non-depressed patients (Carney and Freedland, 2003).

3.5 Health status in myocardial infarction

Mortality associated with myocardial infarction is well described and reflected in the CAD mortality figures described in section 2. However the impact on this disorder also must be considered in relation to health status. In a recent study, Maddox et al (Maddox et al, 2008) reported that almost 1 in 5 patients with AMI experienced ongoing angina 12 months following an infarct. The clinical determinants of this ongoing chest pain included cardiac variables such as a prior history of angina, post-infarct angina during the index hospital admission and previous coronary bypass surgery. Additionally, non-cardiac variables such as younger age, female gender, continued smoking post-infarction, and depression were also important. Indeed depression is not only associated with ongoing symptoms following AMI but is also an important determinant of subsequent HRQoL (Rumsfeld et al, 2001).

3.6 Summary comments

The diagnostic methods and criteria for AMI have evolved in recent years so that more infarcts can be detected with the current technologies. This needs to be considered when interpreting data (especially longitudinal data) concerning myocardial infarction. Despite this, it is clear that AMI is a leading cause of morbidity and mortality worldwide and is responsible for over 12% of deaths each year, with a larger majority of the population suffering from NSTEMI than STEMI. The incidence of AMI has decreased in the industrialised world due to lifestyle changes and therapeutics; however, rates are rising in developing countries such as Asia, Eastern Europe and parts of Latin America. Although the prevalence of AMI is higher in men of all age groups, it is concerning and unexplained why the in-hospital myocardial infarct mortality is higher in women, particularly in the premenopausal era. The factors influencing the occurrence of myocardial infarction have
been well addressed over the past 4-5 decades however the management of factors that influence health status in patients with a recent myocardial infarct require further development.

Percentage of adults with blood cholesterol levels $\geq 5.0\text{mmol/l}$.

Fig. 8A. Prevalence of major biological risk factors by age and sex, in England in 2008.

Hypertension - blood pressure $>140/80$.

Fig. 8B. Prevalence of major biological risk factors by age and sex, in England in 2008.
Diabetes mellitus – both Type I and II. Source a, b & c - British Heart Foundation 2010 report.

Fig. 8C. Prevalence of major biological risk factors by age and sex, in England in 2008.

4. Chronic stable angina

4.1 Defining chronic stable angina

The evaluation of epidemiologic data concerning chronic stable angina is more challenging than assessing CAD mortality or myocardial infarction data. Unlike these other conditions, the diagnosis of chronic stable angina is largely based upon clinical criteria and can only be objectively assessed with specialised investigations such as invasive coronary angiography. As these techniques may not be performed in all individuals with chest pain or angina, the background frequency of the disease is difficult to quantitate. Accordingly, interpretation of data concerning chronic stable angina must be made in the context of the data collected, which may be merely on clinical impression in many studies. This limitation should be considered when reviewing this data.

There exists a certain ambiguity in defining the term ‘angina pectoris’ which has arisen from its use to describe a group of clinical disorders rather than a symptom. First clinical characterised by William Heberden in his 1772 publication entitled ‘Some account of a disorder of the breast’(Heberden, 1772), it refers to a strangling sensation, which usually occurs on exertion, however patients may experience angina without physical activity whereupon it is referred to as rest angina (Maseri, 1995).

In contemporary medicine, ‘angina’ may be used in a more generic context, referring to any coronary heart disease syndrome that results in myocardial ischaemia. These angina syndromes may have different coronary pathophysiological mechanisms responsible for initiating the myocardial ischaemia, including coronary artery spasm and microvascular dysfunction. They may manifest as exertional or rest angina, depending upon the underlying mechanism. The clinical angina syndromes are summarised in Table 3 below.
Epidemiology of Coronary Artery Disease

Table 3. Types of Angina. Source British Heart Foundation, Coronary Heart Disease Statistics, 2010

Table 4. American College of Physicians (ACP) Angina Pectoris Definition

Chest Pain Features

1. **Substernal chest discomfort** – characteristic quality (tightness) & duration (minutes)
2. **Provoking Factors** – exertion or emotional stress
3. **Relieving Factors** – rest or sublingual nitrates

