HEART TIME:
Advancing Heart Failure Management with Sacubitril/Valsartan

Module 1

Contents

1. Introduction 3
2. Incidence and prevalence of heart failure 9
3. Burden of HF in India 18
4. Future directions 22
5. Reference 23

Introduction

Heart failure (HF) is a clinical syndrome marked by a combination of symptoms such as shortness of breath, difficulty breathing when lying flat, and swelling in the lower limbs, along with physical signs like raised jugular venous pressure and fluid buildup in the lungs. It is typically caused by structural or functional problems in the heart, leading to reduced cardiac output or increased pressure within the heart chambers [Ponikoswki p, et al.2016]. HF is categorized into three groups based on left ventricular ejection fraction (EF): HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF), with the respective EF ranges of <40%, 40-49%, and ≥50%. Furthermore, a new category, HF with improved EF, has been introduced, which refers to HF patients who have a baseline EF <40%, experience a 10-point increase in EF from the baseline, and have a follow-up EF measurement of over 40% [Bozkurt B, et al. 2021].

HF is likely to be a significant contributor to death and disability in developing countries due to the rise in vascular diseases and the continued presence of pre-transitional conditions like rheumatic heart disease (RHD) and infectious cardiomyopathies. Unlike Western nations, however, the epidemiology of HF remains largely unstudied in developing countries like India, where no major research has been conducted to assess its prevalence. Despite this, practicing internists and cardiologists recognize that the burden is likely substantial, given that India accounts for 16% of the global population, 25% of the world's coronary heart disease (CHD) burden, 120 million individuals with hypertension, and a significant number of RHD cases. By 2020, cardiovascular disease (CVD) is expected to become the leading cause of morbidity and mortality in India. [Huffman MD, et al. 2010, Reddy KS, et al. 1998].

Heart failure has been described as a global pandemic, with an estimated 64.3 million people affected worldwide in 2017 [Ziaeian B, et al. 2016]. The prevalence of HF is anticipated to rise due to improved survival rates following diagnosis, largely due to life-saving, evidence-based treatments, as well as the increasing life expectancy of the general population. The global financial burden of HF on healthcare systems is alarming. In 2012, the total cost of HF in the United states was estimated at $30.7 billion, with projections indicating a 127% increase to $69.8 billion by 2030, which equates to approximately $244 per adult in the U.S. [Gianlungi S, et al. 2022].

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 comprehensively to describe the epidemiology of HF, providing updated data on its prevalence, incidence,
outcomes, and costs worldwide, while acknossswledging in the availability of limited data in specific geographical areas.

1.1 Classification of heart failure

- **Heart failure with reduced ejection fraction (HFrEF):** symptomatic HF with a left ventricular ejection fraction (LVEF) of ≤40%.
- **Heart failure with mildly reduced ejection fraction (HFmrEF):** symptomatic HF with an LVEF between 41-49%, previously referred to as HF with mid-range ejection fraction.
- **Heart failure with preserved ejection fraction (HFpEF):** symptomatic HF with an LVEF of ≥50%.
- **Heart failure with improved ejection fraction (HFimpEF):** a newly defined category characterized by symptomatic HF, a baseline LVEF of ≤40%, a ≥ 10-point improvement from the baseline, and a follow-up LVEF of >40% (Figure 1).

Figure 1. Classification of HF

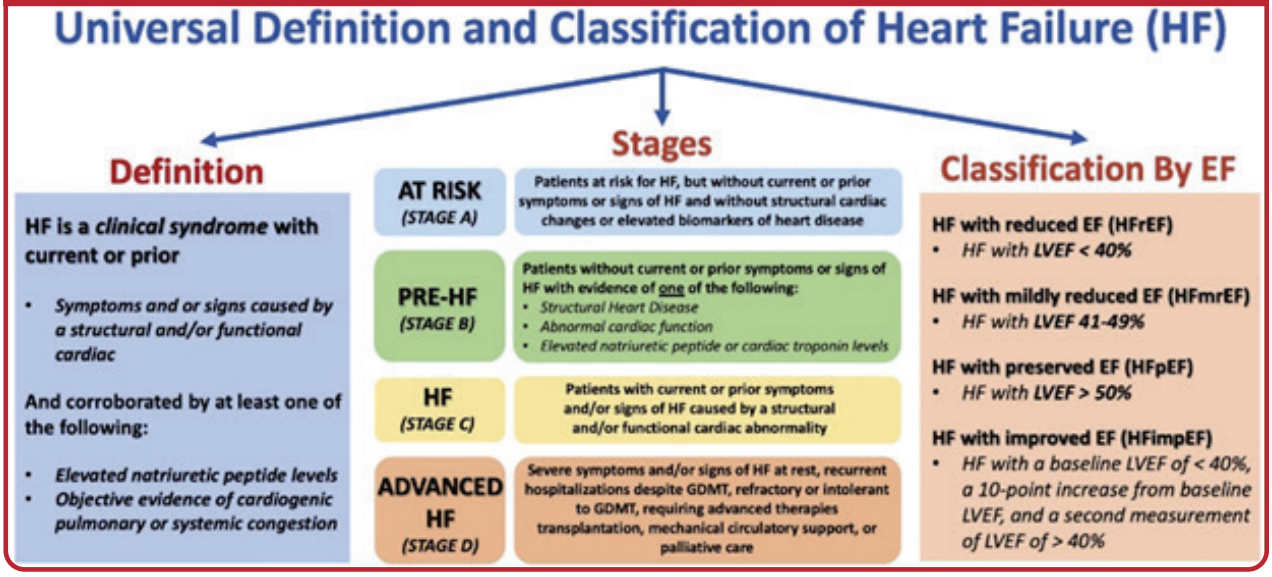

Figure adapted from: Gibson, et al. 2022
HF, heart failure.

1.2 Etiology of HF:

The global burden of disease study identifies 17 primary causes of HF. Over two-thirds of all HF cases are linked to four key conditions: ischemic heart disease, chronic obstructive pulmonary disease (COPD), hypertensive heart disease, and rheumatic heart disease.

