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Epidemiology and risk profile of heart failure

Anh L. Bui, **Tamara B. Horwich**, and **Gregg C. Fonarow**
Ahmanson–UCLA Cardiomyopathy Center, UCLA Medical Center, 10833 Le Conte Avenue, Room 47–123 CHS, Los Angeles, CA 90095-1679, USA

Abstract

Heart failure (HF) is a major public health issue, with a prevalence of over 5.8 million in the USA, and over 23 million worldwide, and rising. The lifetime risk of developing HF is one in five. Although promising evidence shows that the age-adjusted incidence of HF may have plateaued, HF still carries substantial morbidity and mortality, with 5-year mortality that rival those of many cancers. HF represents a considerable burden to the health-care system, responsible for costs of more than $39 billion annually in the USA alone, and high rates of hospitalizations, readmissions, and outpatient visits. HF is not a single entity, but a clinical syndrome that may have different characteristics depending on age, sex, race or ethnicity, left ventricular ejection fraction (LVEF) status, and HF etiology. Furthermore, pathophysiological differences are observed among patients diagnosed with HF and reduced LVEF compared with HF and preserved LVEF, which are beginning to be better appreciated in epidemiological studies. A number of risk factors, such as ischemic heart disease, hypertension, smoking, obesity, and diabetes, among others, have been identified that both predict the incidence of HF as well as its severity. In this Review, we discuss key features of the epidemiology and risk profile of HF.

Introduction

Heart failure (HF) is a major public health issue with a current prevalence of over 5.8 million in the USA and over 23 million worldwide.[1,2] Every year in the USA, more than 550,000 individuals are diagnosed with HF for the first time, and there is a lifetime risk of one in five of developing this syndrome.[1,3] A diagnosis of HF carries substantial risk of morbidity and mortality, despite advances in management. Over 2.4 million patients who are hospitalized have HF as a primary or secondary diagnosis, and nearly 300,000 deaths annually are directly attributable to HF.[1]

From the 1970s to 1990s, a dramatic increase in the prevalence of HF and number of HF hospitalizations was observed,[4–6] and an epidemic was declared.[7,8] Most of the HF burden is borne by individuals aged ≥65 years, who account for more than 80% of the deaths and prevalent cases in the USA and Europe.[6,9] The growing prevalence of HF might reflect increasing incidence, an aging population, improvements in the treatment of acute cardiovascular disease and HF, or a combination of these factors. Promising evidence from national databases as well as community-based cohorts, such as those based in Framingham

Correspondence to: G. C. Fonarow gfonarow@mednet.ucla.edu.

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and Olmsted County,[3,10–16] indicates that the incidence of HF seems to be stabilizing, if not decreasing, for women, and that the length of survival in patients with HF is increasing. Such trends may have resulted from demographic shifts, changes in the prevalence of risk factors, or improvements in the availability and application of HF treatments.[17,18] Furthermore, awareness of and appreciation for HF and preserved left ventricular ejection fraction (LVEF) is increasing. HF and preserved LVEF now represents >50% of HF cases and can have outcomes as poor as those associated with HF and reduced LVEF, but it does not yet have a proven effective management strategy.[19–21] In this Review, we describe the epidemiology of HF, highlighting trends in overall prevalence, incidence, and mortality of HF as a whole and in subgroups. We also highlight how identified risk factors influence both incidence and severity of HF and discuss the impact of HF on the utilization of health services.

Prevalence and incidence

Definitions

HF is the final common stage of many diseases of the heart. Its manifestations, however, can be difficult to diagnose accurately. Many of its features are not organ-specific, and there may be few signs or symptoms early in the disease process.[22,23] This ambiguity has led to multiple criteria being used to define HF in epidemiological studies. Many use the clinical criteria established by the Framingham Heart Study, which require two major criteria, such as elevated jugular venous pressure, pulmonary rales, or a third heart sound, or one major criterion and two minor criteria, including peripheral edema, dyspnea on exertion, or hepatomegaly.[24] Some rely on the clinical criteria of the Cardiovascular Health Study (CHS)[25] or the European Society of Cardiology,[26] whereas others may rely on patient self-report.[1] Many studies incorporate hospital discharge diagnostic coding, with the International Classification of Diseases, 9th Revision, Clinical Modification code 428.xx and diagnosis-related group code 127 having been found to be more specific than all other codes combined.[27,28] These differing criteria might lead to inconsistent estimates of prevalence and incidence. Furthermore, these values are affected by the sampling and data source used to derive these estimates. Large national databases have the advantage of capturing information about an entire population at the expense of less strict definition criteria than smaller cohort studies, which may be more biased in their sampling and, therefore, less representative of the population of interest.[29]

Prevalence and incidence are two measures of disease occurrence. The prevalence of a disease is the proportion of the population affected by the disease at a certain point in time.[30] Incidence, on the other hand, reflects the number of new cases occurring during a period of time in a population at risk for developing the disease.[30] In general, prevalence will equal the incidence of disease multiplied by the average duration of disease, but only in the steady-state situation in which rates are not changing and there is no net migration in or out of a given population.[30] Because HF is a chronic disease state with rare recovery, the duration of HF is directly affected by mortality, which is the incidence of death from a disease within a given time period. Variability in estimated prevalence of HF may, therefore, reflect differences in incidence as well as in survival between population samples.

