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INVITED REVIEW

Global burden of heart failure: a comprehensive and updated review of epidemiology

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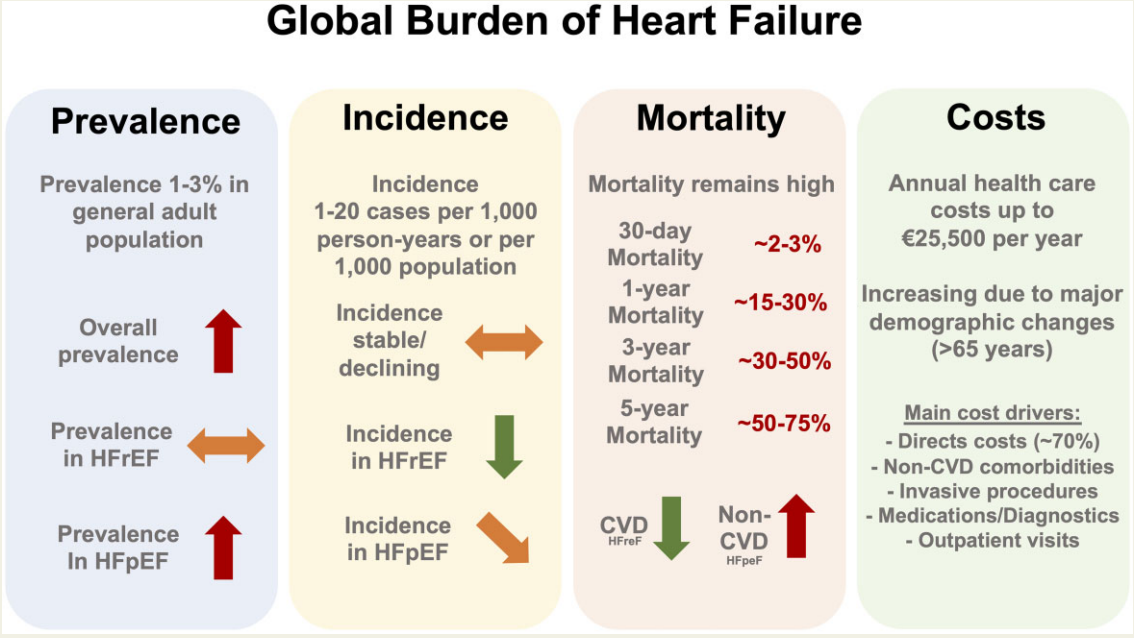
Abstract

Heart Failure (HF) is a multi-faceted and life-threatening syndrome characterized by significant morbidity and mortality, poor functional capacity and quality of life, and high costs. HF affects more than 64 million people worldwide. Therefore, attempts to decrease its social and economic burden have become a major global public health priority. While the incidence of HF has stabilized and seems to be declining in industrialized countries, the prevalence is increasing due to the ageing of the population, improved treatment of and survival with ischaemic heart disease, and the availability of effective evidence-based therapies prolonging life in patients with HF. There are geographical variations in HF epidemiology. There is substantial lack of data from developing countries, where HF exhibits different features compared with that observed in the Western world. In this review, we provide a contemporary overview on the global burden of HF, providing updated estimates on prevalence, incidence, outcomes, and costs worldwide.

Graphical Abstract



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1. Introduction

Heart failure (HF) is a clinical syndrome, which has been traditionally defined as a condition characterized by the reduced ability of the heart to pump and/or fill with blood, or alternatively as an abnormality of cardiac structure/function leading to an inadequate cardiac output or to an adequate cardiac output secondary to compensatory neurohormonal activation and increased left ventricular filling pressure. In 2021, major worldwide scientific bodies proposed a consensus on an universal definition and classification of HF.[1] HF was defined as clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. Based on left ventricular ejection fraction (EF), HF was classified into three EF categories, namely HF with reduced (HFrEF), mildly reduced (HFmrEF), and preserved EF (HFpEF), according to the EF ranges ≤40%, 41–49%, and ≥50%, respectively. Additionally, based on the trajectories of EF over time, a new entity, i.e. HF with improved EF, was introduced and defined as HF with a baseline EF ≤ 40% with a ≥ 10 point EF increase from baseline and a second measurement of EF > 40%.[1]

HF has been defined as a global pandemic, with 64.3 million people estimated to suffer from HF worldwide in 2017.[2] Its prevalence is expected to raise due to the improved survival following a HF diagnosis associated with the availability of life-saving evidence-based treatments and the overall longer life-expectancy of the general population. The burden of HF on health care expenditures worldwide is concerning. In 2012, the total cost for HF was estimated to be $30.7 billion in USA, with projections suggesting an increase in costs by 127% to $69.8 billion, amounting to around $244 for every US adult, in 2030.[3,4]

Despite the limitation of considerable heterogeneity between epidemiological studies on HF, which have analysed different study populations from distinct geographical and socio-economic settings with disparate methods, in this review, we aim comprehensively to describe the epidemiology of HF, providing updated data on its prevalence, incidence, outcomes, and costs worldwide, while acknowledging the availability of limited data in specific geographical areas, such as Africa, South America, and to some extent Asia.

2. Prevalence

Prevalence is the proportion of a population with a specific disease or condition at a defined time point, and therefore provides a measure of the disease burden in the population (*Figure 1*). Furthermore, prevalence is often presented in a standardized manner, e.g. age-standardized or sex-standardized, to allow comparisons across different populations. In particular, in the calculation of age-standardized rates, either one population is mathematically adjusted to have a similar age as the other, or both populations are adjusted to have a similar age as a third population, termed the standard population.[5]

The age-standardized prevalence of HF varies substantially across countries and regions. In 2017, the highest prevalence rates of HF were observed in Central Europe, North Africa, and the Middle East and ranged 1133–1196 per 100 000 people, whereas lower rates were observed in Eastern Europe and Southeast Asia and ranged 498–595 per 100 000 people.[6] In the following paragraphs, we summarize the epidemiological data on the prevalence of HF focusing on different geographical areas.

2.1 Europe and North America

In the 2019 Heart Failure Association (HFA) ATLAS project, the median prevalence of HF was estimated as 17 per 1000 persons across 13 European countries, which reported data, and ranging from ≤12 in Greece and Spain to >30 per 1000 persons in Lithuania and Germany.[7] At a national level, in Portugal, in the EPICA study enrolling 5434 patients attending primary care centres in 1998, the prevalence of HF was overall 4.4%, similar in males and females, and 1.4% in the 25–49 years-old age strata, 2.9% in the 50–59 years-old group, 7.7% in the 60–69 years-old group, and 16.1% in those ≥80 years old. Notably, also the prevalence of systolic and diastolic dysfunction was assessed, which was 1.3% for the first and 1.7% for the latter.[8] Projections anticipate an increase in the prevalence by 30% by 2035 compared with 2011.[9] In the Spanish PRICE study, in 2004–05, of 1776 individuals aged ≥45 years and screened for HF in primary care, the overall prevalence of HF was 6.8%, being 6.5% in males and 7% in females, again with a steep increase with ageing, being 1.3% in those aged 45–54 years, 5.5% in those aged 55–64 years, 8% in those aged 65–74 years, and 16.1% in those aged over 74 years.[10] Another community-based study enrolling 267 231 inhabitants in the South of Spain served by only one hospital, showed that between 2000 and 2007 the prevalence of HF increased from 9.0 to 21.3 per 1000 person-years, and was higher in males vs. females, and for what was termed 'systolic' vs. 'non-systolic' HF. More specifically, the prevalence of non-systolic HF was higher in females vs. males, whereas it was higher

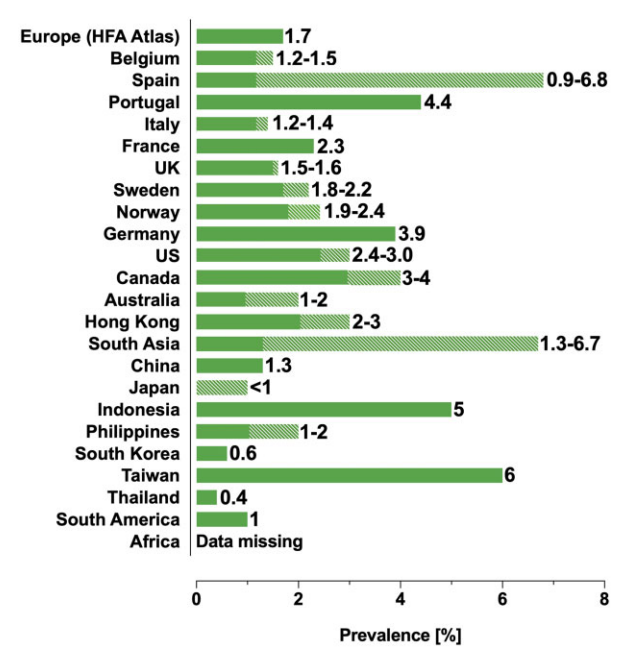

Figure 1 Prevalence of heart failure worldwide. HFA, Heart Failure Association; UK, United Kingdom; US, United States.