1. Ischemic heart disease

Descriptions of angina pectoris date back to 1772, but significant advances in understanding the syndrome's pathophysiology did not occur until the late 19th century, when calcification and thrombosis of the coronary arteries were first recognized. Early research, including the Framingham Heart Study, identified key risk factors for coronary artery disease, such as hypertension, high cholesterol, diabetes, and smoking. Since the 1960s, the death rate from cardiovascular causes has steadily decreased due to better awareness of these risk factors and a stronger focus on primary prevention. The occurrence of ischemic heart disease, hypertension, diabetes, and other chronic conditions tends to rise alongside higher consumption of high-fat, high-sugar foods and a more sedentary lifestyle. Without the implementation of preventive health measures, the incidence and prevalence of these chronic diseases are likely to continue increasing [Ziaeian B, et al. 2016]. This trend of changing disease prevalence is referred to as an epidemiological transition, closely linked to the economic development of a country or region. In 2013, ischemic heart disease was the leading cause of death worldwide, responsible for 15.7% of all age-standardized deaths, which amounted to 8,139,900 fatalities [Ziaeian B, et al. 2016]. The Global burden of disease study indicates that the prevalence of ischemic HF rose from 240 to 270 per 100,000 person-years in men between 1990 and 2010, while remaining stable at 190 per 100,000 in women. Using the estimated rate of myocardial infarctions as a proxy for the incidence of ischemic heart disease, there is evidence of epidemiological transitions in both industrialized and developing countries. From 1990 to 2010, age-standardized rates of myocardial infarction decreased in high-income regions such as Australasia, Europe, and North America, with Eastern Europe experiencing the most significant increase in the number of myocardial infarctions during this period.

2 Hypertensive heart disease

Elevated blood pressure subjects cardiac myocytes to increased mechanical stress and neurohormonal stimulation. This chronic exposure leads to an increase in myocardial mass, ultimately resulting in left ventricular hypertrophy. These adaptations in the heart can progress to HFpEF or HFrEF. Notably, this progression can occur even when there are no obstructive lesions in the epicardial coronary arteries and in the absence of myocardial infarction. Over time, the ongoing strain from high blood pressure can induce structural and functional changes in the heart that predispose individuals to HF, highlighting the complex relationship between hypertension and cardiac health. Data from the NHANES in the USA indicate that from 1999 to 2012, the percentage of patients receiving treatment for hypertension increased from 59.8% to 74.7%. Additionally, the proportion of patients with hypertension who achieved adequately controlled blood pressure rose from 53.3% to 68.9% during the same period. This reflects significant progress in the management of hypertension among the population [Ziaeian B, et al. 2016]. The advancements in blood pressure control are likely linked to the observed decline in the incidence of HF. Despite hypertension being acknowledged as a major cardiovascular risk factor for many years, there continue to be significant gaps in the treatment of high blood pressure across various populations. Hypertension is a widespread issue that affects individuals across all socioeconomic classes. For instance, a clinical evaluation of 1,515 consecutive cardiac referrals in Nigeria revealed that 61% of patients were diagnosed with hypertensive HF, highlighting the substantial burden of this condition within the healthcare system [Ojji D, et al.2013]. However, this study had limitations, as patients did not undergo advanced diagnostic imaging or invasive angiography to accurately confirm the low prevalence of ischemic heart disease. In the PURE study, researchers found that among a sample of patients with hypertension from high-income countries, only 49% were aware of their diagnosis when their blood pressure exceeded 140/90 mmHg. Additionally, 46.7% received treatment, while only 19.0% achieved adequate control of their hypertension. In contrast, in low-income countries, awareness was lower at 40.8%, with 31.7% receiving treatment and only 12.7% managing to achieve adequate control of their blood pressure.

3 Valvular and rheumatic HF

In developed countries, the majority of valvular heart disease cases are degenerative, and the incidence of rheumatic heart disease is extremely low. Echocardiographic studies estimate that the prevalence of any form of valve disease in the USA is approximately 2.5%, with a significant increase in prevalence associated with age, reaching 11.7% among individuals over 75 years old. Clinically diagnosed valvular disease has a prevalence of about 1.8%. In 2010, around 106,000 valve surgeries were conducted in the USA. There is limited data on the prevalence of HF among patients diagnosed with valvular disease, whether clinically or via echocardiography. Worldwide, the most significant burden of valvular disease arises from valvular HF secondary to rheumatic heart disease. In high-income countries, the notable decrease in the prevalence of valvular disease is linked to improvements in living conditions and better access to antibiotic treatments. Consequently, the incidence of rheumatic fever has dropped to fewer than 1 case per 100,000 person-years in developed nations. In contrast, in developing countries, valvular HF due to rheumatic disease remains a major contributor to morbidity and mortality. For instance, in Sudan, the incidence of rheumatic fever exceeds 100 cases per 100,000 person-years. Globally, it is conservatively estimated that around 15.6 million people are affected by rheumatic heart disease, with approximately 470,000 new cases and 233,000 deaths occurring annually when echocardiography is utilized to screen populations in developing countries, the prevalence of rheumatic heart disease can increase tenfold.

4 Chagas cardiomyopathy

Chagas disease is a parasitic condition caused by the protozoan Trypanosoma cruzi, with an estimated 5.7 million people affected globally in 2010, primarily in Latin America. Since 1990, the application of insecticides to decrease the population of the insect vector (Triatoma, commonly known as the kissing bug) has led to a significant reduction in the prevalence of Chagas disease, which had previously reached a peak of 15 to 30 million cases [Ziaeian B, et al. 2016]. Chagas disease continues to be the leading cause of non-ischemic cardiomyopathy in Latin America. In the initial stages of Chagas disease, patients may experience abnormalities in the cardiac conduction system, which can either be asymptomatic or identified following reports of palpitations or syncopal episodes.

Symptoms of HF in these patients typically arise from biventricular dysfunction, with right-sided HF symptoms being more pronounced. Chagas cardiomyopathy is associated with a higher mortality rate compared to other non-ischemic cardiomyopathies, and patients face an increased risk of sudden cardiac death and severe arrhythmias compared to other individuals with HF. Cardiovascular causes account for nearly two-thirds of all deaths related to chagas disease [Ziaeian B, et al. 2016].

1.3 Epidemiology of Heart Failure

India's economic development, industrialization, and urbanization have led to transitions that heighten the overall risk of HF. One significant factor is the aging population; recent advancements in combating communicable diseases have resulted in a growing number of individuals over the age of 60. This demographic is expected to rise from 62 million in 1996 to 113 million by 2016. HF is primarily a condition affecting the elderly, with the lifetime risk of developing HF rising significantly as individuals age. As a result, the overall burden of HF is expected to escalate in tandem with the aging population. This trend is concerning because older adults are more susceptible to a variety of factors that contribute to HF, such as the accumulation of comorbidities, changes in cardiac structure and function, and lifestyle factors that may be prevalent in this demographic.