Prevalence

More than 5.8 million adults in the USA are living with HF.[1] This syndrome affects more men than women, and its prevalence greatly increases with advancing age (Figure 1).[1] Studies estimate the overall prevalence of HF in the population to be about 2–3%. From self-reported data obtained by the National Health and Nutrition Examination Survey, the prevalence in the USA was 2.6% in 2006.[1] Studies with validated diagnoses of HF include

cohort studies, such as the Rochester Epidemiologic Project in Olmsted County, MN, where the prevalence of HF was found to be 2.2%.[31] Here, prevalence increased with age, reaching 8.4% in those aged ≥75 years compared with 0.7% in those 45 to 54 years of age.[31] The Rotterdam cohort showed similar trends, with a HF prevalence of 1% in those aged 55 to 64 years, compared with over 10% in those aged ≥85 years.[32]

The worldwide prevalence of HF seems to have been increasing over the past decades.[6,7,33,34] This trajectory may reflect growing awareness and diagnosis of HF, an aging population, increasing incidence of HF, improvement in the treatment and management of cardiovascular disease, or a combination of some or all of these potential explanations. Curtis and colleagues concluded from a cohort study of more than 600,000 US Medicare beneficiaries that the prevalence of HF increased from 90 to 121 per 1,000 between 1994 and 2003, although the rate of increase has slowed in the past few years, possibly reflecting stabilized incidence and mortality.[34] By contrast, prevalence as measured by HF admission rates declined in Canada between 1994 and 2004; this difference may in part have resulted from higher admission thresholds in Canada during this time period, owing to limited hospital bed availability.[16]

Extrapolating from available evidence, McMurray and colleagues estimate a worldwide prevalence of 23 million individuals living with HF.[2] Incidence and prevalence data for HF in most countries are scarce,[35,36] and current epidemiological data from developing countries are inadequate for making an accurate assessment. Although the magnitude of the HF burden in the developing world is not well quantified, enormous growth in the prevalence of HF is expected as developing countries shift from acute illness to chronic disease, the population ages, and the pervasiveness of HF risk factors, such as hypertension, coronary artery disease, and obesity, increases.[37,38]

Incidence

In the USA, the incidence of HF generally ranges from 2 to 5 per 1,000 person-years, depending on the cohort studied. Like HF prevalence, incidence is greater in males and the elderly. In the Framingham Heart Study, incidence for HF was 5.64 and 3.27 per 1,000 person-years in men and women, respectively,[3] whereas in the Olmsted cohort, comparable rates were 3.78 and 2.89 per 1,000 person-years, respectively.[12] At the age of 40 years, the lifetime risk of developing HF is one in five.[39] In older groups, incidence is higher. Based on the Framingham cohort, the incidence of HF is almost 10 per 1,000 person-years in those >65 years of age.[39] In CHS, which included only those aged ≥65 years, the estimated incidence was 19.3 per 1,000 person-years.[40]

Despite an increasing prevalence, the majority of evidence indicates that the incidence of HF has plateaued and might even be decreasing in some groups. In a population study of more than 5 million people in Scotland, Jhund and colleagues concluded that rates of first hospitalization for HF rose between 1986 and 1994, but declined thereafter.[15] In Olmsted, incidence trends have not significantly changed between 1979 and 2000, with overall incidence of 3.78 and 2.89 per 1,000 person-years among men and women, respectively.[12] Similar conclusions about stabilized incidence were made among the men in the Framingham Heart Study, in which the adjusted incidence of HF was unchanged from 1950 to 1999 (Table 1).[3]

The pattern of HF incidence in women may differ from that in men. In addition to having lower rates of HF than men, women in the Framingham Heart Study also experienced an overall 30% decline in incidence between 1950–1969 and 1990–1999.[3] Levy and colleagues noted, however, that this decline primarily occurred between 1950 and 1979 (Table 1).[3] Such findings of stabilized or declining incidence are in contrast to those suggested by a

community study conducted in Oregon in an older population aged ≥65 years.[10] In this study, the adjusted rate of incident HF increased slightly from 10.0 to 11.3 per 1,000 person-years between 1970–1974 and 1990–1994, respectively, with similar increases in both men (10.7 to 12.7 per 1,000 person-years) and women (8.6 to 11.8 per 1,000 person-years).[10] These differences might reflect an older population and the inclusion of an increasing number of cases diagnosed in the outpatient setting in this latter study.

Because incidence of HF increases with age,[3,13,41] the overall plateau in HF incidence may reflect decreasing incidence in younger individuals, but increasing incidence in older persons. An analysis of the Olmsted cohort found a decline in HF incidence among those aged 60–69 years and an increase in HF incidence in those aged 70–79 between 1981 and 1991.[13] The increasing incidence of HF in the elderly is consistent with trends in hypertension and ischemic heart disease.[33,42] Improved awareness and management of blood pressure from the 1970s to the 1990s may have delayed the onset of HF until later in life.[43] Also, more effective treatments for ischemic heart disease could have increased the surviving pool of older patients, who are then at risk of developing HF in their later years.[44]

In the USA, black individuals tend to have a higher prevalence of HF and present with HF at a younger age than those who are white.[45–47] Analysis of ARIC (Atherosclerosis Risk in Communities),[11] a biracial cohort aged 45 to 65 years at entry, found that HF incidence was lowest in white women at 3.4 per 1,000 person-years compared with 6.0 for white men, 8.1 for black women, and 9.1 for black men. HF incidence was higher for black individuals than white individuals, but these differences were attenuated by adjustment for atherosclerotic risk factors, indicating that the greater incidence observed in black individuals may largely be explained by the higher prevalence of risk factors, such as coronary artery disease, diabetes, and hypertension in this group.[11] Similarly, findings from CARDIA (Coronary Artery Risk Development In young Adults),[47] indicate that early-onset HF before the age of 50 years disproportionately affected black men and women, who have an incidence 20 times that of white individuals.[47] This increased risk was particularly associated with hypertension as well as obesity, chronic kidney disease, and the development of depressed LVEF 10 to 15 years earlier.[47]

Mortality

Despite advances in therapy and management, HF remains a deadly clinical syndrome. In the USA, one in eight deaths has HF mentioned on the certificate, 20% of which have HF as the primary cause of death.[1] Mortality risk steadily increases after a new diagnosis of HF. Based on the Framingham Heart Study, 30-day mortality is around 10%, 1-year mortality is 20–30%, and 5-year mortality is 45–60%.[3] After hospitalization, the prognosis worsens. From a community study in Worchester, MA, the 5-year mortality was more than 75% after the first hospitalization for HF.[48] Studies of prevalent cases in Europe have slightly more favorable estimates, with 1-year and 5-year mortality at 11% and 41%, respectively, from the Rotterdam study,[49] possibly owing to differences in patient selection and definitions of HF leading to inclusion of milder cases.[35] Stewart and colleagues suggested that HF was more ‘malignant’ than cancer in a study of over 30,000 patients hospitalized for HF, myocardial infarction (MI), or four common cancers in Scotland; with the exception of lung cancer, HF was associated with the worst 5-year adjusted mortality.[50]