in males vs. females for systolic HF. The prevalence of both systolic and non-systolic HF increased over time.[11] In the EPISERVE study enrolling patients from primary care in Spain, cardiology and internal medicine units in 2005, the prevalence of HF was 2%, 17%, and 12%, respectively, and 50% of patients with HF had EF ≥ 45%.[12] In France, HF is estimated to affect ∼1 million people, i.e. 2.3% of the entire population.[13] In Sweden, between 2010 and 2014 the age-adjusted prevalence of HF increased from 1.61% to 1.72% according to data from national health registries, and from 2.15% to 2.18% according to electronic health records.[14] In a study considering data from 2.1 million inhabitants from the Stockholm region in Sweden in 2010, crude and demographic composition adjusted prevalence of HF was 1.8% and 2.2%, respectively, similar in women and men.[15] The prevalence in 2.1 million inhabitants from the Stockholm region decreased between 2006 and 2010 in females but remained stable in males.[15] A nationwide registry study in Norway showed crude HF prevalence increasing from 1.98% in 2013 to 2.42% in 2016, being higher in males vs. females (2.88% vs. 1.97%, respectively, in 2016).[16] Age-standardized prevalence was 2.3% in 2013 and 2.8% in 2016, overall higher in males vs. females.[16] In Germany, an analysis of healthcare claims data between 2009 and 2013 highlighted a crude HF prevalence of 4.0%, which was 3.9% after adjustments for age, sex, region, with estimates increasing with age.[17] In the UK, the prevalence of HF standardized by age and sex was stable between 2002 and 2014, ranging between 1.5% and 1.6%, but the absolute number of patients with HF increased by 23%.[18] In Italy, in a primary care setting between 2002 and 2013 prevalence of HF was 1.25%.[19] Another Italian study estimated HF prevalence to be 1.44% in the general population (>16 years old) in 2009, with mainly New York Heart Association (NYHA) functional Class III–IV and with rates increasing with age.[20] Additionally, in a large registry-based study in Belgian general practice between 2000 and 2015, age-adjusted prevalence of the HF stage A (at risk: patients at high risk for developing HF but no functional/structural heart disorder) increased from 27% to 35%, similarly in males and females, whereas for the HF stage B (pre-HF: structural heart disorder but no symptoms) it also increased from 7.6% to 11% but females had a steeper increase compared with males, and for the HF stages C/D (structural abnormalities and severe symptoms managed with medical treatment/advanced HF requiring hospital-based support or heart transplant or palliative care) a general downward trend was observed.[21]

The 2021 American Heart Association Heart Disease and Stroke Statistics based their HF prevalence estimates on the NHANES data collected between 2015 and 2018. Around 6.0 million Americans aged ≥20 years had HF, which increased from around 5.7 million according to NHANES data collected between 2009 and 2012. The prevalence of HF in the USA was 2.4% in 2012, which is projected to rise to 3.0% in 2030.[4] According to data from the Public Health Agency of Canada, age-standardized prevalence of HF among Canadians aged ≥40 years old approximated 3% in females and 4% in males in 2012/2013.[22]

2.2 Asia and Australia

The burden of HF in India is high and estimated prevalence ranges from 1.3 to 4.6 million.[23] Data on HF prevalence in South Asia are very limited, with estimates ranging between 1.3% and 6.7%.[24–26] In the China Hypertension Survey (CHS) enrolling 22 158 participants, prevalence of HF was 1.3%.[27] There are no population-based studies in Japan on the epidemiology of HF but prevalence is estimated to be <1%.[24,28,29] HF prevalence has been estimated to be 2–3% in Hong Kong, 5% in Indonesia, 1–2% in Philippines, 0.6% in South Korea, 6% in Taiwan, and 0.4% in Thailand.[30] Prevalence estimates in Australia range between 1% and 2%.[31]

2.3 South America and Africa

Data from South America (mainly derived from Brazil) document an HF prevalence of 1%.[32] Data on HF prevalence in Africa are currently lacking. In the Heart of Soweto Study cohort enrolled in a hospital serving 1.1 million people, 1960 patients (163 per month) presented with HF in 2006; 43% had incident HF and 23% of these had HFpEF.[33]

2.4 Prevalence according to HF phenotype

Data on the prevalence of the different HF phenotypes, i.e. HFpEF, HFmrEF, and HFrEF, are even more limited due to the unavailability of EF in many data sources. Secular trends in HF prevalence show an overall increase, but when data are analysed according to EF, prevalence has been observed to be increasing for HFpEF but to be stable or even declining for HFrEF.[34] In the European Society of Cardiology (ESC) Long-Term Registry (ESC-HF-LT), 60% of patients were classified as HFrEF (EF < 40%), 24% as HFmrEF (EF 40–49%), and 16% as HFpEF (HF ≥ 50%).[35] In the Swedish HF registry, estimates were 56% for HFrEF, 21% for HFmrEF, and 23% for HFpEF.[36] In the multicentre nationwide Italian Network on HF 23% of patients hospitalized for acute HF had HFpEF (EF ≥ 50%).[37] In a similar setting, rates in Spain were 32% for HFrEF (EF ≤ 40%), 16% in HFmrEF (EF 41–49%), and 52% in HFpEF (EF ≥ 50%).[38]

In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry from USA, enrolling patients hospitalized with new-onset or worsening pre-existing HF, 49% had HFrEF (EF < 40%), 17% had HFmrEF (EF 40–50%), and 24% HFpEF (EF > 50%),[39] whereas corresponding estimates in the Get With The Guidelines-HF (GWTG-HF) were 39% (EF < 40%), 14% (EF 40–50%), and 47% (EF ≥ 50%).[40]

The Global Congestive Heart Failure (G-CHF) registry enrolled 23 047 patients (both in- and outpatients) with a first or prior diagnosis of HF from 40 countries in 8 different geographic regions. HFrEF (EF < 40%) was identified in 54% of the population, HFmrEF (EF 40–49%) in 21%, and HFpEF (EF ≥ 50%) in 24%.[41]

In the ASIAN-HF study enrolling patients with a documented episode of decompensated HF requiring hospitalization or equivalent outpatient treatment within the 6 months before enrolment across 11 Asian regions, 81% had EF < 40%.[42] In Japan, in a multicentre cohort study of 1245 hospitalized patients with decompensated HF between 2013 and 2014, 36% had HFrEF (EF < 40%), 21% had HFmrEF (EF 40–49%), and 43% had HFpEF (EF ≥ 50%).[43] In China, in the CHS study 40% had HFrEF (EF < 40%), 23% had HFmrEF (EF 40–49%), and 36% had HFpEF (EF ≥ 50%).[27]

Pooled data of the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE), the CHARM Preserved (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity), and the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trials highlighted that younger patients with HFpEF were more likely to be Afro-American or Asian males with lower comorbidity burden, whereas older patients with HFpEF were more likely females with a more severe comorbidity status.[44]

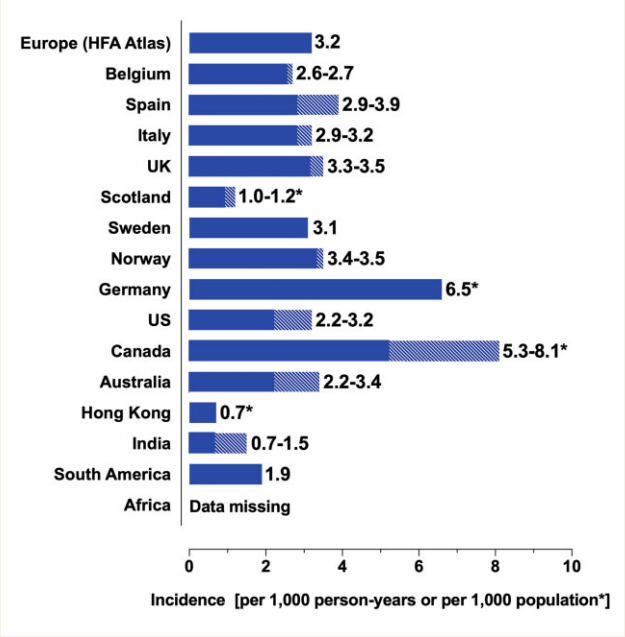

Figure 2 Incidence of heart failure worldwide. HFA, Heart Failure Association; UK, United Kingdom; US, United States.