Secondly, the epidemiological transition signifies shifts in disease patterns that occur as societies undergo development, a concept initially articulated by Omran in 1971. This transition involves a move from communicable diseases being the primary health concerns to a predominance of non-communicable diseases, such as HF, as populations become more urbanized and experience changes in lifestyle, nutrition, and healthcare access [Huffman MD, et al. 2010].

Table 1: epidemiological transitions in various societies

Health transition: Cardiovascular disease example				
Stage	**I**	**II**	**III**	**IV**
Life expectancy (years)	35	50	60	>70
Dominant diseases	Infections, nutritional	Mixed (receding communicable and rising non-communicable)	Chronic (mid-life)	Chronic (elderly)
Contribution of cardiovascular disease to mortality (%)	5–10	15–35	>50	<50
Pattern of cardiovascular disease	Rheumatic, nutritional	Rheumatic, nutritional and stroke (ICH)	Coronary, stroke (both)	Coronary, stroke (THR)
Primary victims	Higher class	All classes	Lower classes	Lower classes

Table adapted from: Huffman MD, et al. 2008

2. Incidence and prevalence of heart failure

2.1 Incidence of heart failure

Variations in incidence can serve as indicators of the effectiveness of preventive measures. Mortality following the diagnosis of a disease can be assessed at various time intervals during follow-up and can provide insights into the impact of treatment. In the context of HF, tracking incidence is particularly useful for evaluating how the occurrence of HF has changed over time due to shifts in risk factors.

Overall, the global incidence of HF varies between 100 and 900 cases per 100,000 person-years, influenced by the specific diagnostic criteria employed and the characteristics of the population being studied [Roger VL, et al. 2013]. In Europe, the HFAATLAS project provided data on incidence rates across 12 member countries of the European Society of Cardiology (ESC). The median annual incidence of HF was found to be 3.2 cases per 1,000 person-years, with rates varying, reaching as high as 6 cases per 1,000 person-years in Estonia and Germany during the years 2018–2019. A comprehensive registry-based study conducted in Belgium, utilizing data from general practitioners, found a non-significant downward trend in the age-standardized incidence of more advanced HF stages C and D, with rates ranging from 2.6 to 2.7 cases per 1,000 person-years. In contrast, the incidence of earlier stages, A and B, exhibited a slight upward trend; specifically, the incidence of stage A increased from 34 cases per 1,000 person-years in 2000 to 38 cases per 1,000 person-years in 2015, while stage B rose from 10 to 13 cases per 1,000 person-years [Gianluigi Savarese, et al. 2022].

India encompasses multiple "ages" along the epidemiological transition spectrum due to its uneven development, yet it seems to be progressing toward the age of delayed degenerative diseases across much of the country. These shifts in population and epidemiological patterns are ultimately evident in the broader health transition, which is illustrated in (Table 1). This table monitors the changes in health status as populations evolve from high rates of infant mortality and fertility to lower rates of both.

Figure 2: Incidence in HF worldwide

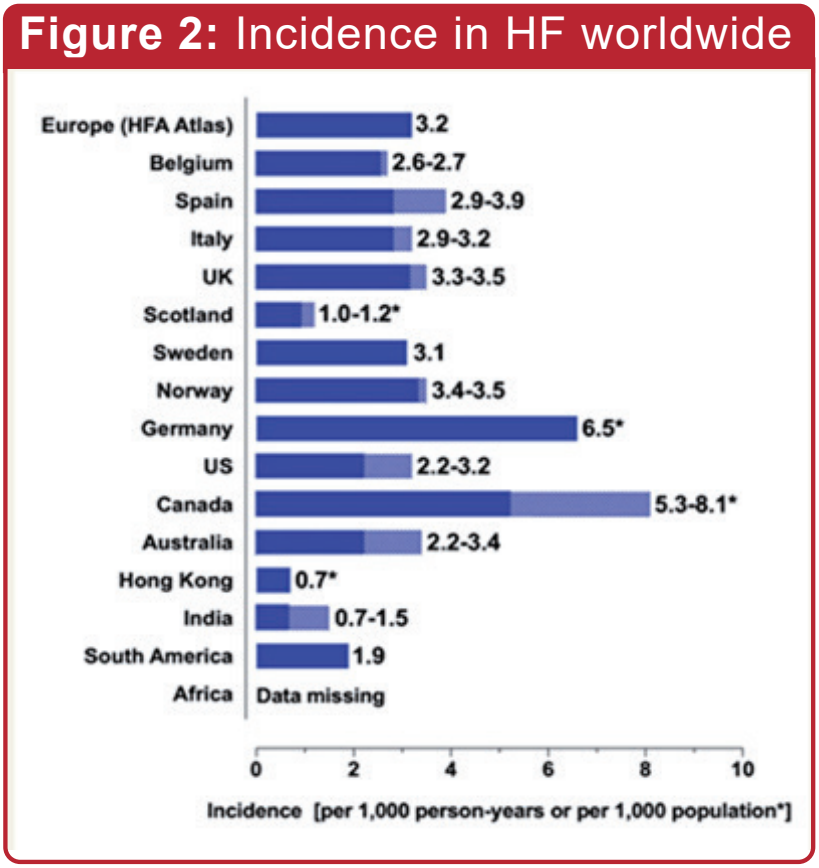

Figure adapted from: Gianluigi Savarese, et al. 2022

Over the past six decades, the incidence of HF in the United States has remained relatively stable, with standardized age-adjusted rates believed to be on the decline. Specifically, data from the Framingham cohort indicates that between 1950 and 1999, the incidence of HF among women decreased from 420 to 327 cases per 100,000 person-years. This decline suggests an improvement in risk factors or treatment strategies for women over this period. In contrast, men did not experience a similar reduction in HF incidence; their rates remained consistently high at approximately 564 cases per 100,000 person-years throughout the same timeframe. This discrepancy highlights potential differences in risk factors, health behaviors, and healthcare access between genders that may influence the development and management of HF

between genders that may influence the development and management of HF From 2000 to 2010, the age-adjusted and sex-adjusted incidence of HF in the Olmsted County cohort decreased from 315.8 to 219.3 cases per 100,000 residents, representing a significant decline of 37.5% over the decade (Figure. 2). Notably, this reduction in HF incidence was more pronounced in women, who experienced a decrease of 43%, compared to a 29% decline observed in men. This difference may reflect varying trends in risk factors, healthcare interventions, or lifestyle changes between genders during this period. The incidence of HF in the USA differs among various ethnic groups. The Multi-Ethnic Study of Atherosclerosis revealed that African American individuals have the highest rates of HF incidence, while white and Hispanic individuals exhibit intermediate rates. In contrast, Chinese American individuals have the lowest incidence rates of HF. These disparities can be attributed to a range of factors, including variations in risk factors such as hypertension and diabetes mellitus, as well as differences in socioeconomic status, all of which contribute to the observed ethnic disparities in HF incidence [Ziaeian B, et al 2016].