In-hospital mortality from HF has generally improved over time.[5,51,52] In ADHERE (Acute Decompensated Heart Failure National Registry),[53] 263 hospitals reported an average hospital death rate of 4.2% in 2001–2003. A study of nearly 7 million fee-for-service US Medicare patients hospitalized with HF showed that in-hospital mortality decreased from 8.5% to 4.3% between 1993 and 2006.[54] Part of the reduction in in-hospital mortality might

have resulted from decreasing lengths of stay, which delays the accounting of these deaths into the post-hospitalization period. However, in more than 77,000 individuals with HF aged ≥65 years followed in Ontario, Canada, in-hospital mortality remained steady and high between 1992 (12.6%) and 2000 (12.3%).[18] These results were replicated in a study of the Canadian National Mortality database, which found minimal adjusted reductions in in-hospital mortality between 1994 (11.1%) and 2004 (10.2%).[16] These incongruent estimates could in part stem from regional variation in patient population, availability of health services, and definitions used to establish a HF admission; such differences would also impact post-discharge outcomes.

Improvements in short-term outcomes have been observed, which include the post-discharge period, as well as longer-term outcomes. In a review of Medicare recipients, 30-day mortality from hospital admission decreased from 12.8% to 10.7% between 1993 and 2006.[54] Though similar declines were seen with 5-year mortality, the 5-year incidence of death from HF remained greater than 60%.[54] In the Scottish population study,[15] there was a decline in 30-day mortality after first hospitalization with HF between 1986 to 2003, from 24.4% to 16.2% in men and 20% to 16.9% in women, with differences persisting at 1-year and 5-year follow-up. Similar trends were seen in Canada[16] and Olmsted County,[12] where the 5-year adjusted survival improved from 43% in 1979–1984 to 52% in 1996–2000. However, most of these improvements were in men and younger adults; the 5-year adjusted mortality in men improved by 15% over this time period compared with only 5% in women. [12] For the population served by the Kaiser Permanente system in Oregon, improvements in HF mortality was also seen in men but not women; the 5-year adjusted mortality improved in men from 82.7% to 68.8% between 1970–1979 and 1990–1994, but remained the same or worse in women with rates from 60.8% to 64.8%.[10] The Framingham Heart Study noted comparable improvement in long-term survival in both men and women (Figure 2).[3] Overall, there was a 12% improvement per decade in the survival rate after the onset of HF.[3]

The general improvements in mortality likely reflect improved recognition, treatment, and management of this chronic syndrome. However, why many of these studies find a greater improvement in men than women is unclear. Women may start with a lower mortality, and incremental improvements from HF therapies are, therefore, less readily seen, or current medical therapies are less effective in women than in men. These differences in mortality might also reflect the greater prevalence of HF and preserved LVEF in women than in men. The mortality reductions observed in national and community-based cohorts over the past 20 years have been smaller than those observed among patients enrolled in randomized clinical trials, where annual mortality is 40–60% lower than those of earlier HF clinical trials.[14,55,56] Selection bias, entry criteria, and optimal background therapy in the placebo and experimental arms are likely factors in explaining the better prognosis of patients in these trials.

Disparities may also exist among racial or ethnic divisions. Mortality in black individuals is consistently higher than in white patients. The death rate from HF for 2006 was 103.7 per 100,000 for white males, 105.9 for black males, 80.3 for white females, and 84.4 for black females.[1] From the ARIC study,[11] case fatality rates were similar for white and blacks individuals in the first 2 years of follow-up, but diverged thereafter; at 5 years, black patients had a significantly higher case fatality rate than white individuals for both men (51.8 versus 41.2) and women (46.1 versus 35.8) (Figure 3). Why these disparities appear after 2 years is unclear, and may be related to medication compliance, hospitalization rates, or faster progression of disease. More research is required to evaluate how differences in factors, such as treatment rates or medication adherence, might contribute to potential disparities by race and ethnicity.

HF and preserved LVEF

Awareness and attention to the HF syndrome in the presence of normal or mildly abnormal LVEF is increasing. Many terms are used to refer to this patient population, including HF and preserved LVEF, HF with normal LVEF, HF with preserved systolic function, HF with diastolic dysfunction, and diastolic HF.[35] The terminology adopted by the Heart Failure Society of America in the 2010 HF guidelines of 'HF and preserved LVEF' is used in this Review.[57] The left ventricle in patients with HF and preserved LVEF may be characterized by concentric remodeling, LV hypertrophy, increased extracellular matrix, abnormal relaxation and filling, decreased diastolic distensibility, and abnormal calcium handling.[58] These patients frequently have evidence of LV diastolic dysfunction, as demonstrated by Doppler echocardiography, cardiac catheterization, or measurement of blood natriuretic peptide levels.[59] HF can occur in these patients as a result of impaired ventricular relaxation, requiring elevated filling pressures to obtain normal LV end-diastolic volumes.[60]

Abnormal diastolic function is not uncommon in the community. In the Olmsted cohort, 20.8% of individuals had mild diastolic dysfunction, 6.6% had moderate dysfunction, and only 0.7% had severe diastolic dysfunction.[31] Comparatively, the prevalence of LVEF <50% was 6.0%, and only 2.0% had LVEF <40%. Overall, 5.6% of individuals had isolated diastolic dysfunction in the presence of normal LVEF. Either systolic or diastolic dysfunction was associated with increased risk for incident HF, but less than half of all patients with moderate to severe diastolic dysfunction or an LVEF <40%, had a validated diagnosis of HF.[31] Similar conclusions were reached in the Rotterdam cohort.[32] Echocardiographic diagnosis alone may indicate those who are at risk of HF, but not necessarily those with clinical HF.