2.5 Key messages on prevalence

In summary, the prevalence of HF ranges between 1% and 3% in the general adult population in industrialized countries and is projected to increase substantially due to the availability of better diagnostic tools ensuring an appropriate diagnosis and life-saving medical treatments prolonging life after diagnosis of HF. Nowadays HF is particularly prevalent among older individuals. There is paucity of data on from South America and Africa. According to registry data mainly from Western Countries, up to roughly 50% of HF patients have HFrEF. While it seems that the prevalence of HFrEF is most likely to remain stable or even decline due to e.g. improved treatments of ischaemic heart disease (IHD), the prevalence of HFpEF is steadily increasing and may become the most common form of HF in the future.

3. Incidence

While prevalence indicates the proportion of the general population affected by HF at a defined timepoint, incidence reflects the number of newly diagnosed HF cases during a certain time period (*Figure 2*). Data on HF incidence and its temporal trends are overall more limited and inconsistent compared with measures of prevalence. In developed countries, incidence rates of HF have reached a plateau during the last decades and are now substantially decreasing.[18]

In the following paragraphs, we summarize the epidemiological data on HF incidence across different geographical areas.

3.1 Europe and North America

In Europe, in the HFA ATLAS project, incidence rates were available in 12 member countries of the ESC. The median annual incidence of HF was 3.2 per 1000 person-years, ranging from <2 in Italy to ≥6 in Estonia and Germany in 2018–19.[7] A large-scale registry-based study from Belgium considering data from general practitioners reported a non-significant downward trend in age-standardized incidence of more advanced HF (stage C/D: 2.6–2.7 per 1000 person-years), whereas the incidence of stages A and B showed a slightly positive trend (stage A: 34 in 2000 to 38 per 1000 person-years in 2015; stage B: 10–13 per 1000 person-years). It is worth noting that the stages A and B are not conventionally defined as HF in most studies but instead as at risk for HF and pre-HF, respectively, and therefore only the incidence data for stage C/D are comparable with the other quoted studies.[21] In the same study, the burden of comorbidities within the HF population was observed to increase during the study period, and the use of HF treatments sharply increased in 2000–08 in patients with incident HF. Based on the Framingham clinical criteria, the incidence of HF was 2.9 per 1000 person-years in 2000 and 3.9 per 1000 person-years in 2007 in Spain.[45] Using health care data from the Italian Lombardy region during 2011, the crude incidence of HF was estimated to be 2.95 per 1000 person-years, with age- and sex-standardized rates being 3.18 in males and 2.0 in females.[46] In a representative cohort of the UK population covering more than 4 million individuals, HF incidence (standardized by age and sex) similarly decreased for females and males by 7% (from 3.58 to 3.32 per 1000 person-years) from 2002 to 2014.[18] After adjustments for age and sex, individuals with the lowest socio-economic status (lowest quintile) had a 61% higher risk of incident HF compared with those with highest socio-economic status.[18] These important socio-economic data are consistent with the findings of a meta-analysis of >6 million individuals where low socio-economic status was associated with an increase in risk of incident HF ranging between 43% and 87% depending on the socio-economic status measure.[47] In Scotland, the age and sex-adjusted incidence rate for HF decreased by 15.2%, from 1.2 per 1000 population in 2008–09 to 1.0 per 1000 population in 2017–18. The highest decrease in rate over the time period, i.e. 25.7%, was reported in the 65–74 age group.[48] In Sweden, the crude incidence of HF was 3.1 per 1000 person-years, similar in males and females, in 2010, whereas adjusted incidences were 3.9 per 1000 person-years in males and 3.7 per 1000 person-years in females.[15] Based on data from the nationwide Norwegian Prescription Database, the annual crude incidence rate of HF was 3.59 per 1000 person-years in 2013 and 3.44 per 1000 person-years in 2016.[16] Notably, the incidence rate was higher in males than in females across all age groups. In another Italian population-based study in a primary care setting, the overall HF incidence rate was 1.9 per 1000 person-years and was slightly higher among females than males (2.0 vs. 1.9).[19] According to the Rotterdam Study, the overall incidence of HF was 14.4 per 1000 person-years and was significantly higher in males (17.6) than in females (12.5), and regardless of sex, the incidence rate increased with age from 1.4 per 1000 person-years in those aged 55–59 years old to 47.4 per 1000 person-years in those aged 90 years or older.[49] In the Dutch Prevention of Renal and Vascular Endstage Disease (PREVEND) community-based cohort study, the cumulative incidence of new-onset HF was 4.4% during 11.4 years of follow-up, which was slightly higher compared with other studies.[50] In Germany, the overall incidence of HF was similar in females and males (6.65 vs. 6.45 per 1000 persons, respectively).[17]

In the USA, in the Olmsted County cohort age- and sex-adjusted incidence of HF declined from 3.2 to 2.2 per 1000 person-years between 2000 and 2010.[51] This decline was greater in females (43%) than in males (29%), and greater in HFrEF (45%) than in HFpEF (28%). After the index age of 45 years, in the Chicago Heart Association Detection Project in Industry study and in the Atherosclerosis Risk In Communities Study incidence of HF was 7.9 and 6.0, respectively, per 1000 person-years, while

it was 21.1 per 1000 person-years after the index age of 65 years in the Cardiovascular Health Study (CHS).[52] According to data from the Framingham Heart Study (FHS) and the CHS covering the time period between 1990 and 2009, the age- and sex-standardized HF incidence rates for 1990–99 and 2000–09 were 19.7 and 18.9 per 1000 individuals, respectively, highlighting stable HF incidence over two decades.[53] However, the incidence of HFrEF declined and the decrease was more accentuated in males than in females although males had higher incidence in each decade, whereas incident HFpEF increased in both males and females.[53]

According to the Report from the Canadian Chronic Disease Surveillance, the age-standardized incidence rate of HF declined from 8.1 per 1000 to 5.3 per 1000 population between 2000–01 and 2012–13. More specifically, the number of persons newly diagnosed with HF fell from about 102 800 to 92 900 individuals.[22]

In a meta-analysis including >10 000 individuals the sex-adjusted cumulative incidence of HF was significantly higher in individuals >75 years old compared to those 65–75 years old over a median follow-up time of 3.5 years.[54] Conversely, in a Danish study enrolling 210 430 individuals with a new-onset HF in 1995–2012, the annual HF incidence was shown to decline in age >50 years, but to increase in age ≤50 years.[55] Most studies on HF epidemiology are conducted on older patient populations. Further population-based studies across the whole age spectrum are needed.

3.2 Asia and Australia

In Australia, in the Heart failure in the Australian Primary carE setting study enrolling a primary care population between 2013 and 2018, the age-standardized annual incidence of 0.348%, which accounted for >66 000 new cases in 2017.[56] The estimated overall incidence of HF was 0.7 per 1000 population in 1997 in Hong Kong. In individuals >85 years old, the incidence was 20 per 1000 population in females and 14 per 1000 population in males.[57] The incidence in India is largely unknown and is reported between 0.5 and 1.7 per 1000 persons per year.[26] However, age-standardized estimates are missing and would be of major interest since the average age of the overall Indian population is younger compared with other countries in North America and Europe.

3.3 South America and Africa

There is lack of population-based incidence studies in Africa where dilated cardiomyopathy is the major cause of HF, and peripartum cardiomyopathy is ubiquitous with high incidence rates ranging between 1/100 and 1/1000 compared with 1/15 000 in the USA.[58–61] The estimated incidence rate of HF was 1.9 per 1000 person-years in South America.[32]

3.4 Incidence according to HF phenotype

Data on the incidence of the different HF phenotypes are even more limited compared with those on prevalence. In the Olmsted County cohort from the USA, 52.5% of patients with incident HF had HFpEF (EF ≥ 50%).[51] Notably, age- and sex-adjusted incidence of HF declined substantially for both HF subtypes from 2000 to 2010 (overall decrease 37%). More specifically, the decrease in incidence was greater in HFrEF (45%) compared with HFpEF (28%).