**ACP Classification:**
- **Typical Angina** – all 3 of above criteria met.
- **Atypical Angina** – only 2 of above criteria
- **Non-cardiac Chest Pain** – only 1 of above criteria
In this section, the data presented concerning ‘angina’ will predominantly focus on patients with chronic stable angina. It will concentrate on the prevalence, incidence, clinical profile, associated morbidity and mortality with this condition. Although the clinical features of the other forms of angina have been alluded to, their epidemiological aspects are less clearly described and unfortunately there are no studies that directly compare the prevalence or incidence of the various forms of angina.

4.2 Prevalence of chronic stable angina

Despite the declining incidence of myocardial infarction, the prevalence of angina remains high with direct costs in the United States in 2000 estimated at over $75 billion (Javitz et al, 2004). Although the exact prevalence of stable angina is unclear, in the UK in 2009, it is estimated that 2.1 million people suffered from angina thus representing a prevalence of approximately 5% of men and 4% of women (BHF, 2010). Coronary heart disease accounts for 1 in 4 deaths in the UK and the lifetime risk for those over 40 years is 49% in men and 32% in women.

Similarly, in the United States, approximately 10.2 million Americans were reported to have angina in 2006 with 4.7% of Caucasian men and 4.5% of Caucasian women over the age of 20 years affected (Lloyd-Jones et al, 2010). These data are primarily based upon patient self-report of a history of angina and thus subject to limited validity.

Although the prevalence of angina in the UK and USA are similar, it is affected by age, gender, ethnicity, and geographic region. As shown in (Figure 9), within the UK, the prevalence is almost 17% amongst males and 12% in females over the age of 75 years but is less than 1% of all those under 45 years of age. Furthermore for all ages, the prevalence of angina in men from Northern Ireland is approximately 6% whereas amongst Welshman it is 4% (BHF, 2010). Ethnic differences in angina occurrence are well illustrated in the United States where the prevalence in men over the age of 20 years is 3.8% in Caucasians, 3.3% in African Americans, and 3.6% in the Hispanic population. The equivalent prevalence amongst females is 3.7%, 5.6% and 3.7%.

4.3 Incidence of chronic stable angina

Based upon surveying general practitioner patient case records, the incidence of newly diagnosed angina in the UK was estimated at 28,000 new cases in 2009 (BHF, 2010). Thus overall, approximately 49/100,000 males were newly diagnosed angina cases and 28/100,000 females. Figure 10 illustrates the age-specific incidence of angina.

4.4 Factors influencing chronic angina

Several large prospective epidemiological studies have provided important insights into the characteristics of patients with chronic stable angina. One of these was the Coronary Artery Disease in gEneral practiCE (CADENCE) study (Beltrame et al, 2009), which recruited 2,031 chronic stable angina patients from general practices across Australia. The sample was representative of this population based upon geographic location. It particularly focussed upon continuing angina symptoms in these patients and surprisingly found that almost 1 in 3 continued to experience angina at least once a week, despite contemporary therapies. This
Fig. 9. Age-specific Prevalence of Angina in the United Kingdom in 2009.

Source British Heart Foundation, Coronary Heart Disease Statistics, 2010

Fig. 10. Age-specific Incidence of Angina in the United Kingdom in 2009.

Source British Heart Foundation, Coronary Heart Disease Statistics, 2010
was similar to that reported in United States (Wiest et al, 2004) and in an international multicentre study (Kirwan et al, 2008).

The clinical characteristics of the chronic stable angina population in the CADENCE study, is summarised in Table 5. As would expected, these are predominantly elderly males with many having conventional cardiovascular risk factors. Their angina symptoms were consistent with ACP defined angina in 72% of the patients. Most had experienced an episode of ACS at some stage of their chronic illness with almost half having experienced an acute myocardial infarction.

Importantly, this study reported that gender or the presence of heart failure or peripheral arterial disease, were independent clinical determinants of ongoing weekly angina in patients with chronic stable angina (Beltrame et al, 2009).