Validating the diagnosis of HF and preserved LVEF is difficult, as it requires evidence of HF in the presence of normal or near normal LVEF. Controversy remains over whether echocardiographic or cardiac catheterization-derived evidence of abnormal LV relaxation, filling diastolic distensibility, or stiffness is also required for diagnosis.[61,62] Early estimates of HF and preserved LVEF prevalence among the total HF population range from 13% to 74%, depending partly on inclusion criteria (particularly LVEF cut-off) and clinical setting.[63] Analyses of more refined population-based echocardiography studies indicate an average of 54%, ranging from 40% to 70%.[64] The overall prevalence of HF and preserved LVEF among the general population in the USA has been estimated at 1.1–5.5%.[64] Study of the Olmsted cohort indicates that, among those with HF, the proportion of patients with HF and preserved LVEF seems to be increasing over time, from 38% in 1986–1990 to 54% between 1996–2001.[21] The prevalence of HF and preserved LVEF now exceeds that of HF and reduced LVEF.[21] The risk profile for HF and preserved LVEF might differ from that of HF and reduced LVEF; those who develop HF and preserved LVEF tend to be older, female, and have a history of hypertension or atrial fibrillation.[19,21,31,65–68] The female preponderance may be a result of the relative contribution of their greater longevity and lower burden of coronary disease than men, sex-related differences in LV remodeling in response to pressure-overload, hormonal factors, and other such differences.[59]

Diastolic dysfunction increases the risk of HF development and all-cause mortality, even after controlling for age, sex, and LVEF. Mild diastolic dysfunction has been associated with eight times the risk of mortality compared with normal cardiac function, and 10 times the risk with moderate to severe diastolic dysfunction.[31] With the development of HF, the 6-month mortality rates are no different between patients with preserved or reduced LVEF.[65] Some studies,[19,21,65,69–71] but not all,[72–75] indicate that long-term outcomes for individuals with HF and preserved systolic function are similarly poor to those with reduced systolic function. Even if the mortality of patients with HF and reduced LVEF is higher, however,

the overall absolute number of deaths attributable to HF and preserved LVEF is likely greater given the aging of the population and the larger proportion of HF and preserved LVEF in the elderly.[70] Potentially reversible clinical features consistently associated with acute decompensation in patients with HF and preserved LVEF include uncontrolled hypertension[67,76] and atrial fibrillation.[76] Clinical deterioration leading to hospital admission results in even higher subsequent mortality.[77] Based on the Olmsted cohort, Owan and colleagues suggest that survival has improved over time for those with HF and reduced LVEF, but not for those with HF and preserved LVEF.[21] The divergence in outcomes for these cohorts might result from therapies that improve outcomes for patients with HF and reduced LVEF. To date, there are as yet no effective therapies proven to change the natural history of HF and preserved LVEF.[20]

Risk factors

In addition to older age, male sex, and ethnicity, multiple other factors indicate increased risk for development of HF (Box 1).

Box 1

Established and hypothesized risk factors for HF

Major clinical risk factors

Age, male sex, hypertension, LV hypertrophy, myocardial infarction, valvular heart disease, obesity, diabetes

Minor clinical risk factors

Smoking, dyslipidemia, chronic kidney disease, albuminuria, sleep-disordered breathing, anemia, increased heart rate, dietary risk factors, sedentary lifestyle, low socioeconomic status, psychological stress

Immune-mediated

Peripartum cardiomyopathy, hypersensitivity

Infectious

Viral, parasitic (Chagas disease), bacterial

Toxic risk precipitants

Chemotherapy (anthracyclines, cyclophosphamide, 5-FU), targeted cancer therapy (trastuzumab, tyrosine kinase inhibitors), cocaine, NSAIDs, thiazolidinediones, doxazosin, alcohol

Genetic risk predictors

SNP (e.g. α2CDel322-325, β1Arg389), family history, congenital heart disease

Morphological risk predictors

Increased LV internal dimension, mass, asymptomatic LV dysfunction

Biomarker risk predictors

Immune activation (e.g. IGF1, TNF, IL-6, CRP), natriuretic peptides (e.g. BNP and NT-BNP), high sensitivity cardiac troponin

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; 5-FU, 5-fluorouracil; HF, heart failure; IGF, insulin-like growth factor; IL, interleukin; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; NT-BNP, N-terminal BNP;

SNP, single-nucleotide polymorphism; TNF, tumor necrosis factor. Adapted from Schocken, D. D. *et al.* Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* **117**, 2544–2565 (2008).

Ischemic heart disease

Ischemic heart disease is thought to be the most important risk factor for HF.[11,40,78–81] In the 7 to 8 years after an MI, more than one-third of patients will develop HF, particularly those with LV dysfunction noted at the time of their heart attack.[82] A history of MI increases the lifetime risk of HF in both men and women.[39] From the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry,[83] ischemia was identified as the primary cause of hospitalization in 15% of patients with HF, and they had worse in-hospital mortality, and also 60-day and 90-day mortality after discharge. Given the strong association between coronary artery disease and HF, it is not surprising that many atherosclerotic risk factors are also risk factors for developing HF.

Advances in management of MI may also impact on HF trends. Better survival after an MI may increase the population at risk for HF, thereby fueling an increase in the number of HF cases. On the other hand, if the severity of MI is declining or if treatment is improving, then the incidence of HF post-MI might also be expected to decrease. In the Olmsted cohort, 36% of patients with incident MI developed HF between 1979 to 1994, with the incidence of HF declining by 2% per year.[81] Administration of reperfusion therapy within 24 h seemed to account for most of the temporal decline in post-MI HF.[82] These findings indicate that improved MI management was associated with less post-MI HF.

