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# Epidemiology and aetiology of heart failure

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**Abstract** | Heart failure (HF) is a rapidly growing public health issue with an estimated prevalence of >37.7 million individuals globally. HF is a shared chronic phase of cardiac functional impairment secondary to many aetiologies, and patients with HF experience numerous symptoms that affect their quality of life, including dyspnoea, fatigue, poor exercise tolerance, and fluid retention. Although the underlying causes of HF vary according to sex, age, ethnicity, comorbidities, and environment, the majority of cases remain preventable. HF is associated with increased morbidity and mortality, and confers a substantial burden to the health-care system. HF is a leading cause of hospitalization among adults and the elderly. In the USA, the total medical costs for patients with HF are expected to rise from US\$20.9 billion in 2012 to \$53.1 billion by 2030. Improvements in the medical management of risk factors and HF have stabilized the incidence of this disease in many countries. In this Review, we provide an overview of the latest epidemiological data on HF, and propose future directions for reducing the ever-increasing HF burden.

Heart failure (HF) remains a rising global epidemic with an estimated prevalence of >37.7 million individuals globally<sup>1,2</sup>. As of 2011, within the USA alone, an estimated 5.7 million individuals live with HF and 870,000 new cases are diagnosed every year<sup>3</sup>. Many developing nations are in the midst of an epidemiological transition as the disease burden rapidly shifts from diseases related to nutritional deficiencies and infections to degenerative chronic diseases observed in the older population<sup>4</sup>. Excluding sub-Saharan Africa, the rates of death from noncommunicable diseases such as HF are increasing worldwide<sup>5</sup>. Data from the Global Burden of Disease Study<sup>5</sup> indicate that approximately 17.3 million people died from cardiovascular causes in 2013, which is a 41% increase from the number of deaths attributed to cardiovascular disease in 1990 (REF. 5). The increase in cardiovascular disease burden is primarily due to demographic shifts, namely an expanding and ageing global population<sup>6</sup>. The ever-increasing incidence of HF in the USA since the 1970s has been described as an epidemic<sup>7,8</sup>. The number of hospitalizations that included HF as a diagnosis in the USA tripled from 1.27 million in 1979 to 3.86 million in 2004 (REF. 9), signifying a substantial economic burden on the health-care system. Although a diagnosis of HF portends increased mortality and loss of quality-adjusted life years, advances in evidence-based therapies and the quality of care in the modern era have substantially improved outcomes for patients. Between 1979 and 2000 in the USA, the absolute 5-year survival rate for HF increased by 9%<sup>10</sup>. In this

Review, we provide an up-to-date overview of the epidemiology of HF, risk factors and aetiologies contributing to the disease burden, and its effect on health-service utilization and health-care expenditures.

## Definition

Diseases of the heart muscle were widely documented in Rudolf Virchow's publication of *Die Cellularpathologie* in 1858, in which he defined nonvalvular heart disease as 'chronic myocarditis', owing to his observation of inflammation on histological sections of diseased hearts<sup>11</sup>. Although the classification terminology for HF has evolved considerably since Virchow's original description, controversies and ambiguities remain. HF is a shared chronic phase of a multitude of cardiac diseases. The ACC Foundation and AHA define HF as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood" (REF. 12). According to their joint guidelines<sup>12</sup>, HF with reduced ejection fraction (HFrEF) is defined as an ejection fraction  $\leq 40\%$ , whereas HF with preserved ejection fraction (HFpEF) is defined as an ejection fraction  $\geq 50\%$ . Patients with an ejection fraction that falls between this range are considered to have borderline HFpEF. Given that this recommendation was published only 3 years ago in 2013, the literature on HFpEF involving the use of echocardiographic imaging data has varied thresholds for left ventricular ejection fraction between 40% and 55%<sup>12</sup>. In 2012, the ESC acknowledged the challenges and uncertainties in defining and diagnosing

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**Key points**

- Heart failure (HF) is the most rapidly growing cardiovascular condition globally
- HF with preserved ejection fraction accounts for an increasing portion of HF in the developed world, and therapies to improve health outcomes are needed
- Improvement in the primary prevention of cardiovascular disease and the treatment of ischaemic heart disease have reduced the age-adjusted prevalence of HF in the developed world
- Advances in HF treatment and prevention have resulted in a decline in mortality in developed nations

HFpEF, even when holistically evaluating patient symptoms, signs, imaging data, and biomarker studies<sup>13</sup>. The ESC guidelines integrate Doppler parameters and biomarker data into the HFpEF diagnostic criteria, and mention the potential of strain and speckle tracking as well as diastolic stress testing to improve categorization of patients with HFpEF<sup>13</sup>.

Although the term ‘cardiomyopathy’ is frequently used in clinical settings to describe ischaemic, valvular, and hypertensive disease, it should be reserved for disease of the myocardium with known genetic or phenotypic patterns. The WHO was among the first to direct a task force to clarify the definition of cardiomyopathies as the scientific understanding of HF aetiologies progressed<sup>14,15</sup>. The term ‘ischaemic cardiomyopathy’ continues to be used instead of the preferred term ‘ischaemic heart disease’ in various guidelines<sup>12,16,17</sup>. In 2006, the AHA published a scientific statement to classify cardiomyopathies as distinct diseases of the myocardium that are predominately genetic and associated with mechanical or electrical dysfunction that frequently progress to HF. Primary cardiomyopathies are generally confined to the heart muscle, whereas secondary cardiomyopathies have both myocardial and systemic multiorgan involvement<sup>18</sup> (BOX 1). In 2008, the ESC provided their own classification of cardiomyopathies — with acknowledged differences from the AHA 2006 statement — based on their morphological and functional phenotypes<sup>19</sup>. In 2013, the World Heart Federation proposed a more specific MOGE(S) nosology system for cardiomyopathies, which describes the morphofunctional phenotype (M), organ involvement (O), genetic inheritance pattern (G), aetiological annotation (E), and functional status (S) of the disease. This classification system allows greater flexibility in categorizing overlapping genetic and phenotypic syndromes<sup>20</sup>. The redefinition of HF taxonomies will continue to evolve concurrently with our understanding of the molecular and genetic pathophysiology of HF.