Figure 3. Incidence of HF in Olmsted County between 2000 and 2010

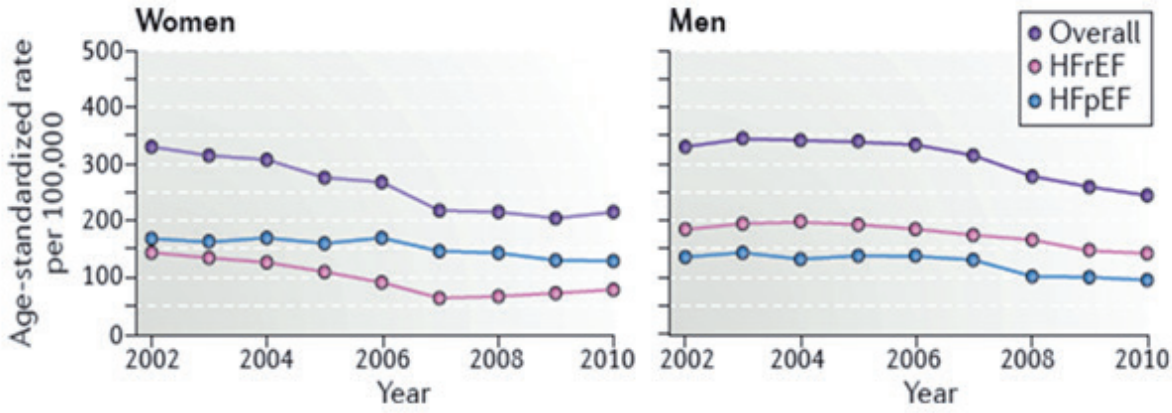

Figure adapted from: Boback Ziaeian, et al. 2016

The annual incidence of HF among patients with coronary heart disease (CHD) ranges from 0.4% to 2.3%. Based on these figures, it is estimated that between 120,000 and 690,000 individuals in India could develop symptomatic HF due to CHD each year, if none of these individuals have HF at baseline and that the population at risk remains constant [Lloyd-Jones D et al. 2010]. If the annual incidence of HF among patients with a systolic blood pressure (SBP) ranging from 144 to 154 mmHg is reported to be between 0.1% and 0.6%, as shown in the hypertension optimal treatment (HOT) and the United Kingdom

Prospective Diabetes Study (UKPDS) trials, this suggests that individuals within this blood pressure range are at a measurable risk of developing HF. These findings underscore the importance of monitoring and managing blood pressure to potentially reduce the incidence of heart failure in this population [Neal B, et al. 2010] respectively, Consequently, the number of new cases of HF attributable to hypertension is projected to rise significantly, from an estimated 118,000 to 708,000 cases per year in 2000, to between 214,000 and 1.3 million cases annually by 2025. This projection assumes conservatively that the majority of patients with hypertension in India have a systolic blood pressure (SBP) in the range of 144 to 154 mmHg. If we consider the incidence of HF based on the year 2000 estimates over a period of five years, the cumulative number of HF patients could range from approximately 590,000 to 3.5 million. Given an estimated mortality rate of 50% at five years, this highlights a substantial burden on healthcare resources.

In addition, the annual incidence of HF associated with obesity, defined as a body mass index (BMI) greater than 30 kg/m², has been estimated to increase by 0.3% in women and 0.5% in men, according to findings from the Framingham Heart Study. This increase is after adjusting for other risk factors such as age, hypertension, left ventricular hypertrophy, myocardial infarction, valvular disease, diabetes, and cholesterol levels. The incidence of HF in India remains largely uncharted, with reported rates ranging from 0.5 to 1.7 cases per 1,000 persons per year. However, there is a notable absence of age-standardized estimates, which would be particularly valuable given that the average age of the Indian population is younger than that of populations in North America and Europe. Such age-standardized data could provide deeper insights into the burden of HF in India and aid in the formulation of targeted healthcare strategies. In India, the annual incidence of HF attributed to various conditions, including coronary heart disease, hypertension, obesity, diabetes, and rheumatic heart disease, has been conservatively estimated to range from approximately 491,600 to 1.8 million cases. This significant figure underscores the substantial health burden posed by these conditions and highlights the urgent need for effective prevention and management strategies to address HF in the country [Huffman MD, et al. 2010].

2.2 prevalence of heart failure

The age-standardized prevalence of HF shows significant variation across different countries and regions. In 2017, the highest prevalence rates were found in Central Europe, North Africa, and the Middle East, ranging from 1,133 to 1,196 cases per 100,000 people. In contrast, lower prevalence rates were reported in Eastern Europe and Southeast Asia, with figures ranging from 498 to 595 cases per 100,000 people.

According to the 2019 Heart Failure Association (HFA) ATLAS project, the median prevalence of HF across 13 European countries that provided data was estimated at 17 cases per 1,000 persons. Within this context, Lithuania and Germany reported the highest rates, with prevalence reaching 30 cases per 1,000 persons [Savarese, et al. 2022].