Analysis of the Framingham Heart Study, however, reached a different conclusion. Comparing 1970–1979 with 1990–1999, Velagaleti and colleagues found that the 30-day incidence of HF after MI rose from 10% to 23.1%, whereas the 30-day mortality after MI declined from 12.1% to 4.1%.[84] Similar trends were seen with the 5-year end points (27.6% to 31.9% for incident HF, and 41.1% to 17.3% for mortality, respectively).[84] These findings indicate that an increase in the incidence of HF coincided with a decrease in mortality after MI. Similarly, the Worchester Heart Attack study[85] reported an increased incidence of HF after MI between the time period from 1975 to 2001, although an earlier study using the same cohort initially reported a modest decline in rates of HF.[86] An earlier study of the Framingham Heart Study also found no change in the incidence of post-MI HF between 1950 and 1989.[87] The interim period between 1990 and 2000 possibly represent years when patients post-MI began to present with HF after advances in reperfusion therapy. Findings of increased post-MI HF in the face of improving mortality after MI are also supported by a cohort study in Canada of more than 7,000 elderly patients hospitalized with acute MI.[88] Between 1994 and 2000, the 5-year mortality after MI decreased by 28%, whereas the 5-year incidence of HF increased by 25%.[88] The growing prevalence of HF may, therefore, in fact be partly owing to the improved survival of patients after MI.

Hypertension

Although the risk of HF associated with hypertension is smaller than that associated with MI, hypertension contributes more to the population burden of HF because of its greater prevalence.[35] In the Framingham cohort, 75% of incident HF cases had antecedent hypertension.[39] Men with hypertension had a twofold increase in risk of developing HF, and

women threefold, whereas the population attributable risk for HF imparted by hypertension was estimated to be 39% in men and 59% in women.[89] The Rotterdam study[32] similarly indicated that hypertension was more of a contributing factor in women than men; hypertensive women were 2.6 times more likely to develop HF than women without hypertension, but hypertensive men were at no higher risk than their nonhypertensive counterparts.[32] Less pronounced findings were concluded from CHS,[40] in which hypertension increased the risk of incident HF by 40% and was associated with a population attributable risk of 13%. Because CHS only included those aged ≥65 years, these lower estimates of the risk attributable to hypertension compared with other studies could reflect the greater presence of other comorbidities, such as ischemic heart disease, when confined to an older population.

The more severe the elevation in blood pressure, the worse the risk of developing HF. The lifetime risk for individuals with blood pressure ≥160/90 mmHg is double that of those with blood pressure <140/90 mmHg.[39] Among people who are hypertensive, risk factors for developing HF include MI, diabetes, LV hypertrophy, and valvular heart disease.[89] In addition, the combined presence of hypertension and HF is associated with worse outcomes; 5-year mortality after the onset of hypertensive HF was 76% in men and 69% in women.[89] Treatment of hypertension, however, can reduce the incidence of HF by almost 50%.[90,91]

Diabetes

Diabetes as well as insulin resistance are also linked to HF development, with diabetes increasing the risk of HF by approximately twofold in men, and up to fivefold in women.[39,80,89,92,93] Further evaluation of the elevated risk particularly in women, was addressed by HERS (Heart and Estrogen/progestin Replacement Study) and its follow-up (HERS II),[94] which included postmenopausal women with a history of coronary heart disease. The investigators concluded that women with diabetes with an elevated BMI or renal insufficiency were at highest risk, having annual HF incidence rates of 7% and 13%, respectively. By contrast, women without diabetes with no other risk factors had an HF incidence of 0.4%. Hyperglycemia (defined as a fasting blood glucose of >300 mg/dL) among patients with diabetes conferred further risk, increasing the hazard by threefold. Not surprisingly, the addition of other risk factors increased the baseline risk. The presence of diabetes was nearly equivalent to the presence of three other traditional atherosclerotic risk factors; the annual incidence of HF in diabetics with no additional risk factors was 3.0% compared with 3.4% in women without diabetes with three or more risk factors. Diabetics with three or more risk factors have an elevated incidence rate of 8.2%.[94]

Diabetes is not only a risk factor for the development of HF, but also portends worse outcomes in the presence of HF. Unfortunately, the convergence of the two diseases has been increasing over time. Based on the Olmsted cohort, the prevalence of concomitant diabetes increased 3.8% every year in patients with HF from 1979 to 1999.[95] This increase was particularly pronounced in older individuals; in those aged >75 years, the odds of having diabetes and HF were nearly fourfold in 1999 compared with in 1979.[95] HF survival is worse in the presence of diabetes—the 5-year survival was 46% in those with HF alone, but only 37% for those with both diabetes and HF.[95]

Dyslipidemia

Elevated cholesterol levels are well recognized as an important independent risk factor for atherosclerotic vascular disease. Dyslipidemia, therefore, is linked to the development of HF. Whereas elevated levels of total cholesterol are not a strong predictor of new-onset HF,[33,40] an increased ratio of total cholesterol to HDL cholesterol is associated with elevated HF risk.[96] Clinical trial evidence also exists showing that lowering LDL cholesterol might

prevent HF. Statin treatment in patients with coronary artery disease reduced HF incidence and decreased all-cause mortality in the subset of patients who developed HF in an analysis of the Scandinavian Simvastatin Survival Study (4S).[97]

Smoking

Tobacco use remains the single largest preventable cause of disease and premature death in the USA. Current smokers have significantly higher risk for the development of HF than ex-smokers and nonsmokers. In CASS (Coronary Artery Surgery Study),[98] smoking was independently associated with a 47% increased risk of developing HF. In the SOLVD trials (Studies Of Left Ventricular Dysfunction),[99] ex-smokers had a 30% lower mortality than current smokers, a benefit that accrued within 2 years after smoking cessation.

Risk factors associated with HF and preserved LVEF

The relative contributions of risk factors and risk profile also differ for patients with HF and preserved LVEF compared with patients with HF and reduced LVEF.[19,21,31,65–68,75,100,101] In a study from Framingham,[65] independent predictors of the onset of HF and preserved LVEF included elevated systolic blood pressure (odds ratio [OR] 1.13 per 10 mmHg), atrial fibrillation (OR 4.23), and female sex (OR 2.29). Prior MI (OR 0.32) and left bundle-branch block morphology (OR 0.21) were associated with reduced odds of HF and preserved LVEF.[65] Cardiovascular disease risk factors, including diabetes, smoking, and hypertension commonly preceded the onset of both HF and reduced LVEF as well as HF and preserved LVEF, but these pre-onset risk factors did not distinguish between the two.[65] Hence characteristics at the time of acute onset were more able to differentiate HF and preserved LVEF versus HF and reduced LVEF than long-standing risk factors.

