

## Review Article

# Heart failure: Epidemiology and prevention in India

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### ABSTRACT

Reliable estimates of heart failure are lacking in India because of the absence of a surveillance programme to track incidence, prevalence, outcomes and key causes of heart failure. Nevertheless, we propose that the incidence and prevalence rates of heart failure are rising due to population, epidemiological and health transitions. Based on disease-specific estimates of prevalence and incidence rates of heart failure, we conservatively estimate the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease to range from 1.3 to 4.6 million, with an annual incidence of 491 600–1.8 million. The double burden of rising cardiovascular risk factors and persistent 'pre-transition' diseases such as rheumatic heart disease, limited healthcare infrastructure and social disparities contribute to these estimates. Staging of heart failure, introduced in 2005, provides a framework to target preventive strategies in patients at risk for heart failure (stage A), with structural disease alone (B), with heart failure symptoms (C) and with end-stage disease (D). Policy-level interventions, such as regulations to limit salt and tobacco consumption, are effective for primordial prevention and would have a wider impact on prevention of heart failure. Clinical preventive interventions and clinical quality improvement interventions, such as treatment of hypertension, atherosclerotic disease, diabetes and acute decompensated heart failure are effective for primary, secondary and even tertiary prevention.

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### BACKGROUND

The incidence and prevalence estimates of heart failure (HF) are unreliable in India because of the lack of surveillance systems to adequately capture these data. This lack of HF surveillance is not unique to India. In 2001, Mendez and Cowie found no population-based HF studies in all developing countries,<sup>1</sup> making global prevalence estimates difficult. Estimating the burden of HF is further hampered by the lack of a standard definition. In fact, the WHO Global Burden of Disease study places HF in several

categories within cardiovascular disease, including ischaemic, hypertensive, inflammatory and rheumatic heart disease (RHD).<sup>2</sup>

The epidemiology of HF in India has likely changed from that reported in 1949 by Vakil, describing hypertension-coronary (31%), RHD (29%), syphilis (12%), and pulmonary (9%) as the primary causes in 1281 patients hospitalized due to HF.<sup>3</sup> More recent evaluations have provided limited insight into the broader HF landscape in India, since these have focused on specific aetiologies of HF (such as HF caused by endomyocardial fibrosis<sup>4</sup> and ST-segment elevation myocardial infarction),<sup>5,6</sup> and HF outcomes in select patients with systolic dysfunction in tertiary care centres,<sup>7</sup> rather than community-based surveillance.

The prevalence of HF in India is possibly on the rise as India remains doubly burdened by the rise in the risk factors of traditional cardiovascular disease (CVD) and by the persistence of pre-transitional diseases such as RHD, endomyocardial fibrosis, tuberculous pericardial disease and anaemia. Prevention of HF—a target that can be overlooked in clinical practice—offers several effective opportunities for clinicians and for patients. In this review, we discuss the (i) epidemiology of HF in India today and the potential reasons for this burden, (ii) staging of HF as a paradigm for prevention of HF, as recommended by the American Heart Association/American College of Cardiology heart failure guidelines, and (iii) interventions for prevention of HF in India.

### EPIDEMIOLOGY

#### Transitions

India's economic development, industrialization and urbanization have been accompanied by transitions that contribute to the increase in the overall risk of HF.

First, the population of India is ageing due to recent successes against communicable diseases such that the number of people >60 years old will increase from 62 million in 1996 to 113 million in 2016.<sup>8</sup> HF is predominantly a disease of the elderly, as the lifetime risk for HF increases with age, so the burden of HF is likely to increase with the ageing population.<sup>9</sup> Second, the epidemiological transition reflects changes in disease patterns as societies develop, as first described by Omran in 1971,<sup>10</sup> and amended by Olshansky and Ault in 1986<sup>11</sup> and Yusuf and colleagues in 2005.<sup>12</sup> The 5 ages include: pestilence and famine, receding pandemics, degenerative and man-made diseases, delayed degenerative diseases, and health regression and social upheaval (the age of inactivity and obesity has recently been proposed as an alternate fifth age).<sup>13</sup> India straddles several 'ages' along this spectrum given its uneven development, but appears to be moving towards the age of delayed degenerative diseases in most of the

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country. These population and epidemiological transitions are finally reflected in the subsequent health transition (Table I), which tracks changes in the health status as populations move from high infant mortality and fertility rates to low infant mortality and fertility rates.