According to data from four large longitudinal American community-based cohorts, 48% of patients with incident HF had HFpEF and 52% had HFrEF.[62] Among Canadian inpatients with new-onset HF from 1999 to 2001 in Ontario, 31% had HFpEF and 56% HFrEF.[63]

In a Dutch community-based cohort study, 4.4% of the study cohort was diagnosed with new-onset HF, of whom 34% had HFpEF (EF ≥ 50%) and 66% as HFrEF (EF ≤ 40).[50]

3.5 Key messages on incidence

Despite limited evidence compared to data available on prevalence, incidence of HF is estimated to be generally 1–20 cases per 1000 person-years or 1000 population, with variations depending on geographical areas and study populations, and most data coming from Europe and North America where incidence seems to be overall 2–3 cases per 1000 population. Data on incidence are limited in South America and missing in Africa. HF incidence rates have been shown to be stable or even declining over time, more in HFrEF and advanced HF than in HFpEF. Several studies, although with some discrepancies, report that the HF incidence significantly increases with age. A lower socio-economic status carries a higher risk of developing HF.

4. Aetiology

HF is a complex, multifactorial syndrome, with several potential underlying aetiologies but common symptoms. The HF aetiology shows considerable geographical variation and more than one specific underlying cause can contribute to the development of this clinical syndrome.

4.1 Ischaemic heart disease

One major risk factor for HF is IHD. The population-attributable risk for HF linked with IHD is 65% for men and 48% for women.[64] Worldwide, IHD accounted for 26.5% of the age-standardized prevalence rate of HF in 2017, with IHD more likely to affect higher income areas.[6] Data from the OPTIMIZE-HF registry reported that IHD was a precipitant factor for hospitalization in 15% of HF patients and was associated with higher risk of mortality after discharge.[65] In the US Nationwide Readmissions Database, women were more likely to be hospitalized for HF within 6 months following an acute myocardial infarction compared with men.[66] In the G-CHF registry, 40% of the study population with HF regardless of EF had ischaemic HF, with the highest estimates in Eastern Europe (57%), Middle East (55%), and South Asia (54%), 50% in East Asia, 43% in Western Europe, 46% in North America, and lowest estimates in Africa (12%).[67] In the ESC-HF-LT registry, the primary HF aetiology of HF was IHD in 49% of patients with HFrEF, 42% in HFmrEF, and 24% in HFrEF.[35] Corresponding estimates in the OPTIMIZE-HF study were 54%, 49%, and 32%.[68] In the Swedish HF Registry, 60%, 61%, and 52% of patients with HFrEF, HFmrEF, and HFpEF, respectively, had IHD, but IHD was associated with higher mortality only in EF < 50%.[64] In the ASIAN-HF registry, an ischaemic aetiology was more common in Southeast Asia (62%) vs. South Asia (35%) vs. Northeast Asia (30%), and in HFrEF vs. HFpEF.[42] In the Middle East, it has been estimated that IHD is aetiology of HF in 50% of patients.[69] Epidemiological data from these and other large registries,[40] highlighting much higher prevalences of IHD in HFrEF and HFmrEF vs. HFpEF, might support a major pathophysiological role for IHD in HFrEF and HFmrEF, which might be only marginal in HFpEF.[70,71] In contrast to what is observed in USA, Europe and Asia, in the THESUS-HF registry considering nine Sub-Saharan countries, non-ischaemic causes were predominant in acute HF (75.5%), although the role of IHD might have been underestimated.[72] Consistently, in the INTER-CHF study, IHD was the underlying cause of HF in 20% of patients enrolled in Africa and in 25% of those from South America.[69,73] However, also in developing regions IHD is emerging as growing

problem reflecting the epidemiological changes accompanying economic and social development, i.e. increasing comorbidity burden and life style associated factors.[74] A meta-analysis of the five landmark ICD trials showed that patients with ischaemic cardiomyopathy have an increased risk of all-cause mortality, dominated by non-sudden cardiac death, compared with HFrEF patients with non-ischaemic cardiomyopathy.[75]

4.2 Hypertension

Hypertension represents a common aetiology for HF. In the OPTIMIZE-HF registry, hypertension was judged as the underlying cause for HF in 17%, 22%, and 31% of patients with HFrEF, HFmrEF, and HFrEF, respectively.[68] In the INTER-CHF, hypertensive heart disease was the HF aetiology in 15% of the overall population, and more specifically in 35% of patients enrolled in Africa, 21% in South America, ∼15% in India, Southeast Asia, and China.[69] In the Swedish HF registry, 56%, 64%, and 72% of patients with HFrEF, HFmrEF, and HFpEF, respectively, had hypertension.[36] In the ASIAN-HF, the prevalence of hypertension was highest in Southeast (67%) and Northeast (55%) Asia and lowest in South Asia (38%), with higher estimates in HFpEF vs. HFrEF.[42] The role of hypertension as an aetiological factor in HF is reinforced by the evidence that treating hypertension reduces the incidence of HF.[76]

4.3 Valvular and rheumatic heart disease

In the ESC-HF-LT registry, 8% of the population had valvular disease as the primary HF aetiology, 4% in HFrEF, 10% in HFmrEF, and 20% in HFpEF.[35] In the INTER-CHF registry, valvular heart disease was the HF aetiology in 11% of the overall population, with the highest rates in South America (13%) and lowest in Middle East (8%).[69] Valvular disease is also highly prevalent in HF patients, with 21% of those with HFrEF and HFmrEF, and 28% with HFpEF suffering from this condition.[36] At the global level, the greatest burden of valvular heart disease on HF is explained by rheumatic heart disease (RHD). RHD represents a complication of rheumatic fever (single severe episode or multiple recurrent episodes). The overall burden of RHD declined over an observation period of 25 years worldwide,[77] likely as a consequence of an improvement in living conditions and the use of antibiotics. In a meta-analysis of screening studies, the prevalence of RHD ranged between 2.7 cases per 1000 population (clinically manifest cases) and 21.1 cases per 1000 population (clinically inapparent cases) in low- and middle-income countries.[78] To date, the remaining burden of RHD mainly appears in low-income countries (e.g. Sub-Saharan African countries) and to some extent also in older patients in higher income countries,[78] with an estimated incidence of acute rheumatic fever in industrialized countries <1 per 100 000 population, and 1.6% of all cardiovascular (CV) deaths explained by RHD.[79,80] In the Sub-Saharan Africa, RHD has been shown to be the HF aetiology in up to ∼40% of the analysed populations.[81] In an analysis from South Africa, the incidence of symptomatic RHD was 24.7 per 100 000 population per annum among adults (>13 years) in Soweto, whereas prevalence of asymptomatic echocardiographic RHD in schoolchildren was 20.2 cases per 1000 children in Cape Town, and 60-day mortality after an admission for acute HF due to RHD was ∼25%.[82] In the 2015 Global Burden of Disease study left and right HF accounts for 25.5% and 5.3% of deaths from RHD.[77]

4.4 Idiopathic dilated cardiomyopathy

In the ESC-HF-LT registry, idiopathic dilated cardiomyopathy accounted for ∼30% of the underlying causes of HF, although potential misdiagnosis should be considered.[35] Corresponding estimates in the OPTIMIZE-HF registry were ∼20%.[68] Idiopathic dilated cardiomyopathy was the HF aetiology in 12% of patients enrolled in the INTER-CHF registry, with slightly higher estimates in Middle East (18%) vs. South America, China, Africa, and India (∼11–15%) and with the lowest representation in Southeast Asia (3%).[69]

4.5 Chagas cardiomyopathy

Chagas disease is caused by the protozoan *Trypanosoma cruzi* and represents a potentially life-threatening disease. Historically, this disease was found only in Central and South America. Approximately 10 million people are infected in these geographical regions.[83] Outside of South America Chagas disease is poorly recognized.[84] The Chagas cardiomyopathy remains the most common cause of non-ischaemic cardiomyopathy in South America.[85] However, immigration makes Chagas disease actual also in other regions, e.g. Europe and USA.[86] In USA, it is estimated that at least 300 000 residents have Chagas disease and the southern half of the country has enzootic cycles of *T. cruzi*.[87] A meta-analysis including 18 studies found that the prevalence of Chagas disease was 4.2% in immigrants from Latin America living in five European countries, and was higher in those emigrating from Paraguay and Bolivia.[88] The Chagas cardiomyopathy is characterized by higher mortality, risk of arrhythmias and of sudden cardiac death compared with other HF aetiologies. As many as 22.4% of patients with Chagas cardiomyopathy are in HF stage C/D; the associated annual risk of all-cause mortality is 7.9%, 3.5% for HF death, and 2.6% for sudden cardiac death.[89,90]