Figure 4. Prevalence of HF in worldwide

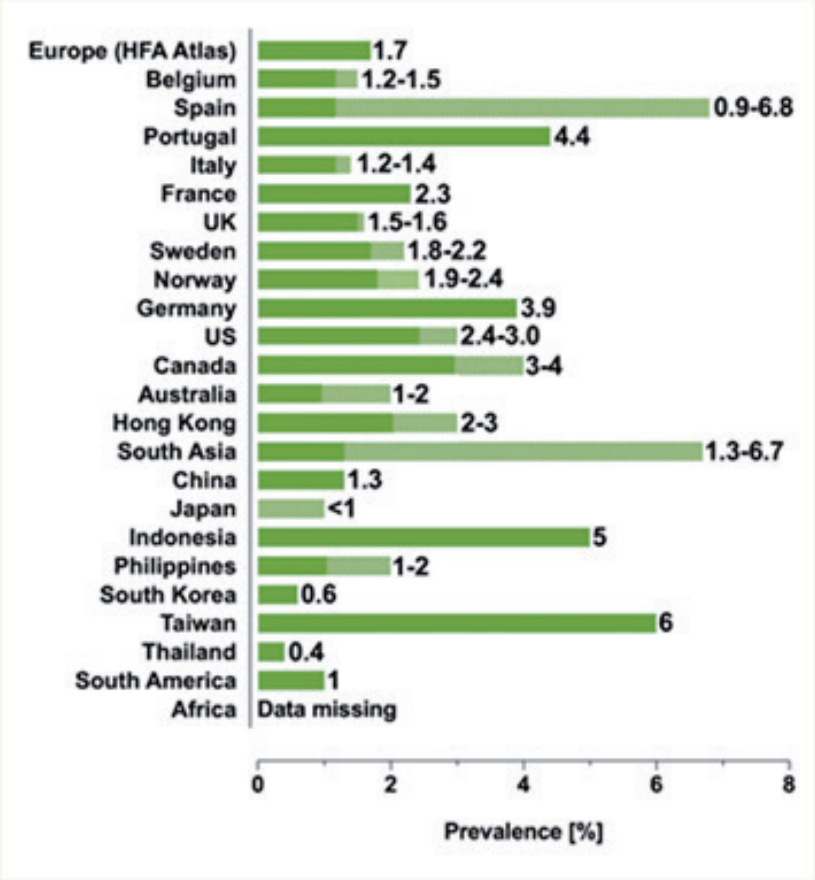

Figure adapted from: Savarese, et al. 2022

It is estimated that approximately 37.7 million individuals worldwide are currently living with HF. This figure highlights the significant global health challenge posed by this condition, underscoring the need for effective management and treatment strategies to improve the quality of life for those affected. In developed countries, the prevalence of HF is typically estimated to range from 1% to 2% of the adult population. This relatively consistent figure underscores the importance of addressing heart failure as a major public health concern within these regions, as it can significantly impact healthcare systems and the quality of life for individuals affected by the condition [Gianluigi Savarese, et al. 2022]. Despite a decrease in the age-adjusted incidence and prevalence of HF, the total number of individuals living with the condition has significantly risen. This increase is largely attributed to changes in the global age distribution and overall population growth. Prior to the 1970s, estimates of HF prevalence in the USA relied on hospital records or death certificates, which lacked reliability due to a considerable amount of care being delivered in outpatient settings. The introduction of the first National Health and Nutritional Examination Survey (NHANES) marked a turning point, allowing for a more accurate national estimation of HF prevalence. During the period from 1971 to 1975, the prevalence of self-reported HF was estimated at 1.1%, while clinically defined HF was reported at 2.0%. [Schocken DD, et al. 1992] In the NHANES study, researchers gathered self-reported data on HF between 2009 and 2012, estimating that around 5.7 million adults, which accounts for approximately 2.2% of the adult population in the USA, are living with this chronic condition. This statistic underscores the significant prevalence of heart failure in the country and highlights the importance of ongoing efforts to manage and treat this health issue effectively.

In Sweden, the prevalence of HF is estimated to be 2.2% for both men and women. Looking ahead, it is projected that by 2030, the prevalence of HF in the USA—without age adjustment—will increase by 46%, surpassing 8 million individuals, which would represent about 2.97% of the population. This anticipated rise emphasizes the growing burden of heart failure and the need for effective healthcare strategies to address this condition in the coming years. [Ziaeian B, et al. 2016]. According to the Global Burden of Disease (GBD) 2019 study, there were approximately 31.89 million prevalent cases of HF in Asia (including Asia and Oceania), with an age-standardized rate (ASR) of 722.45 cases per 100,000 population (with a 95% uncertainty interval [UI] of 591.97 to 891.64 per 100,000).

This ASR for HF in Asia and Oceania is lower than that in America, which stands at 810.42 per 100,000, and Africa at 709.89 per 100,000, but higher than Europe's rate of 606.61 per 100,000. When examining HF prevalence across five distinct Asian regions—East Asia, South Asia, Southeast Asia, Central Asia, and high-income regions of Asia-Pacific—our analysis for 2019 found that East Asia had the highest ASR at 1,014.06 per 100,000 population, while South Asia had the lowest at 389.97 per 100,000. The other regions presented intermediate ASR values, with 455.28 per 100,000 in high-income Asia-Pacific, 544.18 per 100,000 in Central Asia, and 755.95 per 100,000 in Southeast Asia. To quantify the burden of HF in terms of disability, years lived with disability (YLDs) were calculated by multiplying the estimated prevalence of HF by the associated disability weight. YLDs were standardized based on age and gender using the GBD reference population. For comprehensive methodological details, refer to earlier publications [Feng J, et al. 2024]. According to the GBD data, the age-standardized rate (ASR) of HF prevalence varies significantly among countries and territories, ranging from 211.86 to 1,032.84 cases per 100,000 population. In 2019, the nations with the highest prevalence rates of HF were China (1,032.84 cases per 100,000), Indonesia (900.90 cases per 100,000), and Malaysia (809.47 cases per 100,000). In contrast, the lowest prevalence rates were reported in Nepal (211.86 cases per 100,000), Bhutan (255.54 cases per 100,000), and Bangladesh (275.00 cases per 100,000), as illustrated in Figure 5.

