CHAPTER 2
Key therapeutic targets in chronic cardiac care

2.1 Introduction

As described in Chapter 1, the number of elderly individuals developing a chronic cardiac condition (whether it be chronic angina pectoris, CHF or AF), is likely to increase within ageing Western populations. Figure 2.1 outlines the typical case history of a male who had a number of strong risk factors for coronary heart disease in middle age, who eventually experienced a nonfatal acute coronary event (an inferior AMI) that, when combined with a long history of uncontrolled systolic hypertension, ultimately led to CHF, chronic angina pectoris (with a strong decubitus component due to cardiomyopathy), AF and sudden cardiac death. The complexities of managing such an individual with concurrent disease states that complicate the intention and application of treatment cannot be overstated. For example, many patients who would otherwise benefit from the prescription of an angiotensin receptor antagonist or a beta-blocker for CHF secondary to impaired left ventricular systolic dysfunction are unable to tolerate such therapy due to concurrent renovascular disease and/or sick sinus syndrome.

In effectively dealing with chronic cardiac disease, therefore, there are competing priorities that often complicate attempts to draw up clear and precise therapeutic goals from both the patient and treating health care professional's perspective [176]. As indicated by Figure 2.1, however, there are often clear phases in the natural history of chronic cardiac disease that "anchor" the mindset and purpose of supportive and therapeutic management of the underlying disease relative to an individual's life-situation (i.e. middle-age versus beyond normal life-expectancy). These phases include:

- *Primary prevention*. In the absence of any signs of overt symptoms of heart disease there is an onus on someone "at risk" (remembering that any ageing adult man or woman is at risk!) to adopt a healthy lifestyle to prevent its development – particularly sudden cardiac death. Supportive strategies at the primary care level to detect any underlying risk factors (e.g. obesity, Type II diabetes and/or hypertension) and address them via lifestyle advice (e.g. low-fat diet and greater exercise) and/or more active interventions (e.g. lipid-lowering agents) is essential to prevent or even delay the onset of heart disease. Of course, those who see little reason to seek treatment/advice

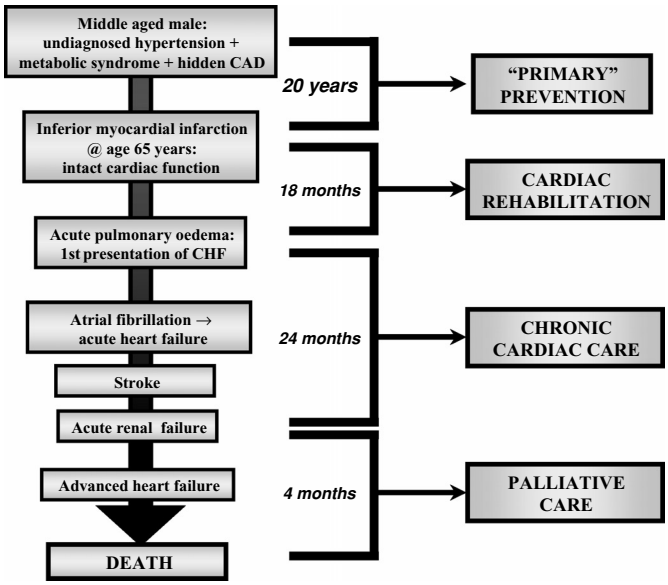

Figure 2.1 A case history of chronic cardiac disease: phases of management.

and/or adopt healthier lifestyles are clearly more likely to develop heart disease and move to the next phase!

- *Secondary prevention/cardiac rehabilitation*. Once an individual has "revealed" that they have underlying heart disease (most commonly due to a nonfatal syncopal attack, cardiac arrest or acute coronary syndrome), the health care system moves into "high alert" to prevent the survivors from rapidly progressing towards a chronic or even rapidly terminal cardiac condition: sometimes this is unavoidable, but, as noted in Chapter 1, there is evidence to suggest that we are becoming more adept, at the population level, at delaying the onset of chronic cardiac disease (most notably CHF). Secondary prevention often occurs in isolation to primary prevention, in that many individuals do not represent "primary prevention failures" but are new to the preventative process: even though it now occurs when they have developed an overt version of the disease. The key principles of modifying major risk factors, however, remain the same with the exception that affected individuals are typically symptom-free once they have received definitive treatment (e.g. undergoing placement of a drug-eluting stent for an occlusive lesion in the left-anterior descending coronary artery that triggered an acute coronary syndrome).
- *Chronic cardiac care*. It is only when an individual is chronically impaired or affected by ongoing symptoms relating to their underlying heart disease that the concept of chronic cardiac care is applied. Often this occurs when "secondary prevention" fails and they suffer a second or even third event (e.g. a

recurrent AMI). Unfortunately, there are very few studies that have examined the natural history of heart disease in a whole population. Anecdotal evidence suggests that the permutations for acute on chronic manifestations of heart disease are complex and that a generic and often "reactive" approach to management is often adopted. Clearly, this book outlines a more individualized and "proactive" approach to management by stressing the importance of maintaining "secondary prevention" and working with the individual and the best aspects of the local health care system in order to optimize treatment strategies (see Chapters 5 and 6) and improve subsequent health outcomes.

- *Palliative care*. Being proactive in terms of dealing with chronic cardiac disease at one end of the spectrum (i.e. when a person first requires careful management) also predicates being proactive at the other end of that disease spectrum: when the underlying heart disease has become terminal and irreversible and preventative and treatment strategies, therefore, have no relevance in terms of improving an individuals quality of life, but when the goal of ensuring a quality *end-of-life* becomes the primary objective of care.

Viewed from a hierarchical perspective, it is pragmatic to consider the principles of management that underpin that phase of the patient's life cycle and cardiac pathology as "active" until clearly superseded by the competing priorities of the subsequent or even distal phase of the disease process (depending on the speed of transition and consolidation of cardiac function). As indicated by the title and articulated more fully in the Preface, this book is dedicated to improving outcomes in those who have already developed chronic cardiac disease. It is important to note, however, that rather than singularly focussing on "disease management" (refer to Chapter 4), this book strongly emphasizes the parallel need to address modifiable contributors (so-called risk factors) to the emergence of confounding and more disabling cardiovascular conditions (e.g. AF-related thromboemobolic stroke), in addition to slowing the progression of the primary cardiac disease state (e.g. coronary artery disease) – (refer to Chapter 3). It also emphasizes the need to consider palliation (i.e. focussing on quality-end-of-life, instead of prolonging life through active interventions) when it is clear that an individual has reached the terminal phase of their disease process.

It is within this context that following sections of this chapter outline the key therapeutic goals that underpin the secondary prevention, treatment, and palliative care management of individuals affected by chronic cardiac disease. These sections are designed to provide an *overview* of the recommendations emanating from expert guidelines published via key organizations, (e.g. the European Society of Cardiology and the American Heart Association). As with other peak organizations dedicated to combating cardiovascular disease at the population level, both have specific processes for producing guidelines and, indeed, implementing them:

- "Get With The Guidelines^{SM} (GWTG) is the premier hospital-based quality improvement program for the American Heart Association and the

American Stroke Association. It empowers health care provider teams to consistently treat patients with the most updated treatment guidelines." [http://www.americanheart.org/presenter.jhtml?identifier=1165–Accessed July 2005].

- "Essential documents for cardiology professionals and the related healthcare industry. ESC Guidelines are the flagship scientific products of the Society." [http://www.escardio.org/knowledge/guidelines/ – Accessed July 2005].

