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CSI Position Statement

CSI position statement on management of heart failure in India

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Preface

The very essence of cardiovascular medicine is the recognition of early heart failure.

Sir Thomas Lewis 1933

Heart failure (HF) is emerging as an important public health problem in India. With the dual burden of traditional diseases like rheumatic heart diseases and the rising burden of new-age diseases like coronary artery disease, the burden of HF in India, is likely to be enormous. Also the varying geographic and ethnic diversity poses a great challenge to the management of HF in our country.

Since our resources are limited and the vast majority of the population spend out-of-pocket for treatment, it is an important responsibility of the cardiologists and all concerned stakeholders to provide the best available therapeutic options in an affordable manner, based on the latest available medical knowledge and practice.

It is in this context that Cardiological Society of India (CSI) decided to bring together a group of experts in HF in India, to develop and publish the 'Position Statement on management of HF in India'. The purpose of this statement is to provide a single document for the whole country which provides the latest available data both from India and the rest of the world. We also have tried to gather data on conditions specific and relevant to the Indian context like rheumatic heart disease, aortoarteritis and endomyocardial fibrosis.

This position statement is recommendatory in nature and carries no statutory status.

1. Preamble, epidemiology and evaluation

1.1. Preamble

Heart failure (HF) affects about 26 million people worldwide[1] and its management poses significant strain on healthcare resources of a country. Ageing population, increasing prevalence of cardiac risk factors and improved survival of patients with acute cardiovascular diseases have resulted in HF becoming a major public health problem, across the world. Improving awareness about the condition, lifestyle modification, early detection, treatment and monitoring are necessary to keep this public health menace in check. A number of guidelines, mostly Western, are available for management of patients with this condition but their uniform implementation may be difficult across all countries because of differences in infrastructure and local practices. Therefore, there is a need for region specific and country-specific guidelines which could more appropriately address such issues.

1.1.1. Magnitude of the problem

There is paucity of data on heart failure burden in India because of the absence of disease surveillance systems in India. HF is not an exception. We have indicators to assume that the incidence and prevalence rates of heart failure are rising due to epidemiological and health transitions. Huffman and Prabhakar in their projections, based on disease-specific estimates projected that a conservative estimate of the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart

disease is in the range from 1.3 to 4.6 million, with an annual incidence of 0.4–1.8 million.[2] Patients with heart failure are younger than in the high income countries, with a mean average age of around 60 years at presentation. They also have a high in-hospital mortality and one year mortality, which are significantly higher than that in the high income countries.[3]

1.1.2. Challenges of management of heart failure in India

The challenge is to make quality healthcare services accessible and affordable to a socioeconomically and linguistically diverse population of more than 1.3 billion[4] spread over 3.287 million km^2, with inadequate infrastructure to deliver services and lack of strict quality control measures. At the 2001 census, 72% of the population lives in villages which are poorly accessible by roads, making delivery of healthcare difficult. Only basic health care facilities are available at most of the primary health centres, which are often understaffed and their services overstretched. Most of the tertiary healthcare resources are concentrated in the large cities and that too mostly in the big Metropolis. This inequality in healthcare distribution is a major impediment for implementation of universal health care in India.

Government of India has cleared the National Health Policy 2017, which promises to increase public health spending to 2.5% of GDP.[5] This is still lower than the government spending in countries such as UK (7.9%), US (8.2%) and Japan (9.6%).[6] Private health care runs parallel with government funded health service, but is expensive and therefore affordability is an issue. As high as 86% of rural population and 82% of urban population are not covered under any insurance scheme whether public or private, to support health expenditure.[7] A study on microeconomics of cardiovascular disease (CVD) in India showed that 79% people have to resort to "distress financing" forcing them to borrow or sell assets when faced with an acute episode of acute coronary syndrome (ACS) or stroke.[8]

In such circumstances, healthcare rationing becomes inevitable. In the private sector, where services come at a premium, it is solely based on the affordability of the patient while in the public sector, which is meant for the masses, it depends on the budgetary allocation for health. We realize that there is a need to move from the 'ability to pay' based rationing to 'need based rationing'. Therefore, whilst issuing a position statement, recommendations for the more expensive treatments need to be judged against the strength of their indications.

One of the striking features of India's health care sector is the variation in range of quality in available services. Apart from infrastructural constraints, low level of provider's knowledge, large gaps between providers' knowledge and the care provided, and poor governance in the healthcare system could be the reasons for poor quality of services.[9] Efforts to improve the quality of care are particularly challenged by the lack of reliable data on quality and by technical difficulties in measuring quality.[10] Moreover, the low overall literacy level (72%) limits awareness and resists adoption of changes.[11]

1.1.3. The need for a position statement

There are many reasons why region specific guidelines in the management of heart failure are necessary. Most of the western guidelines that we follow have been validated for Caucasians. Unfortunately we do not have the wealth of data to confirm the applicability of these guidelines to Indians. Where the strength of evidence is high, the class of indication is unlikely to vary to suit the economic constraints. On the other hand, where the evidence is relatively weak, the cost-effectiveness need to be considered in resource constrained settings. Device therapy in heart failure in the Indian context is a perfect example.

1.1.4. Objective

An expert committee was constituted by Cardiological Society of India (CSI) for formulating the position statement on heart failure. The objective was to provide a consensus statement on heart failure management that could be applied across the country and offer practical suggestions to the problems specific to the country.

1.1.5. Limitations

Lack of adequate data on heart failure in India, remains the main limitation of developing specific guidelines. Moreover, the purpose of this position statement is recommendatory in nature and carries no statutory status.

1.2. *Epidemiology of heart failure (HF)*

Heart Failure (HF) is one of the leading cause of hospitalization in the High Income Countries (HIC), representing 1% to 2% of the total hospital admissions.[1] HF is a disease associated with significant mortality, which is higher than many common cancers like breast or colon. It is also associated with high morbidity, and accounts for a significant share in the healthcare expenditures in the developed world.[11]

Though we have good data on the epidemiology of HF from the HIC, data from the low and middle income countries (LMIC) is very limited and most of them are projections based on western data or based on risk factor levels.[2,12,13]

The 2017 Heart Disease and Stroke update[14] reports that 6.1 million Americans $\geq$20 years of age have HF based on the NHANES data.[15] Projected figures estimate that the prevalence of HF in US will increase by 46% from 2012 to 2030 and the estimated medical costs related to HF will increase almost by 127% to $69.7 billion in 2030.[15]

Some hospital based data on HF has recently emerged from India,[3,16], but there is no significant data on the HF burden in the community. A preliminary estimate on the community-level prevalence of HF in the adult population in India is about 1%.[12] We have certain projections and estimates on HF from India and South Asia.[2,17] Based on these estimates (where US prevalence data is extrapolated to Indian population), the prevalence of HF in India is estimated to be 22.7 million.[17]

When we try to project the burden of HF in India, we have to give consideration to the presence of risk factors of HF. Prevalence of HF is likely to be proportionate to the risk factor levels in the society. India is said to be having the "double burden". On one side there is rise in prevalence of conditions like hypertension, diabetes, and coronary artery disease and on the other side, there is persistence of "traditional " like rheumatic heart disease.[17] There are also specific conditions which are unique to India, like aortoarterits, endomyocardial fibrosis, untreated congenital heart disease, high prevalence of chronic obstructive pulmonary disease (COPD) due to high biomass fuel use which can contribute to the burden of HF.

1.2.1. HF burden – how India is different?

The age at presentation with HF is dependent upon the level of epidemiological transition of that country. In the Trivandrum Heart Failure Registry (THFR) from India,[16] the patients with HF were 10 years younger (mean age 61 years) compared to their western counterparts. In the INTER-CHF study, the mean age among Indians were 56 years, while the patients from sub-Saharan Africa were even younger at 53 years.[18] By contrast, the mean age at presentation was 72 years in USA[19] and the European data – the mean age was 70 years.[20] The Kerala ACS registry also showed the presentation of ACS was at a younger age in India.[21]

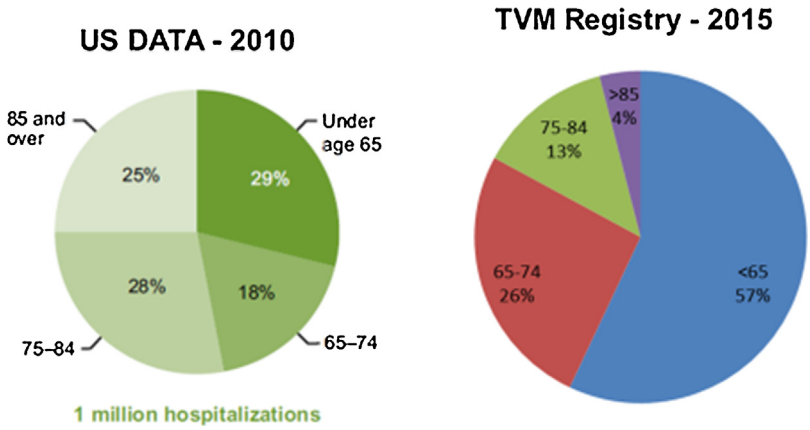

Fig. 1. Difference in the age distribution of patients with HF from India versus United States[3,19].

The age distribution of the patients presenting with HF is also different. (Fig. 1) This data indicates that the burden of HF is in the younger population at productive ages in India. The gender ratio is also different in India compared to US and Africa. Male to female ratio is almost equal proportions in US and Africa, while in India this ratio is 70:30.[16]

The etiology of HF in India is also different from the west. The INTERCHF data shows that CAD is the most common etiology of HF in Asia (48%), while in the Trivandrum Registry IHD accounted for 71%. Table 1 shows the various etiologies in patients from the Trivandrum registry and the INTER-CHF registry.[18] RHD accounts for 8–10% of the burden in India, but it is not a significant problem in the west.[19]

The risk factor prevalence in patients with HF is also different from the west. Type 2 Diabetes(T2DM) is much more prevalent among Indians than westerners as per the Trivandrum Registry.[3]

The prognosis of HF in Indians is worse than the Western population. The in-hospital mortality of 8.4% in THFR is much higher than 4% in the ADHERE registry of USA. But the thirty-day mortality is similar at 30% in both US and Indian populations. The Inter CHF study shows that the one year mortality of in-patients with HF is much higher in India and Africa, about 37% and 60% respectively.[22]

Coming to the management of HF, an important issue is the level of evidence based care. In the Trivandrum registry, it was found that only 25% of the population received guideline directed medical therapy – GDMT (i.e. a combination of BB + ACEI + Aldosterone blockers in HF r EF), and those who did not receive GDMT had higher mortality. This points towards need for quality improvement programs. Fig. 2 summarizes the salient features of HF epidemiology in India.

Table 1
Differences in etiology of Heart failure among large studies form Asia (INTERCHF) and India (Trivandrum HF registry).

	ASIA(INTERCHF)[18]	Trivandrum Registry[16]
ISCHEMIC	48	71
HYPERTENSIVE	14.1	2
DCM	11	15
Rheumatic HD	10	8
ENDOCRINE/METABOLIC	5	
VALVULAR –NONRHEUMATIC	3	2.5
Idiopathic/hypertrophic	2	
CHD	1	1.3
Peripartum Cardiomyopathy		0.25
Right heart failure		1.5

Notes: DCM- dilated cardiomyopathy, RHD- rheumatic heart disease, CHD-Congenital heart disease.

1.3. *Heart failure – definition and types*

Heart failure (HF) is a term easily understood, but is difficult to define. Numerous definitions of HF are proposed with only a few definitions having widespread acceptance.[23] One of the **classical definitions** says "HF is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues or does so only at elevated filling pressures".[24] The **American College of Cardiology (ACC)/American Heart Association (AHA) guidelines**[25] define "HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood". **The ESC guidelines**[26] define HF as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra cardiac pressures at rest or during stress". A more detailed analysis of various definitions of HF may be found elsewhere.[23]

1.3.1. Stages of HF

All the current definitions of HF are restricted to manifest stages with apparent clinical symptoms and signs. However, vast majority of patients have asymptomatic structural or functional cardiac abnormalities like left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, and valve diseases which are well known precursors of HF. It is important to recognize and treat them as established HF has poor prognosis. So, control of these HF

HF presents about a decade earlier in India, most of the burden is in the population below 65 years.

There is a male preponderance with male female ratio of 70:30

Coronary artery disease is the most commonestetiology, followed by idiopathic dilated cardiomyopathy.

Rheumatic heart disease contributes about 10% of the HF burden

The in-hospital mortality is higher in Indian patients.

HF pEF is seen in 25% of the patient population on HF.

Fig. 2. Heart failure Epidemiology – How India is different?.