#### Burden of CVD and risk factors

CVD is currently the leading cause of death in India and its prevalence is projected to rise. In 2000, there were an estimated 30 million people with coronary heart disease (CHD) alone in India, or a nearly 3% prevalence.<sup>8,14</sup> The annual incidence of HF for patients with CHD ranges from 0.4% to 2.3% per year,<sup>15,16</sup> suggesting that 120 000–690 000 Indians could develop symptomatic HF due to CHD every year, assuming none has HF at baseline and the at-risk population does not diminish. After 5 years, the total number of HF patients accrued could range from 600 000 to 3.5 million; with an estimated 50% mortality at 5 years,<sup>17</sup> the prevalence of HF due to CHD alone could be estimated to range from 300 000 to 1.75 million. Nevertheless, as the prevalence of patients with CHD rises, so too will the prevalence of patients with HF.

The prevalence of other risk factors of HF is also rising in India. In addition to the ageing population described above, the prevalence of hypertension is projected to increase from 118 million (2000) to 214 million (2025).<sup>18</sup> If the annual incidence of HF in patients with a systolic blood pressure (SBP) of 144–154 mmHg is 0.1% to 0.6%, as demonstrated in the Hypertension Optimal Treatment (HOT)<sup>19</sup> and United Kingdom Prospective Diabetes Study (UKPDS) trials,<sup>20</sup> respectively, then the number of new HF cases due to hypertension may increase from 118 000–708 000 per year in 2000 to 214 000–1.3 million per year in 2025, conservatively assuming that the bulk of patients with hypertension in India have a SBP in the 144–154 mmHg range. After 5 years of HF incidence based upon year 2000 estimates for hypertension, the total number of HF patients accrued could range from 590 000 to 3.5 million; with an estimated 50% mortality at 5 years, the prevalence of HF due to hypertension alone could be estimated to range from 295 000 to 1.8 million. However, this possibly represents an underestimate, due to conservative estimates of the prevalence of hypertension, as well as the linear relationship between risk of HF and blood pressure that occurs for values even <140 mmHg.

The annual incidence of HF due to obesity (body mass index [BMI] >30 kg/m<sup>2</sup>) has been estimated to increase by 0.3% in women and 0.5% in men, in the Framingham Heart Study, after adjustment for age, hypertension, left ventricular hypertrophy, myocardial infarction, valve disease, diabetes and cholesterol.<sup>21</sup> Few studies in India have used a BMI threshold of 30 kg/m<sup>2</sup>, which

makes it difficult to accurately estimate the prevalence of obesity. Reddy *et al.* estimated the prevalence of obesity (BMI >30 kg/m<sup>2</sup>) in 10 970 participants from urban Delhi and rural Haryana in 2002 to be 6.8%.<sup>22</sup> Using these estimates as a benchmark, a 5% prevalence of obesity (BMI >30 kg/m<sup>2</sup>) in India would lead to an estimated 180 000–300 000 cases of HF annually. After 5 years of the incidence of HF based upon 5% obesity prevalence estimates, the total number of HF patients accrued could range from 900 000–1.5 million; with an estimated 50% mortality at 5 years, the prevalence of HF due to obesity alone could be estimated to range from 450 000 to 750 000.

Similarly, the prevalence of diabetes in India is projected to increase from 32 million (2000) to 70 million (2025).<sup>23</sup> The incidence of HF has been demonstrated to increase from 2.3 per 1000 person-years for a HbA1c <6% to 11.9 per 1000 person-years for a HbA1c >11.9%. Taking the estimate of HF incidence based upon optimal glucose control, the annual incidence of HF due to diabetes may increase from 73 600 (2000) to 161 000 (2025). After 5 years of HF incidence based upon the diabetes estimates for the year 2000, the total number of HF patients accrued could be 368 000; with an estimated 50% mortality at 5 years, the prevalence of HF due to diabetes alone could be estimated at 184 000. However, this is likely to be an underestimate, due to conservative estimates of HbA1c.

#### Unfinished, pre-transition agenda

The unfinished, pre-transition agenda that bookends India's double burden of disease includes a relatively high prevalence of pre-transition diseases, limited healthcare infrastructure, and health disparities, which disproportionately affect people from lower socioeconomic classes and potentially exacerbate disparities further. Prevalence rates for RHD remain high in India, reaching 1.0–5.4 cases per 1000 schoolchildren in one study.<sup>24</sup> Approximately 98 000 people died from RHD in India in 2004,<sup>2</sup> which would add to the total estimated HF prevalence given above. As there is insufficient evidence on the role of secondary prevention of rheumatic fever in preventing the progression of valvular disease in RHD, the risk of HF remains unclear in patients with RHD.<sup>25</sup> Other diseases that can manifest as HF such as endomyocardial fibrosis, tuberculous constrictive pericarditis and infectious endocarditis, appear to be present in greater proportions in India compared with its high-income country counterparts, but data are sparse regarding the prevalence of these diseases in India.