Most of the guidelines now produced by these organizations are available as "downloads" to personal computers and more practically, to handheld computers. However, it is important to reemphasize the need for a structured program to tailor individual management of patients in whom complex decisions need to be made based on the presence of parallel disease states, individual responses to treatment, and the overall context in which a person is living with, or indeed, dying from chronic cardiac disease.

2.2 Minimizing the impact of cardiac risk factors: a lifetime task

As indicated above, the arbitrary use of terms such as "primary" and "secondary" prevention mask the importance of minimizing the impact of modifiable risk factors not only before heart disease has occurred, but also after it has evolved into a chronic manifestation. The only time to stop any efforts to improve a person's risk-factor profile/susceptibility to disease progression, is when a conscious decision has been made to: (i) accept the full consequences of not addressing the "fuel(s)" that typically drive the progression of the disease (and therefore progressively debilitating symptoms) and/or, (ii) shift the focus of management to a predominantly palliative care approach.

The following therapeutic targets in relation to secondary prevention of heart disease are largely based on the following guidelines:

Smith SC Jr., Blair SN, Bonow RO, et al. on behalf of The Healthcare Professionals from the American Heart Association and the American College of Cardiology. AHA/ACC Guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease. 2001 update. *Circulation* 2001; **104**:1577–1579.

De Backer G, Ambrosioni E, Borch-Johnsen et al. on behalf of The Third Joint Task Force of the European and other societies on cardiovascular disease prevention in clinical practice. European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2003; **24**: 1601–1610.

Guiding principles of management. There is little doubt that there is increasing evidence to suggest that "aggressive" risk reduction on therapies for individuals

with and without established cardiovascular disease have steadily reorientated the therapeutic targets (e.g. blood pressure and total cholesterol levels) that will yield the greatest benefits in terms of both "primary" and "secondary" prevention.

Key therapeutic targets. Table 2.1 is adapted from the summary statements issued by the AHA/ACC and ESC statements (listed above) in respect to the key therapeutic targets required to minimize the risk of further cardiovascular events in individuals already affected by the disease. These targets are a *constant* for all affected individuals unless treatment of the underlying process and/or complications from other conditions predicates otherwise. A conscious decision to "abandon" these targets should always be made on a proactive rather than passive basis.

Note: In primary prevention there are well-developed risk assessment tools (e.g. the ESCs Score System and the Framingham Cardiac Risk Assessment Score) to determine an individual's 5- to 10-year risk of experiencing a fatal cardiac event (typically taking into account their age, sex, smoking status, lipid profile, and blood pressure). It must be assumed that any individual who has survived an initial cardiac event and/or developed chronic symptoms is at high risk for a premature fatal event!

2.3 Living with cardiac disease: improving duration and quality of life

As discussed in Chapter 1, the most common manifestations of heart disease in our ageing populations, and the predominant focus of this book, are chronic angina pectoris, CHF, and AF. As such, they often represent the failure of both primary and secondary prevention strategies to completely halt the progressive nature of deteriorating cardiac function and structure due to the inevitable effects of age complicated by increased cardiac stress (e.g. due to systolic hypertension or valvular dysfunction) and/or repeated insults (e.g. due to myocardial ischemia).

Guiding principles. Although these three conditions typically emerge at different stages of the disease process and require distinct therapeutic strategies (see below) the overriding goals of management for these conditions are the same:

1 Slow and even reverse disease progression by addressing precipitating factors.
2 Minimize chronic disabling symptoms and therefore improve quality of life.
3 Minimize acute exacerbations that can impair quality of life and also lead to recurrently and costly hospitalizations and other expensive forms of health care.
4 Prolong survival without compromising on the quality of life.

As represented in Figure 2.1, these goals become progressively harder to achieve in those individuals who typically survive long enough to develop all three forms of chronic heart disease in addition to other significant forms

Table 2.1 Key therapeutic targets in secondary prevention.

Risk behavior/factor	Therapeutic target	Recommended action(s)
Smoking tobacco	Complete cessation	• Self-motivation to quit smoking • Supportive cessation programs • Avoid second-hand smoke • Nicotine replacement or buproprion
Hypertension	Minimum of < 140/90 mmHg OR < 130/80 in those with CHF, renal failure, or diabetes	• Lifestyle modification: weight control, exercise, moderate sodium intake, increase fruit, vegetable, and low-fat dairy products • Antihypertensive therapy on an individual basis
Abnormal lipid profile	Total cholesterol level < 4.5 mmol/L (175 mg/dl) Low density lipids < 2.5 mmol/L (100 mg/dl)	• Dietary modification: reduced fat intake (supplemental omega-3 fatty acids) • Lifestyle modification: weight control and exercise • Lipid lowering agents: statin +/− fibrate
Sedentary lifestyle	Minimum of 30 minutes moderate to high intensity exercise 3–4 times per week	• Assess risk of potential adverse effects (much lower than often predicted) • Self-motivated programs around daily activities • Formal exercise programs
Overweight/obesity*	Body mass index 18.5 to 24.9 kg/m^2 Waist circumference: < 100 cm in men and < 90 cm in women	• Self-motivated program • Dietary modification (as above) • Lifestyle modification (as above) • Formal exercise programs • Formal dietary management programs
Diabetes/metabolic syndrome*	$HbA1_c$ < 7%	• Dietary management • Optimize exercise and lipid profile • Hypoglycemic therapy
Preventative pharmacologic therapies	Antiplatelet therapy	• Aspirin 75 to 325 mg/day in majority of patients • Clopidogrel 75mg/day • Warfarin titrated to INR of 2.0 to 3.0
	ACE inhibitors	• Chronic therapy titrated to highest therapeutic dose in all patients with coronary heart disease: unequivocal recommendation in those with diabetes or left ventricular systolic dysfunction
	Beta-blockers	• Chronic therapy in those with an ACS

of cardiorespiratory disease. The following sections summarize and interpret (as will be noted in Chapter 7, it is important to consult the latest detailed guidelines in developing protocols) therapeutic targets specific to each of these conditions: remembering that any attempts to accommodate the "cookbook" approach offered by expert guidelines becomes progressively harder to apply with competing therapeutic priorities and the needs of the individual [176]. Ultimately, the clinical support and management of affected patients has to take into account those symptoms that most affect them in conjunction with any consequences (i.e. reduced survival) derived from selecting specific therapeutic targets.

The following therapeutic targets in relation to optimizing outcomes in chronic angina pectoris are largely based on the following guidelines:

Task Force of the European Society of Cardiology. Management of stable angina pectoris. *Eur Heart J* 1997; **18**:394–413.

Mannheimer C, Camici P, Chester MR, et al., on behalf of The Joint Study Group on the treatment of refractory angina. The problem of chronic refractory angina. *Eur Heart J* 2002; **23**:355–370.

Gibbon RJ, Abrams J, Chatterjee K, et al., on behalf of The ACC/AHA Task Force on Practice Guidelines (Committee on the management of patients with chronic stable angina). ACC/AHA 2002 Guideline update for the management of patients with chronic stable angina – summary article. *Circulation* 2003; **107**:149–158.