Table 2
ACC/AHA Stages of HF.

Stages	Definitions	Examples
Stage A	At high risk for HF but without structural heart disease or symptoms of HF	Risk factors for HF like hypertension
Stage B	Structural heart disease but without signs or symptoms of HF	LV dysfunction, LV hypertrophy
Stage C	Structural heart disease with prior or current symptoms of HF	Most forms of chronic HF
Stage D	Refractory HF requiring specialized interventions	Advanced/end stage HF

precursor conditions may prevent or delay progression to overt HF. In recognition of the importance of the predisposing conditions in the causation of HF, **the ACC/AHA[25] recognizes 4 stages of HF** (Table 2). Stage C & D are the clinically recognizable forms, while stage A & B are the pre-HF forms. HF may be further classified by underlying etiology, ejection fraction, time course and severity.

1.3.2. Types of heart failure

1.3.2.1. Underlying etiology. A critical component of HF diagnosis is defining the aetiology for HF. Most commonly, LV systolic and/or diastolic dysfunction is the frequent cause of HF across the world. In India, RHD remain one of the common causes of HF.[27] Additionally, pericardial, endocardial, heart rhythm and conduction abnormalities, structural heart defects, and metabolic and systemic conditions may also cause HF. More than one aetiology may contribute to the development and progression of HF in some cases.

1.3.2.2. Heart failure with preserved,mid-range and reduced ejection fraction (Table 3). LVEF remains central to the characterization of HF, despite the shortcomings. Traditionally, HF is classified as HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF). HFrEF is typically defined as LVEF <40% and HFpEF typically considered as LVEF ≥50%. This distinction is very important as both these forms have different underlying etiologies, risk profiles, demographics, and co-morbidities .

The recent ESC guidelines[26] realize that patients of HF with LVEF in the range of 40–49% represent a 'grey area', and have introduced a new term 'HF with midrange EF (HFmrEF)'. Patients with HFmrEF are likely to have mild systolic dysfunction with variable amount diastolic dysfunction. In some of the HFrEF patients, the LVEF may improve with treatment or spontaneously and may be in HFmrEF or HFpEF. However, their prognosis and outcomes may be different. Hence, ACC guidelines categories these patients into HFrEF 'improved'.

HFrEF is easier to diagnose and manage with evidence based guidelines as compared to HFpEF. Most often patients with HFpEF have normal sized LV with EF > 50%, but with an increased LV wall thickness and/or increased left atrial (LA) size on echocardiography along with an evidence of impaired LV filling, hence was referred as diastolic HF. Earlier classification of HF as systolic HF and diastolic HF was simple, but was realised to be less accurate. Most patients with systolic HF also have measurable abnormalities of diastolic function and most patients with diastolic HF also have subtle abnormalities of systolic function using advanced methods of LV systolic function assessment. Moreover, not all patients of HFpEF have measurable abnormalities of diastolic function on echocardiography. Hence, the terms HFrEF and HFpEF are preferred over systolic and diastolic HF.

Table 3
Definitions for Heart failure with preserved, mid-range and reduced EF.[26]

HFrEF (HF with reduced EF)	LVEF ≤ 40%
HFpEF (HF with preserved EF)	LVEF ≥ 50%
HFmrEF (HF with mid-range EF)	LVEF 41–49%

1.3.2.3. Terminology related to the time course of heart failure. Chronic HF and acute decompensated HF (ADHF) are the two most well recognized forms of HF with distinctly varying mortality, morbidity and outcomes. Most of the patients have chronic HF with an insidious onset of symptoms/signs. Acute decompensated HF is the preferred term for patients presenting acutely with HF, which can be defined as 'the sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned office visits, emergency room visits, or hospitalization'.[28] It may be due to a de novo acute onset HF or due to decompensation in a patient with chronic stable HF.

A de novo ADHF may present with an acute or subacute onset. Some conditions like myocardial infarction, myocarditis and acute infective endocarditis are associated with an acute HF with onset within minutes to hours. Dilated cardiomyopathy, infective endocarditis and acute rheumatic fever are classical examples of HF with subacute onset within days to a few weeks. Some of these conditions may resolve completely with or without specific therapy. However, a significant proportion of patients end up having chronic forms of HF. Any worsening of HF in a patient with chronic stable HF also leads to ADHF. Such decompensation of chronic HF is the most common cause of ADHF leading to hospitalization and increased mortality.[28]

Most of the current guidelines[25,26,29] describe an asymptomatic patient with reduced LVEF who never exhibited typical signs and symptoms of HF as having 'asymptomatic LV systolic dysfunction'. However, such patients are at increased risk of mortality and future morbidity and some deaths may occur even before the patient exhibits first signs or symptom of HF. Some of these asymptomatic LV dysfunction patients may have raised biomarkers. It may be prudent to include a category of 'asymptomatic HF' (Stage C, NYHA class I). This identity is also important in a transiently symptomatic patient who became asymptomatic on treatment. Then, HF term may no longer be restricted to patients with manifest signs and symptoms.

1.3.2.4. Terminology related to the symptomatic severity of heart failure. New York Heart Association (NYHA) functional classification (Table 4) remains the most widely used to assess symptomatic severity and exercise tolerance in HF.[30] However, NYHA classification has several limitations. The symptom stages are clearly related survival, yet they correlate poorly with measures of LV function. Moreover, mildly symptomatic patients may also have an increased risk of hospitalization and death.

Patients having a severe form of cardiac dysfunction presenting with severe symptoms and recurrent decompensation is referred as having '**advanced HF**'. Patients with '**end-stage HF**' characteristically have advanced structural heart disease with symptoms of heart failure at rest or upon minimal physical exertion, despite maximal evidence-based treatment. Patients who are continually symptomatic despite maximum tolerated medical therapy are also referred as having '**refractory HF**'.

1.3.2.5. Other commonly used classification terms in HF. Some of the commonly used terms in HF like stable HF, compensated HF, and congestive HF needs further elaboration. Many or all of these previously defined terms may be accurately applied to the same

Table 4
NYHA classification and definitions.[30]

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

patient with HF at different times, depending upon their stage of illness. ESC defines stable/compensated HF as "a treated patient with symptoms and signs that have remained generally unchanged for at least 1 month". Congestive HF is a term used for patients of acute or chronic HF presenting with evidence of volume overload. Congestive HF (CHF) or congestive cardiac failure (CCF) are common terms used in India for chronic HF presenting with clinical signs, but are not specific and are better avoided.

All the components essential for making a complete diagnosis HF are summarized in Fig. 3.

1.4. *Pathophysiology of heart failure*

Heart failure results due to loss of functional myocardial cells (ischemia, myocarditis, cardio myopathies) and also due to extra-myocardial diseases (valvular heart diseases, pericardial diseases, systemic hypertension). On a long run, the extra-myocardial disease processes can also affect the myocardial function by posing pressure and volume overload.

Heart failure due to any etiology is characterised by changes in vascular function, fluid volume and neuro-hormonal status, which serve initially to restore the balance, but are considered to be detrimental over a long term.

1.4.1. Hemodynamic alterations in HF

1.4.1.1. Acute decompensated heart failure. Decrease in cardiac output hikes up the sympathetic nervous tone and inhibit parasympathetic system which attempt to maintain perfusion by

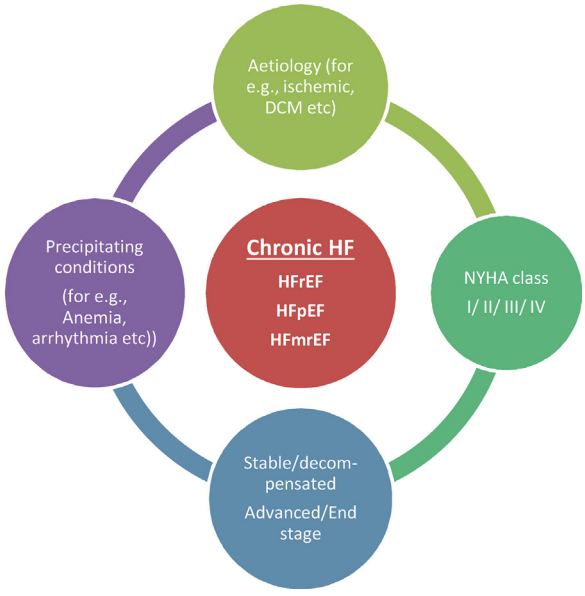

Fig. 3. Components of chronic HF Diagnosis.

increasing peripheral vascular resistance and stimulating the contractile reserve of the remaining myocardium. Vasoconstriction helps to increase the preload and filling pressures. The sarcomere overlap progressively decreases with distension of the chambers and beyond the point of optimal stretch, the volume of blood ejected declines, further worsening the stroke volume and increasing the filling pressures. Salt and fluid retention by kidneys sets in and attempts to increase the preload and tissue perfusion.

1.4.1.2. Chronic heart failure. The variable recovery of the myocardium along with elevated filling pressures enables gradual improvement in cardiac output, thus stabilising the patient. The elevated chamber volume attempts to improve the forward output, but increases the wall stress by the law of Laplace. This stimulates hypertrophy by laying down of sarcomeres in series with lengthening of the myofibres, thereby acting as a counter-measure to decrease the wall stress. Progressive volume overload and/or loss of contractile elements as in myocardial diseases result in gradual loss of efficacy, increased myocardial oxygen demand, sub endocardial ischemia and worsening heart failure.

1.4.2. Basis of compensatory mechanisms in heart failure

A series of systemic compensatory mechanisms are initiated once cardiac injury occurs (Fig. 4). These mechanisms attempt to maintain the cardiac output by affecting the myocardium and vasculature. The adaptive changes in myocardium are collectively termed ventricular remodelling. While the compensatory mechanisms in patients with heart failure with reduced ejection fraction have been documented well, the understanding of pathophysiological processes involved in patients suffering from heart failure with preserved ejection fraction is in an evolving stage.

1.4.3. Ventricular remodelling (Fig. 5)

The term ventricular remodelling encompasses the complex alterations in the ventricle in response to various mechanical, neurohormonal, and immunological stressors on the heart, resulting in alterations in volume, wall thickness and/or shape (). Though initially considered to be protective, adaptive hypertrophic changes over a long term have adverse consequences. Consequent to identification of adaptive mechanisms at molecular and biochemical level, the process has been redefined as "genomic expression resulting in molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury."[31]

1.4.4. Pathophysiology of HF_PEF

In normal hearts, LV pressure rapidly decreases after systole, facilitating rapid filling in diastole with low filling pressures. This is aided by active suctioning effect of left ventricle generated by intraventricular gradients, longitudinal motion of mitral annulus, untwisting of LV during early diastole and elastic recoil of the ventricle after the end of the systole. These are impaired in patients with HF_PEF resulting in decreased rate of pressure decay in LV during isovolumic relaxation phase, progressive.

Initially these may be manifest during exercise only. There is progressive increase in the reliance on atrial systole for ventricular filling, with worsening left atrial hypertension and its consequences, pulmonary venous congestion, pulmonary arterial hypertension and right heart failure. Contractile dysfunction often coexists, not severe enough to depress ejection fraction in resting state. This may become more apparent during exercise.

