Coronary Artery Disease

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Abstract

Coronary heart disease (CHD) is the largest cause of death and disability and the largest single cause of death in Australia and accounted for 21% of all deaths in 2000 and 19% of all deaths in 2004. A single aetiology is rarely found in the majority of old people with CHD. The risks for coronary artery disease increase with age. The damage to the endothelial lining is most often caused by a combination of the following: hypertension, high blood cholesterol, smoking and diabetes. This review discusses the risk factors followed by an update on the clinical management. A large proportion of elderly patients with myocardial ischaemia have atypical manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction. Early diagnosis and prompt treatment are vital in patients with STEMI. Preventing heart disease is an important part of overall management.

Keywords

Coronary heart disease · Risk factors · Unstable angina · Acute coronary syndromes(ACS) · Unexpected sudden death · ST-elevation myocardial infarction (STEMI)

Introduction

In Australia, the incidence of coronary heart disease (CHD) in 2003 was an estimated 49,800 CAD events (non-fatal hospitalisations plus number of deaths in the population) among 40–90 year olds [1]. A 2004–2005 National Health Survey in Australia based on self-reporting revealed that 1.7% of those surveyed had manifestations of CHD, three-quarters of whom had angina and

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one-third reported of having had a heart attack [1]. It is the largest cause of death and disability and the largest single cause of death in Australia and accounted for 21% of all deaths in 2000 [2, 3] and 19% of all deaths in 2004 [2]. CHD accounted for 51% of all cardiovascular deaths and half of them were from acute myocardial infarction [1].

In the United States, the incidence of CHD in 2004 was approximately 1 in 226 or 1.2 million people according to the American Heart Association [4]. Twenty percent of all hospitalisations for myocardial infarction (MI) and 30% of all MI-related hospital deaths occurred in patients above 80 years who constitute only 5% of the US population [5]. The prevalence of chronic ischaemic heart disease in men and women 65 years and over in the United States in 1995 was 83 per 1000 men and 90 per 1000 women. Among those 75 years of age and over, the prevalence was 217 per 1000 for men and 129 per 1000 for women [6].

The blood supply to the heart is from two main coronary arteries, the left and right. Both arise from the root of the aorta. The left coronary artery divides into circumflex and anterior descending branches that perfuse the greater part of the left ventricle and the left atrium. The right coronary artery supplies the inferior surface of the left ventricle, the right ventricle and the right atrium. Branches from both arteries penetrate the myocardium and form a dense capillary bed.

Risk Factors

A single aetiology is rarely found in the majority of old people with CHD. Risk factors for CHD can be categorised into non-modifiable and modifiable, and modification of some of these factors can reduce the risk of CHD (primary prevention) and will be just as helpful in secondary prevention. It is important to identify the non-modifiable risk factors (Box 1) for these may alert the clinician to potentially risk groups. Within this group, treatment of any modifiable factors may be of importance:

(i) Non-modifiable CAD risk factors

The risks for coronary artery disease increase with age. Men are at greater risk than women until women reach menopause when risks become equal for both. Family history is a well-known risk factor in the development of atherosclerosis, and a family history of familial hypercholesterolaemia carries a significant risk. Race may also be important.

(ii) Modifiable CAD risk factors (Box 1)

Among the modifiable CAD risk factors, particular attention is required to identify dyslipidaemia, hypertension and smoking. The Framingham study had shown that when these three risk factors are present, the heart attack rate was seven times greater than when none was present. The Framingham study demonstrated a near linear relationship between total cholesterol levels or LDL level and severity of the atherosclerosis as determined by the mortality rate from CHD and also association with other risk factors such as age, family history, gender and hypertension [7]. The development of CAD has also been shown to be linked with hypertension and smoking [3]. The damage to the endothelial lining is most often caused by a combination of the following: hypertension, high blood, cholesterol, smoking and diabetes [8].

