Preface

It is believed that 20% of the global population suffers from diseases that predispose it to heart failure. The prevalence and hospitalization rates for heart failure continue to increase, in part, because improved therapy has increased life expectancy. Heart failure, now, is the most common hospital discharge diagnosis, and the Medicare budget spends more money for diagnosis and treatment of heart failure than for any other diagnosis. The total and indirect cost of heart failure approaches $30 billion annually in the USA alone.

Although a great deal of progress has been made in the development of both pharmacological and non-pharmacological therapies for this common but potentially fatal disorder, the number of available therapies has increased. But this increase has rendered clinical decision making far more complicated and the timing and sequence of initiating strategies for treatment and the appropriateness of prescribing them in combination more complex. Despite these advances in treatment, the number of heart failure deaths continues to increase.

Keeping this in mind we have assembled a group of experts in the field to put together a state of the art treatise on the management of heart failure. The advantage of this publication is that it is a multiauthor book which brings in perspectives from all around the globe. The other major strength of this publication is that the chapters are relevant to day-to-day clinical practice. In conjunction with volume 2, *Surgical Management of Heart Failure*, this book provides a comprehensive overview of the management of heart failure.

This book is intended for health care providers involved in the prevention and management of heart failure: nurses, physician assistants, house officers, general practitioners, internists, and cardiovascular specialists. We hope that this book will therefore not only contribute to reducing the increasing burden of heart failure worldwide but also serve as a stimulus for new research in the field of heart failure.

Ragavendra R. Baliga
The Ohio State University
Bertram Pitt
University of Michigan Health System
Michael Givertz
Harvard Medical School & Brigham and Women's Hospital

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Epidemiology of Heart Failure

Robert Neil Doughty and Harvey D. White

1.1. Introduction

Heart failure is a complex clinical syndrome occurring as the end result of many different forms of heart disease. There are many different definitions and classifications of heart failure (Table 1.1) but a simple, practical definition of the syndrome of heart failure is that it is characterized by typical symptoms such as shortness of breath, exercise limitation and fatigue and clinical signs of peripheral and/or pulmonary congestion, associated with abnormalities of cardiac structure and function[1]. The syndrome of heart failure results in significant impairment of quality of life, more so than with many other chronic diseases[2], and is associated with high morbidity and mortality. Heart failure frequently occurs in the setting of preserved left ventricular (LV) ejection fraction[3,4] and thus a practical clinical definition of the syndrome[1], rather than reliance on a single factor such as impaired LV ejection fraction, allows identification of the broad group of patients affected by this condition

The recent ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure have taken a new approach to the classification of heart failure (Figure 1.1)[5]. This classification has taken a perspective of the evolution and progression of heart failure as part of the spectrum of cardiovascular disease from patients at high risk of developing heart failure but who do not at that stage have any structural heart disease (Stage A, e.g. patients with hypertension and/or coronary artery disease), through to those patients with structural heart disease and end-stage heart failure (Stage D). In this classification, patients with the clinical syndrome of symptomatic heart failure will fall within Stages C and D (Figure 1.1). This classification is of value for several reasons:

1. Firstly, it clearly places heart failure as a clinical syndrome occurring in patients with structural heart disease
2. Secondly, it recognizes the importance of risk factors and structural heart disease in an asymptomatic patient and that therapy directed towards these abnormalities may help to prevent or delay the onset of the syndrome of heart failure
3. Thirdly, it allows recommendations for treatments of patients at the different stages of their disease process.

When heart failure is classified in this way, the epidemiology of heart failure requires consideration of the epidemiology of each of the four stages A–D. The purpose of this chapter is to review the epidemiology of the syndrome of symptomatic chronic heart failure, and thus only Stages C and D will be considered in detail. However, it is important to recognize that the epidemiology of conditions such as hypertension and coronary artery disease will impact on the syndrome of heart failure.