4.6 Chemotherapy and radiotherapy-induced cardiomyopathy

Treatment with chemotherapeutic and radiotherapy agents has improved the long-term survival of patients with cancer but can cause several CV diseases, and HF in particular. Anthracyclines can lead to left ventricular dysfunction at any dose, and the likelihood of developing dysfunction is higher in presence of CV risk factors and other cancer directed therapies.[91,92] Toxicity due to anthracycline can be acute in ∼1% of the population and is generally reversible, whereas early-onset and late-onset chronic toxicity observed in up to 2.1% and 5%, of cases, respectively, are more likely irreversible.[92,93] Long-term CV mortality in anthracycline-induced cardiomyopathy has been shown to be similar compared to other non-ischaemic dilated cardiomyopathies.[94] The incidence of HF in patients receiving taxanes is usually lower, i.e. up to 1.6% in patients receiving a combination with anthracyclines.[92,95] Among the chemotherapeutic agents targeting the human epidermal growth factor receptor 2, trastuzumab has been shown to induce HF in up to 4.1% of the cases and left ventricular dysfunction in up to 18.6%, with higher rates whether in combination with anthracyclines.[92,95] Reversible left ventricular dysfunction has been observed in ∼15% of patients receiving sunitinib, a vascular endothelial growth factor inhibitor, whereas with bevacizumab there was a five-fold increase in risk of HF.[92] Up to 10% of patients receiving radiotherapy might develop consequent HF, and 64% of women receiving thoracic radiation for breast cancer has been shown to develop HFpEF.[96]

4.7 Congenital heart disease

Advances in surgery and healthcare have improved the prognosis of patients with congenital heart disease (CHD), leading to a growing living population of patients with CHD.[97] A comprehensive meta-analysis including 270 studies reported a prevalence rate of 9.4 cases per 1000 births, which is expected to increase in the future.[98] Despite the success

of surgical or interventional procedures, the morbidity and mortality of patients with CHD is higher than in the general population, and it is related to the development of HF in adulthood (~25%).[97,99]

4.8 Key messages on HF aetiologies

IHD represents the HF aetiology in ~40% of the HF population worldwide, although large geographical variations exist, with very high estimates in Eastern Europe, Middle East, and Southeast Asia (~60%) and very low representation of this HF aetiology in Africa (<15%). IHD is more commonly the HF aetiology in HFrEF and HFmrEF vs. HFpEF. Hypertension is the HF aetiology in 15% of the HF population, with higher estimates in Africa compared with other regions. RHD still represents a major HF aetiology in Sub-Saharan and low-income countries. Chagas cardiomyopathy remains the most common cause of non-ischaemic HF in South America, and emigration has led to this disease being observed also in Europe and US. Epidemiological data on other potential HF aetiologies, e.g. amyloidosis, human immunodeficiency virus, sarcoidosis, and other cardiomyopathies, are more sparse.

5. Outcomes

5.1 Europe and North America

Most data on outcomes in HF patients are available from Europe and North America.[100] In the ESC-HF-LT registry that enrolled 12 440 patients with acute (i.e. either with incident or pre-existing HF in need of diuretics, inotropes or vasodilators) and chronic HF from 21 European countries between 2011 and 2013, 1-year mortality was 23.6% for acute HF and 6.4% for chronic HF. Notably, mortality rates ranged across the different European countries involved in the registry, i.e. between 21.6% and 36.5% in patients with acute HF and from 6.9% to 15.6% in patients with chronic HF.[101]

A further analysis from the ESC-HF-LT registry reported that 1-year mortality was 8.8% in outpatients with HFrEF, 7.6% in HFmrEF, and 6.3% in HFpEF, i.e. higher in HFrEF vs. HFmrEF vs. HFpEF.[35] The highest proportion of deaths due to CV disease at 1 year was observed in patients with HFrEF (53.5%) followed by HFmrEF (50.6%) and HFpEF (47.2%). A different pattern was observed regarding HF hospitalizations at 1 year, with HFrEF and HFpEF reporting higher risk (14.6% and 9.7%, respectively), compared with HFmrEF (8.7%).

In the EuroHeart Failure Survey I (enrolling patients with an HF diagnosis during a hospital admission, an HF diagnosis at any time in the 3 years prior to enrolment, and who received a loop diuretic or pharmacological treatment for HF within 24 h of death or discharge), 90-day mortality was 12% in HFrEF and 10% in HFpEF. However, re-hospitalization rates did not significantly differ between HFrEF and HFpEF (22% vs. 21%, respectively).[102] In the EuroHeart Failure Survey II enrolling patients admitted to hospital due to dyspnoea and HF,[103] the overall in-hospital mortality was 6.7%, consistent with other European surveys.[104,105]

In the Echocardiographic Heart of England Screening (ECHOES) study, which enrolled 6162 patients with HF and/or left ventricular systolic dysfunction, 5- and 10-year survival was 53% and 27%, respectively.[106] Additionally, the degree of EF impairment was associated with lower survival. In particular, 10-year survival was 76.1% in patients with EF ≥ 40% and only 30.8% in those with EF < 40%.

In the nationwide Swedish Heart Failure Registry including patients with clinician-judged, mortality at 30-day, 1 year, and 3 years was lower in HFrEF, i.e. 2.8%, 15.4%, and 28.1%, respectively, compared with HFpEF, i.e. 2.9%, 17.4%, and 32.1%, and HFmrEF, i.e. 2.1%, 14.2%, and 26.9%.[36]

In a Danish nationwide cohort study considering 317 161 patients with first-time inpatient hospitalizations for HF, 1-year mortality declined from 45% to 33% and 1- to 5-year mortality from 59% to 43% between 1983–87 and 2008–12, which was independent of patients' comorbidity burden.[107]

A large-scale population cohort study from the UK investigated 86 833 patients with incident HF between 2002 and 2013. One-year mortality was high (32%) and declined only modestly (27%) during the study period.[108] Interestingly, 1-year mortality due to CV diseases declined from 18% in 2002 to 13% in 2013, whereas non-CV mortality rates increased from 13% to 17%.

The GWTG-HF registry analysed 39 982 patients hospitalized for HF between 2005 and 2009 in the USA.[109] Median survival was 2.1 years and 5-year mortality was 75.4%. However, patients with HFrEF vs. HFpEF had comparable 5-year mortality (75.3% vs. 75.7%, respectively). Re-admission rates were slightly lower in patients with HFrEF compared with HFpEF (82.2% vs. 84.0%, respectively).

An analysis of the OPTIMIZE-HF registry, enrolling patients hospitalized for incident or worsening HF, showed no difference in mortality between HFrEF (EF < 40%) and HFpEF (≥40%), i.e. 9.5% vs. 9.8%, respectively, and re-hospitalization rates, i.e. 29.2% vs. 29.9%, respectively, during 60- to 90-day post-discharge period.[68] Despite similar lengths of hospital stay in patients with HFrEF and HFpEF, unadjusted in-hospital mortality was significantly higher in patients with HFrEF (3.9%) vs. HFpEF (2.9%). However, there was no difference in in-hospital outcomes between HFpEF and HFmrEF (3.0% vs. 2.9%, respectively).

In a systematic review analysing data from 1.5 million patients with chronic or stable HF in any ambulatory setting from 60 studies across high-income countries over the past 70 years,[110] survival estimates at 1 month, 1, 2, 5, and 10 years since HF diagnosis were 95.7%, 86.5%, 72.6%, 56.7%, and 34.9%, respectively. Survival rates among patients ≤65 years were almost 10% higher at 1 year and over 30% higher at 5 years, as compared with those ≥75 years. Additionally, survival rates were higher in studies recruiting participants from secondary vs. primary care.

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial is one of the largest randomized controlled trials in patients with acute decompensated HF enrolling 7141 patients from 2007 to 2010 in 30 countries worldwide. Patients were eligible to participate in this study if they were hospitalized due to acute HF occurring within 24 h before they received their first intravenous treatment for HF. Patients from South America had the highest adjusted 180-day mortality (17.3%), followed by Western Europe (15.1%), North America (13.3%), Asia-Pacific (11.6%), with Central Europe (9.3%) reporting the lowest mortality.[111] Estimates for mortality or HF re-hospitalization at 30 days were 12.7% in North America, 11.0% in Latin America, 7.7% in Western Europe, 7.5% in Asia-Pacific, and 5.1% in Central Europe.