Key therapeutic targets in chronic angina pectoris

A large proportion of the recommendations relating to those affected by chronic angina pectoris are consistent with the therapeutic targets relating to secondary prevention outlined in Table 2.1. Other than addressing the traditional risk factors at the individual level (e.g. smoking and hypertension), it is clear that the emerging role of the "metabolic syndrome" (comprising a number interrelated risk factors and pathological processes) has assumed increasing importance in slowing the progression of coronary artery disease: the concept of "absolute" versus "relative" risk, whereby the combined presence of risk factors is used to calculate the probability (in absolute percentage terms) of a coronary event (fatal or otherwise) occurring with a defined period (usually 10 years). In terms of the active management of this condition, there are three key therapeutic targets or goals:

1 *Accurately determine the extent of the disease*. Coronary angiography remains the gold standard method for determining the presence and extent of the disease. However, a number of investigations including 12-lead ECG, ECG stress testing, ambulatory EGC monitoring, echocardiography (both at rest and stress echocardiography) and nuclear imaging techniques, provide further information concerning the extent of myocardial ischemia, its effects

on myocardial function and, importantly, whether or not revascularization (in the form of coronary angioplasty or coronary artery bypass) will address areas of reversible ischemia (i.e. stunned or hibernating myocardium) as opposed to those areas with fixed perfusion defects or myocardial necrosis.

2 *Optimal pharmacotherapy*. Consistent with the recommendations outlined in Table 2.1 all patients with chronic angina pectoris should have their lipid profile and subsequent suitability for dietary modification and/or prescribed statin therapy assessed in addition to the application of antiplatelet therapy. The three major classes of drug used to reduce the extent of myocardial ischemia and, therefore, anginal symptoms are nitrates (both in terms of acute sublingual therapy for angina pectoris on exertion and as chronic therapy in the form of longer-acting preparations), beta-blockers and calcium antagonists. As noted by the ACC/AHA expert committee, all three forms of pharmacotherapy in appropriate doses can be effectively used to limit anginal symptoms. However, individual variability in respect to both their beneficial and potential adverse effects is common.

3 *Revascularization*. Given an accurate determination of the extent of ischemia and its reversible component, there is a clear role for revascularization – particularly when there are target lesions that can be targeted via a coronary artery bypass or, more frequently in recent years, via percutaneous transluminal coronary angioplasty with the additional use of a drug-eluting stent designed to reduce reocclusion by inhibiting local thrombus formation and fibrosis.

Despite meeting many of the therapeutic goals and targets outlined above, a significant proportion of individuals suffer from chronic refractory angina. Moreover, given the fact that current therapeutics (despite their short-term efficacy) do not address the underlying progression of the disease with age (and contributory conditions) and the progressive ageing of the population, will no doubt lead to an increased number of affected individuals. It is within this context that in the past few years there has been consideration of a new and "novel" range of pharmacologic agents to combat this condition. In particular novel "metabolic" agents that appear to have an "oxygen-sparing" effect and therefore minimize underlying myocardial ischemia appear to markedly improve anginal symptoms in those with refractory angina pectoris. For example, perhexiline an antianginal agent that was first introduced in the 1970s but discarded in the 1980s has been recently reintroduced in patients with refractory angina due to a better understanding of its complex pharmacodynamic and pharmacokinetic profile and safer use of the drug via therapeutic drug monitoring [177]. Perhexiline acts prophylactically in chronic refractory angina via the inhibition of a key enzyme involved in normal cardiac metabolism [178]. This inhibition leads to a change in myocardial metabolism substrate selection from free-fatty acids to glucose. This change improves cardiac efficiency, by reducing oxygen demand and removing intracellular toxins [178]. This "new old" drug has proved to be the forerunner of a range of other "metabolic" agents including trimetazidine, ranolazine, and etomoxir [179].

Note: The metabolic syndrome is defined by the ACC/AHA as the combination of abdominal obesity, abnormal lipid profile (i.e. elevated total cholesterol level and abnormal high versus low density lipid level), hypertension and elevated serum glucose levels.

The following therapeutic targets in relation to optimizing outcomes in CHF are largely based on the following guidelines:

Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, on behalf of the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; **26**(11):1115–1140.

Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, on behalf of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the evaluation and management of heart failure); International Society for Heart and Lung Transplantation; Heart Failure Society of America ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the evaluation and management of heart failure). Developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001; **104**(24):2996–3007.

Krum, H., Jelinek, M., Stewart, S., Sindone, A., Hawkes, A., Atherton, J. On behalf of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Chronic Heart Failure Clinical Practice Guidelines Expert Writing Panel. Guidelines for the Prevention, Detection and Management of People with Chronic Heart Failure in Australia, 2006.

Key therapeutic targets in chronic heart failure

There is little doubt that the complexity of CHF and concurrent disease states that usually complicate its management (see the next section on AF as an example!) means that optimizing the management of this syndrome is extremely challenging. As the frequent "bridge" between the first signs of chronic cardiac disease and death, the purpose and direction of that management can rapidly change. Consistent with this book's consistent emphasis on secondary prevention and delaying the progression of the underlying pathology, it is relevant to refer to the recent update of the AHA/ACC guidelines for the management of CHF. In response to the evolving epidemiologic profile of this syndrome,

this expert committee proposed a more proactive way to classify and tackle a sustained epidemic of CHF. As such, they identified four key stages of heart failure with the following features:

Stage A Individuals at high-risk of developing heart failure: those with pre-existing hypertension, coronary artery disease, left bundle branch block, diabetes and a body mass index of > 30 kg/m^2 (obesity).

Stage B Individuals with previous AMI, asymptomatic valvular disease, and/or asymptomatic left ventricular systolic dysfunction (so-called asymptomatic or "latent" heart failure).

Stage C Individuals with symptomatic heart failure (CHF).

Stage D Patients with severe CHF who have been admitted to hospital.

Once an individual has developed CHF (i.e. a symptomatic form of heart failure), there are a range of therapeutic targets that, if achieved, will *potentially* improve quality of life, reduce morbidity and prolong the life of the affected individual (remembering that there is no cure for CHF). These include:

1 *Accurately determine the presence and extent of the syndrome*. Although there is an evolving role for screening "at risk" individuals via elevated brain natriuretic peptide levels, diagnosis of CHF is based on the combination of clinical features, chest radiography in the acute phase, and objective measurement of ventricular function (most commonly echocardiography) to determine the presence of left ventricular systolic dysfunction or abnormal filling pressures or relaxation indicative of "diastolic heart failure" in the absence of systolic dysfunction. Consistent with the management of chronic angina pectoris, there is also a clear role for nuclear cardiological testing, stress echocardiography, and positron emission tomography to assess potential reversibility of ischemia and viability of myocardium in those with concurrent evidence of active coronary heart disease.

2 *Optimal pharmacotherapy*. Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril) are the cornerstones of pharmacological therapy to prevent disease progression and prolong survival. Similarly, beta-blockers (e.g. carvedilol) prolong survival when added to ACE inhibitors in symptomatic patients. Diuretics (predominantly loop diuretics) provide symptom relief and restoration or maintenance of euvolemia in those individuals who experience cardiopulmonary congestion (as demonstrated by pulmonary or peripheral edema). In those with more advanced CHF (i.e. remain symptomatic despite the application of ACE inhibitors and beta-blockers), digoxin and spironolactone, angiotensin II receptor antagonists (e.g. candersartan), and digoxin have the potential to improve quality of life, prevent morbidity, and prolong survival.

3 *Adjunctive device therapy*. Biventricular pacing may have a role in those individuals in NYHA functional Class III or IV with wide QRS complexes in improving exercise tolerance and quality of life. Moreover, implantable cardioverter defibrillators have been shown to reduce the risk of sudden cardiac death (a major cause of death) in patients with CHF and severe systolic dysfunction of the left ventricle. Pacing may be needed to treat symptomatic bradyarrhythmias and/or sick-sinus syndrome. If possible, atrioventricular

synchrony should be maintained due to the significant contribution of atrial filling to cardiac output in CHF. Upgrading a ventricular pacemaker to a dual-chamber device should be considered in patients with CHF who have maintained sinus rhythm.