1.5. *Clinical evaluation of heart failure patients*

Clinical evaluation is one of the most vital parts of management of patients with heart failure. The purpose of clinical evaluation is

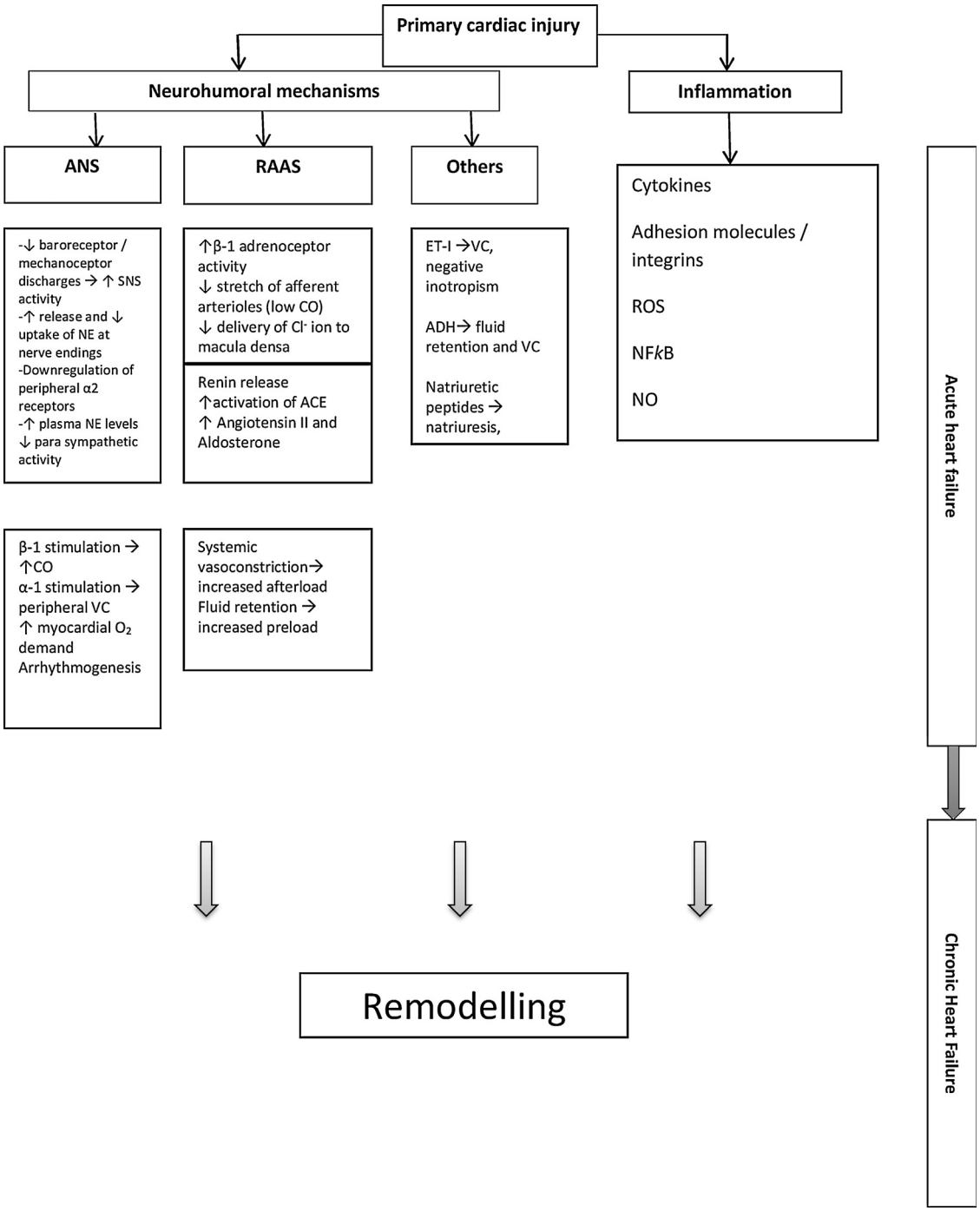

Fig. 4. Various compensatory mechanisms initiated in Heart failure.
ANS – autonomic nervous system; ACE – angiotensin converting enzyme; ADH – antidiuretic hormone, CO – cardiac output; ET – endothelin; NE – norepinephrine; NFκB – nuclear factor kappa beta; NO – nitric oxide; RAAS – renin angiotensin aldosterone system; ROS – reactive oxygen species; SNS – sympathetic nervous system; VC – vasoconstriction

to diagnose heart failure, derive etiological clues, and assess the severity of the condition while taking care to exclude other causes of dyspnea or edema. Clinical evaluation also assesses response of these patients to therapy.

1.5.1. History

Clinical evaluation should start with a good history which will give insights into the etiology of heart failure, the precipitating factors, and the disease severity.

Most common symptoms of HF are dyspnea, symptoms related to fluid retention, palpitation and fatigue (Table 5). Dyspnea initially may be exertional, but can worsen to present as paroxysmal nocturnal dyspnea (PND) or orthopnea or dyspnea at rest. Palpitations can be due to tachycardia, dilated heart or can be due to arrhythmias like atrial fibrillation or ventricular arrhythmias.

Fatigue is due to low cardiac output. Low cardiac output can also manifest as reduced urine output and also lethargy and mental slowing.

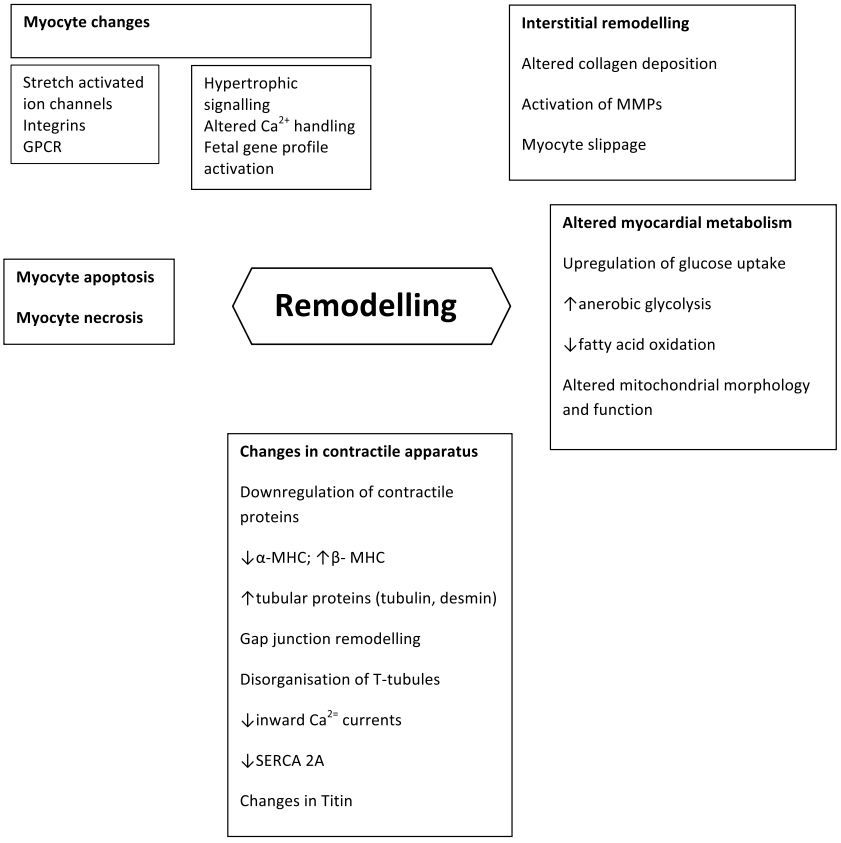

Fig. 5. Molecular and pathological changes seen during ventricular remodelling.
GPCR – G protein coupled receptor; MHC – myosin heavy chain; MMP – matrix metalloproteinase; SERCA – Sarcoplasmic Reticulum Calcium – Adenosine triphosphatase

Fluid retention commonly manifest as dependent edema, ascites or pleural effusion. Gastrointestinal symptoms such as anorexia, early satiety and weight loss are common in patients with HF and are due to visceral congestion. Cardiac cachexia is associated with adverse prognosis. Change in body weight is also very important. Rapid weight gain and development of peripheral edema or ascites suggests volume overload while weight loss during treatment indicates a good therapeutic response and is helpful in establishing the diagnosis of heart failure

One should also elicit history which will give clues to the etiology of HF. History of rheumatic fever in the past, history of myocardial infarction (MI), presence of risk factors like hypertension or diabetes mellitus, history of a recent viral infection, pregnancy, history of habituation to alcohol intake, history of cancer chemotherapy, all can give clues to the etiology.

Recent or frequent prior hospitalizations for HF is associated with adverse prognosis.

It is necessary to assess the compliance to life style, dietary restrictions and physical activity. It is also very important to assess the compliance to drug therapy as it is known to affect the prognosis in HF.

At the same time, one should enquire also about medications that may exacerbate HF (eg NSAIDs) since discontinuation of such medications may represent a therapeutic opportunity.

1.5.2. Physical examination (Table 5)

Physical examination compliments the history and will give clues to the etiology of heart failure. It can confirm the diagnosis of HF and also assess the severity of HF.

General examination can give clues to the etiology, for example evidence of chronic alcohol intake can point towards alcoholic cardiomyopathy. Presence of mucosal pallor indicating anemia, can point towards a precipitating factor.

Table 5
Typical symptoms and signs of Heart Failure.

Symptoms	Signs
Dyspnea	Elevated jugular venous pressure
PND	Hepatojugular reflux
Orthopnea	Third heart sound
Fatigue	Laterally shifted cardiac apical impulse
Palpitations	Dependent edema
Dependent edema	Basal crepitations
Cachexia	Tender hepatomegaly

Height, weight and body mass Index (BMI) should be recorded. Periodic weight monitoring is vital in the management of HF.

Blood pressure (supine and upright) should always be recorded. We should always look for postural changes in blood pressure and heart rate. These will give clues to volume depletion or excess vasodilation from medications. Sinus tachycardia, low blood pressure and reduced pulse pressure indicates a low cardiac output. A pulsus alternans may indicate depressed cardiac function.

One should look for signs of fluid overload in the form of peripheral edema or ascites or pleural effusion. Recent weight gain is a clue.

JVP at rest and following abdominal compression (hepatojugular reflux) is extremely useful part of physical examination to identify systemic congestion.

The most important and specific sign of HF is cardiac enlargement. Size and location of point of maximal impulse

should be looked for and documented. Presence of right ventricular heave suggests significant right ventricular dysfunction and/or pulmonary hypertension

Presence of third heart sound (S3) indicates adverse prognosis in HFrEF and is sometimes the only distinct finding in asymptomatic heart failure patients. Pansystolic murmur of mitral regurgitation may be audible and should be carefully looked for. Other murmurs due to valvular heart disease will give clues to the etiology.

Respiratory rate, rales and presence of pleural effusion should be assessed. It is important to remember that in advanced chronic HF, rales are often absent despite major pulmonary congestion and hence their absence should not eliminate the possibility of heart failure.

Hepatomegaly may be looked for carefully. It indicates venous congestion and can be used to serially monitor the patients. Presence of ascites indicates advanced right heart failure.

1.5.3. Electrocardiogram

ECG is one of the most crucial diagnostic tools in evaluation of patients with HF. A 12 lead ECG is recommended in all patients who are suspected of having HF. Occasionally we may need right sided leads or leads V7 or V8. ECG. Though the ECG may be abnormal in most of the patients, a normal ECG will not rule out HF.

Pre-existing or development of bundle branch block (BBB) is a poor prognostic factor in patients with heart failure. Left bundle branch block (LBBB) prevalence is as high as 25% in patients with chronic heart failure. LBBB causes deterioration of the mechanical function of the left ventricle secondary to asynchronous myocardial activation, which sequentially trigger ventricular remodelling and bad prognosis. Right bundle branch block (RBBB) has been shown in studies to be associated with worse prognosis in patients with chronic heart failure compared to patients with no BBB.

Non-sustained ventricular tachycardia (NSVT) is common among patients with dilated cardiomyopathy with reported prevalence of 30–80%. Though common, the prognostic significance of NSVT as an independent risk factor in heart failure is questionable. Signal averaged ECG and heart rate variability studies have conflicting evidence as a predictor of mortality in dilated cardiomyopathy.

Utility of ECG in HF

1. CAD – Presence of Q waves or loss of R waves or ST segment shift indicates presence of CAD.
2. Arrhythmias can give clues to the etiology – eg. Atrial Fibrillation, bradycardia.
3. ECG can give clues towards electrolyte imbalance
4. ECG – can provide Prognostic information – Eg. Presence of ventricular arrhythmias.
5. It can give clues to chamber enlargement – LVH, RVH, LAE

What to assess in ECG in patients with HF?

Heart rate, PR interval, QRS duration, QT interval, pathological Q waves, evidence of left atrial/right atrial overload, left ventricular/right ventricular hypertrophy, bundle branch block, atrial and ventricular arrhythmias.

CHEST X Ray

As part of the initial assessment of patients with HF Chest X-ray (CXR) stills remains an important diagnostic tool. CXR gives two important clues to HF, presence of cardiomegaly and presence pulmonary congestion, both are very specific to the diagnosis of HF.

What to look for in CXR in HF:

1. Cardio-thoracic ratio
2. Pulmonary congestion
3. Specific cardiac chamber enlargement
4. Pleural effusion
5. Other abnormalities – Lung parenchymal abnormalities, Calcification eg. Pericardial

1.6. *Echocardiography*

1.6.1. Echocardiography

Echocardiography is the critical diagnostic tool in patients with suspected heart failure, where it provides functional and structural information. With the wide availability of echocardiography, it has emerged as the most important tool in the diagnosis, assessment of prognosis and in follow up of patients with HF.

1.6.2. Assessment of structural heart disease

A basic Echocardiographic examination of M-mode, two-dimensional echocardiography, colour Doppler, pulse Doppler and continuous wave Doppler should be performed in all patients with suspected heart failure.