Box 1 Modifiable Risk Factors and Non-modifiable Risk Factors

Dyslipidaemia
Hypertension
Smoking
Diabetes
Obesity
Physical inactivity
Stress
Alcohol consumption
Age
Gender
Family history
Ethnicity/race

The landmark INTERHEART study was a case-control study (15,152 incident cases of AMI and 14,829 controls matched by age and sex with no history of heart disease) that was undertaken in both developed and undeveloped countries (more than 50 countries). The study identified nine easily measured risk factors, namely, hypertension, diabetes, smoking, lipids, obesity, diet, physical activity, alcohol consumption and psychosocial factors that accounted for over 90% of the risk of acute myocardial infarction (AMI) [9, 10].

Dyslipidaemia. Abnormalities of serum lipids especially low-density lipoprotein (LDL) are regarded as atherosclerotic risk factors [11]. There is considerable evidence in support of lowering the lipids in primary and secondary prevention of CAD. Although there is limited data on such treatment strategies in the elderly, recent trials in the elderly have provided data to guide therapy in this population. In the INTERHEART study, the apoB/apoA1 ratio was the strongest factor predicting as opposed to any other cholesterol ratios for estimation of the risk of AMI in both sexes, at all ages and in all ethnic groups. Furthermore, it has the advantage that it can be measured in non-fasting blood samples. ApoA1 reflects the antiatherogenic properties of HDL cholesterol and ApoB the atherogenicity of triglycerides and small dense LDL particles.

Cigarette smoking has long been established as a risk factor for CHD. Smoking was the second strongest predictor, and the INTERHEART study showed that smoking one to five cigarettes daily increases the risk by 40% which increases further with the amount of tobacco smoked per day [9]. Moreover, it obviates the beneficial effects of aspirin and statin in secondary prevention.

Hypertension is present in more than two-thirds of patients older than 65 years, and elderly people are more likely to have poorly controlled blood pressure. It is a major risk factor at all ages for atherosclerosis and more important than hypercholesterolaemia after the age of 45 [12].

Diabetes potentiates the effects of hypercholesterolaemia and markedly increases predisposition to atherosclerosis. In the INTERHEART study, diabetes and hypertension may have been underestimated since these two factors were self-reported [9].

Obesity: The Framingham study revealed that being more than 30% overweight increased the mortality for ischaemic heart disease. The INTERHEART study revealed that abdominal obesity is a greater risk factor than BMI and indicated that the waist-to-hip ratio should replace BMI as an indicator of obesity [9].

Moderate consumption of alcohol raises the HDL level that has a protective effect.

Physical inactivity: Regular exercise reduces premature mortality from cardiovascular disease.

Diet: The INTERHEAT study found high intake of fruit and vegetables to be protective against myocardial infarction [9].

Psychosocial factors: There is a strong and consistent evidence of an independent causal association between depression, social isolation and lack of social support with CHD. The increased risk due to these psychosocial factors was found to be of similar order to the more accepted risk factors such as dyslipidaemia, hypertension and smoking [13]. A low socioeconomic status has been associated with increased CHD mortality [14]. The INTERHEART questionnaire included stress at work or home, financial stress, stressful events, depression and locus of control, and the results indicated that psychosocial factors may contribute a significant proportion of risk for AMI [9, 10].

Clinical Manifestations

Coronary heart disease embraces a wide spectrum of clinical manifestations from stable angina to acute coronary syndromes. Angina is a clinical syndrome with characteristic quality and duration of (i) discomfort in the chest, jaw, shoulder, back or arm, (ii) typically aggravated by exertion or emotional stress and (iii) relieved by nitroglycerin. The symptom complex has been grouped as typical angina, atypical angina or non-specific chest pain [15]. Definite angina satisfies all three

criteria stated above, atypical angina meets two of the characteristics and non-cardiac chest pain meets less than one of the characteristics [15]. The major adverse outcomes are unstable angina, myocardial infarction and sudden death due to arrhythmias.