1.2. Incidence

Data on the incidence of heart failure have mainly been derived from large epidemiological cohort studies such as the Framingham study[6]. The Framingham Heart Study[6] was initiated in 1946

TABLE 1.1. Criteria for diagnosis of heart failure from several studies.

Definition	Framingham Heart Study (7)	Boston HF score (63) (points in parentheses)	ESC criteria (1,64)
Criteria	**Major criteria**	**History**	Symptoms of heart failure, typically breathlessness or fatigue, either at rest or on exercise, or ankle swelling and objective evidence of cardiac dysfunction at rest
	Paroxysmal nocturnal dyspnoea or orthopnoea	Rest dyspnoea (4)	
	Neck vein distention	Orthopnoea (4)	
	Rales	Paroxysmal nocturnal dyspnoea (3)	
	Cardiomegaly	Dyspnoea on walking on level (2)	
		Dyspnoea on climbing (1)	
	Acute pulmonary oedema	**Physical examination**	A clinical response to treatment directed at heart failure alone is supportive but not sufficient for the diagnosis
	S3 gallop	Heart rate (91–110/min, 1; >110/min, 2) (1 or 2)	
	Increased venous pressure 16 cm water		
	Circulation time ≥25 s	Elevated jugular venous pressure (JVP) (>6 cm H_2O, 1; >6 cm H_2O plus hepatomegaly or oedema, 2) (1 or 2)	
	Hepatojugular reflux		
	Minor criteria	Rales (basilar, 1; >basilar, 2) (1 or 2)	
	Ankle oedema	Wheezing (3)	
	Night cough	S3 gallop (3)	
	Dyspnoea on exertion	**Chest radiograph**	
	Hepatomegaly	Alveolar pulmonary oedema (4)	
	Pleural effusion	Interstitial pulmonary oedema (3)	
	Vital capacity ↓1/3 from maximum	Bilateral pleural effusions (3)	
	Tachycardia (rate of ≥120/min)	Cardiothoracic ratio ≥0.5 (3)	
		Upper zone flow redistribution (2)	
	Major or minor criteria		
	Weight loss ≥4.5 kg in 5 days in response to treatment		
	Note: Definitive diagnosis if two major or one major and two minor criteria were present concurrently	**Note:** Not more than 4 points allowed from each of the three categories	
Objective evidence of cardiac dysfunction required	**Not required**	**Not required**	**Required**