Echocardiography gives the diagnosis, confirms the etiology and assesses the severity, which helps in deciding the type of treatment required.[25,26,32–34]

Echocardiography provides insights into all stages (A,B,C and D) of heart failure.[32,33,35]

1.6.3. Assessment of systolic and diastolic function

Two-dimensional echocardiography is the mainstay for the assessment of LV systolic function which includes LV imaging in parasternal long axis view, parasternal short axis views and apical views.[35] LV measurements should be done from two-dimensional echocardiography, and the assessment of LV volume by modified biplane Simpson's method is the most widely accepted method. Area–length method may be used when biplane Simpson method is technically not feasible. Care should be taken to get the correct apical views with visualization of the LV apex and clear identification of the endocardium. In patients with poor image quality, contrast opacification of LV will help to better delineate the endocardium.

M-mode echocardiography should not be used for LV quantification and it should be done from two-dimensional echocardiography. Cube method and Quinones method should not be used for measurement of LV volumes and ejection fraction. Three-dimensional echocardiography when available should be used for measuring LV volume and ejection fraction. LV myocardium is divided into 16 or 17 segments and visualized in parasternal long axis, parasternal short axis and apical views according to the coronary blood supply. Wall motion abnormalities should be described using this nomenclature with wall motion scoring index.

Assessment of LV diastolic function is an equally important requirement of echocardiography.[37] Diastolic dysfunction can be identified by doing a left atrial outflow Doppler sampling between the tips of anterior and posterior mitral leaflets, tissue Doppler from septal and lateral mitral annulus, pulmonary vein velocity, left atrial volume measurement and identification of presence or absence of pulmonary hypertension. Left atrial volume provides incremental information about the severity and chronicity of diastolic dysfunction and is an important prognostic indicator in various groups of heart diseases. Right atrial volume measurement and RV diastolic dysfunction has limited value and not recommended in routine echo.

The LV diastolic dysfunction can be graded into type I abnormal relaxation pattern, type II pseudo normal pattern and type III restrictive pattern and Type IV irreversible restrictive pattern (Table 6).

Table 6
Echocardiographic criteria for assessing grades of Left ventricular diastolic dysfunction.[37]

Diastolic Dysfunction				
	Normal	Grade I	Grade II	Grade III
Mitral E/A	≥0.8	≤0.8	>0.8 to <2	>2
Average E/e ' ratio	<10	<10	10–14	>14
Peak TR velocity (m/s)	<2.8	<2.8	>2.8	>2.8
LA volume index	<34 ml/m^2	Normal or increased	>34 ml/m^2	>34 ml/m^2

Table 7
Echocardiographic criteria for assessing severity of right ventricular function.

RV Function				
	Normal	Mildly abnormal	Moderately abnormal	severely abnormal
RV Diastolic Area (cm^2)	11–28	29–32	33–37	≥38
RV Fractional Area change (%)	32–60	25–31	18–24	≤17
TAPSE	1.5–2.0	1.3–1.5	1.0–1.2	<1.0

1.6.4. Assessment of right ventricular function and pulmonary hypertension

The importance of RV function and RV haemodynamics is being increasingly recognized in the management of HF. Assessment of RV function and hemodynamics is very important to decide about the management of patients, which includes both medical and surgical methods of treatment.[32,33] This information can be obtained from two-dimensional and Doppler echocardiography which is considered now as the non-invasive Swan-Ganz catheter. Pulmonary artery systolic pressure, diastolic pressure and mean pressure can be calculated from tricuspid and pulmonary regurgitation. Right atrial pressure is mainly assessed by using the inferior vena cava dimension and its changes with respiration. RV function can be assessed by surrogate parameters like, TAPSE (Tricuspid annular plane systolic excursion), Tricuspid annular tissue Doppler velocity, RV fractional area change and RV myocardial performance index (Table 7). RV volumes and ejection fraction can be obtained by three-dimensional echocardiography, but it has not come into routine clinical practice yet. Cardiac magnetic resonance imaging (CMRI) is still the gold standard for measuring the RV volumes and ejection fraction.

1.6.5. Tissue d Doppler imaging

Tissue Doppler imaging (TDI) gives information about regional and global function.[32] Tissue Doppler of LV is sampled from mitral annulus and from basal and mid-ventricular myocardial segments. Its use is limited since it's a Doppler based technique and can only be used in apical views. TDI is mainly useful for diastolic function assessment and in the measurement of LV filling pressures (E/e'). It is also useful in assessing LV and RV function by calculation of myocardial performance index since the parameters can be measured in the same heartbeat. Conventional echocardiography plays an important role post CRT for assessing LV function, severity of mitral regurgitation (MR) and adjusting the atrio-ventricular and inter-ventricular delays after CRT.

1.6.6. Speckle tracking echocardiography

TDI and speckle tracking echocardiography (STE) has helped us to understand LV myocardial mechanics[32,33,35] Peak global longitudinal strain (GLS) of LV by STE has come into clinical use, the normal value being −18% to −22%. GLS value of above −16% indicates LV systolic dysfunction (Table 8). Regional peak longitudinal strain pattern of LV myocardial segments can be shown as a Bull's eye diagram with colour coding and numerical values. This may be useful to identify affected segments in various disease conditions. It has also been shown to be useful in identification of areas of fibrosis in patients with dilated and hypertrophic cardiomyopathy. In amyloidosis, it gives a typical pattern of apical sparing with marked decrease of strain in basal and mid myocardial LV segments, the typical "cherry on top of ice cream" appearance.

In patients with HFpEF, even though LV ejection fraction is in the normal range, strain is decreased indicating subclinical LV systolic dysfunction. Strain can also be used to identify sub clinical LV dysfunction after cancer chemotherapy. 25% decrease in GLS compared to the basal values identifies myocardial systolic dysfunction. GLS can also be used to predict early LV systolic dysfunction before ejection fraction decreases in patients with mitral and aortic regurgitation, aortic stenosis, left ventricular hypertrophy due to systemic hypertension, hypertrophic and restrictive cardiomyopathy. Both TDI and STE have shown some utility in assessing patients after cardiac transplant, especially patients who are likely to develop rejection

1.6.7. Three-dimensional echocardiography

Trans-thoracic real time three-dimensional echocardiography (RT3DE)[38] provides accurate LV volume and ejection fraction because the volume is measured by counting the number of voxels present in the LV cast. It is superior since, there is no geometrical assumption and hence no mathematical formula is involved, provided the LV is not foreshortened and LV apex is always

Table 8
Definition of abnormal global longitudinal strain &clinical situations for it's use.

	Global Longitudinal Strain
Abnormal if more than −16% (Normal Range −15.9% to −22.1%)	
It is being used to monitor specific clinical conditions to detect sub clinical LV dysfunction	
	-Cancer induced chemotherapy
	-Aortic stenosis
	-May have a role in cardiac amyloid & Hypertrophic cardiomyopathy

included. RT3DE LV volume correlates well with the gold standard of LV volume by CMR imaging.

1.6.8. Contrast echocardiography

Contrast echocardiography using commercially available contrast agents is useful for LV opacification. Contrast delineates LV endocardium and facilitates more accurate estimation of LV volume and ejection fraction. Contrast echocardiography can be combined with stress echocardiography for identification of wall motion abnormalities with treadmill stress and dobutamine stress echocardiography. It is also useful for identification of thrombus, aneurysm, non-compaction, viable myocardium and apical hypertrophic cardiomyopathy.

1.6.9. Stress echocardiography

Stress Echocardiography may be combined with physical exercise like treadmill test or pharmacological stress like dobutamine stress echocardiography (DSE). Stress echocardiography can be used to identify wall motion abnormalities developing after myocardial ischemia. DSE is useful to identify the biphasic response which indicates viability of myocardium. Stress echocardiography can also be used in patients with asymptomatic and low flow low gradient aortic stenosis. It is also useful in patients with mitral and aortic regurgitation. Stress echocardiography is not recommended for the diagnosis of pulmonary hypertension. In patients with significant dyspnoea with normal resting LV diastolic pressure, diastolic stress test may identify patients with abnormal diastolic dysfunction where an increase in LV end diastolic pressure produces dyspnoea.

1.7. *Biomarkers in heart failure*

1.7.1. Introduction

Although heart failure (HF) remains a fundamentally clinical diagnosis, substantial advances in the understanding of the underlying biology and pathophysiology of this syndrome has led to a greater interest in objective means to quantify its presence, severity, and potential future progression. Among the most intensively studied tools to achieve these goals are circulating biomarkers.

Various remodelling and neurohormonal activation pathways exist whose activity may be leveraged for biological monitoring. (Table 9)

Among the biomarkers, plasma concentration of natriuretic peptides (NPs) is the most commonly used initial diagnostic test in India. It may be used, when and where feasible, particularly when echocardiography is not immediately available Patients with normal plasma NP concentrations are very less likely to have HF. The upper limits of normal levels of NPs in the acute and non-acute settings are discussed below.

So, the use of assay of BNP and NT pro-BNP, is recommended to rule-out HF. However, other biomarkers discussed here, may be used in tertiary care and specialized HF clinic for select group of patients.

1.7.2. Natriuretic peptides

The natriuretic peptides represent the gold standard for biomarkers in HF. The signs and symptoms of HF are non-specific, and many patients who are suspected to have HF referred for echocardiography, finally turned to have no significant cardiac abnormality. In the developing world, like India, where the availability of echocardiography is limited, an alternative approach to diagnosis is to measure the blood concentration of NPs in HF.[36]

Many major studies have examined the threshold levels that can be used as a cut-off to exclude the diagnosis of HF for the two most commonly used natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP).[39–41] Different cut-off values have been proposed for patients presenting with acute decompensated heart failure (ADHF) and those patients presenting with a more gradual onset of symptoms.

For patients presenting with acute decompensated HF, the ideal exclusion cut-off point is proposed to be 300 pg/mL for NT-proBNP and 100 pg/mL for BNP.[42] For patients presenting with chronic heart failure, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP. The sensitivity and specificity of BNP and NT-proBNP for the diagnosis of HF are lower in non-acute settings.[39–41]

The blood levels of these biomarkers, BNP and NT-proBNP come down with treatment of chronic HF, and it correlates with improved clinical outcomes. Thus, the strategy of using BNP or NT-proBNP "guided" therapy versus standard care without natriuretic peptide measurement was compared to find out whether guided therapy renders superior achievement of guideline-directed medical therapy (GDMT) in patients with HF. However, such RCTs have yielded inconsistent results as we discuss below.

These trials comparing the two strategies, which gave mixed results differ primarily in their study populations, with successful trials enrolling relatively younger patients and only those having HFrEF. In addition, the positive "guided trials" aimed at a lower natriuretic peptide goal and/or a substantial reduction in natriuretic peptides during treatment.[43] Although most trials examining the strategy of biomarker "guided" management of patients with HF were small and underpowered, two comprehensive meta-analyses have concluded that BNP guided therapy reduces all-cause mortality in patients with chronic HF as compared to usual clinical care[44,45] especially in patients <75 years of age. The increase in survival could be attributed to the increased achievement of GDMT. In some cases, as we occasionally encounter in our clinical practice, BNP or NT-proBNP levels may not be easily modifiable. If the BNP or NT-proBNP value does not fall after aggressive HF care, we know that the risk for death or re-hospitalization for HF is significantly higher. On the contrary, some

Table 9
Biomarkers of HF.

Myocardial Injury	Neurohormonal Activation	Remodelling
Myocyte Stretch	**Arginine Vasopressin System**	**Hypertrophy/Fibrosis**
NT-proBNP, BNP, MR-proANP	Arginine vasopressin	Matrix metalloproteinases, collagen propeptides, galectin 3, soluble ST2
Oxidative Stress	**Renin Angiotensin System**	**Apoptosis**
Myeloperoxidase, oxidized low-density lipoproteins, MR-proADM	Renin, angiotensin II, aldosterone	GDF-15
Myocardial Injury	**Sympathetic Nervous System**	**Inflammation**
Troponin T, troponin I	Norepinephrine, Chromogranin A	C-reactive protein, tumor necrosis factor α, Fas, interleukins, osteoprotegerin, adiponectin

patients with advanced HF have normal NP levels or have falsely low NP levels because of obesity or they have HF*p*EF.

There are many cardiac and non-cardiac causes which can elevate NP levels that may weaken the diagnostic utility in HF. Atrial fibrillation, age and renal failure are the most important factors which can affect the interpretation of NP measurements. On the other hand, plasma NP levels may be disproportionally low in obese patients, which have to be considered when we interpret NP values.

Treatment with ARNI and monitoring with Natriuretic peptides- Sacubitril/valsartan (ARNI) increases levels of circulating BNP, so BNP is not useful for monitoring the prognosis of these patients who are on ARNI. NT-proBNP is still useful as changes in the levels of this biomarker reflect the reduced pre-proBNP secretion as a result of reduction in the ventricular wall stress in response to HF treatment.