Figure 5. Heart Failure Prevalence in Asia: GBD 2019

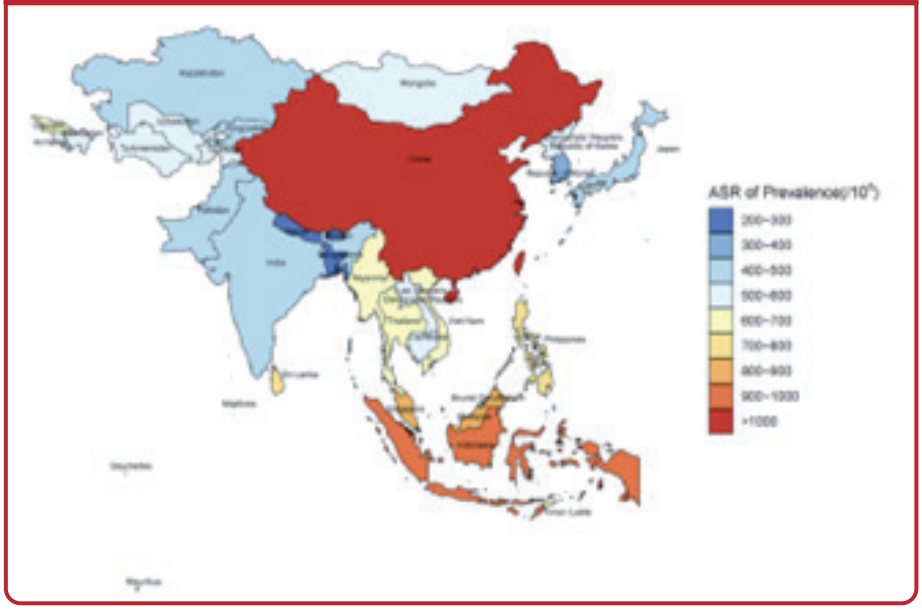

Figure adapted from: Feng J, et al. 2024

Mortality: Determining the number of deaths directly attributable to HF is complex, primarily because HF is often classified as an intermediate stage of underlying conditions, like coronary artery disease, rather than as a primary cause of death. The GBD study utilizes ICD-9 and ICD-10 codes to identify causes of death, but the coding for HF is frequently regarded as a "garbage code." This means it is ambiguous or nonspecific, leading to difficulties in accurately attributing death solely to HF. Consequently, fatalities attributed to HF are commonly reassigned to more definitive underlying causes, such as ischemic heart disease. Additionally, death certificate documentation is similarly constrained by these limitations and may contain inaccuracies. In cases where the etiology of HF is unknown, the recorded cause of death is often categorized under coronary artery disease. [Snyder ML, et al. 2014]. By employing all-cause cardiovascular mortality as a proxy for trends in HF mortality, the GBD Study indicates a significant decline in the age-standardized cardiovascular death rate. Specifically, there was a reduction of 22% from 1990, when the rate was 375.5 deaths per 100,000 person-years, to 2013, when it decreased to 293.2 deaths per 100,000 person-years. This trend suggests improvements in cardiovascular health outcomes over that period [Ziaeian B, et al. 2016]. This reduction in overall cardiovascular mortality might also indicate a decrease in global age-adjusted mortality for HF.

In the USA, during the year 2011, HF was recorded as a contributing factor in one out of every nine death certificates, totaling 300,122 cases [Ziaeian B, et al. 2016]. HF has often been characterized as more "malignant" than cancer due to its significantly lower five-year survival rates. In 1991, the mortality rate associated with HF was found to be 11% higher than that of gastrointestinal cancers during the same time period [Stewart S, et al. 2001]. A systematic review indicated that the comparative five-year age-adjusted and sex-adjusted survival rates for cancer, stroke, and HF are generally similar. Furthermore, it was observed that there have been improvements in survival rates for all three conditions over the past decade [Ziaeian B, et al. 2016]. Despite the high mortality rates associated with HF, there have been significant improvements in survival rates due to advancements in treatment in developed countries. The Framingham Heart Study revealed a decrease in five-year mortality rates for men, dropping from 70% between 1950 and 1969 to 59% from 1990 to 1999. For women, the rates also improved, with a reduction from 57% to 45% during the same periods. Additionally, a community-based cohort study in Olmsted

County found an age-adjusted mortality rate of 20.2% at one year and 56.2% at five years for those newly diagnosed with HF; these rates remained relatively stable between 2000 and 2010. Notably, more than half of the deaths in the HF cohort were due to non-cardiovascular causes, with 14.2% attributed to respiratory diseases, 12.6% to cancers, and 7.1% related to mental health conditions. Similarly, in England, the age-standardized death rates for HF saw a significant decline from 130.6 to 51.8 per 100,000 people between 1981 and 2010. The most pronounced reductions in mortality rates were observed among middle-aged individuals, particularly those aged 55 to 64 years. This trend underscores the impact of medical advancements and public health initiatives aimed at improving heart health within this demographic. In Sweden, national estimates from 2010 indicated that the 5-year survival rate for HF was 48%. Additionally, the mortality rates for HF were reported as 320 deaths per 100,000 person-years for women and 300 deaths per 100,000 person-years for men [Zarrinkoub R, et al. 2013].

Over the past decade, there have been notable improvements in mortality rates for patients hospitalized with HF. In the United States, data spanning from 1999 to 2011 revealed a significant decline in various mortality metrics among Medicare patients with HF: in-hospital mortality rates decreased by 38%, while 30-day mortality saw a reduction of 16.4%, and 1-year mortality rates fell by 13.0%. This trend indicates that advancements in medical care and treatment protocols may be contributing to better outcomes for these patients. In Canada, specifically in Ontario, similar positive trends have been observed for outpatients. Between 1997 and 2007, the 1-year risk-adjusted mortality rate for outpatients with HF decreased from 17.7% to 16.2%. Although there was a nonsignificant decline in mortality for hospitalized patients during the same timeframe, the overall trend suggests improvements in patient care and management strategies for HF across both settings. These statistics highlight the ongoing efforts to enhance HF treatment and management, resulting in better survival rates for affected individuals This rise in mortality rates can be linked to multiple factors. Firstly, the quality of care for HF patients has significantly improved, with a greater emphasis on the implementation of evidence-based medical therapies, which have led to enhanced survival rates among high-risk hospitalized patients. Additionally, hospital systems are now more diligent in reporting HF outcomes and have optimized care processes to better manage these patients.

Moreover, public health initiatives have contributed to a decline in smoking rates, while control over hypertension has seen modest improvements. It is also essential to consider that the observed enhancements in patient outcomes may stem from increased diagnostic sensitivity. Clinicians are now more adept at identifying HFpEF, and changes in coding practices may result in a healthier demographic of HF patients being recorded in contemporary datasets compared to those from earlier decades. These factors collectively paint a more complex picture of HF management and its evolving landscape in recent years [Ziaeian B, et al. 2016].

3. Burdan of HF in India

3.1 Health care costs for HF

The economic impact of HF on global healthcare systems and economies is significant and is projected to grow due to the increasing prevalence of the condition. A comprehensive analysis that examined both direct and indirect costs associated with HF across 197 countries estimated the total economic burden of HF in 2012 to be around $108 billion. In this assessment, direct costs comprised approximately 60% of the total, amounting to $65 billion, while indirect costs represented about 40%, equating to $43 billion.

Focusing on specific regions, healthcare costs related to HF in Germany were reported to be €3,150 per patient annually in 2011. A substantial portion of these expenses was attributed to hospitalizations, which accounted for €2,128 (or 74% of total costs) (figure 5). In contrast, expenditures for rehabilitation, medication, and outpatient visits were significantly lower, with rehabili tation costing €294 (9%), medication €290 (9%), and outpatient visits €238 (8%). This data underscores the considerable financial strain that HF imposes on healthcare systems, emphasizing the need for effective management strategies to mitigate these costs.

In a comparison of healthcare expenditures based on the New York Heart Association (NYHA) functional classification, it was found that the average cost per patient rose significantly with advancing stages of HF. For instance, patients classified as NYHA class I incurred expenses of €2,474. As patients progressed to NYHA class II, costs increased by 14%, to 48% for those in class III, and reached a staggering 71% for patients in class IV.