Clinical and research definitions of HF are wide-ranging and prone to misclassification. Diagnostic criteria for HF can include physician assessment, laboratory tests, advanced cardiovascular imaging, or invasive haemodynamic catheterization. In 1971, the Framingham Heart Study provided clinical criteria for HF diagnosis based on physical examination and physician adjudication<sup>21</sup>. Framingham researchers utilized major and minor criteria to establish definite, probable, or questionable diagnoses for congestive HF<sup>22</sup>.

The Carlson criteria, published in 1985, uses a points system based on patient history, physical exam, and chest radiography to determine the certainty of HF, mainly for research purposes<sup>23,24</sup>. Investigators in other studies, such as the Cardiovascular Health Study<sup>25</sup>, have diagnosed HF on the basis of a physician panel review of all pertinent medical records, including chest x-ray and echocardiograms<sup>25</sup>. The latest guidelines on the echocardiographic assessment of left ventricular function from the American Society of Echocardiography, published in 2015, recommend that ejection fraction should be considered abnormal when it is  $\leq 52\%$  for men and  $\leq 54\%$  for women<sup>26</sup>. Validation studies to assess the sensitivity and specificity of several HF criteria have yielded variable results<sup>27,28</sup>.

Health-service utilization and hospitalization rates associated with HF frequently depend on medical provider billing information in the community. The limitations on available administrative data have been described, with concerns for the underestimation of HF admissions, misspecification of diagnoses, unbundling of medical conditions, and upcoding<sup>29–31</sup>, leading some to question the accuracy of International Classification of Disease, Ninth Revision (ICD-9) codes, designed to facilitate international comparability in the collection and presentation of mortality statistics. An estimated one-third of patients hospitalized with HF lack relevant ICD-9 codes as a primary or secondary diagnosis for acute exacerbations<sup>29</sup>. ICD-10 codes were found to be highly predictive of acute HF compared with physician adjudication (using the Carlson criteria), and were similar to ICD-9 coding reliability with a positive predictive value of 90.2%, negative predictive value of 97.2%, sensitivity of 68.6%, and specificity of 99.3%<sup>31</sup>. Over time, upcoding and misclassification might substantially misrepresent trends in incidence and prevalence. Improved diagnostic accuracy might confound outcomes such as hospitalization rates and mortality<sup>8</sup>. More routine utilization of echocardiography and advancements in echocardiographic imaging have led to increased diagnosis of both HFrfEF and HFpEF in hospitalized patients, which makes comparing cohorts between eras increasingly challenging.

**Epidemiology****Incidence**

Estimates of HF incidence and trends in the global population are scarce and unreliable<sup>32</sup>. Most of the literature on HF epidemiology and management is derived from high-income, developed nations. In these countries, HF incidence in particular populations has shown signs of stabilization and possible reduction. Improvements in the primary prevention of cardiovascular diseases and the treatment of ischaemic heart disease are the primary drivers of this trend<sup>33,34</sup>. In general, the global incidence of HF ranges from 100 to 900 cases per 100,000 person-years depending on the diagnostic criteria used and population studied<sup>8</sup>. Investigators in the Atherosclerosis Risk in Communities Study<sup>3</sup>, who assessed trends in hospitalization and case fatality rates, estimated 915,000 new cases of HF in the USA in 2012.

Community-based cohorts, such as Framingham and Olmsted County, might provide more reliable information on the incidence and prevalence of HF through their use of case validation sampling strategies. Cases can be confirmed by reviewing medical record, findings on physical exams, and physician panel review. For >65 years, the Framingham Heart Study has reported on risk factors, prevalence, and trajectories of numerous cardiovascular diseases<sup>35</sup>. Importantly, their diagnostic criteria and methods have remained uniform over time, rendering their reported trends for risk factors and cardiovascular diseases more consistent. However, as both the Framingham and Olmsted County cohorts are predominately made up of white individuals, the trends measured using these cohorts cannot be generalized to more ethnically diverse populations<sup>32,35</sup>.

Over the past 60 years, the incidence of HF in the USA has stabilized, and standardized age-adjusted rates are thought to be decreasing. Between 1950 and 1999, the incidence of HF in women from the Framingham cohort reduced from 420 to 327 cases per 100,000 person-years<sup>35</sup>. However, this reduction was not observed for men, whose HF incidence remained at approximately 564 cases per 100,000 person-years<sup>35</sup>. Between 2000 and 2010, the age-adjusted and sex-adjusted incidence of HF declined from 315.8 to 219.3 per 100,000 residents in the Olmsted County cohort, a 37.5% decline over the decade<sup>32</sup> (FIG. 1). A greater decline in HF incidence was observed in women (43%) than in men (29%)<sup>32</sup>. The incidence of HF varies between ethnic groups in the USA. The Multi-Ethnic Study of Atherosclerosis<sup>36</sup> reported the highest incident rates of HF among African-American individuals, intermediate rates among white and Hispanic individuals, and the lowest rates among Chinese-American individuals. Differences in risk factors (including hypertension and diabetes mellitus), as well as socioeconomic status, contribute to this ethnic disparity in the incidence of HF<sup>36</sup>.

Similar reductions in HF incidence have been observed in Europe. More than 8,000 participants from the community-based PREVEND cohort study<sup>34</sup> from Groningen, the Netherlands recruited in 1997–1998 were followed up for 11 years for assessment of cardiovascular risk factors and disease epidemiology. Using the ESC criteria to diagnose HF, the incident rate of HF was 387.4 cases per 100,000 person-years, with 34% of all cases categorized as HFpEF<sup>37,38</sup>. A Swedish study using data from an administrative health register in Stockholm comprising 2.1 million inhabitants reported 380 new cases of HF per 100,000 person-years in 2010, with an absolute reduction of 90 cases compared with their 2006 national health data<sup>39</sup>.