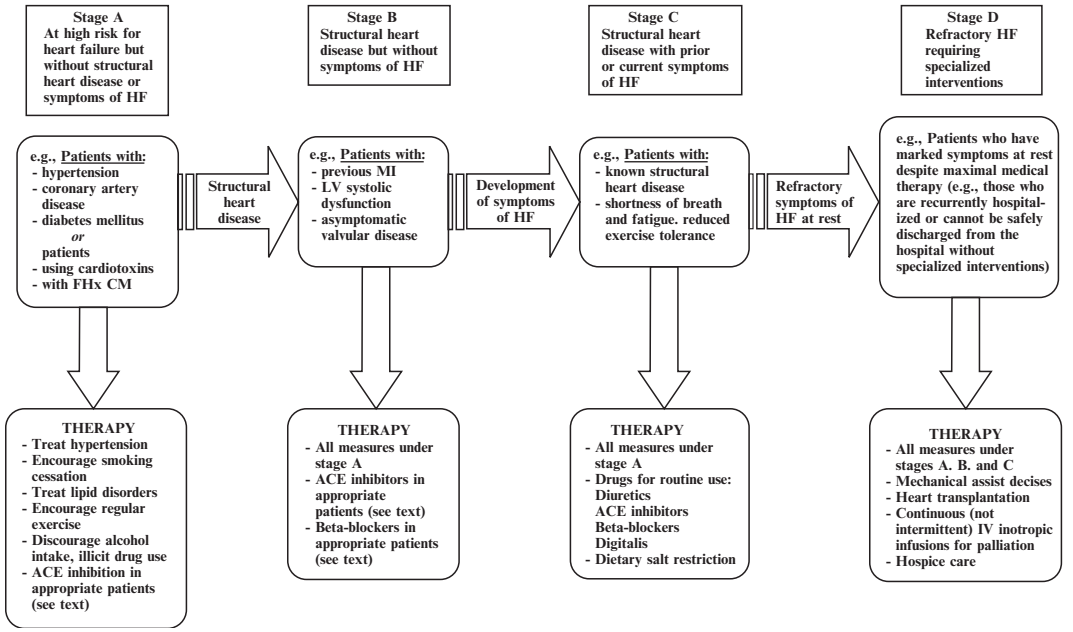

FIGURE 1.1. Stages in the evolution of heart failure and recommended therapy by stage. Reproduced with permission from reference (5). Copyright 2001, with permission from Elsevier

for the purpose of defining risk factors for and the natural history of cardiovascular disorders. An early report from the 5,209 people in the original Framingham cohort based a diagnosis of heart failure on selected clinical criteria (Table 1.1)[7]. Based on these criteria, 3.5% of men and 2.1% of women (total of 142 people) developed heart failure over 16 years of follow-up. The development of heart failure was strongly associated with advancing age.

In 1971, children of the original study participants and the spouses of these children were entered into the Framingham Offspring Study[8] and data regarding heart failure, using the same definition, from these two cohorts were reported in 1993[9]. Among these 9,405 participants followed from 1948 to 1988, congestive heart failure developed in 652 (6.9%). Age-adjusted incidence rates among persons aged over 45 years were 7.2 cases/1000 men and 4.7 cases/1000 women. Incidence rates increased markedly with increasing age.

The Eastern Finland Study (1986–1988) reported that the age-adjusted annual incidence of heart failure in a rural community was 4.1/1000 in men and 1.6/1000 in women[10]. In this study, heart failure was defined by Framingham and Boston criteria (Table 1.1). The difference between men and women in this population was accounted for by an excess of ischemic heart disease in men. The Rotterdam Study was a prospective, population-based cohort study involving 7,983 people over the age of 55 years recruited between 1989 and 1993 and followed until 2000. In this study, heart failure was defined according to the European Society of Cardiology criteria[1]. The overall incidence rate of heart failure in this study was 14.4/1000 person-years and was higher in men (17.6/1000 man-years) than in women (12.5/1000 woman-years). The incidence rates were strongly age-related, increasing from 1.4/1000 person-years in those aged 55–59 years to 47.4/1000 person-years in those aged 90 years or over.

In a cross-sectional study in primary care in Scotland (1999–2000), the incidence of heart failure was 2/1000 people, increasing to 90/1000 among patient over the age of 85−years[11]. The incidence of heart failure obviously varies somewhat between these studies, differences that may in part be explained by differences in the definition of heart failure that was used, the methodology, geographical location or time period of the study. While the studies cannot be directly compared, they consistently demonstrate that heart failure is a common problem, and one that increases markedly with advancing age.

Few studies have reported the changes in incidence of heart failure over time[12,13]. The study by Senni et al. reported that the incidence of heart failure was unchanged from 1981 to 1991[12]. Such studies are difficult due to the need for long-term follow-up of cohorts over several decades, with standardized methodology, including standardized definition of heart failure, over time. A recent analysis of data from the Framingham study has suggested that since the 1950s and 1960s the incidence rate of heart failure has remained unchanged in men but has decreased by about one third in women[13]. However, it appears that this decline in incidence in women occurred in the 1970s and that over the last 20 years incidence rates in women have remained unchanged[13]. It thus appears that incidence rates have remained unchanged over recent decades, although it should be acknowledged that long-term data are relatively limited.

1.3. Prevalence

In the USA, there has been a doubling of the prevalence of heart failure over the last 20 years. It is currently estimated that ~71.3 million people (24% of the population) are affected by cardiovascular disease and that 5 million people have heart failure[14], representing about 1.6% of the total population. This compares to the estimated prevalence of heart failure in 1983 of ~2.3 million persons[15].