Figure 5: Healthcare costs of HF worldwide

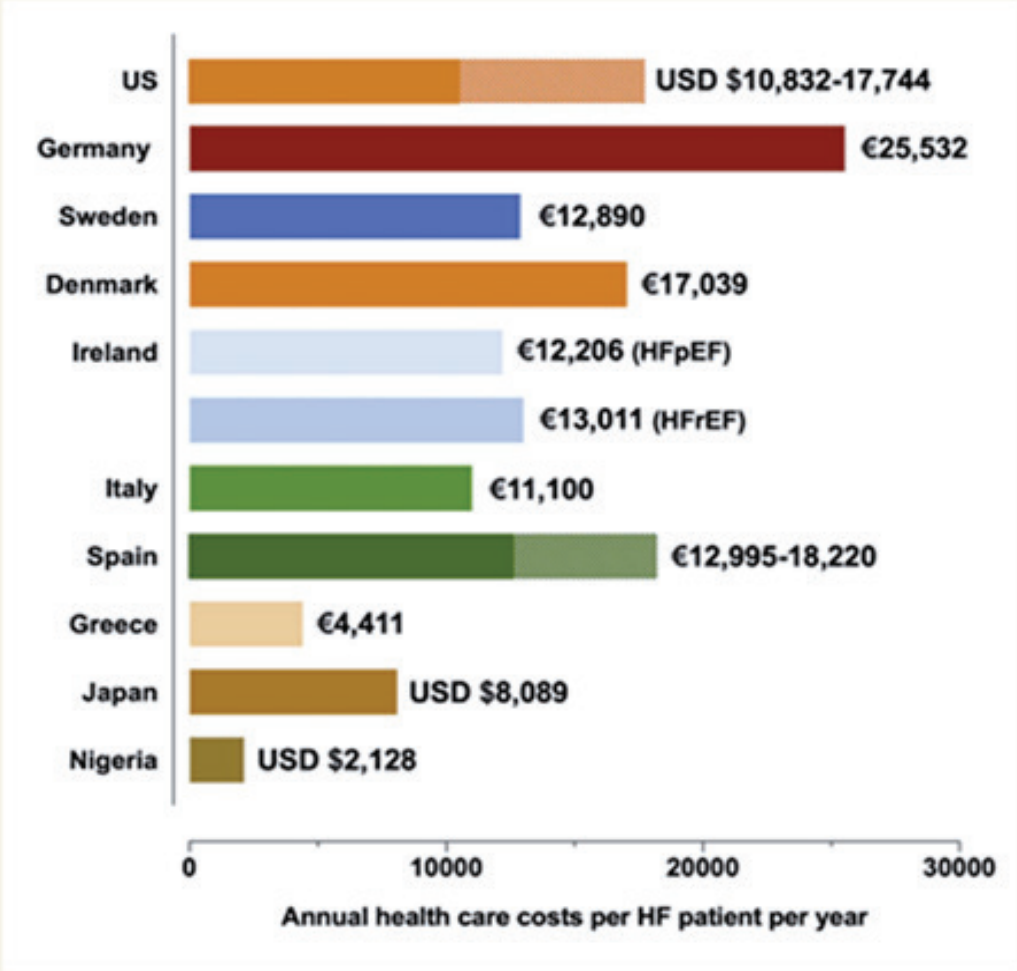

Figure adapted from: Savarese, et al. 2022

This trend of rising costs is further exacerbated by demographic shifts and the overall increase in the prevalence of HF in the United States. According to a nationwide survey conducted by the American Heart Association in 2013, it is projected that the direct and indirect costs associated with HF will rise dramatically from $20.9 billion in 2012 to $53.1 billion by 2030, marking a 2.5-fold increase. This significant financial burden highlights the urgent need for effective prevention and management strategies to address the growing impact of HF on healthcare resources.

Figure 7: Global cost of HF per capita in 2012

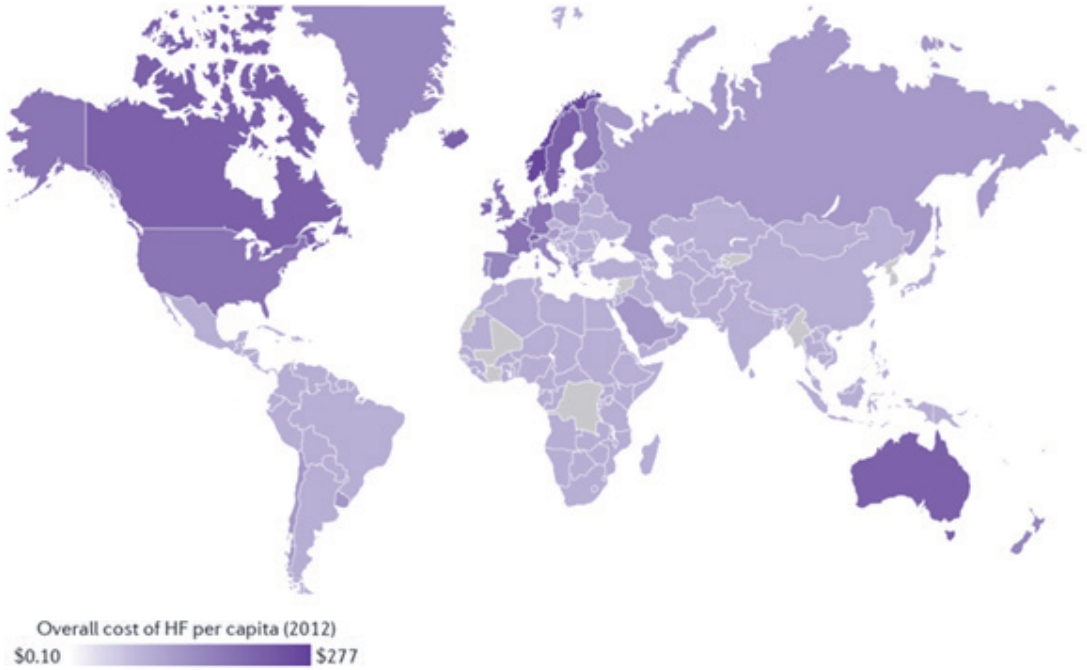

Figure adapted from: Boback Ziaeian, et al. 2016

3.2 Impact of comorbidities on costs for HF patients

The presence of comorbidities significantly influences annual healthcare costs for patients with HF. For instance, the estimated annual cost for patients with HF and hypertension is approximately $19,537, while those with HF, hyperkalemia, and on dialysis face much higher expenses, averaging around $77,214. Dialysis, although required by only a minority of HF patients, contributes substantially to the overall costs associated with HF management. A retrospective case-control study conducted in the United States in 2010 revealed that annual healthcare expenditures for HF patients without type 2 diabetes mellitus (T2DM) averaged $22,230. However, this figure rose considerably for patients with comorbid T2DM, reaching $32,676. Between 2010 and 2013, the mean costs associated with HF-related hospitalizations were reported as $12,915 for patients with T2DM, compared to $10,103 for those without. This trend held true regardless of the type of HF, whether HFpEF or HFrEF.