Approximately 80% of the global cardiovascular disease burden occurs in middle-income and low-income countries<sup>5,40,41</sup>. Projects such as the INTERNATIONAL Congestive Heart Failure study<sup>38</sup>, the PURE study<sup>39</sup>, and the Global Burden of Disease Study<sup>40</sup> aim to measure the burden of HF in these countries<sup>5,40,41</sup>. The PURE study involves a cohort of 156,424 individuals from three high-income, 10 middle-income, and four low-income nations, and is designed to assess factors related to the development of chronic conditions. After a mean

follow-up of 4.1 years, the PURE investigators reported 271 new cases of HF per 100,000 person-years<sup>41</sup>. Among African patients hospitalized for cardiovascular disease, acute decompensated HF was the most common diagnosis<sup>42</sup>. Improvements in public-health infrastructure and further research are needed to improve monitoring of the cardiovascular disease burden in these middle-income and low-income nations.

### Prevalence

An estimated 37.7 million people are living with HF globally<sup>2</sup>. The estimates of HF prevalence in developed countries generally range from 1–2% of the adult

#### Box 1 | Taxonomy of heart failure aetiologies<sup>18,132</sup>

##### Ischaemic

Coronary artery disease  
Coronary dissection  
Coronary embolism

##### Valvular

Rheumatic heart disease  
Degenerative valvular disease

##### Hypertensive (both HFpEF and HFpEF)

##### Primary cardiomyopathies

###### Genetic

- Hypertrophic cardiomyopathy
- Arrhythmogenic cardiomyopathy
- Left ventricular noncompaction
- Mitochondrial myopathies
- Ion-channel disorders (long QT syndrome, Brugada, etc.)

###### Acquired

- Tachycardia-induced
- Peripartum
- Stress-induced (Takotsubo)
- Substance-abuse-induced (e.g. alcohol, cocaine)
- Toxin-related (e.g. anthracycline)
- Myocarditis (inflammatory)
- Chagas
- HIV
- Viral
- Giant cell myocarditis

##### Secondary cardiomyopathies

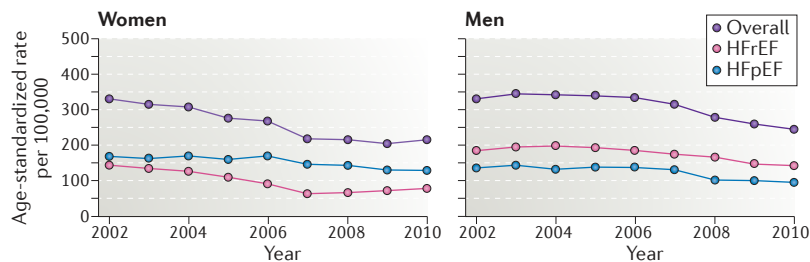
Amyloidosis  
Sarcoidosis  
Storage disease (e.g. haemochromatosis, Fabry disease)  
Connective tissue disorder (e.g. scleroderma)  
Thyroid disease  
Endomyocardial fibrosis  
Nutritional deficiencies (e.g. selenium, beriberi, kwashiorkor)  
Anaemia  
Arteriovenous fistula

##### Congenital heart disease

##### Pericardial disease

##### Other

HFpEF, heart failure with preserved ejection fraction;  
HFrEF, heart failure with reduced ejection fraction.



**Figure 1 | Incidence of heart failure in Olmsted County between 2000 and 2010.** A decrease in the age-adjusted rate of HF for both men and women was observed between 2000 and 2010. This decrease is most notable for HFrEF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. Modified from Gerber, Y. *et al.* A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern. Med.* **175**, 996–1004 (2015), with permission from the American Medical Association.

population<sup>43</sup>. Although the age-adjusted incidence and prevalence of HF are decreasing, the absolute number of patients with HF has drastically increased, secondary to shifts in the global age distribution, as well as general population growth<sup>6</sup>.

Before the 1970s, the prevalence of HF in the USA was estimated using hospital records or death certificates with limited reliability, owing to a large proportion of care being provided on an outpatient basis. The development of the first National Health and Nutritional Examination Survey (NHANES) facilitated a more accurate estimation of HF prevalence nationally<sup>44</sup>. The prevalence of self-reported and clinically defined HF in 1971–1975 was estimated to be 1.1% and 2.0%, respectively<sup>44</sup>. Investigators in the NHANES study compiled self-reported HF data between 2009 and 2012, and estimated that approximately 5.7 million adults (2.2%) in the USA live with the chronic condition<sup>3</sup>. Consistent with this figure, the prevalence of HF in Sweden was estimated to be 2.2% for both men and women<sup>39</sup>. By 2030, the prevalence of HF (not adjusted for age) in the USA is projected to increase by 46% to >8 million people (2.97%)<sup>45</sup>. An ageing national population is the primary driver for the mounting HF burden.

The HF burden is disproportionately distributed among the elderly. Over half of patients hospitalized with HF are aged >75 years<sup>46</sup>. The prevalence of HF generally doubles for each decade of life. The prevalence is <1% for those aged <40 years, and >10% for those aged >80 years<sup>3</sup>. The lifetime risk of developing HF is approximately 20% between the ages of 40 and 80 years for both men and women<sup>47</sup>. Improvements in medical management have delayed the onset of HF, and prolonged the lives of those who develop the condition. These shifting demographics highlight the importance of integrating geriatric medicine into HF management. Furthermore, as trials have tended to exclude or under-represent older populations, further research on improving outcomes in this age cohort is needed<sup>48</sup>.

In the USA, the prevalence of HF varies considerably by ethnicity, socioeconomic status, and geographical region. Lower socioeconomic status is associated with higher rates of HF when controlling for known cardiovascular risk factors<sup>49,50</sup>. African-American individuals have a threefold increased risk of developing dilated

cardiomyopathy when controlling for socioeconomic factors and comorbidities<sup>3,12</sup>. The unadjusted prevalence of HF is similar among white individuals and Hispanic individuals in the USA, and is lowest among Chinese-American individuals<sup>31</sup>. The southeastern region of the USA, spanning from Georgia in the east to Oklahoma in the west — commonly referred to as the ‘stroke belt’ owing to elevated rates of cerebrovascular events in this region — has a 69% higher age-adjusted mortality from HF than the national average<sup>52</sup>. Such large variations in disease rates by ethnicity, region, and socioeconomic status suggest that targeting health services might improve the prevention and management of cardiovascular diseases in high-risk communities<sup>53</sup>.