Other risk factors

Obesity also increases the risk of HF, and estimates suggest that having a BMI ≥30 kg/m^2 doubles the risk of HF.[47,81,102] Among those with established HF, however, there is evidence that obesity is associated with improved outcomes.[103,104] In an analysis of nearly 8,000 patients in the Digitalis Investigation Group Trial,[104] obese patients had a 19% lower risk of death than individuals of normal weight. This paradox has not been well explained and may be related to the earlier age at which patients with obesity present with HF, the highly catabolic nature of the HF disease state, or other factors.[105]

Renal failure, even in the early stages, confers incremental risk. From the Physicians Health Study,[106] early kidney disease, as measured by elevated cystatin C levels, increases the odds of incident HF by 80%, though this effect is attenuated by adjustment for blood pressure. Among those with HF, kidney disease is a strong predictor of mortality. In the HERS study, poor renal function (creatinine clearance <40 ml/min) was associated with a 53% higher hazard of death than in those with normal renal function.[107] Use of angiotensin-converting-enzyme (ACE) inhibitors seemed to attenuate this increased risk.

Other risk factors include psychological stress and environmental factors, such as a low socioeconomic status.[108] Additionally, a variety of biomarkers, alterations in cardiac morphology, and genetic factors identify patients who are at high risk for developing HF. Biomarkers associated with higher HF risk include natriuretic peptide and ultrasensitive troponin levels.[108] Cardiac morphological parameters that identify individuals at higher risk for HF include increased LV size and mass.[108] An increasing number of genetic factors, from single mendelian mutations to genetic polymorphisms, are also associated with HF.[108]

These conditions not only increase the risk for developing HF, but contribute to the morbidity and mortality for patients with established HF. As elderly individuals are

disproportionately affected by HF, multiple other comorbid conditions are frequently present in patients with HF.[109,110] In a study of elderly US Medicare beneficiaries hospitalized for HF, comorbidities were common, including hypertension (61%), coronary artery disease (56%), diabetes (38%), chronic obstructive pulmonary disease (33%), and atrial fibrillation (30%).[111] Therefore, practitioners must deal not only with managing HF, but also with multiple other conditions and the resultant risk of adverse effects from polypharmacy. The risk of preventable hospitalizations and mortality is strongly increased with the number of comorbid conditions.[112]

Impact on health services

The resources used to treat HF vary by country and context, and so discussions relating to health services are location-specific. Because there is a relative paucity of data regarding the burden and costs of HF outside the USA, most of the information reported here is from this setting.

Hospitalizations

HF places a heavy and growing burden on the health-care system. In the USA, HF is the most common condition for hospital admission in people aged >65 years, followed by pneumonia, cancer, cerebrovascular disease, and then coronary atherosclerosis.[113] Of the patients first diagnosed with HF in the outpatient setting in Olmsted County, 74% were hospitalized within a mean of 1.7 years.[12] In the USA, there were over 1.1 million hospital discharges of patients with a primary diagnosis of HF in 2006, with 2.4–3.6 million having HF as a primary or secondary diagnosis.[1] Data from national registries indicate that approximately 46–51% of hospitalized patients with acute HF have HF and preserved LVEF.[67,68,76]

Based on the National Hospital Discharge Summary, adjusted hospitalization rates for HF as the primary diagnosis increased by 79% between 1979 and 2004; a twofold increase was observed when considering hospitalizations where HF was listed anywhere on the discharge conditions (Figure 4).[5] Not all studies consistently find a continuing rise in hospitalizations; Stewart and colleagues concluded that the hospitalization rate in Scotland steadied in the 1990s,[114] after nearly 60% increase between 1980 to 1990.[115] Similarly, hospitalization rates remained stable in Oregon between 1991 and 1995,[51] and in Ontario, Canada, between 1992 and 2000.[18]

Other changes to admission of patients with HF have been made. The median length of stay has declined, from 8 days in 1980–1984 to 5 days in 2000–2004.[5] A decline has also been seen in the percentage of patients discharged from hospital to home (70.6% to 57.3%) and an increase in transfers to both short-term and long-term facilities (12.3% to 26.0%) over the same time period.[5] Thus, while the number of hospitalizations is potentially growing, this observation could be related to shorter lengths of stay in hospital. Patients are also being transferred to facilities for continued care, rather than being improved to the point where they can go home.

Furthermore, advances in medical care are allowing people to live with more comorbidities. The management of other chronic diseases in patients with HF, therefore, becomes increasingly important. Among hospitalized patients in whom HF was listed anywhere on the discharge diagnosis, only 30% had HF listed as the primary diagnosis.[5] Thus, patients with HF are primarily hospitalized for other conditions, one of the most common of which includes respiratory diseases, such as pneumonia and chronic obstructive pulmonary disease.[5] However, the addition of multiple comorbidities adds to the complexity of managing patients with HF. Not only is there a high frequency of comorbid conditions in patients with

HF,[111] therapies for chronic conditions may be limited when treatments that are beneficial in one condition are detrimental in another; for example, β-blockers in the presence of lung disease, ACE inhibitors in the presence of kidney disease, or nonsteroidal anti-inflammatory drugs for arthritis are contraindicated in HF.[110,116]

Readmissions constitute a substantial portion of the hospitalization burden. Among the US Medicare fee-for-service population, HF was the most common cause of readmission, with 27% of patients being readmitted within 30 days.[117] In another study of US Medicare patients, Bueno and colleagues found reductions in length of stay and in-hospital mortality between 1993 and 2006, but there were fewer patients discharged to home and an increase in 30-day readmission rates from 17% to 20%.[54] Similar increases in rehospitalization rates were observed in Canada during this period.[118] Economic incentives to reduce hospital length of stay may have led to suboptimal in-patient management, resulting in more frequent readmissions and overall increased rates of hospitalization. Patients with HF and preserved LVEF are also frequently readmitted, with 60 to 90 day readmission rates of 29%.[67]

There remains considerable individual hospital variability in conforming to quality of care indicators. In one study of adherence to the performance standards established by the US Joint Commission on Accreditation of Healthcare Organizations, hospital adherence rates varied from 0% to 100%.[119] Considerable variability was also observed in median length of stay, ranging from 2.3 days to 9.5 days, and in in-hospital mortality, from 0% to 11.1%.[119] Thus, despite published guidelines, a gap between guidelines and actual care remains, which may be associated with high variability in outcomes.