Since patients have uneven and limited access to healthcare in India, the healthcare infrastructure itself may play a role in the rising burden of HF.<sup>26</sup> The public healthcare system is often

TABLE I. The cardiovascular disease health transition that results from population and epidemiological transitions in many societies

Stage	Health transition: Cardiovascular disease example			
	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

Model developed by Omran; modified by Olshansky and Ault ICH intracranial haemorrhage THR thrombotic

overloaded, which makes access to basic services difficult. India has <2% penetration of health insurance (government employees are an exception),<sup>27</sup> making the out-of-pocket costs for prevention of HF relatively expensive. Emergency services are not widely available in India, such that patients who experience acute cardiac events, such as acute coronary syndrome (ACS), typically have longer symptom-to-door and door-to-needle times than in other countries.<sup>28</sup> This combination of inaccessibility, unaffordable treatment and treatment delay possibly increases the incidence of HF in India.

Xavier and colleagues evaluated the association between ACS care and socioeconomic status (SES) in the India-based CREATE ACS registry.<sup>29</sup> Patients with a lower SES were less likely to undergo coronary angiography, percutaneous coronary intervention, and coronary artery bypass graft surgery and were less likely to receive medications for secondary prevention of CHD. These disparities contributed significantly to the 2.7% absolute increase in 30-day mortality seen in the poorest stratum compared with that in the richest stratum. However, these differences in mortality were abolished after adjusting for risk factors of CHD, location of infarct, and treatments, suggesting that uniform distribution of CHD and treatment of risk factors of CHD offers an opportunity to improve care. Important social determinants of health such as poverty, lack of empowerment, and healthcare inequalities<sup>30</sup> impede these efforts and are likely to exacerbate the burden of HF in India.

Taken together, the estimated prevalence of HF due to CHD, hypertension, obesity, diabetes and RHD alone in 2000 ranges from 1.3 million to 4.6 million, with an annual incidence ranging from 491 600 to 1.8 million. Both estimates are projected to rise and do not account for other important causes of HF such as alcoholic, familial, hypertrophic and idiopathic dilated cardiomyopathies, pericardial disease and endomyocardial fibrosis. The estimated prevalence of HF in India remains lower than that in the USA (5.8 million),<sup>17</sup> but the rate for potential increase and subsequent morbidity and mortality strengthens the case for prevention of HF in India.

### STAGES OF HEART FAILURE: GOALS

In 2005, the American Heart Association (AHA) and American College of Cardiology (ACC) introduced updated HF clinical practice guidelines that moved beyond the New York Heart Association (NYHA) classification system to include four new stages of HF—A through D.<sup>31</sup>

*Stage A* represents patients who do not have structural heart disease nor do they have symptoms of HF but are at high risk for developing HF. These patients include those with hypertension, diabetes, atherosclerotic disease, obesity, metabolic syndrome, family history of cardiomyopathy, or exposure to cardiotoxic drugs (e.g. anthracyclines). The primary goals of treating stage A patients include treatment of hypertension and dyslipidaemia, cessation of tobacco, alcohol and illicit drug use, encouragement of exercise and management of metabolic syndrome. Anticholinesterase inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) are recommended for patients with concomitant diabetes and/or vascular disease.

*Stage B* represents patients with evidence of structural heart disease in the absence of symptoms of HF (such as left ventricular hypertrophy, left ventricular dysfunction or valvular heart disease). The primary goals of treating stage B patients are similar to those for stage A patients. ACE-I or ARBs and beta-blockers are recommended for appropriate patients with left ventricular

dysfunction and/or vascular disease, as well as implantable cardioverter defibrillators (ICDs), in selected patients.

*Stage C* represents patients with a history, symptoms and clinical signs consistent with HF and fall into the NYHA classification system (I–IV). The primary goals of treating stage C patients include all the goals of stages A and B, as well as dietary salt restriction. Aldosterone antagonists, digoxin, hydralazine/nitrate combination therapy, and biventricular pacemaker/ICDs are recommended for selected patients.

*Stage D* represents patients with advanced HF who have marked symptoms at rest despite maximal medical therapy. These patients are often hospitalized repeatedly and cannot be discharged without specialized therapies. The primary goals of treating stage D patients include all the goals of stages A, B and C, as well as decisions regarding the appropriate level of care. Clinicians and patients in India can use this paradigm to help guide their goals and strategies, particularly in stages A and B patients where prevention of HF is achievable.