Cross-sectional and cohort studies conducted in developing countries have identified risk factors and aetiologies for HF, but more detailed epidemiological data are unavailable<sup>54–60</sup>. Although reliable estimates for middle-income and low-income nations are lacking, evidence from the current literature suggests that HF is the fastest growing cardiovascular condition globally<sup>61,62</sup>. Of the 1.63 billion people who live in South Asia, 30 million would have had HF in 2011, if the prevalence of HF in South Asia is assumed to be the same as that in the USA<sup>63</sup>. However, this assumption is purely hypothetical and requires validation.

**Mortality**

Estimating the number of deaths attributable to HF alone is challenging, because HF is commonly categorized as an intermediate stage of an underlying condition such as coronary artery disease, and not the actual cause of death. The Global Burden of Disease Study<sup>5</sup> defines the causes of death using ICD-9 and ICD-10 codes. However, the code for HF is treated as a ‘garbage code’ — an ambiguous or vague code associated with a non-specific cause of death. Death caused by HF would often be reassigned to the most likely underlying cause, such as ischaemic heart disease. Death certificate documentations have the same limitations and might also be subject to inaccuracies. For HF of unknown aetiology, the cause of death is frequently reassigned to coronary artery disease<sup>64</sup>. Using all-cause cardiovascular mortality as a surrogate for HF mortality trends, the Global Burden of Disease Study estimates that the age-standardized cardiovascular rate of death was reduced by 22% between 1990 (375.5 deaths per 100,000 person-years) and 2013 (293.2 deaths per 100,000 person-years)<sup>5</sup>. This reduction in overall cardiovascular mortality might also indicate a decrease in global age-adjusted mortality for HF.

In the USA in 2011, one in nine death certificates (*n* = 300,122) listed HF as a cause of death<sup>3</sup>. A diagnosis of HF has previously been described as more ‘malignant’ than cancer, given the comparatively low 5-year survival rates<sup>65</sup>. In 1991, 5-year mortality from HF was 11% higher than the corresponding rates for gastrointestinal cancers<sup>65</sup>. Comparative 5-year age-adjusted and sex-adjusted survival rates for cancer, stroke, and HF were found to be generally similar in a systematic review, with observed improvements in survival for all three diseases over the past decade<sup>66</sup>.



Despite the high fatality rates for patients with HF, survival rates have increased remarkably with treatment advances in the developed world. The Framingham Heart Study reported a decline in 5-year mortality from 70% between 1950 and 1969 to 59% between 1990 and 1999 for men, and a reduction from 57% to 45% for women during the respective periods<sup>35</sup>. The community-based cohort from Olmsted County reported a 20.2% age-adjusted mortality for incident HF at 1-year and 56.2% at 5 years; these rates did not change significantly between 2000 and 2010. More than half of the HF cohort died from noncardiovascular causes; 14.2% of deaths were related to respiratory disease, 12.6% to neoplasm, and 7.1% to mental health<sup>32</sup>. Earlier analyses from Olmsted also noted a temporal improvement in overall 5-year mortality in the time period since 1979 (REF. 10). Likewise, in England between 1981 and 2010, age-standardized death rates for HF decreased from 130.6 to 51.8 per 100,000 people<sup>67</sup>. The steepest declines were noted among middle-aged individuals between 55 and 64 years<sup>67</sup>. National estimates for Sweden in 2010 reported the 5-year HF survival rate as 48%, with 320 deaths per 100,000 person-years for women and 300 deaths per 100,000 person-years for men<sup>39</sup>. In Germany, the unadjusted 1-year mortality for patients first hospitalized with HF was 23% in 2006 (REF. 68).

Mortality for hospitalized HF has also improved over the past decade. Between 1999 and 2011, in-hospital mortality decreased by 38%, 30-day mortality by 16.4%, and 1-year mortality by 13.0% for Medicare patients with HF in the USA<sup>69</sup>. Similarly, in Ontario, Canada, 1-year risk-adjusted mortality for outpatients decreased from 17.7% to 16.2% between 1997 and 2007; a nonsignificant decline was also noted for inpatients during the same period<sup>70</sup>. This increase in mortality might be attributable to several factors. The quality of care and expanded use of evidence-based medical therapies has increased survival for high-risk hospitalized patients. Hospital systems now regularly report HF outcomes and improved care processes<sup>71</sup>. The rates of smoking have declined, and hypertension control has improved marginally<sup>72,73</sup>. Furthermore, the improvements in observed outcomes might reflect greater diagnostic sensitivity, increased recognition of HFpEF by clinicians, and shifts in coding practices that create a healthier pool of patients with HF in the current era compared with previous decades<sup>74,75</sup>.

Estimates of HF mortality in the developing world are limited. Fatality rates for HF are estimated to be 3.72 times higher in low-income countries and 2.61 times higher in middle-income countries than in high-income countries after adjusting for age and sex<sup>41</sup>. A higher threshold for case definitions, greater disease severity, and limited availability of evidence-based therapies might explain these higher fatality rates in developing nations.

### HFpEF

Patients with HFpEF comprise a large and important and subpopulation of individuals with HF. Patients with HFpEF frequently experience delayed diagnosis and limited treatment options. As this population

presents with a unique phenotype that is distinct from HFrEF, special attention will be given to the known epidemiology of HFpEF in the following section.

HFpEF is a clinical syndrome defined as HF with normal ejection fraction and impaired diastolic function on objective imaging. For an accurate diagnosis of HFpEF, the HF symptoms in these patients must not be secondary to another condition. HFpEF has received increased attention in the literature as patients diagnosed with this clinical syndrome have unique trajectories and management challenges. The greatest risk factor for HFpEF is hypertension<sup>12,76</sup>, and additional risk factors include older age, female sex, and diabetes. Rare aetiologies for HFpEF include hypertrophic cardiomyopathy, infiltrative cardiomyopathies such as amyloidosis, and iron-storage diseases such as haemochromatosis. Medical interventions specifically targeting the disease course of HFpEF are lacking<sup>37,77</sup>.