1.7.3. Biomarkers of myocardial injury: cardiac troponin T or I

Higher levels of circulating cardiac troponin are found in patients with HF, without any evidence of myocardial ischemia and frequently in those without underlying CAD. This suggests the presence of ongoing myocyte injury or necrosis in these patients with HF. In chronic HF, elevation of cardiac troponin levels is associated with impaired hemodynamics, progressive LV dysfunction, and increased mortality rates. The data is similar in patients with acute decompensated HF also, where elevated cardiac troponin levels are associated with higher clinical adverse events and mortality. Data also shows that decrease in troponin levels over time while on treatment is associated with a better prognosis than persistent elevation in patients with chronic or ADHF. In India CAD contributes to the majority of HF burden hence, the measurement of troponin I or T should be routine in patients presenting with acutely decompensated HF syndromes. Inflammatory CMP should be considered if troponins are elevated.

The other biomarkers which are being evaluated in HF and their pathophysiological mechanism is given in Table 10. None of these biomarkers have consistently shown usefulness like BNPs.

1.8. *Non-Invasive imaging other than echocardiography*

Echocardiography remains the cornerstone of HF evaluation, however, other non-invasive imaging techniques magnetic resonance imaging, FDG PET as well as nuclear imaging plays an important role in specific situations.

An overview of the potential role of these imaging techniques are discussed below.

1.8.1. Ischemic heart disease

1.8.1.1. Viability assessment. Patients with severe left lentricular dysfunction are known to improve after revascularization, suggesting the presence of viable myocardium.[46] Viability assessment can be done by many imaging techniques such as 18F-FDG PET-CT, Cardiac MRI, SPECT-CT imaging, and dobutamine stress echocardiography. Thallium201 (Tl-201) imaging is an established procedure for the detection of viable myocardium and various protocols like stress-redistribution, rest-delayed, rest-reinjection are used for this purpose.

For the last several years many studies have come up which tested for viability with Technetium (Tc) agents. Tc agents have the advantage of superior imaging characteristics of 99mTc and hence this allows more doses to be given, along with reduced tissue attenuation of Tc-agents.[47] Though initial studies have revealed that Tc labelled tracers are less accurate than Tl-201 for detection of viable myocardium,[48] recent studies have shown that using nitroglycerin and 99mTc-myocardial agents, it is possible to achieve comparable sensitivity and specificity for myocardial viability detection as with the use of Tl-201.[49,50]

F-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography-Computed Tomography scan (PET-CT) is also one of the commonly used investigation for accurate assessment of viable myocardium.

FDG PET requires proper patient preparation. Depending on blood glucose level, glucose load or intravenous insulin as per sliding scale has to be administered according to standard protocol. If the patient's blood glucose level is more than 140 mg/mL, they have to rescheduled after control of blood glucose levels.

1.8.1.2. Inflammatory myocardial disease. Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The current diagnostic criteria for cardiac sarcoidosis includes gadolinium-enhanced MRI which was added as a minor criterion for the clinical diagnosis.

Imaging using 18F-FDG PET, in conjunction with perfusion imaging to assess fibro granulomatous replacement of the myocardium in sarcoidosis is found to have high sensitivity and specificity.

In general, PET/CT imaging for cardiac sarcoid disease should be considered in patients having second or third-degree atrioventricular block of unknown etiology in patients <55 years of age and when non-ischemic, monomorphic ventricular tachycardia manifests. In particular, an early identification of cardiac sarcoid involvement with PET/CT imaging may be crucial to install immunosuppressive therapy and thereby prevent the development of severe cardiomyopathy and heart failure symptoms.[51]

1.8.1.3. Radionuclide ventriculography. With the advent and routine use of gated myocardial perfusion studies (MPS) and highly improved cardiac computed tomography and magnetic resonance imaging, a number of previous applications of radionuclide ventriculography using MUGA(Multigated acquisition) or ERNA(equilibrium radionuclide angiography) have almost gone into oblivion or add little to the practical management of cardiac patients at present.[52,53]

1.8.2. Role of cardiac magnetic resonance imaging (CMR) in evaluation of patients with heart failure

Over the last two decades Cardiac Magnetic Resonance (CMR) imaging has established itself as the imaging of choice especially in patients with limited echo windows or right ventricular pathology.

CMR is excellent in providing accurate anatomical and functional data without exposure to ionising radiation. It is also recognised as the gold standard modality in assessment of left ventricular ejection fraction (LVEF).[55]

Table 10
Novel Biomarkers.

	Biomarker	Pathophysiological pathway
1	Mid-regional pro adrenomedullin (MR-pro ADM)	Sympathetic nervous system activation
2	Copeptin	Arginine-vasopressin system activation
3	Soluble ST-2 (Soluble suppression of Tumorigenicity −2)	Cardiac Fibrosis – Considered as a marker of long term prognosis.
4	Galectin-3 (Gal −3)	Cardiac Fibrosis
5	Kidney Injury Molecule-1	Indicates renal involvement in HF

CMR is unique in its ability to characterise myocardial morphology using T1/T2/T2*(star) mapping wherein relaxation times of different myocardial pathologies can be used to establish a diagnosis without the use of contrast. Delayed enhancement (DE) imaging is also unique for CMR wherein imaging is performed 10–15 min after giving contrast. Abnormal tissue enhances more than normal myocardium and is depicted as bright region in the background of normal dark myocardium. CMR can characterize underlying cause of heart failure based on the pattern and location of enhancement/scar/interstitial fibrosis with DE imaging.

1.8.3. Ischemic heart disease

CMR can help in making important decisions with regards to revascularisation and guiding further therapy by selecting patients who would benefit from surgical or interventional revascularisation. CMR can assess myocardial viability and potential to recover by using various markers- wall motion abnormality, myocardial thinning, delayed enhancement imaging for transmurality of infarction and by assessing contractile reserve.

Myocardial segments with wall motion abnormalities and no/mild (<25%) scar have good likelihood of functional recovery following revascularisation. Segments with more than 75% hyper enhancement have been shown to have little or no potential for functional recovery following revascularisation.[54] Transmurality of scar is the second most important predictor of functional recovery. Scar volume by CMR, also predicts survival and all-cause mortality independent of the left ventricle ejection fraction.[55–57] Viability and potential recovery of myocardium post revascularisation can also be assessed with the use of low dose Dobutamine stress by establishing myocardial contractile reserve. Flow reserve can also be determined with CMR using vasodilator stress and establishing the functional significance of indeterminate coronary artery stenosis.

CMR clearly depicts the transition zone and represents the gold standard for patient selection for aneurysmectomy.[58]

1.8.4. Non-Ischemic myocardial disease

1.8.4.1. Dilated cardiomyopathy (DCM). Presence of mid-myocardial delayed gadolinium enhancement suggests fibrosis and is associated with higher incidence of arrhythmia, adverse events, hospitalisation and mortality.[59] CMR also provided accurate assessment of LV and RV volumes, mass and systolic function. It is also very useful in ruling out common other mimics of DCM, especially ischemic cardiomyopathy in older patients.

1.8.4.2. Myocarditis. Presence of global/regional dysfunction, myocardial oedema and contrast enhancement in mid myocardial/subepicardial distribution are commonly seen imaging findings in myocarditis. Parvovirus B19 myocarditis produces lateral wall enhancement and recovery within a few months, but herpesvirus-6 myocarditis produces septal enhancement and rapid progression to cardiac failure.[60]

1.8.4.3. Granulomatous cardiomyopathy. Two most common causes of granulomatous cardiomyopathy are sarcoidosis and tuberculosis. CMR can accurately demonstrate myocardial edema and/or fibrosis along with evidence of extra cardiac involvement of sarcoidosis. Noncaseating granulomas in cardiac sarcoidosis may involve the LV free wall, basal ventricular septum, right ventricle, papillary muscles, right and left atria. The clinical manifestations depend on the site and extent of these granulomas. Also, LGE imaging can act as a guide to decide the site of endomyocardial biopsy. In spite of extensive myocardial involvement, pericardial involvement is uncommon and asymptomatic. Presence of mediastinal adenopathy may be seen and provides an accessible site for biopsy for histopathological confirmation.[61,62]

Myocardial tuberculosis is considered an uncommon clinical entity and is only infrequently diagnosed ante-mortem. Pathologically, there are three patterns of involvement:

- Miliary tuberculosis, with the heart being just one of the many organs involved
- Diffuse infiltrating interstitial disease.
- Caseating nodular disease (tuberculoma).

The miliary form is by far the commonest; tuberculomas are much rarer. The lesions may involve the atria, the ventricles, or the interventricular septum and may lead to heart block. It may also present as intracavitory mass lesion, commonly within the atria. Mediastinal adenopathy and pericardial involvement with pericardial effusion and pericarditis are common imaging findings.[63,64]

1.8.5. Non-ischemic myocardial disease

1.8.5.1. Hypertrophic cardiomyopathy: HCM. CMR will accurately depict various phenotypes of HCM- symmetrical, asymmetrical, apical, mid cavity etc. The apical variety and RV involvement is often difficult to diagnose on echocardiography due to poor echo window and CMR is useful. Typical pattern of LGE in HCM is midwall patchy or punctate hyper enhancement in a thickened myocardium in a noncoronary distribution.[65]

Two common types of HCM progression to the burned-out phase are seen at imaging: a dilated form where the LV is most commonly affected and a restrictive pattern where atrial dilatation is the most prominent morphologic finding. Both patterns of progression lead to heart failure, which is commonly unresponsive to available therapies and ultimately necessitates cardiac transplant.

CMR allows effective assessment of septal thickness, quantification of ejection fraction and identification of fibrosis. Cardiac MR imaging can also demonstrate morphologic abnormalities of the mitral valve apparatus and papillary muscles, which are important contributors to development of sub aortic gradients and LVOT obstruction. CMR also can accurately quantify the amount of mitral regurgitation, which can help in deciding surgical management. Since the most devastating complication of HCM is SCD, cardiac MR imaging allows prediction of which patients require ICD implantation.[66]

1.8.5.2. Iron overload cardiomyopathy. Heart failure due to iron overload is the most common cause of death in patients with thalassaemia major worldwide.

Iron assessment by T2* relies on the measurement of T2* relaxation from gradient echo (GRE) sequences. T2* values in the mid-septum have been calibrated to myocardial tissue iron levels in [Fe] milligrams per gram dry weight and indicate a strong inverse linear relationship.[67]

T2* monitoring is now internationally recommended in the annual monitoring of transfusion-dependent patients at risk of developing myocardial iron loading. In this way, T2* imaging of cardiac iron loading has progressed from a research technique to a clinically validated tool and has transformed clinical outcomes in β-thalassaemia major.[68]

1.8.5.3. Arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is characterised by fibro fatty infiltration of the right or both ventricles. Recently published international task force guidelines emphasise assessment of regional wall motion abnormality and RV volumes and ejection fraction.[69] CMR can contribute to one major or one minor criteria towards the diagnosis of ARVC according to the Task Force. LV involvement can also be accurately demonstrated by CMR.

1.8.5.4. Cardiac amyloidosis. Cardiac amyloidosis is characterized by thickened myocardium, atria, and interatrial septum, with diminished systolic function and biatrial enlargement. Delayed enhancement is typically global subendocardial progressing to transmural, but can also occasionally be patchy.[70] A unique feature of cardiac amyloidosis is the alteration of T1 kinetics of gadolinium distribution, with nulling of the myocardium before the blood pool due to diffuse amyloid infiltration, resulting in higher gadolinium uptake and T1 shortening

1.8.5.5. Left ventricular non-compaction. This is characterised by prominent trabeculations in the LV cavity with deep intertrabecular recesses. Patients present with heart failure, arrhythmias or embolic events. There is lack of consensus in diagnostic criteria for LV non-compaction especially due to overlap with DCM and apical HCM. Both CMR and echo can depict hypertrabeculated myocardium but CMR can depict biventricular anatomy/function, can exclude other anomalies and also demonstrate fibrosis.[71]

1.9. *Invasive evaluation of heart failure*

Vast majority of patients with HF can be evaluated using non-invasive modalities like echocardiography and CMR. But we have to resort to invasive techniques occasionally as we discuss below.

1.9.1. Indications for invasive testing in heart failure

a) To resolve diagnostic uncertainties in patients with inconclusive clinical findings.
b) For evaluation of pulmonary vascular disease.
c) To look for coronary anatomy when ischemia is suspected as a cause of heart failure
d) To assess for suitability for advanced therapies in chronic heart failure like work-up for cardiac transplant

1.9.2. Modalities for invasive assessment of heart failure

Invasive evaluation of heart failure (HF) can be discussed under the following headings- Right heart catheterization (RHC), Coronary arteriography, Endomyocardial biopsy and Implantable hemodynamic monitoring devices.