Additionally, an analysis of a nationwide readmission database that included 2,645,336 patients hospitalized for HF between 2010 and 2014 identified coronary artery disease and valvular disease as the strongest predictors of healthcare costs among cardiac comorbidities. This underscores the significant financial burden that accompanies HF, particularly when compounded by other health conditions [Gianluigi Savarese, et al. 2022].

Figure: 6 Epidemiological factor

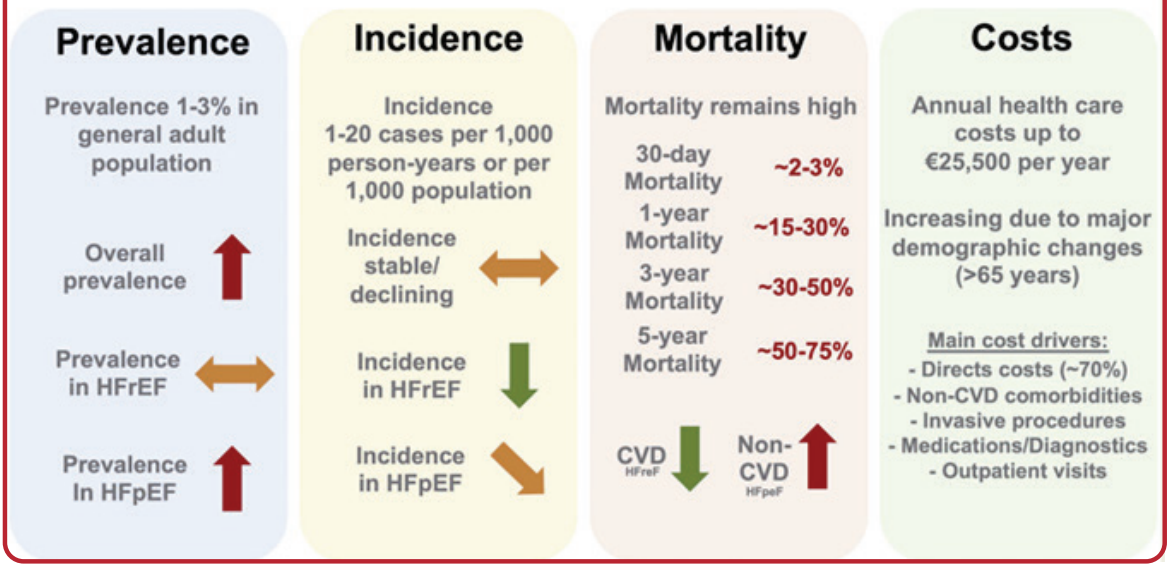

Figure adopted from: Ziaeian, et al. 2016

Hospitalizations: In high-income countries, HF is the most common diagnosis among elderly patients aged over 65 years. HF accounts for 1–2% of all hospital admissions. In the United States, HF stands as the leading primary cause for hospitalization, with around 1 million discharges annually between 2000 and 2010. The number of hospital admissions where HF was a contributing factor tripled from 1979 to 2004. During this period, age-adjusted hospitalization rates for HF as the primary diagnosis rose from 219 to 390 per 100,000 person-years. In the Olmsted County cohort, patients with HF experienced an average of 1.34 hospitalizations per person per year, with 63% of these hospitalizations related to non-cardiovascular conditions.For Medicare patients in the U.S., the hospitalization rate for HF declined from 1,390 to 925 per 100,000 person-years between 1999 and 2011, and the average length of hospital stay dropped from 3.1 days to 1.9 days during this time [Ziaeian B, et al. 2016].

Ambulatory care: n 2011, there were 553,000 emergency department visits for HF recorded in the USA, and in 2012, HF was the primary diagnosis for 1,774,000 outpatient visits. In the UK, a typical general practitioner manages approximately 30 HF patients and diagnoses an additional 10 cases each year. The quality of outpatient care for HF patients has been evaluated by examining the use of guideline-recommended treatments in eligible patients. These guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin-receptor blockers (ARBs), beta-blockers, mineralocorticoid-receptor antagonists, anticoagulant therapy for atrial

fibrillation or flutter, cardiac resynchronization therapy, implantable cardioverter-defibrillators, and education on HF self-management. Adherence to these seven recommended measures has been shown to lower 2-year mortality rates [Ziaeian B, et al. 2016].

If we assume that the causes of HF, such as age, coronary heart disease (CHD), hypertension, and diabetes, are similar globally, insights from the U.S. population can be applied to the Indian context. However, given the different age structures between the two countries, projections need to be stratified by age groups. In the U.S., the overall prevalence of HF is approximately 1.76% (around 4.8 million people), increasing from 2% in those aged 40–59 years to 5% in the 60–69 age group, and 10% for those aged 70 and older. Using these figures for India, the estimated HF prevalence would be around 10 million people, or roughly 0.9% of the total population.

Additionally, the prevalence of self-reported myocardial infarction (MI) in the U.S. is about 4%, ranging from 0.8% in individuals aged 18–44, to 4.8% in those aged 45–64, and 12.9% in individuals aged 65 and above. Applying these numbers to the Indian population suggests that approximately 21 million Indians over the age of 19 may have a history of MI. Since 10–40% of those with MI develop HF, this translates to an estimated HF burden in India of between 2.1 million and 8.4 million individuals, with a reasonable estimate of around 4–5 million [Chaturvedi V, et al. 2016].

4. Future directions

Shifting demographics and epidemiological changes predict a significant increase in the number of HF patients. The most effective way to improve quality of life and reduce healthcare costs is through primary prevention of HF. For both developed and developing countries, better hypertension control, reducing tobacco use, and addressing lifestyle factors are key strategies to lower HF incidence and prevalence [Yusuf S, et al. 2014]. Enhancing adherence to evidence-based outpatient practices is expected to be the most effective approach to improving HF management, potentially offering greater benefits than novel treatments. Tailoring prevention and treatment strategies to local populations is crucial for maximizing benefits, and additional research and resources should be allocated to low-income countries, where preventable HF presents the greatest burden [Cohn JN, et al. 2014].

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