HFpEF is estimated to comprise between 44% and 72% of all cases of HF<sup>78</sup>. Differences in case definitions over time have contributed to variations in the reported incidence and prevalence of HFpEF. The prevalence of HFpEF in middle-income and low-income countries is not well characterized<sup>76</sup>. International trial data that include patients from North America, Europe, and Russia suggest that the prevalence of HFpEF is highest in the USA and Canada, intermediate in Western Europe, and lowest in Eastern Europe and Russia<sup>79</sup>. In the Olmsted County cohort, the proportion of HFpEF among incident cases of HF increased from 38.0% in 1986 to 47.8% in 2000, and to 56.9% in 2010. Additionally, the decline in the incidence of HFpEF was less than the decline in the incidence of HFrEF<sup>32,80</sup>. Using data from the AHA's Get With The Guidelines — Heart Failure project, investigators found that the proportion of patients hospitalized with HFpEF increased from 33% in 2005 to 39% in 2010 (REF. 75). Mortality for HFpEF is slightly lower than that for HFrEF (121 deaths versus 141 deaths per 1,000 patient-years) after adjusting for age, sex, and comorbidities<sup>81</sup>; however, observed readmission rates are higher for HFpEF than for HFrEF<sup>82</sup>. To date, no effective therapies are available to improve survival of patients with HFpEF.

### Aetiologies

A wide range of cardiac conditions, hereditary defects, and systemic diseases can result in HF (BOX 1). Patients with HF can have mixed aetiologies, which are not mutually exclusive, and HF aetiologies vary considerably between high-income and developing countries<sup>41,83</sup>. HF has an estimated 17 primary aetiologies, as determined by the Global Burden of Disease Study<sup>84</sup>. More than two-thirds of all cases of HF can be attributed to four underlying conditions: ischaemic heart disease, chronic obstructive pulmonary disease, hypertensive heart disease, and rheumatic heart disease. Although the Global Burden of Disease Study aims to approximate the burden of right-sided HF from chronic obstructive pulmonary disease, studies estimating the prevalence of right-sided HF are limited and require further study<sup>84</sup>. High-income regions are

disproportionally affected by ischaemic heart disease and chronic obstructive pulmonary disease compared with low-income regions, which in turn are primarily affected by hypertensive heart disease, rheumatic heart disease, cardiomyopathy, and myocarditis<sup>2</sup>. The assessment and management of cardiovascular risk around the world requires the tailoring of policies to population-specific risks and underlying aetiologies<sup>33</sup>.

### **Ischaemic heart disease**

Medical descriptions of angina pectoris date back to 1772, but understanding of the pathophysiology underlying the syndrome did not progress until the late 19<sup>th</sup> century, when calcification and thrombosis of the coronary arteries were first described<sup>85,86</sup>. Early studies, such as the Framingham Heart Study, identified the risk factors for coronary artery disease, including hypertension, hyperlipidaemia, diabetes, and smoking. The rate of death from cardiovascular causes has steadily declined since the 1960s with increased recognition of cardiovascular risk factors and greater attention to primary prevention<sup>87</sup>. The incidence of ischaemic heart disease, hypertension, diabetes, and other chronic diseases tends to parallel the increased consumption of food high in fat and sugar, and sedentary behaviour. The incidence and prevalence of these chronic diseases tend to increase unless preventive health strategies are implemented<sup>4</sup>. This pattern of shifting disease prevalence is described as an epidemiological transition that is strongly associated with the economic development of a country or region.

Ischaemic heart disease was the leading underlying cause of death globally in 2013, accounting for 15.7% of all age-standardized deaths, equating to a total of 8,139,900 deaths<sup>5</sup>. The Global Burden of Disease Study estimates that the prevalence of ischaemic HF between 1990 and 2010 increased from 240 to 270 per 100,000 person-years in men, and was stable at 190 per 100,000 in women<sup>88</sup>. Using the estimated rate of myocardial infarctions as a surrogate for the incidence of ischaemic heart disease, there is evidence for epidemiological transitions among both industrialized and developing nations. Age-standardized rates of myocardial infarction decreased between 1990 and 2010 in high-income countries in Australasia, Europe, and North America<sup>88</sup>. Within these regions, the greatest increase in the number of myocardial infarctions was in Eastern Europe<sup>88</sup>. In Sweden, the prevalence of ischaemic heart disease among patients with HF declined between 2006 and 2010 by approximately 7–8%<sup>39</sup>. In the Olmsted County cohort, the proportion of ischaemic HFrEF declined from 39.8% to 29.4% between 2000 and 2010, whereas the proportion of ischaemic HFpEF increased from 29.0% to 32.6% in this same time period<sup>32</sup>. The decrease in the proportion of patients with HFrEF is likely to be attributable to a reduction in myocardial infarction through both primary and secondary prevention strategies. Furthermore, patients with active myocardial infarction are more swiftly treated with percutaneous coronary intervention and other medical therapies<sup>89</sup>. With respect to the global burden of ischaemic heart disease, the incidence of acute myocardial infarction worldwide is highest in

Eastern Europe and Central Asia, with >340 cases per 100,000 person-years for men and 180 cases per 100,000 person-years for women<sup>88</sup>. The lowest rates of acute myocardial infarction were observed in high-income nations in Asia<sup>88</sup>.

### **Hypertensive heart disease**

An increase in blood pressure exposes cardiac myocytes to elevated mechanical stress and neurohormones, which increase myocardial mass and result in left ventricular hypertrophy. These cardiac changes can further progress to HFpEF or HFrEF, even in the absence of obstructive epicardial coronary arteries and myocardial infarction<sup>90</sup>. NHANES data from the USA show that, between 1999 and 2012, the proportion of patients treated for hypertension improved from 59.8% to 74.7%, and the proportion of patients with hypertension and adequately controlled blood pressure improved from 53.3% to 68.9%<sup>73</sup>. This improvement in blood pressure control is likely to have contributed to the decline in the incidence of HF. In the Olmsted County cohort, 73.6% of patients with HFrEF had hypertension compared with 89.3% of patients with HFpEF<sup>32</sup>. The lifetime risk of HF for individuals with blood pressure >160/90 mmHg is double that of those with blood pressure <140/90 mmHg<sup>47</sup>. Early randomized trials on hypertension control reported that effective treatment of moderate ( $\geq 140/90$  mmHg) and severe hypertension ( $\geq 180/110$  mmHg) reduces the risk of HF by 87%<sup>91</sup>. In the USA, antihypertensive treatment has reduced the incidence of HF by approximately 50%<sup>35</sup>.