The Rotterdam Study (1989–2000) reported prevalence rates of between 6.5% and 7.0% in a population over the age of 55 years[16]. Prevalence was higher in this study in men (8%) than in women (6%). Prevalence increases with advancing age; for example, from the Rotterdam Study prevalence was 0.9% in those aged 55–64 years compared with 9.7% in those aged 75–84 years[16]. A similar age gradient in the prevalence of heart failure was observed in the study of men born in 1913 (a population study of men living in Gothenburg): prevalence was 2% at age 50 and 13% at age 67[17]. Data from the Framingham study showed an approximate 'doubling by decade', with prevalence of heart failure in the age group 50–59 years being 1% compared with about 10% in those aged 80–89 years[18].

The prevalence of heart failure is also increasing as the population ages and the proportion of the population over the age of 65 increases[19]. The US Census estimates that there will be 40 million Americans aged 65 and older by 2010. In New Zealand, a population of ~4 million people, it is projected that the proportion of the population over the age of 65 years will increase from 12% in 2001 to 14% in 2011 and 18% in 2021 (Figure 1.2)[20]. Assuming a prevalence of heart failure of ~10% in those aged 65 and over, it can be expected that the number of people affected by heart failure will increase by ~50% over the next few decades. This increase in prevalence will increase the burden of heart failure on health care resources over coming decades.

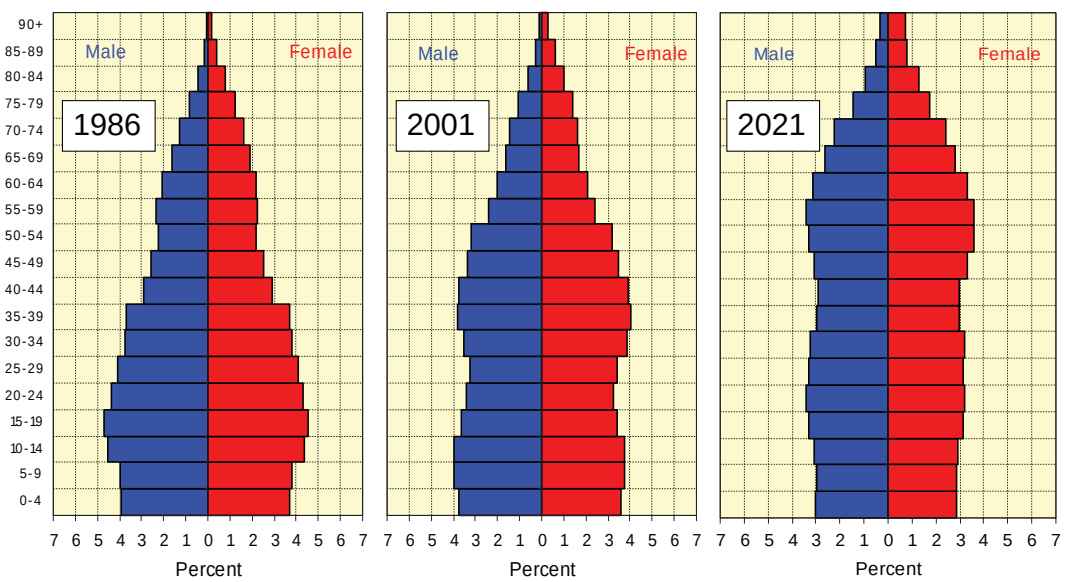

FIGURE 1.2. Aging of the population in New Zealand (*See Color Plates*)

1.4. Lifetime Risk of Heart Failure

Long-term population-based cohort studies allow the estimation of lifetime risk of developing heart failure. The Framingham study reported that the lifetime risk of developing heart failure was 20% at age 40[21]. In this study, the remaining lifetime risk did not change because of rapidly increasing incidence rates of heart failure with increasing age. The Rotterdam Study reported lifetime risk of developing heart failure of 33% for men and 29% for women at age 55[16]. Lifetime risk decreased with advancing age in both men and women to ~23% who reached age 85 years. Differences observed between these two studies may be accounted for by methodological differences between the studies (e.g. definition of heart failure and age ranges studied) and that the studies were conducted during different eras (Framingham study 1971–1996 and Rotterdam Study 1989–2000). Despite these differences, these two studies demonstrate high lifetime risk of developing heart failure of between one in four and one in three people over the age of 40–55.