4 *Optimal nonpharmacological strategies*. A range of adjunctive strategies can be used to improve the quality of life of affected individuals and, potentially, avoid clinical crises and prolong survival. These include careful fluid management: wherever possible, determine the patient's ideal "dry or euvolemic" weight (when a patient who has had signs of fluid retention after diuretic treatment reaches a steady weight at which there are no further signs of fluid overload). Using this ideal weight as a goal, encourage patients to weigh themselves daily, record it in a diary and adjust their fluid intake and use of diuretic therapy (as a flexible regimen) accordingly. As malnutrition, cardiac cachexia, and anemia are common problems that contribute to the debilitating symptoms of weakness and fatigue associated with CHF-affected individuals need to be thoroughly investigated for the underlying cause (e.g. intestinal malabsorption due to chronic ischemia, hepatomegaly, or iron-deficiency) and referred to specialist dietary intervention/nutritional support via a qualified dietician (e.g. to be prescribed a specific sodium restricted diet plus supplemental vitamins). Contrary to conventional thinking, there are also theoretical benefits of promoting exercise in CHF to reverse associated deconditioning of peripheral and respiratory muscles in addition to improving endothelial function. Meta-analyses demonstrate that inhospital and home exercise training programs for CHF can be successfully applied without significant adverse effects. Improved outcomes associated with reported programs include increased exercise capacity, decreased resting catecholamines, improved heart rate variability and, most importantly, quality of life.

The following therapeutic targets in relation to optimizing outcomes in AF are largely based on the following guidelines:

American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the management of patients with atrial fibrillation). ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: executive summary. *Circulation* 2001; **104**:2118–2150.

Key therapeutic targets in atrial fibrillation

Because AF typically emerges in much older individuals in whom chronic cardiac disease is already well established, there is a natural temptation to concentrate solely on passively controlling this arrhythmia. However, as emphasized

in the previous sections, unless there has been a conscious decision to adopt a palliative approach, there are strong clinical and pathological reasons why *proactively* targeting the typical precursors and risk factors that "drive" AF: particularly in terms of preventing "malignant" paroxysmal events and/or increasing the likelihood of the underlying cardiac rhythm evolving into persistent AF.

It is within this context that there are three overriding principles that underpin the management of AF:

1 Reestablish normal sinus rhythm.
2 If unable to permanently reestablish normal sinus rhythm, minimize the absolute time spent in AF and aggressively control the underlying ventricular rate.*
3 Minimize the thromboembolic risk imposed by AF.

Unfortunately, all three are difficult to achieve given the combination of the typical age of affected individuals, the need for close surveillance/monitoring, the fine line associated with the risk-benefits provided by current therapeutics and the presence of confounding comorbidities. In terms of the active management of this arrhythmia, there are a number of therapeutic targets or goals:

1 *Accurately determine what form of AF is present.* An immediate diagnosis of AF requires documentation of a single-lead ECG. However, vital information (e.g. LV hypertrophy, bundle branch block) is gained from a 12-lead ECG. If there is evidence of sporadic events or indeed a more permanent form of AF, a 24-hour Holter monitor should be applied and carefully analyzed. Additional electrophysiology studies, where appropriate, will determine whether of not the arrhythmia can be terminated (e.g. via an ablation procedure), clarify the mechanism of an associated wide QRS-complex tachycardia and identify any predisposing arrhythmias such as paroxysmal supraventricular tachycardia. Similarly, exercise testing can provide vital information in terms of an "inducible" component with exercise and/or the adequacy of ventricular rate control.
2 *Determine the extent of thromboembolic risk*. Given the close association between AF and stroke, it important to categorize the risk of a future thromboembolic event. Overall, individuals with nonvalvular AF have a six-fold increased risk of thromboembolism: the major risk factors for an ischemic stroke and systemic embolism being prior history of the same, hypertension, CHF, advancing age (particularly beyond 65 years of age), diabetes and coronary artery disease. In this context, transesophageal echocardiography is also vital to determine the presence of thrombus in the left atrial appendage

*There is still debate concerning the relative merits of aggressively controlling the ventricular rate in AF versus administering potentially toxic pharmacologic agents to maintain sinus rhythm. This issue further emphasizes the need for individually tailored management.

(this is a contraindication for electrical cardioversion). As thyrotoxicosis also increases the risk of AF and resistance to cardioversion, thyroid function should also be routinely assessed and appropriately managed. Any individual aged 65 years or more with any of the above risk factors should be considered as "high risk" in this regard.

3 *Determine the extent of associated cardiac dysfunction*. A range of other standard cardiorespiratory investigations, including chest radiography and transthoracic echocardiography should be used to determine any contributory cardiac abnormalities (e.g. valvular dysfunction, left ventricular systolic dysfunction, and chronic respiratory disease).

4 *Converting the AF to sinus rhythm*. This can be attempted with either electrical or pharmacological cardioversion: the latter appears to be more efficacious when initiated within seven days of the onset of AF and the former is particularly indicated in paroxysmal AF associated with a rapid ventricular response and a hemodynamic/ischemic crisis. Within seven days of onset, the most effective agents include dofetilide (a Type III antiarrhythmic that is also effective when applied to more prolonged AF), flecanide, ibutilide, and propafenone.

5 *Maintaining sinus rhythm*. There is a range of pharmacological agents used to maintain sinus rhythm, once achieved. These include sotalol, amiodarone, and dofetilide. The major consideration is risk-benefit based on the number of concurrent disease states/precipitants that may trigger new episodes of AF, the extent of cardiac compromise associated with these events and the safety profile and, indeed, individual response to the selected agent.

6 *Controlling the ventricular rate in persistent or permanent AF*. If the ventricular rate is elevated beyond normal physiologic parameters (after a careful assessment of the underlying ventricular rate both at rest and during exercise), a beta-blocker or calcium antagonist should be prescribed. Digoxin is indicated in those patients with concurrent left ventricular systolic dysfunction.

7 *Reducing the risk of subsequent thromboembolic events*. All patients (excepting younger individuals with "lone" AF) should receive either antiplatelet (i.e. aspirin) or anticoagulation (i.e. warfarin) therapy. Given the narrow therapeutic margins associated with warfarin (with the need for regular monitoring of INRs to maintain levels of 2.0 to 3.0 in those aged < 75 years and 1.6 to 2.5 in older individuals) with increased risk of bleeding events (e.g. intracranial hemorrhage), a careful assessment based on risk (see above) should be used to decide whether aspirin is a more appropriate agent in this regard.

2.4 Dying from cardiac disease: optimizing the of end-of-life

Not surprisingly, the advanced stages of chronic cardiac disease can have a devastating effect on a patient's quality of life. Unfortunately, many patients with nonmalignant disease states have little or no access to palliative care

programs. Nor are potentially useful palliative strategies applied. These issues have been particularly highlighted in relation to CHF, but apply equally to those dying from other forms of heart disease. The reasons for the absence of palliative care services include a lack of resources and expertise, and problems associated with determining prognosis.

Guiding principles of management

Predicting the illness trajectory in patients with end-stage CHF and other forms chronic cardiac disease is much harder when compared to those with terminal malignancy. This creates uncertainty and can potentially prevent doctors telling patients when they have reached the terminal phase of their illness and from planning appropriate care. The emerging literature surrounding this subject, particularly in relation to CHF, clearly identifies the following goals of management in this context:

1. Availability of protocols for the management of end-stage/refractory heart disease to ensure that a reversible component of the disease process has not been overlooked, and that all reasonable treatment options have been considered.
2. Clear guidelines to determine when it is appropriate to talk to the patient and their family/carers about the prospect of death and their preferences in this regard (e.g. advanced directives and living wills). It has been suggested that any individual considered to be at high risk of dying within 12 months should be considered for palliation.
3. Identifying the most appropriate management to provide quality end-of-life (i.e. symptom relief, diuretics, pain control).
4. Identifying what is inappropriate management (i.e. inotropes, dialysis, central lines, artificial ventilation and urinary catheters – unless the patient has a retention or for his/her comfort not just to monitor urinary output).
5. Good coordination and continuity of care by a single health care professional.