The pain in unstable angina compared with stable angina is generally more severe and lasts longer, occurring spontaneously at rest, with less effort and is progressive. It is due to the rupture of the atheromatous plaque with platelet adhesion. The classic pathology of unstable angina is that of a non-occluding thrombus. The pain at rest is due to a number of mechanisms. The episodes of pain from myocardial ischaemia are caused by bursts of platelet emboli, spasm at the site of injury or intermittent growth of thrombus to occlude, followed by recanalisation by natural lysis [16]. NSTEMI has been considered as a more severe state of the same clinical syndrome [17].

The term acute coronary syndromes (ACS) encompasses the clinical manifestations for unexpected sudden death to unstable angina to ST-elevation myocardial infarction (STEMI) also referred to as major Q-wave myocardial infarction or non-ST-elevation acute coronary syndromes (NSTEACS) on the basis of ECG findings. NSTEACS is subdivided into non-STEMI and referred to as non-Q myocardial infarction and unstable angina according to the cardiac enzyme results. In three-quarters of the patients with ACS, there is plaque disruption of a minor stenotic lesion and in the remainder plaque erosion in a more severe stenotic lesion [18, 19]. Sudden death without previous symptoms occurs in about 10% of patients with CHD. If the patient presents within 3 h of evolving acute myocardial infarction and electrocardiogram shows unequivocal ST-segment elevation, the patient is subjected to thrombolysis or coronary angioplasty.

Atypical presentations are more common in the elderly with MI and symptoms may be more subtle [20]. Dyspnoea, fatigue and heart failure symptoms were more frequently the first symptoms than typical chest pain unlike that in younger patients [21]. In the elderly, STEMI was more common, and non-STEMI was diagnosed and more common in women and in patients previously diagnosed with ischaemic heart disease, diabetes and hypertension [21] so were the presence of cerebral and peripheral vascular diseases and renal failure [22].

Primary diagnostic precondition is differentiating ACS from non-cardiac chest pain. Patients with all three characteristics of typical angina have a possibility of having ACS. The initial assessment of a patient presenting with chest pain is a history that focuses on the anginal symptoms and risk factor evaluation, physical examination, electrocardiogram and biomarkers of cardiac injury with early risk stratification. Risk stratification is of vital importance in patients presenting with UA/NSTEMI [17]. The primary aim is in evaluating patients with non-STEMI. The aim is to exclude or confirm acute myocardial infarction and risk stratification for further investigations and treatment. The AHCPR categorised UA for death or MI into low, medium and high largely based on the history, physical and ECG findings [23].

The likelihood of ACS (low, intermediate, high) should be determined in all patients presenting with chest pain. TIMI (Thrombolysis in Myocardial Infarction) score and GRACE (Global Registry of Acute Cardiac Events) score are the best systems for risk stratification for unstable and non-STEMI. The seven TIMI score predictors are age 65 years or older, at least three CAD risk factors (family history of CAD, hypertension, hypercholesterolaemia, diabetes and current smoking), known coronary stenosis of 50% or more, use of acetylsalicylic acid in the past 7 days, at least two severe angina episodes in the previous 24 h, ST changes on ECG at presentation and elevated serum cardiac markers [24]. The variables of the GRACE risk score are age, heart rate, systolic blood pressure, cardiac arrest, Killip class, serum creatinine, ST-segment changes and cardiac biomarkers [25].

A large proportion of elderly patients with myocardial ischaemia have atypical manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction [26, 27]. In the elderly with MI, there is a frequent substitution of dyspnoea for chest

discomfort, and this atypical presentation especially in women may partly explain the high rate of unrecognised MI in this age group [28]. Patients presenting with acute pulmonary oedema are generally older than those manifesting typical anginal symptoms [29, 30].

Patients who have acute myocardial infarction often delay hospital admission. Early treatment in acute myocardial infarction is crucial. There have been several studies on delayed arrival in the hospital with suspected myocardial infarction. The reasons for delay have been attributed not only to clinical and logistics factors but also to race, female sex, older age, diabetes and socioeconomic characteristics [31, 32]. There have been several suggestions to address this such as educational interventions; targeting specific populations, namely, the elderly, female and patients with cardiac risk factors; and the prompt use of emergency medical transport services [26].