1.5. Hospitalizations for Heart Failure

Heart failure is characterized by high rates of hospital admission in most Western countries[22-32]. In the USA, it is estimated that there are about 900,000 hospital admissions with a primary diagnosis of heart failure each year and about 2.6 million admissions for heart failure as a primary or secondary diagnosis[(33)]. Heart failure is the most common diagnosis in patients over the age of 64 years hospitalized in the USA[33]. Readmissions for worsening heart failure are common following first admissions for heart failure, reported at about 30% in Scotland at 12 months[23] and about the same proportion in the USA within 6 months[30].

Hospital admissions for heart failure have increased over the 1980s and 1990s in many developed countries[22-25,27-30,32]. This pattern has been mirrored in New Zealand with steady increases in age-standardized hospitalizations for heart failure over the last 15 years (Figure 1.3). The reasons for this are probably multi-factorial and may be associated with an increased number of elderly individuals in the population, and improved survival following

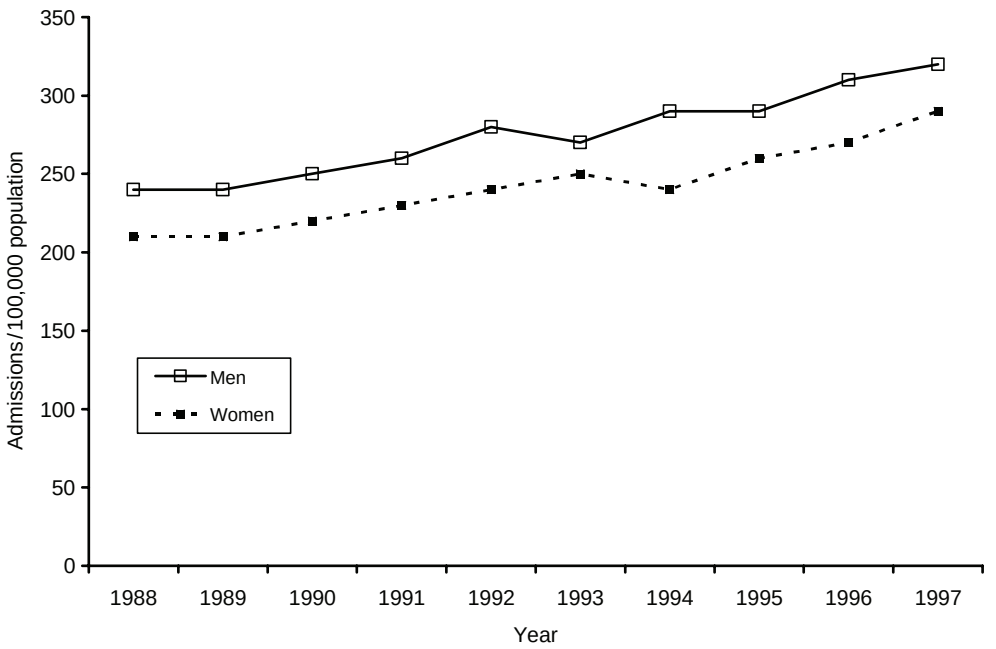

FIGURE 1.3. Age-standardized hospital admissions for congestive heart failure in New Zealand

acute myocardial infarction. Recent indications are that the increase in admissions observed in the 1980s and 1990s is now stabilizing, although hospitalization data need to be followed closely over the next few years to determine whether these trends will continue, or whether further increases will occur. Several studies have reported that most of the increase in hospital admissions observed over recent years has been in the elderly[22,27]. Elderly patients also have longer hospital stay[23] and higher rates of hospital readmission[34,35] than do younger patients.