Key therapeutic targets in terminal chronic cardiac disease

There are very few guidelines to facilitate the optimal management of those dying from terminal cardiac disease. However, it is reasonable to suggest the following therapeutic targets in this context:

1. Effective communication between the health care team, the patient and their family/carers (where appropriate) to determine the patient's health care and quality of life priorities at the end-of-life.
2. Supportive management to maintain the patient's independence as long as possible.
3. Adequate analgesia and other palliative care strategies to minimize pain and discomfort.
4. Psychological support and counseling to minimize emotional and psychological distress.
5. A peaceful death!

2.5 Summary

The combined pages of expert recommendations and opinion used to derive the key therapeutic targets listed above number more than *one hundred* and the studies and papers on which they are based in the *thousands*. Unfortunately, this does not mean that we know exactly what to do in order to fully attenuate the impact of chronic cardiac disease on quality of life, morbidity and premature mortality. However, there is a growing recognition that if we were to spend as much time applying what we know now, as opposed to generating new therapeutic options (i.e. freezing "curative" research in favor of "translational" research), we would be able to make a substantial impact on the individual and societal burden imposed by common disease states such as chronic cardiac disease. Certainly, there is ample evidence to suggest that "malignant" conditions such as CHF [180] and AF [181] are routinely undertreated and mismanaged. This first section of the book has attempted, therefore, to firstly establish the size of the problem in relation to chronic cardiac disease and, secondly, outline what can be done to subsequently improve health outcomes. The remaining sections of the book will subsequent examine the individual and organizational factors that further influence health outcomes in relation to chronic cardiac disease (Section 2), the evidence in favor of programs of care that have the potential to both delay the progression and severity of the disease and successfully improve day-to-day management of symptomatic patients (Section 3), before bringing together all the aspects of the preceding sections to describe what is most likely to be cost-effective when establishing a service targeting individuals affected by chronic cardiac disease (Section 4).

References

1 Yusuf S, Reddy S, Onupuu S, et al. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors and impact of urbanisation. *Circulation* 2001; **104**:2746–2753.

2 Yusuf S, Reddy S, Ounupuu S, et al. Global burden of cardiovascular diseases, part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001; **104**:2855–2864.

3 Murray CJL, Lopez AD, eds. *The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020*. Boston, MA: Harvard School of Public Health, 1996**.**

4 Omran AR. The epidemiological transition: a theory of the epidemiology of population change. *Milbank Mem Fund Q* 1971; **49**:509–538.

5 World Health Organisation. *Atlas of heart disease & stroke* (Chapter 13, Global burden of coronary heart disease). Geneva: World Health Organisation, 2005. http://www.who.int/cardiovascular_diseases/resources/atlas/en/print.html. Accessed June 2005.

6 Lloyd-Jones DM, Larson MG, Alexa B, et al. Lifetime risk of developing coronary heart disease. *Lancet* 1999; **353**:89–92.

7 Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; **351**:1328.
8 Hsue PY, Giri K, Erickson S, et al. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. *Circulation* 2004; **109**:316–319.
9 United Nations world population prospects: the 1998 revision. 2005. Accessed online 21 June 2005. http://www.abs.gov.au/Ausstats/abs@.nsf/Lookup/93D90E2E55DFA003CA256A7100188A7C
10 Carroll K, Majeed A, Firth C, et al. Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. *J Public Health* 2003; **25**:29–35.
11 Knopp RH. Risk factors for CAD in women. *Am J Cardiol* 2002; **89**:28E–35E.
12 Kannel WB, Feinleib M, McNamara PM, et al. An investigation of heart disease in families: the Framingham Offspring Study. *Am J Epidemiol* 1979; **110**:281–290.
13 Bhopal R, Hayes L, White M, et al. Ethnic and socio-economic inequalities in coronary heart disease, diabetes and risk factors in Europeans and South Asians. *J Public Health Med* 2002; **24**(2):95–105.
14 Rutter MK, Meigs JB, Sullivan LM, et al. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004; **110**:380–385.
15 Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. *Circulation* 2003; **107**:499–511.
16 Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J* 2004;**147**(3):398–400.
17 Bostom AG, Silbershatz H, Rosenberg IH, et al. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. *Arch Intern Med* 1999; **159**:1077–1080.
18 Bunker SJ, Colquhoun DM, Esler MD, et al. "Stress" and coronary heart disease: psychosocial risk factors. National Heart Foundation of Australia position statement update. *Med J Aust* 2003; **178**:272–276.
19 Wells AJ. Passive smoking as a cause of heart disease. *J Am Coll Cardiol* 1994; **24**:546–554.
20 Kannel WB, Feinleb M. Natural history coronary of angina pectoris in the Framingham Study. Prognosis and survival. *Am J Cardiol* 1972; **29**:154–163.
21 Voss R, Cullen P, Schulte H, et al. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Munster Study (PROCAM) using neural networks. *Int J Epidemiol* 2002; **31**:1253–1262.
22 Salomaa V, Keonen M, Koukkunen H, et al. Decline in out-of-hospital coronary heart disease deaths has contributed the main part to the overall decline in coronary heart disease mortality rates among persons 35 to 64 years of age in Finland. *Circulation* 2003; **10**:691–696.
23 Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339**:1349–1357.
24 Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *JAMA* 1998; **279**:1615–1622.

25 Ballantyne C, Arroll B, Shepherd J. Lipids and CVD management: towards a global consensus. *Eur Heart J* 2005 (E-pub Jun 21): In press.
26 Karpe F, Boquist S, Tang R, et al. Remnant lipoproteins are related to intima-media thickness of the carotid artery independently of LDL cholesterol and plasma triglycerides. *J Lipid Res* 2001; **42**:17–21.
27 Hamsten A, Silveira A, Boquist S, et al. The Apolipoprotein CI content of triglyceride-rich lipoproteins independently predicts early atherosclerosis in healthy middle-aged men. *J Am Coll Cardiol* 2005; **45**:1013–1017.
28 Walldius G, Junger I, Holme I, et al. High apolipoprotein B, low apolipoprotien A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS) study: a prospective study. *Lancet* 2001; **358**:2026–2033.
29 American Heart Association – National and international statistics. Accessed online 15 June 2005. http://www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf
30 Chobanian AV, Bakris GL, Black HR, et al. and the National high blood pressure education program coordinating committee. The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure: The JNC 7 Report. *JAMA* 2003; **289**:2560–2572.
31 The American Heart Association 2005: Diabetes http://www.americanheart.org/presenter.jhtml?identifier=4546. Accessed June 2005.
32 British Heart Foundation Coronary Heart Disease Statistics. Accessed online June 25 2005. http://www.bhf.org.uk/professionals/index.asp?secondlevel=519
33 Liese AD, Schulz M, Moore CG, et al. Dietary patterns, insulin sensitivity and adiposity in the multi-ethnic insulin resistance atherosclerosis study population. *Br J Nutr* 2004; **92**:973–84.
34 Vasan RS, Sullivan LM, Wilson PF, et al. Relative importance of borderline and elevated levels of coronary heart disease risk factors. *Ann Intern Med* 2005; **142**:393–402.
35 Marsh SA, Coombs JS. Exercise and the endothelial cell. *Int J Cardiol* 2005; **99**(2):165–169.
36 Spencer CG, Martin SC, Felmeden DC, et al. Relationship of homocysteine to markers of platelet and endothelial activation in "high risk" hypertensives: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *Int J Cardiol*. 2004; **94**:293–300.
37 Agatisa PK, Mathews KA, Bromberger JT, et al. Coronary and aortic calcification in women with a history of major depression. *Arch Intern Med* 2005; **165**(11):1229–1236.
38 Onupuu S, Negassa A, Yusuf S., for the INTERHEART Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**:937–952.
39 Rosengren A, Hawken S, Ounpuu S, et al. for the INTERHEART Investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13,648 controls from 52 countries (the INTERHEART Study): case control study. *Lancet* 2004; **364**:953–962.
40 MacIntyre K, Stewart S, Capewell S, et al. Heart of inequality – the relationship between socio-economic deprivation and death from a first acute myocardial infarction: a population-based analysis. *BMJ* 2001; **322**: 1152–1153.
41 Wilson DK, Kirtland KA, Ainsworth BE, et al. Socioeconomic status and perceptions of access and safety for physical activity. *Ann Behav Med* 2004; **28**(1):20–28.