A. Role of RHC in heart failure –

There is no role of routine RHC in management of heart failure[72] as most therapies in treatment of HF are based on either symptomatic improvement or survival benefit rather than their effect on hemodynamic variables. Routine use of pulmonary artery catheter insertion to manage heart failure was not found to improve morbidity and mortality in landmark ESCAPE trial.[72] Thus, it is no longer recommended to use right heart catheterization routinely in every patient.[26,27] Hemodynamic monitoring can be considered in patients with clinically indeterminate volume status and those refractory to initial therapy.

The Subset of patients, which might get benefit from RHC include –

1. Patients with persistent severe symptoms despite optimum medical therapy.
2. Dependence on intravenous inotropic infusion after initial clinical improvement.
3. Patients with cardiogenic shock requiring vasopressor therapy and being considered for mechanical circulatory support.
4. Patients being evaluated for heart transplantation

B. Role of Coronary arteriography

Those with previous history of angina and CAD and who are considered suitable for potential coronary revascularization should preferably have an invasive coronary angiogram in order to establish the diagnosis of CAD and its severity. In view of the high prevalence of CAD in young population in India, it is better to err on the side of doing a CAG rather than not doing it.

Patients with malignant arrhythmia and survivors of sudden cardiac death are candidates for coronary angiogram. Those who have recent worsening of symptoms of CAD also earn a coronary angiogram even if prior angiograms are unremarkable.

1.10. *C. Endomyocardial biopsy -*

Given the limited diagnostic yield, routine use of Endomyocardial biopsy (EMB) is not indicated. It should be considered only when a specific diagnosis is being suspected, that is likely to impact the therapy. Endomyocardial biopsy should not be performed in the routine evaluation of HF.

Adult and pediatric patients who present with the sudden onset of severe left ventricular failure within 2 weeks of a distinct viral illness and who have typical lymphocytic myocarditis on EMB have an excellent prognosis. Therapy with combinations of immunosuppressive agents has been associated with improved outcome in giant cell myocarditis and necrotizing eosinophilic myocarditis. EMB can be helpful in identifying those patients. (Cooper et al. European Heart Journal (2007) 28, 3076–3093).

EMB is useful for

1. Rapidly progressive heart failure that worsens despite optimum medical therapy:
   a Unexplained new-onset heart failure (HF) of less than two weeks.
   b Unexplained new-onset HF of two weeks with a dilated left ventricle and new ventricular arrhythmias or heart block.
2. Suspected cardiac rejection after heart transplantation
3. Suspected myocardial infiltrative disorder

Important considerations while planning EMB -

1. Anticipated yield of the procedure as well as the risk of sampling error and procedure related complications.
2. The availability of effective therapy for the diagnosis that is obtained.
3. EMB is recommended in when the unique prognostic and diagnostic value of the information gained is likely to outweigh the procedural risk.
4. Facilities and personal who can interpret the biopsy specimens.

1.10.1. Role of implantable hemodynamic monitoring devices in heart failure

Newer devices permit the measurement of ambulatory hemodynamics with implantable monitors. These devices include RV leads that measure intrathoracic impedance and pressure, wireless pulmonary artery pressure monitors, and left atrial pressure sensors. These devices are based on the principle that rise in LV filling pressure commonly occurs days before symptoms, changes in weight, or hospitalization. However currently there is no established role of these devices in heart failure management. The commonly available devices are the Chronicle device (Medtronic, Inc., Minneapolis), and CardioMEMS^{TM} device.

1.11. Diagnostic evaluation: evaluation protocol for heart failure suited to India –

1.11.1. Introduction

The patients of heart failure require a detailed evaluation for etiology, prognostication, and assessment of treatable co-morbidities that can improve outcomes in these patients.

1.11.2. Evaluation in patients with HF

After a detailed clinical evaluation, all patients suspected of having HF should have an ECG, Chest X-Ray and an echocardiogram as discussed. We will be able to diagnose and prognosticate most of the patients with these three investigations. But we need further evaluation in a sub-group of patients, one group where we could not reach a diagnosis and the other group where we need to further quantify or qualify the disease or the associated co-morbidities.

Some of the patients need advanced imaging modalities like CMR, cardiac CT or invasive cardiac catheterization. Few patients need to be referred to other sub-specialties for evaluation. Examples include thyroid dysfunction related cardiomyopathy, hemochromatosis, sarcoidosis and amyloidosis. Holter monitoring may be required in patients suspected of having tachycardiomyopathy. Obstructive sleep apnea is a common co-morbidity encountered with HF and that needs evaluation and prompt treatment.

A proposed algorithm for the work-up of patients and follow-up is given below.

HEARTFAILURE–PROPOSED INVESTIGATION PROTOCOL

FIRST LEVEL–FOR ALL PATIENTS

1. Height and Weight – at each visit
2. Heart rate, Supine and standing BP(at each visit)
3. Chest X Ray and ECG(Initial visit and to be reviewed periodically)
4. Echocardiogram-(Initial visit and to be reviewed periodically)
5. Holter – (If atrial fibrillaion or ventricular arrhythmias are suspected or suspected tachycardiomyopathy)
6. Complete blood count
7. ESR
8. Serum BNP or NT Pro-BNP(to be repeated as and when required)
9. LFT (Liver function tests) – S bilirubin, SGPT
10. RFT (Renal function test) – Creatinine with serum electrolytes to be repeated as required
11. Virology- HIV/HBsAg/AntiHCV antibody
12. Thyroid profile – Screening with TSH levels.
13. 6 min walk test(ambulant patients)

SECOND LEVEL INVESTIGATIONS- IN SELECTED CASES

1. Cardiac Cath[Right atrial mean pressure, Pulmonary Capillary Wedge, pulmonary artery -PA(systolic/diastolic /mean), Left ventricular end-diastolic pressure (LVEDP), pulmonary vascular resistance (PVR), Coronary angiogram, Coronary venogram, left and right ventricular (LV and RV) angiogram as required
2. Cardiac MRI(with hepatic screening for hemochromatosis)

SECOND LEVEL WORKUP- AS PER PHENOTYPE ON Echocardiography.

Expansion of Short forms. HRCT – High Resolution computed Tomography, S.ACE – Serum Angiotensin converting enzyme, S.Ca – Serum calcium, S.Ph – Serum Phosphorus, ASO Titer – Antistreptolysin O Titer, S.Ca – Serum calcium.

DCM	HCM	RCM
Family screening	Family screening	
S Ferritin		S. Ferritin
Echo–dyssynchrony		
Viral Titres (Coxsackie/Enterovirus)		
If conduction abnormality/VT: Sarcoidosis to be ruled out- S.Ca /S.Ph /HRCT Chest / S.ACE		If conduction abn/ VT: Sarcoid- S.Ca/S.P/ HRCTchest/S.ACE
If ECG/Echo suggestive: Amyloid workup- Abdominal Fat pad Biopsy		If ECG/Echo suggestive: Amyloid workup- Abdominal Fat pad Biopsy
Pediatric age: ASO titre		

2. Management of heart failure

2.1. *Non-pharmacological management*

Nonpharmacological management occupies an important place in heart failure therapy. However, most of the recommendations are based on consensus expert opinion or are derived from limited trial data.

2.1.1. Sodium restriction

Increased salt consumption is one of the most important causes of worsening of heart failure.[73,74] Dietary sodium restriction results in reduction in dose of diuretic which helps in reducing plasma renin activity and improves overall outcome.[75] Observational data suggest an association between dietary sodium intake with fluid retention and risk of hospitalization.[76,77] Other studies have reported worsening neurohormonal profile with sodium restriction in heart failure.[78] Majority of the studies have been performed in patients with HFrEF except one which has been performed on HFpEF.[79] These data have been mostly obtained from a predominantly white population and hence may not be fully extrapolated to the Indian context. The scenario has been further complicated by the results shown by 2 randomized control trials that lower sodium intake is associated with worse outcome in patients with HFrEF.[80,81]

American Heart Association and the United States Department of Agriculture (USDA) recommend sodium intake of 2.3 gm (equivalent to 5.7 gm of common salt) per day for the general population, and 1.5 gm for those with hypertension, blacks and middle-aged and older people.[82] In India it is reasonable to limit daily sodium intake to 2–3 gm. In severe cases of heart failure sodium intake may be restricted to 500 mg/day[83]

2.1.2. Obesity

Obesity has generally been defined as body mass index (BMI) $\geq$30 kg/m$^{2.}$ For Asian Indians 25 kg/m2 is accepted as the upper level of normal BMI. However, HF patients with BMI between 30-35 kg/m^2 have lower mortality and hospitalization rates as compared to those with BMI in normal range.[84] It has been shown that overweight (25–29.9 kg/m^2) and obese patient with heart failure have better survival than patients with ideal body weight (BMI 18.5 to 24.9 kg/m^2).[85,86] Low BMI (<18.5 kg/m^2) subjects with HF appear to have the highest mortality. Reasons for this "obesity paradox" remain unexplained. Until further data are available, caloric restriction as part of the treatment of the severely obese patient with HF and weight stabilization or reduction in overweight and mildly obese patients seem reasonable.

2.1.3. Fluid intake

Fluid restriction is indicated in setting of symptomatic hyponatraemia whether or not it is caused by pharmacological therapy. In the outpatient setting, fluid restriction generally is indicated for advanced HF refractory to high doses of oral diuretic agents. Most HF management programs monitor patient volume status reliably and effectively by measuring daily morning weight.

Non-adherence with dietary sodium restriction or pharmacological therapy for HF, use of non-steroidal anti-inflammatory agents and glitazones and excessive high fluid intake (>6 l per day) are the usual causes of diuretic refractoriness.

2.1.4. Nutritional management

Cardiac cachexia is associated with stimulation of cytokines, tumor necrotic factor-α and chronic low cardiac output state. Special nutritional recommendations have been made regarding frequency and size of meal to ensure high energy diet. There is no evidence for use of anabolic steroids.

Multivitamin and mineral supplementation, especially thiamine, may be recommended as all patients, who are on diuretic therapy, are usually deficient of essential vitamins and minerals.[87,88]

Naturoceutical products including ma huang, ephedrine metabolites, hawthorne or imported Chinese herbs are contra-indicated in HF.[89]

2.1.5. Lifestyle modification

The diagnosis of HF and its prognosis usually provoke anxiety. Relaxation techniques like meditation and yoga may improve patient daily functioning.[90]

Standard heart failure therapy may worsen sexual dysfunction leading to discontinuation of HF therapy and deterioration of HF symptoms. Phsophodiesterase – 5 inhibitors can be safely used in compensated HF patient but not with nitrates.

The reversal of ventricular remodelling and normalization of left ventricular ejection fraction after cessation of alcohol consumption are established facts.[91,92]

2.1.6. Exercise rehabilitation

Several studies have reported that physical conditioning by exercise training improves functional aerobic capacity, health related quality of life and hospitalization rate in patients with HF. One large randomized controlled trial has reported a modest but non-significant reduction in primary composite outcome of all – cause mortality or all – cause hospitalization.[93,94] In a recent Cochrane review on exercise training which included 33 trials with 4740 patients with HF (majority HFrEF), it was reported that there was trend of reduction in mortality.[94] Regular aerobic exercise and inspiratory muscle training programs are recommended.

2.1.7. Other therapies

2.1.7.1. Continuous positive airway pressure. Sleep disorders are highly prevalent in HF patients. It is therefore recommended that formal sleep evaluation should be undertaken in patients who remain symptomatic despite optimal HF therapy. It has been shown that use of continuous positive airway pressure (CPAP) reduces edema, daytime muscle sympathetic nerve activity, systolic blood pressure, frequency of ventricular premature beats during sleep and improves LV function.[95–97] A Canadian trial found that patients randomized to CPAP had increased LVEF, improved nocturnal oxygenation and improved 6 min walk distance but no survival benefit was reported.[98] However, CPAP may be harmful in presence of central sleep apnoea.

2.1.7.2. Supplemental O_2. Oxygen supplementation is a useful adjunct in hospitalized HF patients during acute decompensation. Resting or exertional hypoxemia due to pulmonary congestion requires increased dose of diuretic agent rather than supplemental O_2 therapy.

2.1.7.3. Vaccination. Polysaccharide and conjugated pneumococcal vaccine every 5 years and influenza vaccination every year are recommended in all HF patients who do not have any known contradictions.[573]

2.2. *Pharmacological management of acute HF*

2.2.1. Aims of management

- Identification of the hemodynamic profile of patient (by assessing the volume status and adequacy of systemic perfusion),
- Identification of the precipitating factor,
- Relieving symptoms,
- Directly improving short- and long-term outcomes,
- Initiation and optimization of long-term therapies.