Although hypertension has been recognized as a potent cardiovascular risk factor for many decades, gaps in the treatment of high blood pressure still remain. Hypertension affects all socioeconomic classes. Clinical evaluation of 1,515 consecutive cardiac referrals in Nigeria resulted in a diagnosis of hypertensive HF in 61% of patients<sup>92</sup>. However, this study was limited in that patients did not receive advanced diagnostic imaging or invasive angiography to confirm the low prevalence of ischaemic heart disease. Investigators in the PURE study<sup>93</sup> found that, within a sample of patients with hypertension from high-income countries, only 49% of patients with blood pressure >140/90 mmHg were aware of their diagnosis, while 46.7% received treatment, and 19.0% had adequate control of their hypertension. In low-income countries, the rate of awareness was 40.8%, 31.7% received treatment, and 12.7% had adequate control<sup>93</sup>. These rates reflect the opportunity for improved management of hypertension globally in reducing preventable cardiovascular diseases.

### **Valvular and rheumatic HF**

In developed countries, most cases of valvular heart disease are degenerative in nature, and the incidence of rheumatic heart disease is exceedingly low. The prevalence of any valve disease diagnosed using echocardiography is estimated to be 2.5% in the USA; prevalence increases substantially with age to 11.7% in individuals aged >75 years<sup>94</sup>. The prevalence of clinically diagnosed valvular disease is 1.8%<sup>94</sup>. In 2010, approximately 106,000 valve surgeries were performed in the USA<sup>3</sup>.

Data on the prevalence of HF among patients with clinical or echocardiographic diagnosis of valvular disease is scarce. Globally, the greatest burden of valvular disease is valvular HF that is secondary to rheumatic heart disease. In high-income nations, the substantial decline in prevalence of valvular disease is attributable to improvements in living conditions and availability of antibiotic therapy. The incidence of rheumatic fever has fallen below 1 case per 100,000 person-years in developed nations<sup>95</sup>. In developing countries, however, valvular HF resulting from rheumatic disease contributes substantially to morbidity and mortality. In Sudan, the incidence of rheumatic fever is >100 cases per 100,000 person-years<sup>95</sup>. A conservatively estimated 15.6 million people have rheumatic heart disease globally, with 470,000 new cases and 233,000 deaths per year<sup>96</sup>. When echocardiography is used to screen affected populations in developing countries, the prevalence of rheumatic heart disease increases tenfold<sup>97</sup>. Despite the high prevalence of rheumatic heart disease in low-income countries, the global age-standardized mortality has decreased 22% from 375.5 to 293.2 deaths per 100,000 between 1990 and 2013 (REF. 5).

### Cardiomyopathies

Quantifying the global burden of cardiomyopathy is difficult given variations in diagnostic capabilities and coding practices<sup>5</sup>. A study of an Italian outpatient cohort estimated that the distribution of HF aetiologies was 36.0% dilated cardiomyopathy, 45.6% ischaemic cardiomyopathy, 12.9% hypertensive cardiomyopathy, and 5.5% from other causes<sup>83</sup>. The prevalence of cardiomyopathy in low-income countries is also poorly understood, and larger epidemiological studies are required<sup>98</sup>. The available data suggest that infectious, inflammatory, and nutritional deficiencies cause HF more commonly in sub-Saharan Africa than in middle-income and high-income countries<sup>99</sup>. An estimated 26.0% of the HF cases in sub-Saharan Africa have been attributed to the cardiomyopathies, specifically idiopathic dilated cardiomyopathy, HIV-related cardiomyopathy, hypertrophic cardiomyopathy, and endomyocardial fibrosis. Endomyocardial fibrosis is an endemic cardiomyopathy primarily described in Uganda and other regions with profound malnutrition from low protein and high cassava diets. An estimated 24% of dilated cardiomyopathies observed in sub-Saharan Africa might be secondary to myocarditis and autoimmune disorders<sup>60,100</sup>. Myocarditis has an estimated prevalence of 0.5% to 4.0% globally, and aetiologies vary depending on the region<sup>101</sup>.

### Chagas cardiomyopathy

Chagas disease is an endemic parasitic disease caused by the protozoan *Trypanosoma cruzi*, and was estimated to affect 5.7 million people worldwide in 2010, mostly in Latin America. The use of insecticides to reduce the numbers of the insect that spreads the parasite (*Triatoma*, commonly referred to as the kissing bug) since 1990 has reduced the prevalence of Chagas disease from a peak of 15–30 million<sup>102,103</sup>. The Global Burden of Disease Study estimates that the age-standardized

mortality for Chagas disease decreased by 51.7% between 1990 and 2013 (REF. 5). In 2005, an estimated 300,000 immigrants were living with Chagas disease in the USA<sup>104</sup>.

Chagas disease remains the most common cause of nonischaemic cardiomyopathy in Latin America<sup>104</sup>. A cohort study observed that 38.3% of patients with Chagas disease progressed to being diagnosed with HF after a 10-year follow-up period<sup>105</sup>. In the early stages of the disease, patients are likely to develop abnormalities of the cardiac conduction system that can be asymptomatic or detected after reported palpitations or syncope events. HF symptoms are typically caused by biventricular dysfunction with a greater prominence of right-sided HF symptoms. Chagas cardiomyopathy has a higher mortality than other nonischaemic cardiomyopathies, and patients are at greater risk of sudden cardiac death and malignant arrhythmias than other patients with HF. Deaths from cardiovascular causes account for nearly two-thirds of all Chagas-related deaths<sup>106</sup>. Antiparasitic treatment with benznidazole in patients with Chagas cardiomyopathy did not improve clinical outcomes or 5-year mortality<sup>107</sup>. The recommended management for Chagas cardiomyopathy is based on strategies for HFrEF<sup>107</sup>.