42 Bos V, Kunst AE, Garssen J, et al. Socioecconomic inequalities within ethnic groups in The Netherlands, 1995–2000. *J Epidemiol Community Health* 2005; **59**(4):329–335.
43 Pekkanen J, Uutela A, Valkonen T, et al. Coronary risk factor levels: differences between educational groups in 1972–87 in eastern Finland. *J. Epidemiol Community Health* 1995; **49**:144–149.
44 Tenconi MT, Devoti G, Comelli M, and RIFLE research group. Role of socioeconomic indicators in the prediction of all causes and coronary heart disease mortality in over 12,000 men – the Italian RIFLE pooling project. *Eur J Epidemiol* 2000; **16**:565–571.
45 Kim MC, Kini A, Sharma SK. Refractory angina pectoris mechanism and therapeutic options. *J Am Coll Cardiol* 2002; **39**(6):923–934.
46 Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 Guideline update for the management of patients with chronic stable angina – summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the management of patients with chronic stable angina). *Circulation* 2003; **107**:149–158.
47 European Society of Cardiology Guidelines on the management of stable angina pectoris. Recommendation of the task force of the European Society of Cardiology. *Eur Heart J* 1997; **18**:394–413.
48 Abrams J. Chronic stable angina. *New Engl J Med* 2005; **352**:2524–2533.
49 Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina. Report from the ESC Joint Study Group on the treatment of refractory angina. *Eur Heart J* 2002; **23**:355–370.
50 Stewart S. Refractory to medical treatment but not to nursing care: can we do more for patients with chronic angina pectoris? *Eur J Cardiov Nursing* 2003; **2**:169–170.
51 Lewin RJ. Improving quality of life in patients with angina. *Heart* 1999; **82**:654–655.
52 Lewin RJ, Furze G, Robinson J, et al. A randomised controlled trial of a self-management plan for patients with newly diagnosed angina. *Br J Gen Pract* 2002; **52**:194–201.
53 Campeau L. Grading of angina pectoris (letter). *Circulation* 1976; **54**:522–523.
54 Bertrand ME, Simoons ML, Fox KAA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000; **21**:1406–1432.
55 Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962; **27**:645–658.
56 Jackson G. Clinical benefits of a metabolic approach to the management of coronary patients. *Eur Heart J Suppl* 1999 **1**:O28–O31.
57 Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the committee on vascular lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1994; **89**:2462–2478.
58 Ross R. The Pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; **362**:801–809.
59 McGill HC, McMahan CA, Herderick EE, et al.Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 2000; **72**(5):1307S–1315S.

60 Kavey RM, Daniels SR, Lauer RM, et al. American Heart Association Guidelines for Primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation* 2003; **107**:1562–1566.
61 Stary HC, Chandler AB, Glagov S, et al. A definition of advanced types of atherosclerotic lesions and a histiological classification of atherosclerosis. A report from the Committee on vascular lesions of the council on arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol* 1995; **15**:1512–1531.
62 Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischaemic death. *N Engl J Med* 1984;**310**(18):1137–1140.
63 Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005; **85**:1093–1129.
64 Stanley WC, Chandler MP. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart Fail Rev* 2002; **7**(24):115–130.
65 Lee L, Horowitz JD, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. *Eur Heart J* 2004; **25**(7):634–641.
66 Lopaschuk GD, Belke DD, Gamble J, et al. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta* 1994; **1213**:263–276.
67 Liedtke, AJ. Alterations of carbohydrate and lipid metabolism in the acutely ischaemic heart. *Prog Cardiovasc Dis* 1981; **23**(5):321–336.
68 Stanley WC. Partial fatty acid oxidation inhibitors for stable angina. *Expert Opin Investig Drugs* 2002; **11**(5):615–629.
69 Taegtmeyer H, Roberts AF, Raine AE. Energy metabolism in reperfused heart muscle: metabolic correlates to return of function. *J Am Coll Cardiol* 1985; **6**(4):864–870.
70 Depre C, Vanoverschelde JL, Taegtmeyer H. Glucose for the heart. *Circulation* 1999; **99**(4):578–588.
71 Lampe FC, Whincup PH, Wannamethee SG, et al. The natural history of prevalent ischaemic heart disease in middle-aged men. *Eur Heart J* 2000; **21**:1052–1062.
72 Hemingway H, Shipley M, Britton A, et al. Prognosis of angina with and without a diagnosis: 11-year follow-up in the Whitehall II prospective cohort study. *BMJ* 2003; **327**:895.
73 Rose G, Hamilton PS, Keen H, et al. Myocardial ischaemia, risk factors and death from coronary heart disease. *Lancet* 1977; **1**:105–109.
74 Murphy NF, Stewart S, Hart CL, et al. A population study of the long-term consequences of angina: 20 year follow-up of the Renfrew-Paisley study. *Submitted for publication.*
75 Sigurdsson E, Sigfusson N, Agnarsson U, et al. Long-term prognosis of different forms of coronary heart disease: the Reykjavik Study. *Int J Epidemiol* 1995; **24**:58–68.
76 Rosengren A, Wilhelmsen L, Hagman M, et al. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Goteborg, Sweden. *J Intern Med* 1998; **244**:495–505.
77 Wood P. *Diseases of the Heart and Circulation*. London: Chapman and Hall, 1968.
78 Braunwald E, Grossman W. Clinical aspects of heart failure. In: Braunwald E, ed. *Heart Disease*, 4th edn. New York: WB Saunders,1992, p. 444.
79 Packer M. Survival in patients with chronic heart failure and its potential modification by drug therapy. In: Cohn J, ed. *Drug Treatment of Heart Failure*, 2nd edn. Secaucus, New Jersey: ATC International, 1988, p. 273.