### INTERVENTIONS FOR PREVENTION IN INDIA

#### *Primordial prevention of HF*

Policy-level interventions targeting HF and risk factors for HF could have a major impact on the burden of disease in India through primordial prevention. First, regulations to limit the salt content of foods have a great potential to reduce the burden of hypertension, CHD and subsequent incidence of HF across a wide spectrum of the population. A 2010 study modelling a 3 g reduction in salt intake across the population of USA estimated an annual reduction in myocardial infarction by 54 000–99 000, stroke by 32 000–66 000, and overall mortality by 44 000–92 000.<sup>32</sup> Subsequently the incidence of HF should also decrease, though this was not specifically modelled. Whether reduction of salt intake in India would be safe and effective needs further study.

Second, tobacco taxation that includes *bidis* and smokeless tobacco provides the most powerful tool to immediately reduce consumption of tobacco and helps decrease the overall CVD burden, including HF.<sup>33</sup> *Bidis* and smokeless tobacco account for over 80% of tobacco consumption in India but only 12% of the excise tax.<sup>34</sup> *Bidis* attract little excise tax because they are usually produced by small manufacturers who are dispersed throughout the country; excise duties effectively cover only branded *bidis*.<sup>34</sup> Tobacco taxation has been shown to reduce consumption in high-income countries,<sup>35</sup> but the reductions may be higher in India due to higher price sensitivity of tobacco consumers in India.

Both salt reduction and tobacco control are the two cost-effective strategies for reduction of CVD that are ready for scale-up in countries such as India and should be adopted as quickly as possible.<sup>36</sup> However, to monitor and evaluate any interventions, community-based surveillance of HF and risk factors of HF is required to help clinicians, researchers and policy-makers understand the burden of HF in India more clearly rather than through crude estimates such as those detailed above. Ongoing data collection and monitoring would provide policy-makers with the framework to evaluate the impact of HF- and HF risk factor-associated policy decisions<sup>37</sup> and to appropriately allocate patient care and research funding in a timely, responsive fashion.

#### *Primary prevention*

Effective clinical interventions for prevention of HF in asymptomatic patients target the three major, modifiable HF risk factors for stage A patients, namely hypertension, atherosclerotic disease and diabetes. Stage B patients, particularly those with

asymptomatic left ventricular dysfunction, represent another group that derive even greater benefit from preventive efforts because of their increased absolute risk. Landmark hypertension trials such as Swedish Trial in Old Patients with Hypertension (STOP),<sup>38</sup> Systolic Hypertension in the Elderly Program (SHEP),<sup>39</sup> and Systolic Hypertension in Europe (Syst-Eur)<sup>40</sup> demonstrated a 1.5%–2.5% absolute risk reduction in the incidence of HF over the 2–4 year follow up period with antihypertensive therapy. The number of patients needed to treat (NNT) to prevent one HF incident event ranged from 40 to 65. The patients had a mean age of  $\geq 70$  years in all three trials and a starting mean SBP  $> 170$  mmHg, conferring a high short term absolute risk for HF.

Drugs used in these three trials included thiazide diuretics, ACE-I, calcium channel blockers, beta-blockers and reserpine. While the Joint National Commission VII recommends using a thiazide diuretic as the first-line agent for hypertension,<sup>41</sup> ACE-I or ARBs are also recommended for patients with atherosclerotic disease or diabetes by the AHA/ACC.<sup>42</sup> Beta-blockers are typically reserved only for patients who have a history of myocardial infarction or angina.<sup>42,43</sup>

Patients with atherosclerotic disease can also be treated with lipid-lowering therapies to reduce their risk of HF, in addition to decreasing their mortality risk. The Scandinavian Simvastatin Survival Study (4S),<sup>44</sup> Cholesterol And Recurrent Events (CARE),<sup>45</sup> and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)<sup>46</sup> trials all demonstrated reduction in the incidence of HF with statins in patients with atherosclerotic disease. However, the majority of the risk reduction appeared to be mediated via a concomitant reduction in recurrent vascular events such as myocardial infarction, since the relative risk reductions were similar. The NNT to prevent one HF event ranged widely from 31 to 500 in these three trials.