Several studies have shown the impact of socio-economic factors on outcomes in HF.[112] A prospective study including 1802 patients with chronic HF recruited in four UK hospital showed that socio-economic deprivation was associated with increased risk of all-cause and non-CV mortality but not with CV mortality, and with all-cause but non-HF-specific hospitalization in patients with HF (EF ≤ 45%) over a follow-up time of 3 years.[113] In a large population-based study from UK, all-cause mortality, as well as the risk of all-cause hospitalization, was significantly higher in most deprived patients vs. the most affluent group, i.e. 8% and 34% relative risk difference.[114] In the Swedish HF registry, 16% of the population had three socio-economic risk factors (lower income, no/

compulsory degree, and living alone) and lower socio-economic status was associated with higher risk of mortality/HF hospitalization, overall CV and non-CV events across the EF spectrum.[115] In Denmark, income was inversely related to 1-year mortality.[116] In the US National Inpatient Sample low SES (homelessness or lowest quartile of median neighbourhood income) was associated with a 2% increased risk of all-cause mortality.[117]

5.2 Asia, Australia, South America, and Africa

Contemporary data on outcomes in HF across Asia are limited. In the Japanese Cardiac Registry of Heart Failure in Cardiology enrolling 2675 patients hospitalized for worsening HF in 164 hospitals, unadjusted in-hospital mortality was higher in patients with HFpEF vs. HFrEF (6.5% vs. 3.9%, respectively).[118] After multivariate adjustments, no significant differences were observed. Moreover, in-hospital mortality rates in patients with HFmrEF were similar to those with HFrEF or HFpEF.

Among 3466 participants to the Korean Heart Registry including >1500 HFrEF patients hospitalized for signs/symptoms of HF, in-hospital mortality was 6.6%, 60-day mortality was 3.8%, and 1-year mortality was 9.2%. Rates for mortality/re-admission were 4.6% at 60 days and 14.1% at 1 year.[119]

In the prospective multicentre China-HF Registry enrolling patients hospitalized for HF, crude in-hospital mortality was 4.1% and significantly higher in patients with HFrEF vs. HFpEF (4.0% vs. 2.4%, respectively).[120]

In the ASIAN-HF registry, crude 1-year all-cause mortality was 9.6% in patients with symptomatic HF, i.e. with at least one episode of decompensated HF in the previous 6 months requiring hospital admission or treatment in an outpatient clinic. Asian patients with HFrEF had more impaired 1-year mortality than those with HFpEF (10.6% vs. 5.4%, respectively). One-year all-cause mortality was highest in Southeast Asian patients (13.0%), followed by South Asian patients (7.5%) and Northeast Asian patients (7.4%).[42] In the same registry, higher country- and patient-level socio-economic indicators were associated with higher quality of life and lower risk of all-cause mortality/HF hospitalization.[121]

In a meta-analysis of 12 studies enrolling 67 255 patients hospitalized for HF between 1990 and 2016 in Australia,[122] the 30-day and 1-year all-cause mortality rates were 8% and 25%, respectively.

The INTER-CHF study enrolled 5823 in- and outpatients with a clinical diagnosis of HF between 2012 and 2014 and assessed 1-year mortality in patients with HF in Africa, China, India, the Middle East, Southeast Asia, and South America.[69] Overall mortality rate was 16.5%, highest in Africa (34%) and India (23%), intermediate in Southeast Asia (15%), and lowest in China (7%), South America (9%), and the Middle East (9%). Notably, regional differences persisted after multivariable adjustments. However, patients in Africa, India, and Southeast Asia were on average 10 years younger than those in South America and China but had higher mortality rates. Mortality rates slightly differed between the INTER-CHF and Asian-HF registries, which might be due to marked differences in patient characteristics.

There is paucity of data on HF epidemiology in Africa. However, some studies on epidemiology of CV diseases, such as the PAN-African SCD, are planned.[123] Results of the THESUS-HF cohort study in nine African countries showed an in-hospital mortality of 4.2% in patients hospitalized due to acute HF (i.e. admitted with dyspnoea and diagnosed with HF based on symptoms and confirmed by echocardiography) between 2007 and 2010.[72] The estimated 180-day mortality was 17.8% and the mean EF was 39.5%.

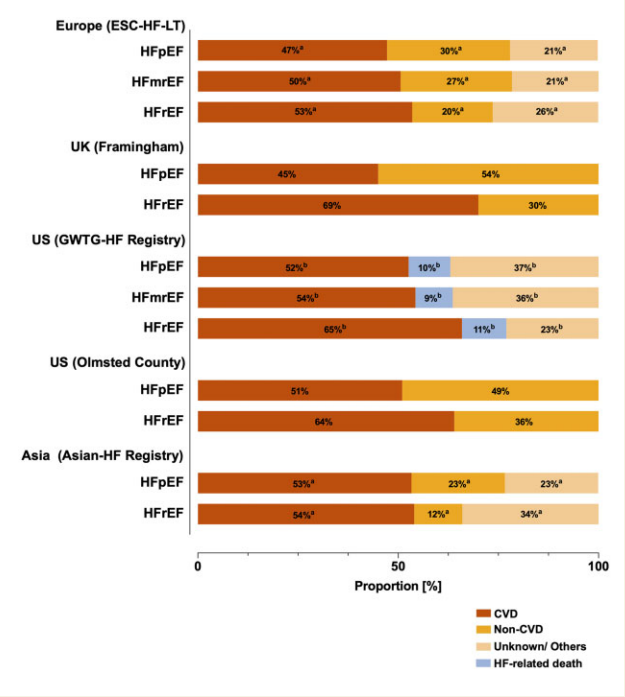

Figure 3 Causes of death in heart failure patients worldwide. [a]—proportion of all-cause deaths at 1 year; [b]—proportion of all-cause deaths at 5 years. CVD, cardiovascular death; HF, heart failure. Definitions of HF phenotypes according to data sources: Europe (ESC-HF-LT): HFrEF EF < 40%, HFmrEF EF 40–50%, HFpEF EF>50%; UK (Framingham): HFrEF EF≤40%, HFpEF EF>40%; US (GWTG-HF Registry): HFrEF EF≤40%, HFmrEF EF 41–49%, HFpEF EF≥50%; US (Olmsted County): HFrEF EF < 50%, EF≥50%; Asia (Asian HF-Registry): HFpEF EF<40%, HFpEF EF≥50%.

5.3 Causes of death

The different causes of death might reflect the heterogeneity of the HF population in term of age, comorbidity burden and therefore HF phenotypes (*Figure 3*). In the ESC-HF-LT registry, CV death was the leading cause of death at 1 year. Notably, CV death was more frequent in HFrEF (53.5%) vs. HFmrEF (50.6%) vs. HFpEF (47.2%). Conversely, non-CV mortality was higher in HFrEF (20.1%) vs. HFmrEF (27.8%) vs. HFpEF (30.7%) at 1 year.[35]

In the GWTG-HF registry, among patients hospitalized for HF, primary causes of death substantially varied across the EF spectrum, with patients with HFrEF most likely to report CV death, i.e. 65.9% in HFrEF vs. 52.6% in HFpEF at 5 years. In addition, patients with HFrEF were more likely to die of CV mortality within 1-year post-admission compared to patients with HFpEF.[109]

In the ECHOES study, the main causes of death were CV/cerebrovascular deaths (46.4%), with 16.7% being due to myocardial infarction and 16.3% to HF, followed by respiratory disease associated deaths (17.5%), and cancer (21.4%). Comorbidities, such as diabetes, valvular disease, use of diuretics, smoking, and obesity were identified as important independent predictors of mortality.[124]

In a community-based sample from the FHS, between 1971 and 2004 CV death was the most frequent underlying cause of death (66.1%). Stratified by EF, CV death was observed in 44.5% of HFpEF patients and in 69.9% of those with HFrEF. Notably, a history of myocardial infarction

was associated with higher risk of CV death in female but not male HF patients.[125]

In an epidemiological study from Olmsted County enrolling patients between 1979 and 2002, the most frequent underlying cause of death was non-CV (49%) in patients with HFpEF (EF ≥ 50%), whereas it was coronary heart disease in patients with HFrEF (43%; EF < 50%). CV mortality decreased by 29% in patients with HFpEF, whereas patients with HFrEF reported only a modest 13% non-statistically significant decrease in risk over the follow-up (>20 years).[126] Although men and women experienced a comparable age-adjusted all-cause mortality, male patients had higher CV mortality compared to females, while HF hospitalization rates were lower in females vs. males HF.[51] The risk of CV death was also higher in males vs. females in the I-PRESERVE trial, which was also paralleled by a higher risk of sudden cardiac death, non-CV death, and all-cause death.[127]

In a comprehensive systematic review, only 19 studies reported causes of deaths. In 14 of them death was due to CV diseases for over 50% of the total deaths, and HF tended to be the most frequent cause of death but widely ranging between 8% and 64%. Five-year survival in patients with HFrEF was lower compared to patients with mixed EF (including patients with HFrEF, HFmrEF, HFpEF, and no EF assessment), but there was no difference in survival for HFpEF compared with HFrEF at 1 and 5 years.[110]