The central hemodynamic components of decompensated heart failure are the elevation of filling pressures and the reduction of cardiac output. The assessment of these hemodynamic profiles helps to direct the pharmacotherapy.[99] Profile B, "warm and wet," with congestion and adequate perfusion is the most common type. (Figs. 6 and 7)

2.2.2. Optimizing volume status

The rate of diuresis should achieve desirable volume status without causing a rapid reduction in intravascular volume, which may result in symptomatic hypotension or renal dysfunction. Diuretics are the mainstay of therapy in acute decompensated heart failure to decrease volume overload. To date, diuretics have

LOW PERFUSION AT REST? (COLD FOREARMS & LEGS, OBTUNDATION, DIZZINESS, NARROW PULSE PRESSURE, PULSUS ALTERNANS, DECLINING Na LEVEL, WORSENING RENAL FUNCTION)			
		NO	YES
CONGESTION AT REST? (ORTHOPNOEA, OEDEMA, ELEVATED JVP, S3, RALES, ASCITES)	NO	WARM & DRY	COLD & DRY
	YES	WARM & WET	COLD & WET

Fig. 6. Evaluation of heart failure profiles[99].

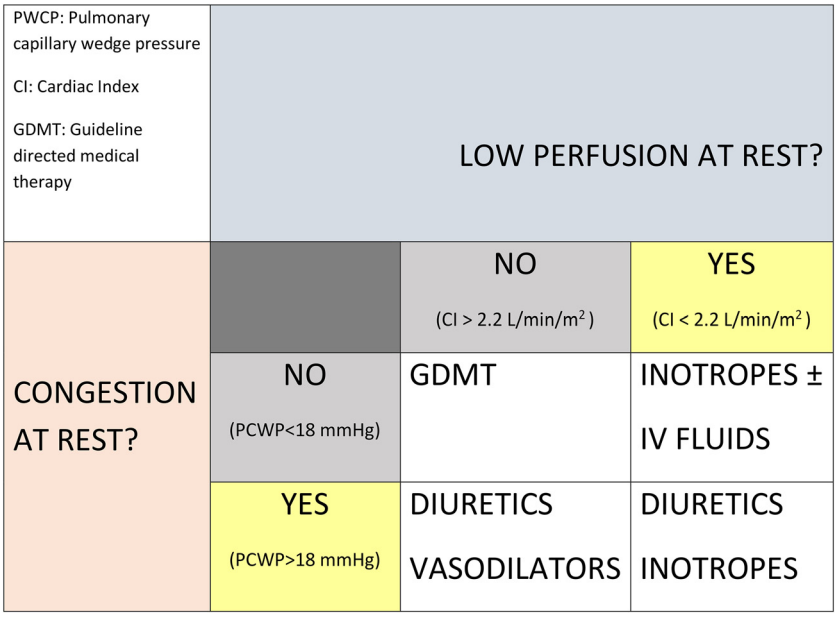

Fig. 7. Treatment outline for heart failure profiles[99].

not improved survival in HF patients. Current guidelines recommend intravenously administered diuretics as first line therapy for volume overload.[100] Loop diuretics are initial diuretics of choice. DOSE Trial randomized diuretic administered as continuous infusion or twice daily intravenous bolus. The co primary endpoints, patient global assessment of symptoms and mean change in serum creatinine at 72 h, were not significantly different between treatment groups. High dose bolus injection may cause vestibular toxicity. For secondary endpoints, higher doses were associated with significantly improved net urine output, weight loss, and dyspnea balanced by worsening renal function.[101] (Tables 11 and 12)

In patients who are refractory to high dose loop diuretics, combining a loop diuretic with a distal tubule acting agent such as oral metolazone or intravenous chlorthiazide produces a synergistic diuretic effect. Inotropic therapy should generally be reserved for patients with evidence of low cardiac output. Administration of low dose dopamine to enhance diuresis has been abandoned. Results from the DAD II suggested no difference between high-dose furosemide, low-dose furosemide, and low-

Table 11
Use of Diuretics for correction fluid overload.[101]

Diuretic naïve: Furosemide 20–40 mg iv bolus.
Previously taking diuretic: Furosemide 2.5 x previous dose (max 180 mg) (1–2 x previous dose if declining renal function, low albumin or SBP <90 mm Hg).
If inadequate diuresis consider:
- Increasing iv dose or
- Switching to continuous iv infusion or
- Add diuretic with different mechanism (e.g. metolazone, hydrochlorthiazide, chlorthalidone)

Table 12
Comparison of commonly used Diuretics available for management of HF.

	Furosemide	Bumetanide	Torsemide	Metolazone	Chlorothiazide
Mechanism of action	Loop Diuretic	Loop Diuretic	Loop Diuretic	Thiazide-like diuretic	Thiazide diuretic
Bioavailability	40%–70%	80%–95%	80%–90%	65%	N/A
Dose Equivalents	PO: 40 mg. IV:20 mg	1 mg	20 mg	N/A	N/A
Usual oral dosing	40–80 mg once or twice daily, max 600 mg/d	1–2 mg once or twice daily, max 10 mg/d	20–40 mg once or twice daily, max200 mg/d	2.5–5 mg once daily, max 10 mg/d	N/A
Usual intravenous bolus dosing	Diuretic naïve: 40–80 mg q8–24 h Diuretic PTA: 1–2.5 x PO dose PTA*. May repeat in 2–3 h. Max 600 mg/d	Diuretic naïve:0.5–1 mg q8–24 h Diuretic PTA: 1-2.5 x PO dose PTA* May repeat in 2–3 h. Max 10 mg/d	Diuretic naïve: 10–20 mg q8–24 h Diuretic PTA: 1-2.5 x PO dose PTA* May repeat in 2–3 h. Max 200 mg/d	N/A	250mg–500 mg q12–24 h,max 2 gm/day
Usual intravenous continuous infusion dosing	40–80 mg IVB load, then 5–10 mg/h.max 40 mg/hr	1–2 mg IVB load,then 0.5–2 mg/h.max 2 mg/hr	20–40 mg IVB load,then 5–20 mg/h.max 20 mg/hour	N/A	N/A
Duration of action	4–6 h	6–8 h	12–16 h	12–24 h	6–12 h

IVB = intravenous bolus, PO = oral,PTA = prior to admission.

dose furosemide plus dopamine, on mortality or readmission for ADHF.[102]

The EVEREST Trial randomized 4133 patients with ADHF (LVEF ≤40%) to tolvaptan or placebo.[103] The primary outcome was significantly improved with tolvaptan; however, this benefit was driven primarily by reduction in weight loss.

Ultrafiltration reduces pulmonary artery pressure and increases diuresis. Complications of ultrafiltration include those associated with central venous access and intravascular depletion. Beneficial effect on weight loss as compared to diuretics is not full proof. Plasma creatinine increases more than with diuretics.[104,105]

At present the role of ultrafiltration is restricted to diuretic resistant cases and dyselectrolytemia.

2.2.3. Vasodilators

Intravenous vasodilators often provide rapid symptom resolution, especially in patients with acute pulmonary edema or severe hypertension. Vasodilators should be avoided in patients with reduced filling pressures or symptomatic hypotension. But there is little evidence for improved outcome. Nitroglycerin exhibits primarily venodilation at low doses and mild arterial vasodilation at higher doses; thus, it is the preferred agent for preload reduction.[106]

Nitroprusside is a balanced arterial and venous vasodilator which results in augmentation of cardiac output and reduction in filling pressure with greater reduction in pulmonary artery pressure, systemic vascular resistance, and blood pressure. It is used primarily in patients with high systemic vascular resistance and often requires invasive hemodynamic monitoring. The primary disadvantages of nitroprusside are hypotension, tachyphylaxis and risk of cyanide and thiocyanate accumulation. In patients with substantial hepatic or renal impairment, this agent should be avoided or dose and duration of therapy should be minimized.

Nesiritide or human B-type natriuretic peptide produces dose-dependent venous and arterial vasodilation with increase in cardiac output and natriuresis. This agent should be used for selected patients (Table 13).[107–109]

2.2.4. Inotropic agents

Dobutamine stimulates β-adrenergic receptors with little effect on α-adrenergic receptors, so that contractility is increased with peripheral and pulmonary vasodilation. It is started at a high dose and de-escalated to the lowest dosage to maintain the desired effect. Patients receiving chronic maintenance infusions generally exhibit tachyphylaxis and require increasing dosages over time.

Dopamine stimulates β-receptors, α-receptors and dopaminergic receptors that cause vasodilation in renal and peripheral vasculature. At dosages of 3 μg/kg/min or less, dopamine is predominantly vasodilatory. Alpha-adrenergic stimulation dominates when dopamine doses reach 5 μg/kg/min, or when other vasopressors are given. When blood pressure support is the initial need, dopamine should be started at a dosage of at least 4 μg/kg/min. Similarly, when patients are weaned from the use of dopamine as a pressor agent, it may be necessary to discontinue it once a dosage of 3 μg/kg/min is reached.

Milrinone is a phosphodiesterase-III inhibitor that blocks degradation of cAMP. Milrinone is the drug of choice in patients receiving chronic beta-blocker therapy because its inotropic effects don't involve stimulation of beta-receptors. In patients with cardiogenic shock on beta blockers, initial noradrenaline followed by milrinone is recommended.[110–113]

Epinephrine and Norepinephrine provide significant additional inotropic and blood pressure support for short-term life-saving intervention. Both norepinephrine and epinephrine stimulate type 1β-adrenergic receptors and α-adrenergic receptors, increasing contractility, heart rate, and peripheral vascular resistance, while promoting cardiac arrhythmias and ischemia. These should not be administered except in true emergency situations.

Vasopressin is used increasingly to potentiate the effects of catecholamines in patients who remain severely hypotensive despite high-dose pressor support.[114,115] Vasopressin has been used for days, in doses of 0.05 to over 0.1 U/min. Although vasopressin is considered an antidiuretic hormone, its use in critical settings is sometimes associated with profound water diuresis that reverses after discontinuation of the drug. (Table 14)

Levosimendan sensitises troponin C to calcium thereby improving myocardial contractility and haemodynamics. Levosimendan also has vasodilatory and anti-ischaemic properties.[116–118] Levosimendan is currently used in cardiogenic shock in combination with other vasopressors and over dobutamine only if reversal of beta-blockers is needed to improve the hypo perfusion.

2.2.5. Ventilatory support

Supplemental oxygen and assisted ventilation should be reserved for patients with hypoxaemia. In the very few studies that have systematically examined effects of increasing FiO2, oxygen supplementation causes a fall in cardiac output and increases in SVR and cardiac filling pressures. In a study by Gray et al., 1069 patients with AHF admitted with cardiogenic pulmonary oedema and arterial pH of less than 7.35 were randomised to standard oxygen therapy, continuous positive airway pressure (CPAP), or non-invasive intermittent positive

Table 13
Vasodilators for management of acute heart failure.

	Nitroglycerin	Nitroprusside	Nesiritide
Mechanism	Increase NO synthesis and cGMP	Increase NO synthesis and cGMP	Activate guanylate cyclase-linked NP receptor A to increase cGMP
Clinical effects	Vasodilator (venous arterial)	Vasodilator (venous = arterial)	Vasodilator (venous = arterial)
Indication	Warm & wet. Cold & Wet. HTN Crises. ACS	Warm & wet. Cold & Wet. HTN Crises	Warm & wet. Cold & Wet
Usual dosing	10-30mcg/min and titrate by 10–20 mcg/min every 10–20 min to max 200 mcg/kg/min	0.1-0.2mcg/kg/min and titrate by 0.1-0.2 mcg/kg/min every 10–20 min to max 2 mcg/kg/min	0.1mcg/kg/min and titrate by 0.005 mcg/kg/min every 3 h. to max 0.03 mcg/kg/min
Onset.	1–5 min	1 min	15–30 min
Half-life	1–4 min	10 min	20 min
Elimination	Inactive metabolites in urine (no renal/hepatic adjustment)	Cyanide (hepatic). Thiocynate (renal)	NP receptor C (no renal/hepatic adjustment)

ACS = acute coronary syndrome.cGMP = cyclic guanosine monophosphate.HTN = hypertensive.NO = nitric oxide.NP = natriuretic peptide.

Table 14
Hemodynamic effects of ionotropic agents.