For asymptomatic patients with evidence of structural heart disease (Stage B patients), specifically left ventricular dysfunction, the benefits of preventive therapy are even greater. The Studies of Left Ventricular Dysfunction (SOLVD) prevention arm demonstrated a 9% absolute risk reduction with the use of enalapril in patients with asymptomatic left ventricular dysfunction after 4 years of treatment (NNT=11).<sup>47</sup> Likewise, the Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE) and Trandolapril in Patients with Reduced Left-Ventricular Function after Acute Myocardial Infarction (TRACE) trials studied the effects of ACE-I (enalapril, ramipril and trandolapril) on patients following a myocardial infarction and demonstrated a combined 3.6% absolute risk reduction in the incidence of HF over a median of 31 months (NNT=28).<sup>48</sup> The Carvedilol Post-Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) study demonstrated a more modest 2% absolute risk reduction (NNT=50) with carvedilol in the incidence of hospitalization due to HF, but the follow up period was for only 1.3 years.<sup>49</sup> In comparison, the NNT for glycoprotein IIb/IIIa antagonists to prevent one death or myocardial infarction at 30 days ranges from 32 to 250 in patients with unstable angina/non-ST-segment elevation myocardial infarction, depending on the timing of drug administration and concomitant treatment strategy (invasive v. non-invasive).<sup>50</sup>

Patients with diabetes can be treated with ramipril to decrease the incidence of HF, as demonstrated in the Heart Outcomes Prevention Evaluation sub-study (MICRO-HOPE).<sup>51</sup> Ramipril decreased the incidence of HF by 2.3% over 5 years (NNT=43), though the risk of severe HF requiring hospitalization was not decreased with ramipril compared with placebo. ARBs have also

been shown to decrease the incidence of HF in people with diabetes when compared with beta-blockers,<sup>52</sup> but this difference appears to be mediated through a differential reduction in blood pressure. While observational data have demonstrated a decreased incidence of HF with better glycaemic control, neither the ADVANCE nor the ACCORD studies demonstrated a difference in incidence of HF between the standard and intensive glucose control arms.<sup>53,54</sup>

RHD requires a broader effort targeting primary antibiotic prophylaxis<sup>55</sup> or development of an effective group A streptococcal vaccine<sup>56</sup> to prevent HF, particularly since secondary prevention with penicillin has not been clearly shown to prevent the progression of valvular disease, as previously mentioned.<sup>25</sup> Major reductions in RHD in Cuba<sup>57</sup> and Costa Rica<sup>58</sup> have been demonstrated through comprehensive programmes that increase community awareness of group A streptococcal infections and integrate clinical diagnostics and single dose benzathine penicillin treatment in primary care settings. While this strategy may not be easy to adopt throughout India, it may be more cost-effective than secondary prevention alone.<sup>59</sup>

Treatment of tuberculosis provides another opportunity to prevent HF, through the prevention of symptoms due to constrictive pericarditis. No studies have evaluated the treatment benefit in the primary prevention of HF, but the advent of antituberculous drugs for treatment of pericardial tuberculosis has been associated with a decline in estimated case fatality rate from nearly 100% to as low as 8%.<sup>60</sup> The forthcoming Investigation of the Management of Pericarditis in Africa (IMPI Africa) Pilot Study should provide further insight into the prevention of HF from tuberculosis.<sup>61</sup> The investigators aim to evaluate the safety of a 6-week course of adjunctive prednisolone which, if positive, will provide preliminary data for a larger trial that will evaluate the efficacy of prednisolone in reducing pericardial complications (death, constriction or tamponade requiring drainage) in tuberculosis patients with pericardial effusions.

#### *Secondary and tertiary prevention of HF through clinical quality improvement*

Clinical quality improvement programmes—often organized through professional societies<sup>62</sup>—can help standardize and improve clinical care for patients at risk for asymptomatic HF (stages A and B), as well as those patients with symptomatic HF (stages C and D) to prevent HF and its complications, including hospitalization and death. Participation in practice improvement programmes has been shown to increase use of evidence-based care, adherence to performance measures, and decreased length of stay (for hospitalized HF patients) and may improve clinical outcomes.<sup>63,64</sup>

Appropriately trained and supported non-physician health workers (NPHWs) may be able to play a complementary role in the support and delivery of these programmes in the future.<sup>65</sup> India also currently lacks cardiovascular clinical practice guidelines, as well as nationally representative quality improvement initiatives to improve care for CVD. Development of guidelines and quality improvement programmes through professional societies offers a potential avenue for clinicians and researchers to improve prevention of HF through the establishment and implementation of India-specific practice standards.

#### CONCLUSION

The burden of HF in India appears high, and estimates of prevalence range from 1.3 million to 4.6 million, with an annual incidence of 491 600–1.8 million. However, reliable data are lacking because of inadequate surveillance systems. Population, epidemiological

and health transitions will continue to play an important role in the future burden of HF in India. The formulation of stages of HF (A to D) provides a preventive framework across the spectrum of patients with HF, from at-risk to end-stage. Incorporating effective, comprehensive (primordial through tertiary) prevention of HF provides the best opportunity to curb the projected rise of HF in India.

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