Data on length of hospital stay quoted in studies of hospitalized patients with heart failure is highly dependent on the method of data collection and the health care system in which the study was performed. For example, mean length of stay in Scotland in 1990 was 20 days[23] compared with 5 days in Oregon, USA, in 1991[31]. Despite methodological differences between studies, it has been clearly demonstrated that length of hospital stay for heart failure has progressively decreased during the 1980s and 1990s[23,26,31], with average length of stay now ~1 week. The length of stay is strongly age-related; for example, in Scotland in patients aged 25–44 mean length of stay was ~7 days compared with 26 days in patients over the age of 75 years[23]. There is a risk that the length of stay could become too short with patients being discharged before being stabilized and, if post-discharge care is inadequate, earlier readmission occurring. The optimal length of hospital stay is uncertain and will depend at least in part on the local health care environment (both hospital and community).

The total and indirect/direct cost of heart failure in the USA has been estimated to be approximately $29.6 billion in 2006[36]. The cost of heart failure is high due largely to the large number of hospitalizations[36,37]. Hospital admissions associated with heart failure constitute 1–2% of total annual health spending in most developed nations[26,38,39].

1.6. Heart Failure Prognosis

Heart failure is associated with poor survival[7,9,16]. Early data from the Framingham Heart Study (1950s and 1960s)[7] suggested that mortality rates were high, with less than 50% of men being alive 5 years after the diagnosis of heart failure. A further report from the Framingham study followed 9,405 subjects for a median of 14.8 years during the 1970s and 1980s, during which time 652 (6.9%) people developed heart failure[9]. These patients with heart failure were followed for a mean of 3.9 years after the onset of heart failure during which time 551 died (84.5%). Median survival was 1.7 years for men and 3.2 years for women. Increasing age was associated with increasing mortality, with a 27% increase in mortality per decade of advancing age in men and a 61% increase per decade in women.

The extent of the severity of mortality associated with heart failure has often been underestimated. The poor survival rates associated with high profile conditions such as cancer often receive considerable attention but the comparative mortality of heart failure has not until recently been determined. A recent report from Scotland has compared mortality among 16,224 men and 14,842 women presenting with heart failure, acute myocardial infarction or cancer (lung, large bowel, prostate, bladder or breast)[40]. With the exception of lung cancer, heart failure was associated with the worst 5-year survival rates (~25%). This population-based study has clearly demonstrated that heart failure is a ‘malignant’ disease process, with outcome worse than many different forms of cancer. This information reinforces the need for aggressive, preventive and therapeutic strategies across the stages of heart failure (Figure 1.1).

No temporal changes in mortality rates were observed in earlier reports from the Framingham cohort[9]. The follow-up in the Framingham study was almost exclusively before the widespread use of evidence-based therapies such as neurohormonal antagonists and device-based therapy proven to decrease mortality[5] and does not therefore address the effect of widespread implementation of interventions on survival in heart failure patients. The series of major mortality trials have demonstrated progressive declines in overall mortality in patients with heart failure enrolled in these trials as multiple therapies have been added in sequence (Figure 1.4). However, these data do not determine the temporal trends in mortality in patients with heart failure.

Several recent reports, from population-based datasets rather than randomized trial cohorts, have now demonstrated that mortality from heart failure is declining (Table 1.2)[13,41-44]. The Framingham