Data from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) trial[77] indicate that the frequency of hospitalization itself is associated with increased mortality. In patients with chronic HF, the risk of death is greatest in the earliest period after discharge and directly related to the duration and frequency of HF hospitalizations.[77] Those with more comorbidities are also more likely to be readmitted; in a cross-sectional study of US Medicare beneficiaries, nearly 40% of HF patients had five or more comorbidities, and this group accounted for 81% of the total hospital days experienced by all patients with HF.[112]

Ambulatory care

HF has been reported to be second only to hypertension as a cardiovascular reason for an office visit, and results in 12 to 15 million outpatient visits annually in the USA.[120] In a study of 1,516 outpatients in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study),[121] Chan and colleagues found that HF outpatients with reduced LVEF after an MI incur substantial costs within the following year, with mean costs ranging from $9,628 to $18,476 per patient. Improved outpatient follow-up in addition to avoiding premature hospital discharge could have a positive impact on reducing rehospitalization rates.[122,123] However, as an international survey in 15 countries showed, substantial variation in practice is found across countries with inconsistencies between physician knowledge and actual prescription patterns in the outpatient setting.[109]

Cost

At present, developed countries devote 1–2% of all health-care expenditures towards HF.[124] Costs to the National Health Service in the UK were estimated to be 1.9%.[125] The estimated cost of HF for 2010 is $39.2 billion,[1] which includes health-care services, medications, and lost productivity. This estimation is likely understated because it is based on data for HF as the primary diagnosis or underlying cause of death and ignores secondary diagnoses and other indicators. Over a 5-year period, patients with HF and preserved LVEF will consume

as many health-care resources as those with HF and reduced LVEF.[126] Hospitalizations are the main driver of total HF costs,[127] and because approximately 80% of HF hospitalizations occur among the US Medicare population who are aged ≥65 years,[5] the costs to US Medicare are likely to rise with the aging population.

Future directions

As the prevalence of HF continues to increase, it will be necessary to more effectively prevent the occurrence of HF to address the global burden of this syndrome.[128] More needs to be done to improve identification of those at risk for HF, modify the risk factors that contribute to HF pathogenesis at both the individual and population level, as well as better appreciate the interactions of age, sex, and race in order to not exacerbate existing disparities. Developing an understanding of whether, and to what degree, differences in treatment rates and medication adherence might contribute to disparities in HF incidence and outcomes by race and ethnicity is also important. Use of medications, such as ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers together with device therapies in selected patients, have improved survival in those with prevalent HF and reduced LVEF. However, no therapy has as yet been shown to improve survival in those with HF and preserved LVEF. There is a critical need to identify and implement therapies for patients with HF and preserved LVEF. Further progress in understanding the epidemiological and pathophysiological differences between patient subgroups could allow for improved and more targeted preventive and management therapies.

Developing better insight into the drivers of HF hospitalizations and preventable readmissions will also be important for improving individual care and addressing its broader economic impact. Such efforts may require changes in discharge planning or disease management at home.[129,130] The fact that many hospitalizations of patients with HF are precipitated by ischemia, arrhythmias, chronic obstructive pulmonary disease, bronchiectasis, lower respiratory disease, asthma, and acute and chronic renal failure[110] suggests that more can be done to manage the comorbidities that occur with HF. There may be an underutilization of effective HF therapies in patients with contraindications, such as lung or kidney disease.[131] More work is needed to identify effective management strategies in these vulnerable subgroups.

Conclusions

HF is, and will continue to be, a substantial burden on health-care systems and societies. Although age-adjusted incidence has generally not been found to have increased in recent years, the prevalence of HF will likely continue to rise given the substantial aging of the population, improved survival with HF, and improved survival after MI. With these changes come increasing rates of hospitalizations and rehospitalizations, as well as their associated costs to society and the individual's quality of life. HF and preserved LVEF represents over half of prevalent HF and likely has outcomes as poor as those associated with HF and reduced LVEF, but as yet has no effective therapies. Further study of the epidemiology of HF, particularly of its subgroups and the interactions between risk factors, will not only better inform the prognostication and treatment of the individual patient with HF, but also allow for more effective global prevention efforts.

Key points

- Heart failure (HF) is a major public health issue that affects nearly 5.8 million individuals in the USA and 23 million worldwide

- The prevalence of HF is increasing owing to the aging population and improved management of heart disease, but the age-adjusted incidence of HF seems to have plateaued
- HF and preserved left ventricular ejection fraction (LVEF) has an increasingly prominent role in HF, representing more than half of HF cases, with outcomes similar to HF and reduced LVEF
- Although mortality from HF has improved over the past few decades, it still results in a high 5-year mortality that rivals that of many cancers
- Risk factors, such as ischemic heart disease, hypertension, smoking, obesity, and diabetes increase the risk of incident HF and predict poor outcomes in the setting of the disease
- HF is a major source of health services utilization, being a leading cause of hospitalizations, readmissions, and outpatient visits at a cost of over $39 billion annually in the USA

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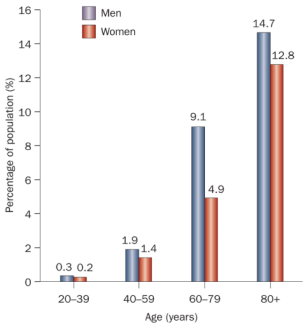

Figure 1.