Management

Early diagnosis and prompt treatment is vital in patients with STEMI. Several randomised trials have validated primary angioplasty and stents as the optimal therapy for these patients as primary percutaneous coronary intervention (PCI) yields >90% TIMI 3 flow in the infarct-related vessel compared to about 50% after thrombolytic therapy [33]. If STEMI patients cannot be treated with PCI, thrombolytic therapy is the preferred initial therapy [33]. After thrombolysis, it is expedient for patients to be referred for coronary angiogram and revascularisation between 2 and 24 h [34]. Glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide or abciximab) are beneficial in STEMI patients, and intracoronary bolus administration is usually reserved for high-risk patients [33] especially patients with diabetes undergoing PCI. Antiplatelet drugs improve the survival of patients with acute coronary syndrome. Aspirin (300 mg) should be administered immediately and is usually continued indefinitely. Clopidogrel can be used if there is aspirin allergy. A loading dose of 300–600 mg clopidogrel as early as possible is given prior to primary PCI thereafter a maintenance dose of 75 mg/d and continued for this regimen long term, for example, a year [35]. Granules containing adenosine diphosphate (ADP) bind to the P2Y12 receptor on the surface of the platelets initiating platelet aggregation. Two newer ADP-receptor inhibitors including prasugrel and ticagrelor have been studied in STEMI patients compared to clopidogrel [33]. Clopidogrel and prasugrel are thienopyridines and they bind to the P2Y12 receptor irreversibly. Whereas ticagrelor is a non-thienopyridine, it is a reversible P2Y12 receptor antagonist [33]. Randomised trials have shown the newer antiplatelet agents compared to clopidogrel to be superior in patients with STEMI and would benefit more from them following primary PCI [33]. A loading dose of 150 mg of ticagrelor is administered followed by 90 mg twice daily. Maximal platelet inhibition is achieved in approximately 30 min with prasugrel [36], whereas ticagrelor takes 2 h and clopidogrel takes 2–8 h depending on the dose [37]. The risk of haemorrhage is higher with the newer antiplatelet agents compared to clopidogrel. Bivalirudin, a transient and reversible thrombin inhibitor, should be considered as the preferred anticoagulant for patients undergoing primary PCI [33].

In patients with NSTEMI or unstable angina in addition to aspirin in combination with clopidogrel and anticoagulant therapy, a platelet glycoprotein (GP) IIb/IIIa receptor antagonist is administered if PCI is to be performed [35]. Anticoagulant drugs reduce the risk of thromboembolic complications and are done with the use of low molecular weight, unfractionated heparin (dalteparin, enoxaparin or fondaparinux) for a period of usually 8 days. Medium- to high-risk patients should be considered for early coronary angiography and revascularisation. For low-risk patients' medical treatment and for those who do not respond to medical treatment, coronary angiography and revascularisation should be considered.

There are significant differences in coronary artery lesions between younger and older persons with the latter more likely to have calcified, ostial, tortuous, multi-vessel and left main

lesions [38]. Older persons are also more likely to have co-morbid conditions such as renal impairment, cognitive impairment and frailty, and as a result, they are under-represented in clinical revascularisation trials. They also have higher risk of complications during and after coronary revascularisation. Evidence however suggests older persons derive significant benefits, both in terms of mortality and quality of life, from revascularisation as do the younger cohort.

The Trial of Invasive versus Medical Therapy in Elderly Patients with chronic symptomatic CAD (TIME) showed that among 305 patients 75 years or over with symptomatic CAD, investigation and treatment group had better symptom relief and quality of life in addition to fewer major events (49% vs. 19%) [39]. Evidence from the GRACE registry which included over 15,000 patients over the age of 70 with non-ST-elevation MI showed significant differences in in-hospital mortality, combined end point of death, myocardial infarction and stroke at 6 months between groups treated with PCI versus medical therapy [40]. In a meta-analysis which included 410 octogenarians with STEMI, PCI was also shown to be superior to thrombolysis in having a lower incidence of all-cause mortality (18.3% vs. 26.4%) at 30-day follow-up [41]. It must be noted however that subjects included in these studies are highly selected.