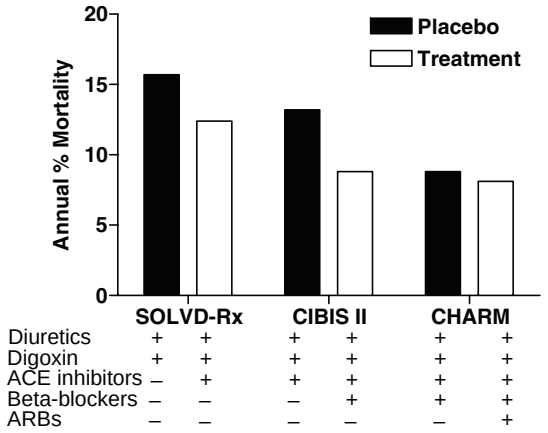

FIGURE 1.4. Changing mortality in the large trials of neurohormonal antagonists. Studies referenced are the large-scale randomized trials, including SOLVD treatment trial [46], CIBIS II[47], and the CHARM Programme[49]. Annualized mortality rates for the placebo and treatment arms in these trials are quoted. ARBs = angiotensin receptor blockers

study has reported significant declines in mortality associated with heart failure over the last 40 years, reductions equivalent to ~12% per decade[13]. However, mortality remains high with 1-year mortality rates from the Framingham study of 28% for men and 24% for women in the 1990s. Hospital-based cohorts have also recently demonstrated improved survival associated with heart failure following hospitalization for heart failure[41-44]. Despite these improvements in outcome, current mortality associated with heart failure remains high, with estimated mortality 1 year following hospitalization for heart failure of between 26%[44] and 38%[43].

The benefits of angiotensin-converting enzyme (ACE) inhibitors[45,46], beta-blockers[47,48] and angiotensin receptor antagonists[49] in patients with heart failure have been demonstrated in large, placebo-controlled trials. Widespread implementation of these and other evidence-based therapies should contribute to the improved survival that has been observed for patients with heart failure. Encouragingly, a recent report from Canada has demonstrated that improvement in mortality in patients over the age of 65 years with heart failure during the 1990s in Alberta, Canada, was associated with the use of neurohormonal antagonists. Widespread use of appropriate medical- and device-based therapy for patients with heart failure remains an important component of strategies to continue to improve the outcome for patients with this malignant condition.

1.7. Etiology of Heart Failure

Coronary artery disease now appears to be the most common cause of heart failure[50,51], occurring in approximately two thirds of patients with impaired LV systolic function. Many patients with coronary artery disease have preceding hypertension, as hypertension is one of the common risk factors for the development of coronary artery disease. In the Framingham cohort, most of the population-attributable risk for heart failure was accounted for by hypertension, with myocardial infarction having a higher risk ratio but lower overall prevalence and hence lower population-attributable risk[52]. However, determining the underlying cause of heart failure is often difficult; many patients with established heart failure are not subject to extensive investigations and hence the exact underlying etiology is never determined. Whatever the exact proportions, coronary artery disease and hypertension remain major causes of heart failure and are likely to remain so over coming decades with the aging of the population.

Heart failure occurring in the setting of acute myocardial infarction has long been recognized as being associated with poor outcome[53]. Recent data from large registries have provided data on the impact of existing or new heart failure in the setting of acute coronary syndromes, and established that heart failure remains a major contributor to outcome[54-56]. The Second National Registry of Myocardial Infarction (NRMI-2) reported data from 190,518 patients admitted to US hospitals with acute ST elevation myocardial infarction, 19% of whom had heart failure on admission[54]. Heart failure was associated with markedly higher in-hospital mortality (21.4%) compared with that in those without heart failure (7.2%). The VALIANT Registry included 5,573 consecutive patients with acute myocardial infarction at 84 hospitals in nine countries between 1999 and 2001[55]. Forty-two per cent of these patients had heart failure and/or LV systolic dysfunction during hospitalization; in-hospital mortality rate among these patients was 13% compared

TABLE 1.2. Temporal changes in mortality associated with heart failure.