80 Poole-Wilson PA. Changing ideas in the treatment of heart failure: an overview *Cardiology* 1987; **74**:53–7
81 Hunt SA, Baker Dw, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. (Committee to revise the 1995 guidelines for the evaluation and management of heart failure) 2001. Accessed online 29 June 2005. http://www.acc.org/clinical/guidelines/failure/II_characterization.htm#II_A
82 Swedburg K, Cleland J, Dargie H, et al. ESC Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology. *Eur Heart J* 2005; **26**:1115–1140.
83 Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. *Lancet* 2003; **362**:147–158.
84 Krum H, Jelinek M, Stewart S, Sindone A, Hawkes A, Atherton J. On behalf of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Chronic Heart Failure Clinical Practice Guidelines Expert Writing Panel. Guidelines for the Prevention, Detection and Management of People with Chronic Heart Failure in Australia, 2006.
85 Brixius K, Reuter H, Bloch W, et al. Altered hetero- and homeometric autoregulation in the terminally failing human heart. *Eur J Heart Fail* 2005; **7**:29–35.
86 Taylor MR, Bristow MR. The emerging pharmacogenomics of the beta-adrenergic receptors. *Congest Heart Fail* 2004; **10**:281–288.
87 Narula J, Kolodgie FD, Virmani R. Apoptosis and cardiomyopathy. *Curr Opin Cardiol* 2000; **15**(3): 183–188.
88 Schrier RW, Abraham WT. Mechanisms of disease: hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**(8): 577–585.
89 Suresh DP, Lamba S, Abraham WT. New developments in heart failure: role of endothelin and the use of endothelin receptor antagonists. *J Card Fail* 2000; **6**(4): 359–368.
90 Blum A, Miller H. Pathophysiological role of cytokines in congestive heart failure. *Ann Rev Med* 2001; **52**:15–27.
91 Aukrust P, Gullestad L, Ueland, Damas JK, Yndestad A. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. *Ann Med* 2005; **37**:74–85.
92 Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions – results from the medical outcomes study. *JAMA* 1989; **262**:907–913.
93 Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam health outcomes study – initial catalog of health-state quality factors. *Med Dec Making* 1993; **13**:89–102.
94 Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002; **87**:235–241.
95 Koenig HG. Depression in hospitalized older patients with congestive heart failure. *Gen Hosp Psych* 1998; **20**:29–43.
96 Levenson JW, McCarthy EP, Lynn J, et al. The last six months of life for patients with congestive heart failure. *J Am Geriatr Soc* 2000; **48**:S101–S109.

97 Krumholz HM, Phillips RS, Hamel MB, et al. Resuscitation preferences among patients with severe congestive heart failure: results from the SUPPORT project. *Circulation* 1998; **98**:648–655.
98 Krumholz HM, Phillips RS, Hamel MB, et al. Resuscitation preferences among patients with severe congestive heart failure: results from the SUPPORT project. *Circulation* 1998; **98**:648–655.
99 Murray SA, Boyd K, Kendall M, et al. Dying of lung cancer or cardiac failure: a community-based, prospective qualitative interview study of patients and their carers. *BMJ* 2002; **325**:931–34.
100 Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: national hospital discharge survey 1985–1995. *Am Heart J* 1999; **137**:352–60.
101 Westert GP, Lagoe RJ, Keskimaki I, et al. An international study of hospital readmissions and related utilization in Europe and the USA. *Health Policy* 2002; **61**:269–278.
102 Stewart S, MacIntyre K, McCleod ME, et al. Trends in heart failure hospitalisations in Scotland, 1990–1996: an epidemic that has reached its peak? *Eur Heart J* 2001; **22**: 209–217.
103 MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case-fatality in 66,547 patients hospitalised between 1986 and 1995. *Circulation* 2000; **102**:1126–1131.
104 Ho KKL, Anderson KM, Karmel WB, et al. Survival after the onset of congestive heart failure in the Framingham Heart Study subjects. *Circulation* 1993; **88**:107–115.
105 Stewart S, MacIntyre K, Hole DA, et al. More malignant than cancer? Five-year survival following a first admission for heart failure in Scotland? *Eur J Heart Failure* 2001; **3**:315–322.
106 Peeters A, Mamun AA, Willekens F, et al. for NEDCOM. A cardiovascular life history: a life course analysis of the original Framingham Heart Study cohort. *Eur Heart J* 2002; **23**:458–466.
107 Jong P, Vowineckel E, Liu PP, et al. Prognosis and determinants of survival in patients newly hospitalised for heart failure: a population based study. *Arch Intern Med* 2002; **162**:1689–1694.
108 Cowie MR, Wood DA, Coats AJS, et al. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2001; **83**:505–510.
109 Lynn J. An 88-year-old woman facing the end of life. *JAMA* 1997; **277**(20):1633–1640.
110 Brenna TD, Haas GJ. The role of prophylactic implantable cardioverter defibrillators in heart failure: recent trials usher in a new era of device therapy. *Curr Heart Fail Rep* 2005; **2**:40–45.
111 Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**:1397–1402.
112 Jouven X, Desnos M, Guerot C, et al. Idiopathic atrial fibrillation as a risk factor for mortality. The Paris Prospective Study. *Eur Heart J* 1999; **20**:896–899.
113 Fuster V, Ryden LE, Asinger RW, et al. for the ACC, AHA, ESC & NASPE. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Circulation* 2002; **104**:2118–2150.
114 Coumel P. Neural aspects of paroxysmal atrial fibrillation. In: Falk RH, Prodrid PJ,

eds. *Atrial Fibrillation: Mechanisms and Management*. New York: Raven Press, 1992, pp. 109–125.

115 Frost L, Johnsen SP, Pedersen L, et al. Seasonal variation in hospital discharge diagnosis of atrial fibrillation: a population-based study. *Epidemiology* 2002; **13**:211–215.

116 Murphy NF, Stewart S, MacIntyre K, et al. Seasonal variation in morbidity and mortality related to atrial fibrillation. *Int J Cardiol* 2004; **97**:283–288.

117 Wolf PA, Benjamin EJ, Belanger AJ, et al. Secular trends in the prevalence of atrial fibrillation: The Framingham Study. *Am Heart J* 1996; **131**:790–795.

118 Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; **82**:2N–9N

119 Bharti S, Lev M. Histology of the normal and diseases atrium. In: Falk RH, Prodrid PJ, eds. *Atrial Fibrillation: Mechanisms and Management*. New York: Raven Press, 1992, pp. 15–39.

120 Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959; **58**:59–70.

121 Moe GK, Abildskov JA. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. *Circ Res* 1964; **4**:447–460.

122 Berry C, Stewart S, Payne EM, et al. Electrical cardioversion for atrial fibrillation: outcomes in 'real life' clinical practice. *Int J Cardiol* 2001; **81**:29–35.

123 Skanes AC, Mandapati R, Berenfeld O, et al. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation* 1998; **98**:1236–1248.

124 Yue L, Feng J, Gaspo R, et al. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. *Circ Res* 1997; **81**:512–525.

125 Manios EG, Kanoupakis EM, Mavrakis HE, et al. Sinus pacemaker function after cardioversion of chronic atrial fibrillation: is sinus node remodeling related with recurrence? *J Cardiovasc Electrophysiol* 2001; **12**:800–806.

126 Redfield MM, Kay GN, Jenkins LS, et al. Tachycardia-related cardiomyopathy a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clin Proc* 2000; **75**:790–795.

127 Wolf P, Mitchell J, Baker C, et al. Impact of atrial fibrillation on mortality, stroke and medical costs. *Arch Intern Med* 1998; **158**:229–234.

128 Lip GY. The prothrombotic state in atrial fibrillation. New insights, more questions and clear answers needed. *Am Heart J* 2000; **140**:348–350.

129 Lip GY. Does atrial fibrillation confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999; **33**:1424–1426.

130 Stewart S, Hart CL, Hole DA, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley Study. *Am J Med* 2002; **113**:359–364.

131 Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002; **87**:235–241.

132 Stewart S, MacIntyre K, McCleod MC, et al. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J* 2001; **22**:693–701.