### Congenital heart disease

Global estimates of the prevalence of congenital heart disease range from 0.4% to 5.0% of all births<sup>108</sup>. In the USA, the prevalence of congenital heart disease is estimated to be approximately 1%<sup>108</sup>. Patients with congenital heart disease tend to under-report their HF symptoms compared with patients with noncongenital HF<sup>109</sup>. Exercise testing is usually required to understand functional limitations in patients with congenital heart disease, because echocardiographic criteria for HFrEF and HFpEF might not be relevant in this patient cohort. Among adult patients with congenital heart disease, 51% reported NYHA class II to III HF symptoms, and exercise testing revealed further functional limitations<sup>109</sup>. HF is seen more commonly in patients with congenital heart disease and single or systemic right ventricles<sup>108</sup>. Adults with six major categories of congenital heart defects (atrial septal defects, congenitally corrected transposition of the great vessels, tetralogy of Fallot, transposition of the great arteries, Ebstein anomaly, and Fontan circulation) all had markedly reduced exercise capacity on cardiopulmonary exercise testing<sup>110</sup>.

The global burden of congenital heart disease has been underappreciated in low-income countries. Most congenital lesions are not diagnosed at birth and might present only after progression to severe symptoms, and the limited availability of imaging technologies in the developing world further restricts diagnostic capabilities<sup>111</sup>. Echocardiographic studies in school-aged children in Africa reported high rates of rheumatic and congenital heart disease<sup>111</sup>. Another small study, in which echocardiography was used to diagnose congenital heart disease in Mozambique, reported a prevalence of 230 cases per 100,000 in school-aged children, with 80% of cases being newly diagnosed<sup>112</sup>.



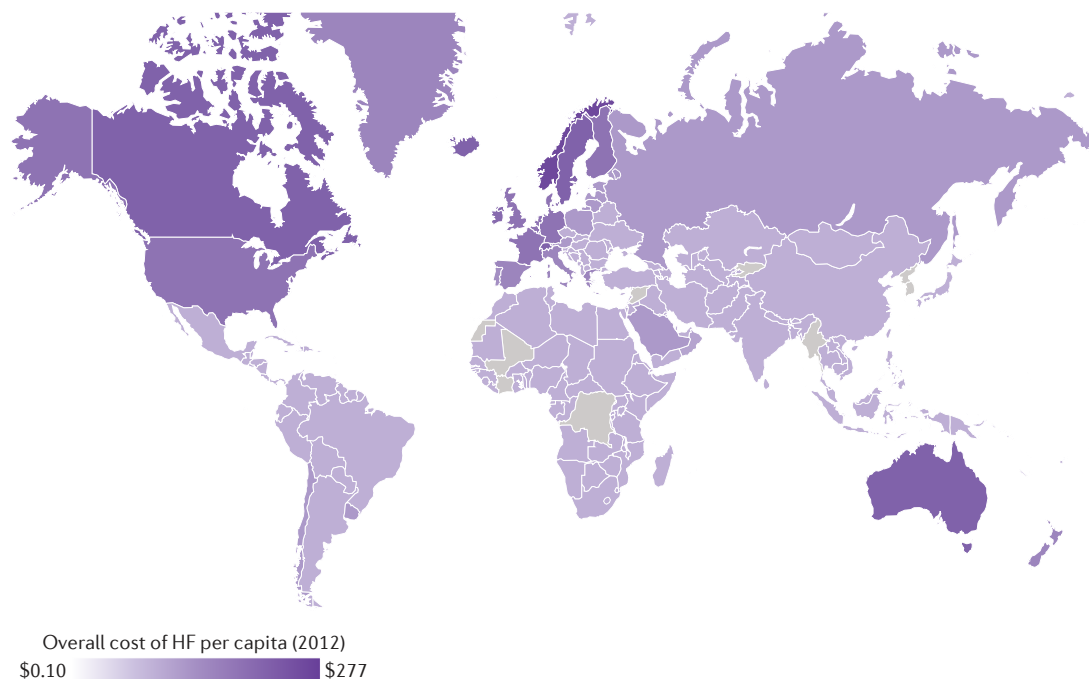


Figure 2 | **Global cost of HF per capita in 2012.** The map shows the estimated per capita cost of HF based on reported national health-care expenditures and expected HF burden. HF, heart failure. Modified from Cook, C. *et al.* The annual global economic burden of heart failure. *Int. J. Cardiol.* **171**, 368–376 (2014), with permission from Elsevier.

## Burden on health services

### Hospitalizations

In high-income countries, HF is the most common diagnosis in hospitalized elderly patients aged >65 years (REF. 113). HF hospitalization represents 1–2% of all hospital admissions<sup>114</sup>. In the USA, HF is the leading primary diagnosis for hospitalization, with approximately 1 million discharges every year between 2000 and 2010 (REF. 3). The number of hospitalizations that included HF as a reason for admission tripled between 1979 and 2004 (REF. 9). In this time period, age-adjusted hospitalization rates for a primary diagnosis of HF increased from 219 to 390 per 100,000 person-years<sup>9</sup>. In the Olmsted County cohort, an average 1.34 hospitalizations occurred per person-year among patients with HF, and 63% were secondary to noncardiovascular causes<sup>32</sup>. Between 1999 and 2011, the HF hospitalization rate among Medicare patients in the USA decreased from 1,390 to 925 per 100,000 person-years<sup>69</sup>, and the average length of stay shortened considerably from 3.1 days to 1.9 days<sup>69</sup>.

Similar trends in hospitalization rates for HF have also been observed in Europe. In France, the age-standardized hospitalization rate for HF was 246.2 per 100,000 population in 2012 (REF. 115). Rates of hospitalization were stable between 2000 and 2010, whereas standardized inpatient mortality decreased by 3.3% per year on average<sup>115</sup>. The number of hospital admissions for HF peaked in the 1990s in the Netherlands, Scotland, and Sweden, followed by a decline<sup>114</sup>. In the UK, 5% of all admissions from the emergency department to the hospital are for HF<sup>116</sup>. HF hospitalizations are projected to increase by >50% by the year 2035, owing to an ageing population<sup>116</sup>.