In the ASIAN-HF registry, the most common cause of death was CV (60.9%) followed by unknown/presumed CV (25.9%) and non-CV (13.2%). Risk of CV death was slightly higher in HFrEF (54.0%) vs. HFpEF (53.3%), whereas non-CV death was more frequent in HFpEF (23.3%) vs. HFrEF (12.0%) at 1 year.[42]

In the INTER-CHF Registry enrolling patients between 2012 and 2014, cardiac death were more common than non-cardiac death, i.e. 46% vs. 16%, respectively (38% unknown).[69]

Although CV death is predominant in HF, growing evidence has highlighted a gradual shift towards non-CV death over the last two decades. In a Spanish HF cohort of HFrEF and HFmrEF patients, non-CV deaths accounted for 17.4% of deaths in 2002 and for 65.8% in 2018. Among patients dying from non-CV events, a diagnosis of cancer represented the most common cause of death, followed by infections, and respiratory disease. Notably, the proportion of CV deaths decreased over time, which was mainly explained by the decrease in risk of sudden cardiac death, without any change in deaths for myocardial infarction or stroke.[128] A decrease in risk of sudden cardiac death over time has been shown in two analyses of data from landmark HFrEF trials as well.[129,130] A report from USA analysing causes of death between 2000 and 2014 confirms an increase in non-CV vs. CV mortality in HF patients >45 years old.[131] In a large population-based analysis from UK, CV death was higher than non-CV death for the first few years after an HF diagnosis, but at around 3–5 years follow-up risk of non-CV death surpassed the one of CV death.[114] In a further analysis from UK of ∼90 000 patients with a first diagnosis of HF between 2002 and 2013, risk of CV death declined by 27% over time, which was paralleled by an increase in risk of non-CV death by 22%, with cancer, respiratory conditions and infections being the major non-CV causes of death.[108]

5.4 Hospitalizations

Hospitalizations due to HF represent 1–2% of all hospital admissions in the Western world.[103] Additionally, HF is the most frequent cause of hospitalization among individuals >65 years.[132] Approximately 30–40% of HF patients have a history of hospitalization for HF[101,133] and 50% are re-admitted with 1 year within their initial diagnosis of HF.[114,134]

In the Olmsted County cohort, hospitalizations in patients with HF were common (1.34 per person-year) and mostly due to non-CV causes (63%).[51] CV hospitalization rates were stable between 2000 and 2010.[51]

Nationwide data (National Inpatient Sample) from the USA reported 12 783 478 HF hospitalizations between 2002 and 2013.[135] Age-adjusted HF hospitalization rates decreased by 30.8% between 2002 and 2013, while data substantially varied due to racial and ethnic differences with nearly 2.5-fold higher HF hospitalization rates in black vs. white patients.

In a large-scale Danish population-based cohort study enrolling 317 161 patients with first-time hospitalizations for HF during 1983–2012, the standardized HF hospitalization rate decreased between 1983 and 2012 by 25% for females (from 192 to 144 per 100 000 persons) and by 14% for males (from 217 to 186).[107]

The comprehensive Cardiovascular Disease Project in Norway analysed incident and recurrent HF hospitalizations between 2000 and 2014.[136] Age-standardized rates for incident HF hospitalizations declined on average 1.9% per year in males and 1.8% per year in females. However, after a first HF hospitalization, 6.1% of males and 5.6% of females had a HF recurrence with 30 days.

Consistently, a Scottish long-term study on incident HF hospitalization including 5.1 million people between 1986 and 2003 confirmed that previously rising age-adjusted rates of first HF hospitalization clearly declined over time.[137]

A recent report from Sweden analysing 3878 patients with incident HF between 2005 and 2013 highlighted that recurrent HF hospitalizations were associated with an increased risk of CV and all-cause mortality. In HF patients with one recurrent HF hospitalization, the annualized mortality rates for CV mortality increased from 29 to 53 deaths per 100 person-years at risk.[138]

5.5 Associations between comorbidity status and outcomes

Both cardiac and non-cardiac comorbidities are common in HF patients and associated with adverse outcomes, such as reduced quality of life, hospitalizations, and fatal events. Comorbidity burden has been repeatedly shown to be heavier in HFpEF vs. HFmrEF vs. HFrEF.[36,139] The cumulative number of comorbidities is a strong predictor of mortality/morbidity in patients with HF regardless of EF.[140,141]

Atrial fibrillation is common in HF regardless of EF. In the ESC-HF-LT registry prevalence was 20% in HFrEF, 22% in HFmrEF, and 32% in HFpEF, with corresponding estimates in the OPTIMIZE-HF being 28%, 33%, and 32%.[35,36] Although in the Swedish HF registry atrial fibrillation was associated with ∼10–20% increased risk of all-cause mortality without any significant difference across the EF spectrum, in the ESC-HF-LT registry, it predicted increased mortality/HF hospitalization in HFpEF and HFmrEF but not in HFrEF.[142,143]

Diabetes is highly prevalent in patients with HFrEF and HFpEF, i.e. ∼30%.[144] Patients with HF and with vs. without diabetes have higher mortality and morbidity in both ambulatory and in-hospital setting.[145–149] In the CHARM program diabetes was associated with a higher relative risk of CV death or HF hospitalization in patients with HFpEF vs. HFrEF, but with no difference in all-cause mortality.[150] In the Swedish HF registry type 2 diabetes (T2DM) similarly increased CV and non-CV events but did so generally less in HFpEF, except for the increase in HF hospitalization which was consistent regardless of EF.[141]

Chronic kidney disease (CKD) is common in patients with HF and worsening renal function is associated with poor clinical outcomes.[151] In

a meta-analysis CKD had a prevalence of 32% while worsening renal function was observed in 23% of the HF population, and they were associated with a ~two-fold increased risk of all-cause mortality, with greater magnitude of the association whether EF was higher.[152] Conversely, in the Swedish HF registry, CKD was associated with a 50% increased risk of death in HFrEF and HFmrEF vs. a 30% increased risk in HFpEF.[153] Similarly, the increase in risk with CKD in terms of overall risk of CV and non-CV events was greater in HFmrEF and HFrEF vs. HFpEF.[141]

Chronic obstructive pulmonary disease (COPD) and HF often coexist in patients. The prevalence of unrecognized HF is about ~20% in patients with COPD.[154,155] In the ESC-HF-LT registry, prevalence of COPD was 15% in HFrEF, 12% in HFmrEF, and 14% in HFpEF.[35] COPD is an independent risk factor of all-cause mortality and non-CV mortality in patients with HFpEF and HFrEF.[156–160] In the BIOSTAT-CHF study, it was associated with worse quality of life, all-cause mortality and hospitalization regardless of EF.[139]

Anaemia is a common comorbidity in HF, with higher prevalence in HFpEF (~40%) vs. HFmrEF and HFrEF (~30%), and represents an independent predictor of HF hospitalization and mortality in patients with HF regardless of EF.[161] Notably, iron deficiency, which represents the most common cause of anaemia, has a prognostic role in HF patients regardless of anaemia, being associated with exercise capacity, quality of life, and survival.[162,163]

There is growing evidence for an interplay between cancer and HF, although with conflicting findings. In the Women's Health Initiative HF was associated with a 28% increased risk of cancer, and more in particular of obesity-related and for some site-specific (colorectal and lung) cancers, but not of tobacco-related and breast cancers. When EF was analysed, HFpEF but not HFrEF was associated with the risk of developing cancer.[164] Conversely, in the Physicians' Health Study, which enrolled only males, there was no association between HF and incident cancer, raising questions regarding potential sex-based differences in the relationship between cancer and HF.[165] Cancer has been shown to increase mortality in patients with HF by >50%.[166]

5.6 Key messages on outcomes

In the past decades, the prognosis of HF has slightly improved, but mortality remains high, with 1-year risk ranging 15–30% and 5-year risk up to 75% in specific populations, without great differences in risk between HFpEF and HFrEF.

Although CV death still represents the major underlying cause of death in HF patients, it has been decreasing over time. Non-CV deaths are also frequent and increasing, in particular in patients with HFpEF. Additionally, both cardiac and non-cardiac comorbidities are frequent in patients with HF and associated with worse outcome. Patients with HF experience frequent hospitalizations, which has been slightly improving over time. Incident and recurrent HF hospitalizations are associated with increased risk of mortality.