Prevalence of heart failure by age and sex in the USA. Based on the National Health and Nutrition Examination Survey, 2003–2006. With permission from Lloyd-Jones, D. *et al.* Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* **121**, e46–e215 (2010).

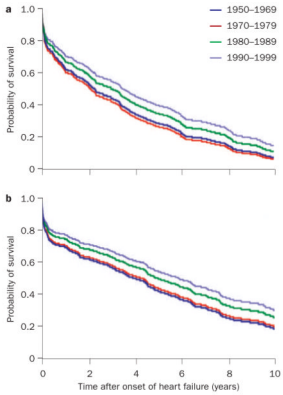

Figure 2.

Age-adjusted survival after the onset of heart failure in **a** | men and **b** | women over time, from 1950 to 1999, based on the Framingham Heart Study. Estimates shown are for patients aged 65 to 74 years. Reproduced with permission from Levy, D. *et al.* Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.* **347**, 1397–1402 © 2002 Massachusetts Medical Society. All rights reserved.

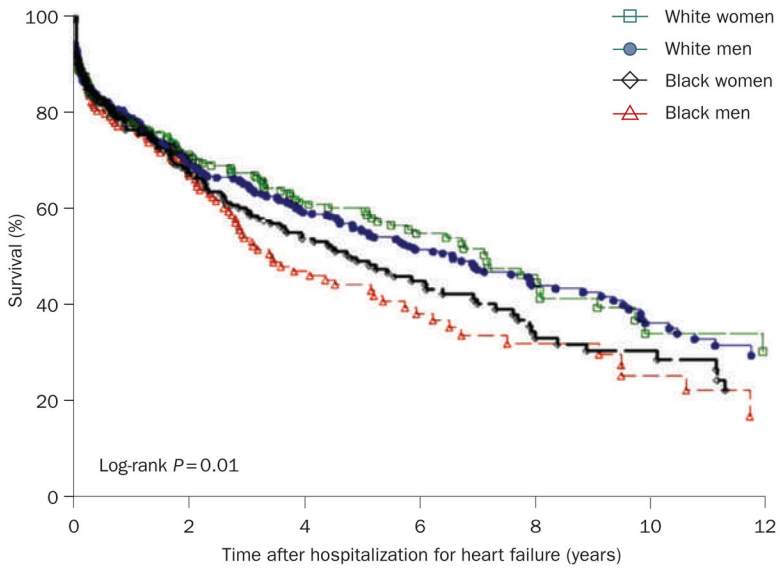

Figure 3.

Survival after incident heart failure hospitalization by race and sex, based on the ARIC (Atherosclerosis Risk in Communities) Study, 1987–2002. Reprinted from *Am. J. Cardiol.* **101**, Loehr, L. R. *et al*. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study), 1016–1022 © 2008, with permission from Elsevier.

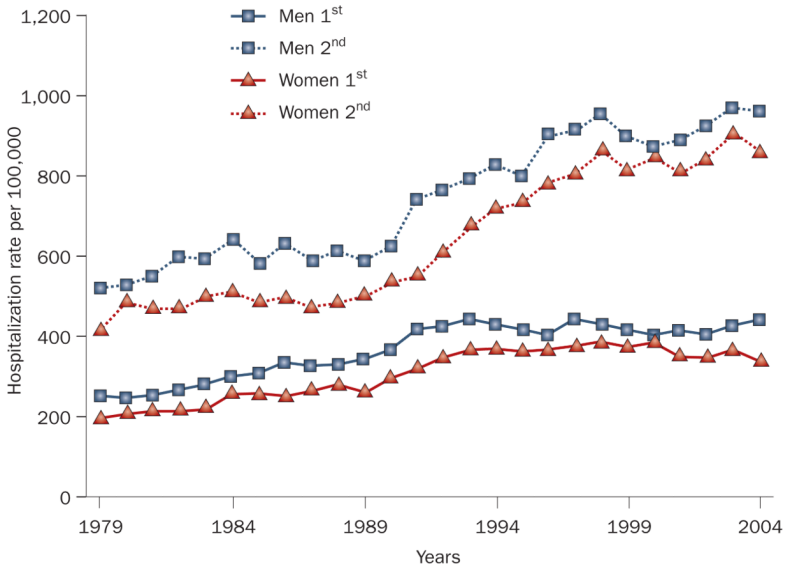

Figure 4.

Time trends of age-adjusted hospitalization rates in men and women, based on the National Hospital Discharge Survey, 1979–2004. Trends shown for heart failure as the first-listed or additional (2nd to 7th) diagnosis for men and women. Reprinted from *J. Am. Coll. Cardiol.* **52**, Fang, J. *et al*. Heart failure-related hospitalization in the U.S., 1979 to 2004, 428–434 © 2008, with permission from Elsevier.

Table 1

Temporal trends in the age-adjusted incidence of HF based on the Framingham Heart Study*

Period	Men		Women	
	Incidence of HF (rate per 100,000 person-years)	Rate ratio	Incidence of HF (rate per 100,000 person-years)	Rate ratio
1950–1969‡	627 (475–779)	1.00	420 (336–504)	1.00
1970–1979	563 (437–689)	0.87 (0.67–1.14)	311 (249–373)	0.63 (0.47–0.84)
1980–1989	536 (448–623)	0.87 (0.67–1.13)	298 (247–350)	0.60 (0.45–0.79)
1990–1999	564 (463–665)	0.93 (0.71–1.23)	327 (266–388)	0.69 (0.51–0.93)

*All values were adjusted for age (<55, 55–64, 65–74, 75–84, and ≥85 years). Values in parentheses are 95% CI.

‡This period served as the reference period.

Abbreviation: HF, heart failure. Reproduced with permission from Levy, D. *et al.* Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.* **347**, 1397–1402 © 2002 Massachusetts Medical Society. All rights reserved.