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Artery Disease Risk Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71 ± 11 years</td>
</tr>
<tr>
<td>Male gender</td>
<td>64%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>78%</td>
</tr>
<tr>
<td>Previous or current smoker</td>
<td>59%</td>
</tr>
<tr>
<td>Obesity (BMI and/or waist circumference)</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Associated Cardiovascular Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Previous acute coronary syndrome</td>
<td>70%</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>22%</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>17%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Angina Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Substernal chest discomfort</td>
<td>93%</td>
</tr>
<tr>
<td>Pain provoked by exertion</td>
<td>73%</td>
</tr>
<tr>
<td>Pain provoked by emotional stress</td>
<td>26%</td>
</tr>
<tr>
<td>Pain relieved by rest</td>
<td>54%</td>
</tr>
<tr>
<td>Pain relieved by sublingual nitrates</td>
<td>51%</td>
</tr>
</tbody>
</table>

Table 5. Clinical Characteristics in Stable Angina Patients. Data from (Beltrame, Weekes et al. 2009).

4.4.1 Gender

In a gender sub-analysis of the CADENCE study, significant gender disparities in coronary risk factors, clinical features, diagnostic investigations and management were observed as well as differences in angina-related health outcomes (Dreyer et al, 2011). Although women had more frequent angina which was associated with greater physical impairment and a poorer quality of life, they were less extensively investigated, prescribed fewer cardio-protective agents, less likely to achieve guideline lipid or weight targets and were less likely to receive...
any specialist cardiology review (Figure 11). The predilection for women having more frequent angina is likely to be multi-factorial and may include biological, clinical presentation and assessment differences between genders (Bairey Merz et al, 2006). For example, women may have smaller coronary arteries that are less amenable to revascularisation therapies. Furthermore, coronary microvascular dysfunction is more prevalent in women and angina resulting from this is less responsive to conventional anti-anginals.

Fig. 11. Gender comparisons in the clinical management of stable angina patients. Age adjusted frequency data for (a) cardiology review, (b) pharmacological therapy and (c) revascularisation therapy, in 2005 stable angina patients categorised by gender. (male vs. female: *p < 0.05, **p < 0.01, ***p < 0.001). Data from Dreyer et al (2011). Copyright permission gained Elsevier 30/09/2011

4.4.2 Co-morbidities

As shown in Table 5, many chronic stable angina patients have a history of a previous MI and their cardiac prognosis will be influenced by this event. In chronic stable angina patients who have not previously experienced a myocardial infarct, the risk of myocardial infarct or all-cause death has been described as 1.7%/year and 1.9%/year, respectively (Lampe et al, 2000).

Co-existing heart failure and/or peripheral arterial disease have been shown to be important determinants of on-going angina symptoms in patients with chronic stable angina (Beltrame et al, 2009). This potentially reflects the more extensive disease in these patients. Certainly, patients with chronic stable angina and co-existing peripheral arterial disease were more physically limited and a poorer quality of life than those without co-existing peripheral arterial disease (Wilson et al, 2011).
4.5 Impact of chronic stable angina on health status

The CADENCE study not only demonstrated that many patients with chronic stable angina have frequent ongoing symptoms but also that frequent angina is associated with reduced physical limitations and a poorer quality of life (Beltrame et al, 2009). Although the CADENCE study utilised a threshold of angina of at least once week, the relationship is a continuum as shown in Figure 12. Thus the more frequent the angina, the greater the impairment in physical limitation and quality of life. Hence enquiring about angina frequency may provide useful clinical insights into the impact of the disorder on the patient’s quality of life.

While enquiring about the frequency of angina provides some insights into the disability associated with the disorder, it does not replace a detailed history and evaluation identifying the full impact of the condition on the patient. Unfortunately clinicians may not be completely aware of the angina burden experienced by their patients as alluded to in the CADENCE study. In this study, the clinicians reported that 80% of their patients had optimally controlled angina and that 61% had minimal impairment in their physical activity by the angina. In contrast, patient questionnaires demonstrated that only 52% of patients reported being angina-free and only 47% described their angina as not limiting their enjoyment in life. Hence further efforts are required to bridge this gap between the patient’s experience and the clinician’s perception of the disability associated with angina.