133 Frost L, Vestergaard P, Mosekilde L, et al. Trends in incidence and mortality in the hospital diagnosis of atrial fibrillation or flutter in Denmark, 1990–1999. *Int J Cardiol* 2005; **103**:78-84.

134 Stewart S, Murphy N, McGuire A, et al. The current cost of angina pectoris to the National Health Service in the United Kingdom. *Heart* 2003; **89**:848–853.
135 British Heart Foundation Coronary Heart Disease Statistics: http://www.bhf.org.uk/professionals/index.asp?secondlevel=519. Accessed June 2005.
136 American Heart Association – national and international statistics: http://www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf. Accessed June 2005.
137 McMurray JJV, Stewart S. The burden of heart failure. *Eur Heart J* 2003; **5**:I3–I113.
138 McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997; **350**: 829–833.
139 Davies M, Hobbs F, Davis R, et al. Prevalence of left ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening Study: a population based study. *Lancet* 2001; **358**:439–444.
140 Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population: the Rotterdam Study. *Eur Heart J* 1999; **20**:447–455.
141 Schunkert H, Broeckel U, Hense HW, et al. Left ventricular dysfunction. *Lancet* 1998; **351**:372.
142 Gardin JM, Siscovick D, Anton-Culver H, et al. Sex, age and disease effect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. *Circulation* 1995; **91**:1739–1748.
143 Devereux RB, Roman MJ, Paranicas M, et al. A population based assessment of left ventricular systolic dysfunction in middle-aged and older adults: the Strong Heart Study. *Am Heart J* 2001; **141**:439–446.
144 Nielsen OW, Hilden J, Larsen CT, et al. Cross-sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. *Heart* 2001; **86**:172–178.
145 Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; **33**:1948–1955.
146 Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA Study. *Eur J Heart Fail* 2002; **4**:531–539.
147 McMurray J, McDonagh T, Morrison CE, et al. Dargie HJ. Trends in hospitalization for heart failure in Scotland 1980–1990. *Eur Heart J* 1993; **14**:1158–1162.
148 Rodriguez-Artalejo F, Guallar-Castillon P, Banegas Banegas JR, et al. Trends in hospitalization and mortality for heart failure in Spain, 1980–1993. *Eur Heart J* 1997; **18**:1771–1779.
149 Abraham WT, Adams KF, Fonarow GC. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46**:57–64.
150 Eriksson H, Wilhelmsen L, Caidahl K, et al. Epidemiology and prognosis of heart failure. *Z Kardiol* 1991; **80**:1–6.
151 Doughty R, Yee T, Sharpe N, et al. Hospital admissions and deaths due to congestive heart failure in New Zealand, 1988–91. *NZ Med J* 1995; **108**:473–475.
152 Reitsma JB, Mosterd A, de Craen AJM, et al. Increase in hospital admission rates for heart failure in The Netherlands, 1980–1993. *Heart* 1996; **76**:388–392.

153 Stewart S, MacIntyre K, McCleod ME, et al. Trends in heart failure hospitalisations in Scotland, 1990–1996:An epidemic that has reached its peak? *Eur Heart J* 2001; **22**:209–217.
154 Mosterd A, Reitsma JB, Grobbee DE. ACE inhibition and hospitalisation rates for heart failure in The Netherlands, 1980–1998. The end of an epidemic? *Heart* 2002; **87**:75–76.
155 Ng TP, Niti M. Trends and ethnic differences in hospital admissions and mortality for congestive heart failure in the elderly in Singapore, 1991 to 1998. *Heart* 2003; **89**:865–870.
156 Swedberg K, Köster M, Rosen M, et al. Decreasing one-year mortality from heart failure in Sweden: data from the Swedish Hospital Discharge Registry – 1988–2000. *J Am Coll Cardiol* 2002; **41**:190A.
157 Westert GP, Lagoe RJ, Keskimaki I, et al. An international study of hospital readmissions and related utilization in Europe and the USA. *Health Policy* 2002; **61**:269–278.
158 Murray J, Hart W, Rhodes G. An evaluation of the cost of heart failure to the National Health Service in the UK. *Br J Med Econ* 1993; **6**:91–98.
159 Stewart S, Jenkins A, Buchan S, et al. The current cost of heart failure in the UK: an economic analysis. *Eur J Heart Fail* 2002; **4**:361–371.
160 Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002; **347**(5):305–313.
161 Stewart S, MacIntyre K, Capewell S, McMurray JJV. An ageing population and heart failure: an increasing burden in the 21st century? *Heart*. 2003; **89**:49–53.
162 Kelly DT. Our future society: a global challenge. *Circulation* 1997; **95**:2459–2464.
163 Bonneux L, Barendregt JJ, Meeter K, et al. Estimating clinical morbidity due to ischaemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Publ Health* 1994; **84**:20–28.
164 Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med* 1995; **155**:469–473.
165 Stewart S, Murphy N, Walker A, et al. The cost of an emerging epidemic – an economic analysis of atrial fibrillation in the UK. *Heart* 2004; **90**:286–292.
166 Stewart S, Hart CL, Hole DA, et al. Population prevalence, incidence and predictors of atrial fibrillation in the Renfrew/Paisley Study. *Heart* 2001; **86**:516–521.
167 Wihelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med* 2001; **250**:382–89.
168 Anonymous. Atrial fibrillation as a contributing cause of death and medicare hospitalization–United States, 1999. *MMWR Morb Mortal Wkly Rep* 2003; **52**:130–131.
169 Stewart S, MacIntyre K, McCleod MC, Bailey AE, McMurray JJV. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J* 2001; **22**:693–701.
170 Stewart S. Atrial fibrillation in the 21st Century: The new cardiac "Cinderella" and new horizons for cardiovascular nursing. *Eur J Cardiovasc Nursing* 2002; **2**:115–121.
171 Stewart S, McMurray JJV. Atrial fibrillation and the ageing population: an emerging epidemic? *Eur Heart J* 2002; **23**:617.
172 Youman P, Wilson K, Harraf F, et al. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003; **21**:43–50.

173 Hravnak M, Hoffman LA, Saul MI, et al. Resource utilization related to atrial fibrillation after coronary artery bypass grafting. *Am J Crit Care* 2002; **11**:228–238.
174 Maier W, Windecker S, Boersma E, et al. Evolution of percutaneous transluminal coronary angioplasty in Europe (1992 – 1996). *Eur Heart J* 2001; **22**:1733–1740.
175 Stewart S, Blue L, Walker A, et al. An economic analysis of specialist heart failure management in the UK – can we afford not to implement it? *Eur Heart J* 2002; **23**:1369–1378.
176 Tinetti ME, Bogardus ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med* 2004; **351**(27):2870–2874.
177 Horowitz JD, Sia STB, Macdonald PS, et al. Perhexiline maleate treatment for severe angina pectoris- correlations with pharmacokinetics. *Int J Cardiol* 1986; **13**:219–229.
178 Kennedy JA, Unger SA, Horowitz JD. Inhibition of Carnitine Palmitoyltransferase-1 in rat heart and liver by perhexiline and amiodarone. *Biochem Pharmacol* 1996; **52**:273–280.
179 Lee L, Horowitz JD, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. *Eur Heart J* 2004; **25**:634–641.
180 Gupta R, Tang WH, Young JB. Patterns of beta-blocker utilization in patients with chronic heart failure: experience from a specialized outpatient heart failure clinic. *Am Heart J* 2004; **147**:79–83.
181 Zimetbaum P, Reynolds MR, Ho KK, et al. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. *Am J Cardiol* 2003; **92**:677–681.