There is some evidence to suggest that drug-eluting stents reduce MI and target lesion revascularisation but not all-cause mortality, stroke or major haemorrhages [42]. The choice of device should consider the nature of the lesion, the underlying co-morbidities and whether there are relative or absolute contraindications for dual antiplatelet therapy. The use of a radial versus femoral access has been shown to reduce the rate of local vascular complications [43].

With the ageing of population, almost 25% of all patients undergoing CABG are >70 years of age. In spite of the widespread reluctance of subjecting an older person to cardiac bypass surgery due to the increased risk and slower post-operative recovery period, appropriately selected older subjects can derive similar benefit, in terms of mortality and health-related quality of life from cardiac surgery. In a review of 18 studies performed in a number of countries, elderly patients have improved early and late HRQOL following CABG, better post-operative in comparison to pre-operative HRQOL scores and attain similar HRQOL in aged-matched general population [44]. Potential patients for CABG should be evaluated on the basis of the cognitive, functional state as rather than purely on their chronological age.

Prevention

Preventing heart disease is an important part of overall management. One concept that has been advanced in Europe and particularly in the UK is total risk management. The concept is a multifactorial assessment and intervention on the basis of absolute risk. The European Society of Cardiology task force report had defined priorities for coronary prevention [45]. In one category of patients with established coronary disease or any other symptomatic manifestation of atherosclerosis and a second category comprising healthy individuals who are at high risk of developing coronary disease, intervention in both groups should take account of all risk factors and not a single one in isolation. There is no distinction between the groups which should be managed equally. The claim is that the distinction between primary and secondary prevention is artificial in biological terms and that common goals should be set [45]. Total risk management directs that individuals with symptomatic atherosclerotic disease or who are asymptomatic or those at high absolute risk should all receive similar lifestyle guidance, have their risk factors reduced to the same targets and, where appropriate, be offered proven drug therapies [46]. It tends to avoid treatment of single risk factors in people at low multifactorial risk (Box 2).

Box 2 Primary Prevention of CAD
Cessation of smoking
Avoidance of excessive drinking
Regular exercise
Eat balanced diet, low-fat diet
Avoid overweight and obesity

(*continued*)

Box 2 Primary Prevention of CAD (continued)
Have a regular life and manage stress
Regular follow-up for regular illnesses, e.g. hypertension, diabetes, dyslipidaemia

Smoking: Adaptation of measures to quit smoking which are effective in younger individuals has also been proved to be equally effective in the elderly cardiovascular patient. These include physician's advice, behavioural counselling, self-help materials, telephone counselling and the use of pharmacological therapies [47, 48].

Hypertension: Hypertension is a major risk factor in coronary heart disease and is common among the elderly of both sexes. Systolic blood pressure is more predictive of risk than diastolic blood pressure; in the elderly, elevated systolic blood pressure has more significance than diastolic blood pressure. The Systolic Hypertension in the Elderly Program (SHEP) [49] and the European Trial on Hypertension in the Elderly [50] trials were conducted in elderly patients with isolated hypertension. The SHEP trial at the end of 5 years revealed a statistically significant reduction in adverse events related to coronary heart disease, congestive heart failure and overall cardiovascular disease following treatment of the hypertension in the elderly with isolated hypertension. The European trial stopped after 2 years because of a marked decrease in non-fatal and total strokes and a trend towards reduction of coronary artery disease and heart failure although no statistical significance was achieved. The SHEP trial also demonstrated that antihypertensive therapy reduced coronary artery disease in elderly patients with normal or high cholesterol.