6. Costs of care

6.1 Health care costs worldwide for HF

The economic burden of HF on worldwide healthcare systems and economies is substantial and is even expected to increase due to the raising prevalence of the disease (*Figure 4*).[167]

A comprehensive study comparing direct and indirect costs of HF worldwide in 197 countries found that the overall economic costs of HF in 2012 were estimated to amount to $108 billion.[168] In particular, direct costs accounted for about 60% ($65 billion) and indirect costs for about 40% ($43 billion).

HF-related health care costs per patient were €3150 per year in 2011 in Germany and were mainly linked with hospitalizations (€2328; 74%), while costs of rehabilitation (€294; 9%), medication (€290; 9%), and outpatient visits (€238; 8%) were considerably lower.[169] Compared with €2474 spent per patient in NYHA class I, there was a significant cost increase together with more advanced NYHA class, i.e. 14% in NYHA class II, 48% in NYHA class III, and 71% in NYHA class IV.

Based on demographic changes and the overall increasing prevalence of HF in the USA, a nationwide survey from the American Heart Association in 2013 reported that direct and indirect costs attributed to HF will significantly increase from $20.9 billion in 2012 to $53.1 billion in 2030 (2.5-fold increase).[4] In the USA population, the highest increase of costs is expected in HF patients >65 years old of age (three-fold), whereas it will be milder for younger age groups (a 1.6-fold increase for those aged 45–64 years and a two-fold increase for those aged 18–44 years), with a majority of costs linked with hospitalizations (>70%).[4] Furthermore, indirect costs are also expected to increase substantially, i.e. from $9.8 billion to $16.6 billion (increase of 69%) over the same time period.

A systematic review including 16 international studies from 2004 to 2016 estimated an overall lifetime health care costs due to HF of $126 819 per patient.[170] However, expenditures significantly differed across the countries considered in this study, with highest total annual prevalence-based costs in Germany ($25 532)[171] and lowest in South Korea ($868).[172]

In Spain, in a prospective multicentre study including 274 patients with symptomatic HF, estimated total medical costs per patient for 1-year follow-up ranged from €12 995 to €18 220 in 2010.[173]

According to data from Danish nationwide registries including 176 067 HF patients between 1998 and 2016, total annual health care costs per HF patient were €17 039 (direct costs: €11 926; indirect costs:

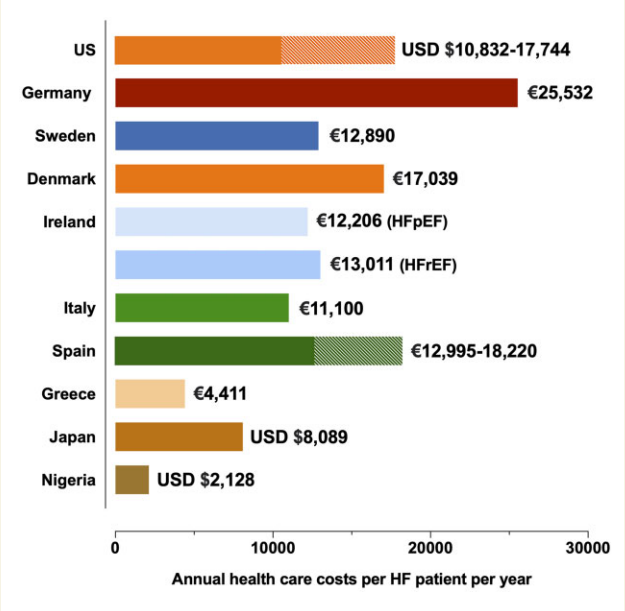

Figure 4 Health care costs of heart failure worldwide. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

€5113),[174] and were significantly higher than in the general population (€5936). Notably, costs were highest in HF patients with a history of HF <1 year.

Using data from a large population from Northern Italy in 2011, the estimated average annual costs due to HF per patient were €11 000, of which €4300 for the index hospitalization (39%), €5900 for recurrent hospitalizations (53%), and the remaining €900 for outpatient care (8%).[46]

In Portugal in 2014, estimated direct costs for treating HF patients were €299 million (39% for hospitalizations, 24% for medicines, 17% for diagnostics, 16% for consultations, and the rest for other healthcare needs, including emergencies and long-term care), whereas indirect costs were estimated to be €106 million.[175] The overall mean costs for prescribed medications per HF patient were €287.

Data from a prospective HF registry from Ireland reported slightly higher annual costs for patients with HFrEF (€13 011) vs. patients with HFpEF (€12 206), whereas average costs per patient due to emergency non-CV admissions were higher in patients suffering from HFpEF (€655) vs. HFrEF (€584).[176] Additionally, annual costs of re-hospitalizations were significantly higher in HFpEF (€5396) vs. HFrEF (€4287) indicating the high burden of comorbidities in patients with HFpEF.

In Sweden between 2005 and 2014, health care costs per HF patient for the first year were €12 890 and decreased to €5588 per patient per year by year 2 after diagnosis. Additionally, overall healthcare costs were mainly driven (~90%) by hospitalizations, and HFpEF needed a greater use of health care resources compared to patients with HFrEF or unknown EF.[177]

A cross-sectional study using data from the Japanese Registry of All Cardiac and Vascular Diseases between 2012 and 2014 reported median costs per HF patient amounting to $8089, and were higher in age >75 years.[178] Additionally, several international studies have shown that the costs due to hospitalizations were 5–31% higher in patients with HF aged <65 vs. ≥65 years old.[179–182]

Data on health care costs in countries with low- to middle income are very limited. In Nigeria, the total computed costs for HF care were $2128 per patient per year between 2009 and 2010.[183]

6.2 Impact of comorbidities on costs in HF patients

The presence of comorbidities has a relevant impact on annual health care costs in patients with HF, i.e. $19 537 for patients with HF and hypertension to USD, and $77 214 for patients with HF, hyperkalaemia and on dialysis.[184–186] In terms of procedural costs, dialysis accounts for significant costs in HF care, even if used only in a minority of patients.[187]

In a retrospective case–control study in 2010 in the USA, annual costs related to HF amounted to $22 230 per patient in absence of T2DM, whereas expenditures substantially increased in presence of comorbid T2DM ($32 676).[188] In the USA between 2010 and 2013, mean costs for HF-related hospitalizations were $12 915 in patients with T2DM and $10 103 in those without T2DM, and were higher with T2DM regardless of EF (HFpEF or HFrEF).[189] In the US nationwide re-admission database including 2 645 336 patients hospitalized for HF between 2010 and 2014, strongest predictors of costs among cardiac comorbidities were coronary artery disease and valvular disease.[190] Pulmonary disease, fluid and electrolyte disorders, liver disease, bleeding, cancer, and renal failure represented most important predictors of costs among non-CV comorbidities during a hospital admission. Notably, 12.6% of these patients hospitalized for HF underwent an invasive procedure or treatment. Inpatient costs varied substantially depending on the procedure or treatment performed during the hospital admission ($129 547: circulatory support, $119 769: intra-aortic balloon pump, $251 110: left ventricular assist device, and $293 575: heart transplantation).[190]

6.3 Key messages on costs of care

Annual health care costs per HF patient amount up to €25 000 in the Western world. The majority of costs is linked with directs costs [inpatient care and (re-)hospitalizations] and non-CV comorbidities. Additionally, an important pattern of increasing HF hospitalizations, especially in women, might highlight potential later presentation and limited evidence-based therapies in HFpEF. Based on major demographic changes and the overall increasing prevalence of HF, direct and indirect costs are expected to significantly increase, especially in HF patients >65 years old of age. Data on costs based on the EF phenotype are currently limited, but the impact of HFpEF on hospitalization costs might be higher.

7. Conclusions

HF is a major healthcare problem and is associated with a high use of resources and health care costs. Although incidence has remained stable or has even slightly declined over time, prevalence is increasing due to the improved HF treatments and longer life-expectancy in the population. Despite significant enhancements in HF therapies, morbidity and mortality still remain high. Although CV mortality is decreasing over time, it remains the leading cause of death in HF patients, whereas increasing non-CV mortality has been observed, which might be explained by the increasing burden of comorbidities, in particular in HFpEF.

HF is the leading cause of hospitalizations in patients >65 years and accounts for 1–2% of all hospitalizations in the Western world. A better understanding of the causes of hospitalizations might contribute to set preventive strategies leading to improve patients' prognosis and reduce HF burden on health care costs. Improving care and treatment of HFpEF is a priority since this is expected to represent the major player on the HF stage in the next years.

Finally, epidemiological data on HF in developing countries, where HF has different characteristics compared with the Western world, are needed.

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