	Beginning of cohort		End of cohort		Percent change	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Community-based studies						
Levy, Framingham[13]						
Years	1950–1969		1990–1999			
30-day mortality	12%	18%	11%	10%	−8.3%	−44.4%
1-year mortality	30%	28%	28%	24%	−6.6%	−14.3%
Hospital-based studies						
MacIntyre, Scotland[a 41]						
Years	1986		1995			
30-day mortality	19.9%		18.6%		−6.5%	
1-year mortality	46.7%		42.4%		−9.2%	
Baker, MediCare USA[a 42]						
Years	1991–1992		1997			
30-day mortality	9.3%		7.9%		−15.3%	
1-year mortality	36.6%		31.3%		−14.6%	
Blackledge, England[a 43]						
Years	1993/1994		2000/2001			
30-day mortality	28%		18%		−35.7%	
1-year mortality	55%		38%		−30.9%	
Schaufelberger, Sweden[44]						
Years	1988		2000			
30-day mortality	15%	16%	10%	12%	−33.3%	−25%
1-year mortality	40%	43%	26%	30%	−35%	−30.2%

[a] Data not available for men and women separately.

with 2.3% in those patients without heart failure and normal LV systolic function.

The GRACE Registry has recently reported data on the impact of heart failure among 16,166 patients with acute coronary syndromes admitted to 94 hospitals in 14 countries[56]. Heart failure on admission was associated with poor survival rates compared with that in patients without heart failure both in hospital (12% vs. 2.9%) and at 6 months post-discharge (8.5% vs. 2.8%). Heart failure was also associated with increased mortality rates even in those patients with normal cardiac biomarkers. The presence of heart failure at admission in each of these registries was associated with longer hospital stay, and lower rates of procedures and use of therapies proven to reduce mortality[54–56].

These large registries provide data on the impact of heart failure in the contemporary setting of acute coronary syndromes and reinforce the importance of heart failure and LV systolic dysfunction in this group of patients[54–56]. Worryingly these patients appear to be under-treated compared to those without heart failure, despite being a group at higher absolute risk who will have potentially greater gains from the proven therapies. Early identification of such patients is important to allow appropriate evidence-based therapies to be utilized to improve patient outcomes.

1.8. Future Burden of Heart Failure

As discussed, heart failure is a major burden in the population and to the health care systems of most developed countries. The combined effects of aging of the population and improved survival for

patients with cardiovascular disease (including for those with heart failure) are projected to increase this burden. By 2020, it has been projected that first hospitalizations for heart failure will increase 34% in men and 12% in women in Scotland[57]. The epidemic of diabetes and metabolic syndrome will continue to fuel an increase in the incidence of cardiovascular disease including heart failure. Diabetes is a significant independent risk factor for the development of heart failure[58] and occurs in ~20–30% of patients with heart failure[59,60]. The incidence of diabetes is projected to increase over the next few years, with estimates that 5.4% of the adult population worldwide will have diabetes by 2025[61]. Obesity is another important risk factor for heart failure which is increasing with the increase in sedentary lifestyle[62]. Thus, all indications are that heart failure will remain a major public health problem for years to come. Attention to the patients at risk of developing heart failure (Stage A, Figure 1.1) will be an important part of the strategy to prevent or delay the onset of heart failure. Meanwhile, aggressive management of patients with established heart failure is essential to decrease the morbidity and mortality associated with this condition.

1.9. Summary and Key Points

- Approximately one in three or one in four people in the general population will develop heart failure during their lifetime.
- The incidence of heart failure in the population is ~1–2/1000 population per year, but increases steeply with advancing age.
- The overall prevalence of heart failure in the general population is ~1% but increases markedly with increasing age to ~10% in the over 80-year-olds.
- Incidence rates have remained stable over the last 30 years but prevalence is expected to rise as the population ages.
- Hospitalization rates for heart failure have risen over the last 20 years
- Costs associated with heart failure account for ~1–2% of the total health budget in most Western countries.
- While the prognosis for patients with heart failure appears to be improving, heart failure remains a malignant disease with 1-year mortality rates of 26–38% following first admission for heart failure.
- Therapeutic strategies to prevent heart failure include management of the common conditions which cause heart failure, including coronary artery disease, hypertension and diabetes.

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