In the USA, differences in HF hospitalization rates between ethnic groups have been described. The likelihood of hospitalization for HF is 50% higher for African-American individuals, 20% higher for Hispanic individuals, and 50% lower for Asian individuals than for white individuals<sup>117</sup>. These reported ethnic differences in hospitalization rates were not controlled for socioeconomic factors, which might explain the variations in hospitalization rates.

National registries have provided insight into international practice variations for the treatment of HF and identified areas for quality improvement. Adherence to evidenced-based therapies for HF is highest in North America, Western Europe, and Japan<sup>118</sup>. However, the use of mineralocorticoid-receptor blockers was found to be lower in North America than in other high-income regions. The lowest rates of adherence to HF therapy were in Eastern Europe and Asia (excluding Japan)<sup>118</sup>. In the Get With The Guidelines — Heart Failure project, quality of care for all ethnic groups in the USA was similar, but in-hospital mortality was notably lower for African-American and Hispanic individuals<sup>119</sup>. In 2013, the median risk-standardized 30-day hospital readmission rate for HF was 21.9%, and ranged from 17.0% to 28.2%. The median hospital readmission rate for HF decreased by 1.5% between 2010 and 2013 (REF. 120).

### Ambulatory care

In 2011, a total of 553,000 emergency department visits for HF were recorded in the USA<sup>3</sup>, and in 2012, a primary diagnosis of HF was charted for 1,774,000 outpatient visits. In the UK, the average general practitioner

cares for 30 patients with HF and diagnoses HF in an additional 10 patients annually<sup>116</sup>. The quality of outpatient care for patients with HF has been assessed by studying the frequency of guideline-recommended practices for eligible patients. Guideline-recommended therapy includes use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers,  $\beta$ -blockers, mineralocorticoid-receptor antagonists, anticoagulant therapy for atrial fibrillation or flutter, cardiac resynchronization therapy, implantable cardioverter-defibrillators, and education on self-management of HF. Treatment compliance with these seven guideline-recommended measures was found to reduce 2-year mortality<sup>71</sup>.

### Financial burden

Accurate estimates for the global financial burden of HF are challenging given data limitations. Attempts have been made to calculate the global cost of HF using known national health expenditures. A study published in 2014 estimated that US\$108 billion was spent on HF globally in 2012, 60% of which was spent directly on medical costs<sup>121</sup>. A majority of the worldwide expenditure for HF (86%) was attributed to high-income regions that constitute only 18% of the global population<sup>121</sup> (FIG. 2). The prevalence of HF in the USA is projected to increase by 46% between 2012 and 2030, with total medical costs predicted to rise from US\$20.9 billion to \$53.1 billion. Nearly 80% of these projected expenses are attributed to increased hospitalizations. Indirect costs of lost productivity from morbidity and premature mortality are estimated to increase from US\$9.8 billion to \$16.6 billion by 2030, and total direct and indirect medical costs will increase from US\$30.7 billion to \$69.8 billion<sup>122</sup>. The prevalence of HF among Medicare's highest-cost patients was 44% in 2010, and HF admissions were the costliest preventable hospitalization for those beneficiaries<sup>123</sup>. The mean cost per hospital admission for HF in the USA was \$10,775 in 2011. The highest-expenditure patients were found to have more comorbidities and higher inpatient mortality<sup>124</sup>.

The UK's Centre for Economics and Business Research estimates that the cost of cardiovascular disease in Europe will increase from €102.1 billion in 2014 to €122.6 billion by 2020 (REF. 125). In Sweden and the UK, 2% of the entire national health-care budget is spent managing HF<sup>116,126</sup>. In Sweden, 31% of HFpEF medical expenditures were for outpatient care, 29% for primary cardiac hospitalizations, and 40% were for non-cardiac hospitalizations<sup>127</sup>. In the developing world, an estimated US\$15.1 billion was spent on HF in 2012.<sup>121</sup> A small Nigerian cohort study reported US\$2,128 in

expenditures per case of HF in 2009. Outpatient costs comprised 56% of total expenditure owing primarily to transportation expenses for monthly visits<sup>128</sup>.

### Future directions

Shifting demographics and epidemiological transitions foretell a rapid rise in the number of patients with HF. Primary prevention of HF is the most effective means of improving quality of life and reducing health-care expenditure<sup>41</sup>. For both developed and developing nations, improved control of hypertension, reduction in tobacco use, and targeting of lifestyle factors are the most effective means of reducing HF incidence and prevalence. Although evidence indicates that the incidence and prevalence of HF is stabilizing in high-income countries, large gaps remain in what we know about the control of known risk factors for earlier identification of at-risk patients, to allow for expedited intervention that might further reduce the HF burden<sup>129</sup>. Maximizing adherence to evidence-based practices for outpatients will prove to be the best strategy to improve the management of HF; the potential gains from novel therapeutics will pale in comparison to what can be gained by improving primary prevention and treatment-adherence strategies<sup>130</sup>. These strategies should be tailored to local populations for maximal benefits<sup>131</sup>, and more research and resources should be directed towards low-income nations that harbour the largest burden of preventable HF.

### Conclusions

HF is the most rapidly growing cardiovascular condition globally, conferring a substantial burden on health-care systems worldwide. In high-income nations, improvements in public health have shifted demographics towards an ageing population with a high prevalence of chronic diseases. Elderly individuals are living with HF longer than ever, which necessitates improved systems to manage chronic disease, improve health outcomes, and reduce health-care expenditures. HFpEF is accounting for an increasing share of the prevalence of HF in the developed world, but therapies to reduce mortality in affected patients have not been discovered. Meanwhile, preventable childhood diseases are transitioning to preventable cardiovascular diseases in developing nations. Although more reliable epidemiological data are required, low-income nations have a disproportionately high incidence of preventable causes of HF, such as hypertensive heart disease and rheumatic heart disease. Future research should be aimed at addressing the ever-expanding challenges in HF prevention and management in this new era.

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