SAQ = Seattle Angina Questionnaire. Adapted from (Beltrame et al, 2009). Copyright gained 30/09/2011.

Fig. 12. Relationship between Angina Frequency and Patient-assessed Quality of Life Indices.

4.6 Summary comments

Although data concerning the epidemiology of chronic stable angina must be interpreted with caution considering the objectivity of the data source, substantial information is available primarily based upon patient self-report and general practitioner clinic surveys. In developed countries, the estimated prevalence of stable angina is 4-5% and the incidence of new cases approximately 46/100,000 population. The chronic nature of this condition results
in significant impairment in patient health status with a recent study reporting that almost a third of patients have angina once a week. Since there is an inverse relationship between symptom frequency and its related physical limitation and quality of life, these patients have substantial health status impairment that warrants more attention.

5. Key facts in the epidemiology of coronary artery disease

Coronary artery disease (CAD) is the global leading cause of death and may manifest clinically as an acute coronary syndrome such as AMI, or a chronic coronary syndrome such as chronic stable angina.

**Concerning CAD Mortality:**
- It is estimated that 7.2 million people died world-wide in 2004 from CAD (i.e. approximately 12% of all deaths).
- In developing countries the CAD mortality is rising but in developed countries it has been falling since the 1960’s.
- CAD mortality varies with age, gender, geographic region, socioeconomic status and depression.

**Concerning Myocardial Infarction:**
- The prevalence of myocardial infarction within developed countries is approximately 3-4%.
- The incidence of new myocardial infarction within developed countries is approximately 200/100,000 population.
- Factors influencing the frequency of myocardial infarction within the community include (a) demographic – age, gender, (b) lifestyle/biological – lipid profile, smoking status, blood pressure, diabetic status, obesity, fruit/vegetable intake, alcohol consumption, and (c) psychosocial factors.
- Approximately 1 in 5 patients continue to experience angina 12 months following an AMI. The frequency of these ongoing symptoms is not only influenced by cardiac factors (such as a pre-infarction history of angina) but also non-cardiac factors such as age, gender and depression.

**Concerning Chronic Stable Angina:**
- The prevalence of chronic stable angina within developed countries is approximately 4-5%.
- The incidence of newly diagnosed angina within developed countries is approximately 46/100,000 population.
- Factors that influence the frequency of angina symptoms in patients with chronic stable angina include female gender and co-existing heart failure or peripheral arterial disease.
- Despite contemporary therapies in developed countries, almost 1 in 3 patients with chronic stable angina continue to experience angina at least once a week. Since angina frequency is inversely related to physical limitation and quality of life, these patients have a considerably impaired health status.
6. Appendix: definitions

ANGINA PECTORIS – a strangling sensation in the chest resulting from myocardial ischaemia.

CORONARY HEART DISEASE – a group of clinical disorders involving coronary circulatory dysfunction resulting in impaired coronary blood flow and thus myocardial ischaemia. This includes coronary atherosclerosis, coronary artery spasm and/or microvascular dysfunction.

CRESCENDO ANGINA – angina pectoris that is occurring more frequently or with greater intensity, or with less provocation. It is a form of unstable angina.

EXERTIONAL ANGINA – angina pectoris precipitated by exertion.

INCIDENCE – the number of new episodes of a disorder over a period of time (eg new myocardial infarcts in 2007)

MIXED PATTERN ANGINA – angina pectoris occurring during exertion but also on occasions at rest.

MYOCARDIAL INFARCT – a pathological condition where inadequate coronary blood flow results in myocardial necrosis.

MYOCARDIAL ISCHAEMIA – a pathological condition where an insufficient coronary blood flow results in inadequate oxygen supply and the accumulation of wastes products in the myocardium.

PREVALENCE – the number of patients with the disorder at any particular time (eg patients with a myocardial infarct in Britain).

REST ANGINA – angina pectoris occurring at rest.

7. References


Montalescot, G. Dallongeville, J et al. (2007). STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J* 28(12): 1409-1417.


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Cardiovascular disease is ranked as the leading cause of death worldwide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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