Dyslipidaemia: There is strong evidence supporting lipid lowering in the primary and secondary prevention of CHD. Because these studies have not been specifically oriented towards the elderly, the value of such therapy in older individuals has been questioned. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [51] revealed a significant reduction in rates of CHD-related mortality and non-fatal MI in high-risk patients 70 years and older with pravastatin. A subgroup analysis of the Heart Protection Study [52] supported the use of statins in elderly patients with CHD. Simvastatin significantly reduced rates of all-cause mortality, coronary death and non-fatal MI in patients older than 70 years including patients with LDL cholesterol levels less than 3.00 mmol/L.

Diabetes: The prevalence of diabetes is increasing, and diabetes is a strong predictor of recurrent ischaemic events in patients with CHD. The recommended interventions are similar to all age groups and include good glycaemic control, use of pharmacological therapies aimed at reducing the HbA1c level to less than 7% and achieving a near-normal fasting blood sugar level, dietary counselling, weight control and exercise.

Physical Activity: Reduces the chance of being overweight, decreased blood pressure and a more favourable lipid profile. Brisk walking for about 30 min on most days is recommended.

Impact

In the UK, according to the British Heart Foundation [53], 180,000 people died of cardiovascular disease and around 80,000 of them are from coronary heart disease. Likewise in the European Union, CHD is the most common cause of death [4]. The cost remains an enormous problem in almost every nation. It is the cause of premature death and disability amounting to 36% of all hospitalisation for cardiovascular disease in Australia [1]. The annual cost equates to 2.8% of the total recurrent health expenditure which includes the cost of specialist medical services, hospital stays and medications [3], and the direct health system costs in Australia was $630 million in 1993–1994 [2]. This is considered to be the average indication of the average cost, even today [2]. In the UK, CHD costs over 1.7 billion pounds per year [53] (Box 3).

Box 3 Key Points: Coronary Artery Disease
A large proportion of elderly patients with myocardial ischaemia have atypical

(*continued*)

Box 3 Key Points: Coronary Artery Disease (continued)

manifestations including dyspnoea and worsening heart failure in addition to an excess occurrence of unstable angina and non-Q wave myocardial infarction [27, 28].

Risk stratification is of vital importance in patients presenting with UA/NSTEMI [17].

Early treatment in acute myocardial infarction is crucial.

Total risk management directs that individuals who are asymptomatic or those at high absolute risk should all receive similar lifestyle guidance, have their risk factors reduced and where appropriate be offered proven drug therapies [47].

Multiple Choice Questions

1. The following complications of acute myocardial infarction are true, except:
   A. Mitral regurgitation
   B. Rupture of the papillary muscle
   C. Cardiac failure
   D. Pneumonia
2. A large proportion of elderly with myocardial ischaemia have atypical manifestations. The following are true, except:
   A. In the elderly with myocardial ischaemia, there is a frequent substitution of dyspnoea for chest discomfort.
   B. The elderly with myocardial ischaemia arrive early in the hospital.
   C. Patients presenting with acute pulmonary oedema are generally older.
   D. Elderly patients with myocardial ischaemia have an excess occurrence of unstable angina.
3. The following with regard to risk factors for coronary artery disease (CAD) are true, except:
   A. Among the modifiable risk factors, particular attention is required to identify dyslipidaemia, smoking and hypertension.
   B. In the Framingham study when the above-mentioned risk factors are present, the heart attack rate is seven times greater than when none are present.
   C. Diabetes is a strong predictor of recurrent cardiovascular events in patients with CAD.
   D. Quitting smoking by elderly cardiovascular patient is not as effective as in younger individuals.

MCQ Answers

1 = D; 2 = B; 3 = D

Short Answer Questions

1. List four complications of the atheromatous plaque.
2. List four functions of the vascular endothelium.

SAQ Answers

1. (i) Calcification of the plaque; (ii) Ulceration or rupture; (iii) Thrombosis; (iv) Haemorrhage into the plaque
2. (i) Prevents intravascular clotting; provide a permeability barrier; regulate vascular tone; produce NO

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