	CO	PCWP	SVR	MAP	HR
Dobutamine	↑↑↑	↓/←→	↓	↓/←→	↑/←→
Dopamine- moderate	↑↑	↑/←→	↑/←→	↑↑	↑
Dopamine- high	↑	↑	↑↑↑	↑↑	↑↑
Milrinone	↑↑	↓	↓↓	↓/←→	↑/←→
Levosimendan	↑↑↑	↓↓	↓↓	↓	↑

pressure ventilation (NIPPV). Compared to standard oxygen therapy, non-invasive ventilation (CPAP or NIPPV) did not alter 7- and 30-day mortality, but did lead to greater reduction in dyspnoea, heart rate, and hypercapnia[118]. A subsequent meta-analyses on the use of non-invasive positive pressure ventilation (NIPPV) showed a reduction in hospital mortality compared to standard treatment.[119] This is not suitable for mentally obtunded patients.

Apart from above measures the guideline directed therapies being taken by patient for heart failure before decompensation also needs to be titrated according to need. (Table 15)

2.3. *Pharmacotherapy of heart failure with reduced ejection fraction (HFREF)*

The major goals of treatment in patients with HFrEF are to improve symptomatic status and functional capacity, prevent recurrent hospitalizations and reduce mortality. This section discusses the pharmacotherapy of HFrEF, Stage C with special focus on:

A. Renin-Angiotensin System (RAS) inhibition
A1. ACE Inhibitors (ACEI)
A2. Angiotensin receptor blockers (ARB's)
A3. Is a combination of ACEI/ARB recommended for HFrEF?
B. Angiotensin receptor-Neprilysin inhibitors (ARNI)
C. Beta-blockers
a. What first: ACEI or beta-blocker or simultaneous initiation of both?
D. Mineralocorticoid receptor antagonists (MRA's)
E. Diuretics
F. Ivabradine
G. Digoxin
H. Hydralazine and Isosorbide di nitrate
I. Diuretics
J. Pharmaco-economic aspects of HF in India
K. Summary

A 1 RAS Inhibition (RAS) with ACEI

- Therapy with ACEI leads to symptomatic improvement, reduced hospitalization and significantly reduces adverse outcomes in patients with HFrEF. Various randomized controlled trials (RCTs) have established the role of ACE inhibition in patients across the spectrum of HF (mild, moderate and severe HF) in those with and without coronary artery disease.[120–125] Meta-analysis of previous ACEI trials have reported lower all-cause mortality (odds ratio [OR], 0.77 $P < 0.001$) as well as lower mortality and HF hospitalization (OR, 0.65 $P < .001$) in those receiving ACEI.[126] All ACEI's are reported to reduce the combined end point of mortality and hospitalization for HF, suggesting a "class effect" with no significant differences among the available ACEI in their effects on symptoms.
- Clinical Use:
  - ACEI should be started at low doses (listed in Table 16) and titrated upward (as tolerated) to doses shown to reduce the risk of cardiovascular events in clinical trials. Dose adjustments may be made at 1–2 weekly intervals. In case maximal doses are not tolerated, the immediate lower doses should be tried.
  - Caution should be exercised in patients with low systemic blood pressure, renal insufficiency (serum creatinine SCr > 2.5 mg/dl), and elevated serum potassium (>5.0 mEq/L). Careful monitoring of serum potassium and S Cr is imperative; renal function and electrolytes should be measured at initiation and with each dose adjustment. Although a slight increase in SCr often occurs after initiation of ACEI, an exact threshold for discontinuing therapy has not been

Table 15
Optimizing therapies for chronic heart failure during acute decompensation.

Medication	Transition in Hospital	Monitoring
Diuretics	Continue or augment(if indicated).unless signs/symptoms of dehydration	Daily weight (standing) Strict intake and output Vital signs(BP,HR,RR,O2 saturation) including orthostatic BP,HR BUN. Serum creatinine Serum potassium and magnesium
Beta blockers and ARBs	Continue unless decompensation due to recent addition or dose increase (in which case reduce dose) Discontinue if significant hypotension,bradycardia, or overt cardiogenic shock	BP and HR including orthostatic BP, HR
ACE inhibitors and ARBs	Continue. unless hypotension or acutely worsening renal function	BP and HR including orthostatic BP,HR Strict intake and output BUN. Serum creatinine Serum potassium
MRAs	Continue unless K >5.5 CrCI <30 ml/min	BP and HR including orthostatic BP,HR Strict intake and output BUN. Serum creatinine Serum potassium
Digoxin	Continue unless acutely worsening renal function. Significant bradycardia (HR <45bpm), Or signs/symptoms of toxicity Note:half-life = 36 h if normal renal function (minimum of 5–7 days to reach steady state post initiation or dose change)	HR Serum Creatinine Serum potassium, magnesium, and calcium Serum digoxin concentration (at least 6 h post dose) if not recently obtained, change in renal function, or addition/removal of interacting medication
Hydralazine + Isosorbide dinitrate	Continue unless significant hypotension	BP and HR including orthostatic BP. HR

ACE = angiotensin converting enzyme, ARBs = angiotensin receptor blockers, BP = blood pressure, BUN = blood urea nitrogen, CrCI = creatinine clearance, HR = heart rate, K^+ = potassium, MRAs = mineralocorticoid receptor antagonists, O_2 = oxygen,RR = respiratory rate.

Table 16
Commonly Used drugs in HFrEF and their dose schedules.

ACE inhibitors	Initiating dose	Maximum dose
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Ramipril	1.25 to 2.5 mg once	10 mg once
ARBs		
Losartan	25 to 50 mg once	50 to 150 mg once
Valsartan	20 to 40 mg twice	160 mg twice
ARNI: Sacubitril/valsartan	49/51 mg sacubitril/valsartan bd OR lower dose 24/26 mg BID)	97/103 mg BID (sacubitril/valsartan)
Beta blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	50 mg twice
Carvedilol CR	10 mg once	80 mg once
Metoprolol succinate extended release	12.5 to 25 mg once	200 mg once
Aldosterone antagonists		
Spironolactone	12.5 to 25.0 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Ivabradine	5 mg bd	7.5 mg bd
Loop diuretics		
Bumetanide	0.5 to 1.0 mg od/bd	10 mg
Furosemide	20 to 40 mg od/bd	600 mg
Torsemide	10 to 20 mg od	200 mg
Thiazide diuretics		
Chlorothiazide	250 to 500 mg od/bd	1000 mg
Chlorthalidone	12.5 to 25.0 mg od	100 mg
Hydrochlorothiazide	25 mg od/bd	200 mg
Indapamide	2.5 mg od	5 mg
Metolazone	2.5 mg od	20 mg
Potassium-sparing diuretics		
Spironolactone	12.5 to 25.0 mg od	50–100 mg
Eplerenone	25 mg od	50 mg od
Triamterene	50 to 75 mg bd	200 mg
Amiloride	5 mg od	20 mg
Hydralazine/isosorbide dinitrate Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily
Digoxin	0.125 mg	0.25 mg (serum level < 1.0 ng/mL)

established. Up to 50% increase in SCr and increase in potassium not >5.5 mEq/L is generally considered acceptable.
  - Important side effects in patients with HF relate to hypotension and azotemia. However both are well tolerated and asymptomatic hypotension does not usually require lowering the dose or drug discontinuation. The azotemia is frequently due to the relative volume-depletion accentuated by concomitant diuretics and is therefore often improved by reduction in diuretic dose. Other side effects include cough in 15–30% (a higher incidence has been reported amongst Indians as compared to Western cohort)[127] and angioedema (which may occur in <1% of patients) the latter often necessitating drug withdrawal. It is important to distinguish the ACEI induced cough from that due to pulmonary congestion from worsening HF or cough due to bronchospasm induced by concomitant beta blocker use. In occasional cases, if the cough significantly impacts the patient's quality of life, a change to an ARB, is needed.
  - ACEI should not be administered to pregnant patients or those planning to become pregnant.
  - An abrupt withdrawal of ACEI can often precipitate clinical deterioration and should be avoided.
- Recommendations: All patients with prior or current symptoms of HFrEF regardless of etiology, should be started on an ACEI, unless there is a contraindication.

A 2 RAS Inhibition with ARB's

- Angiotensin-receptor blockers offer an alternative approach to the inhibition of the RAS. and are known to produce favourable hemodynamic, neurohormonal, and clinical effects as substantiated in different RCT's.[128–132]
- Analysis of trials in which ARBs were compared with placebo without background ACEI therapy, confirmed a benefit of ARBs in reducing mortality and hospitalization although this was only a non-significant trend.[133] Direct comparison with ACEI did not however reveal any superiority of ARB's in reducing either mortality or hospitalization[135]
- In patients of chronic HF on ACEI and also receiving beta-blockers, no significant effect of ARB's on mortality or combined endpoint of mortality and morbidity was reported.[134]
- In one of the more recent meta-analysis of ACE/ARB's in HF by Tai et al. (n = 47,662 patients), ACEI reduced all-cause mortality by 11% and cardiovascular mortality by 14%. In contrast, ARBs had no beneficial effect on reducing all-cause or cardiovascular mortality.[135]
- Hence, based on current evidence, ACEI/beta-blockers should be considered as first-line therapy to limit morbidity and mortality outcomes in patients with HF and there is no additional benefit of adding ARB's in patients taking both ACEI and beta-blockers, and tolerating them well.
- Clinical Use:
  - ARBs also need to be started at low doses and gradually titrated upward (see Table 1), and all attempts should be made to use doses that have been shown to reduce cardiovascular events in RCT's. Titration is generally achieved by doubling the doses every few days; it is important to monitor renal function at initiation and with any dose titration.
  - Similar to the recommendations for ACEI, ARBs should be given with caution to patients with low blood pressure, azotemia or

elevated serum potassium. Unlike ACEI, ARBs do not inhibit kininase and are hence associated with a lower incidence of cough.
  - Although ARBs are a good alternative for patients with ACEI-induced angioedema, patients may also develop angioedema with ARBs and hence these drugs are best avoided in patients with ACEI induced angioedema.
- Recommendations: Patients with prior or current symptoms of chronic HFrEF who are intolerant to ACEI (due to cough) are candidates for ARB's.

A3 Combination of ACEI and ARB:

- Combination therapy with ARBs and ACEI has no added total mortality benefit in chronic HFrEF. Rather, this increases the side effects and should be avoided.

B RAS Inhibition with ARNI's: A deeper understanding of the role of natriuretic peptides in HF led to the development of the combination drug ARNI containing an ARB (valsartan) and a neprilysin inhibitor (sacubitril). The PARADIGM-HF trial demonstrated that sacubitril/valsartan (200 mg twice daily, with the ARB component equivalent to valsartan 160 mg) was superior to ACEI (viz. enalapril target dose 10 mg bd) in patients with HFrEF.[136]

- Clinical Use: In patients already on ACEI, it is important to discontinue these 48 h prior to initiating sacubitril/valsartan to avoid the risk of angioedema.
  - The usual starting dose is 49 mg/51 mg bd with attempt to double to target dose of 97 mg/103 mg bd at 2–4 weeks as tolerated by the patient. In ACEI/ARB naïve patients, the starting dose is lower (24/26 mg bd with a slower titration schedule; double every 3–4 weeks).
  - Although the PARADIGM-HF trial enrolled patients with high baseline BNP/NT-proBNP, it is not mandatory to estimate these biomarkers prior to initiation of ARNI. It is however important to remember that since BNP levels are elevated in patients receiving sacubitril/valsartan (due to neprilysin inhibition), NT-proBNP should be used if biomarker estimation is contemplated for monitoring treatment and assessing HF severity.
  - Do not initiate therapy with ARNI if baseline serum potassium level is >5.4 mmol/L, SBP <100 mmHg or there is past history of angioedema.
  - In patients with mild renal impairment (eGFR 60–90 ml/min/1.73 m2), no dose adjustment is required. In patients with moderate (eGFR 30–60) and severe renal impairment (eGFR <30), caution should be exercised and consider starting dose of 24 mg/26 mg bd, with subsequent slow titration, assuming there is no deterioration in renal function. The drug should be avoided in patients with end stage renal disease.
  - In patients with mild hepatic impairment, no dose adjustment is required. In patients with moderate hepatic impairment, a lower starting dose (as above) should be used. The drug should not be used in patients with severe hepatic impairment, cirrhosis or cholestasis.
  - Potential adverse effects include cough, dizziness, angioedema, hypotension, renal impairment and hyperkalaemia. If after initiating sacubitril valsartan, there is symptomatic hypotension, SBP <95 mm Hg, hyperkalaemia or renal dysfunction, adjust other medications (eg diuretics) or temporarily down-titrate or discontinue sacubitril/valsartan.
- Recommendations: In all patients with chronic symptomatic HFrEF, ACEI (or ARB) and beta-blockers remain the first line agents. In patients who remain symptomatic despite optimal therapy with an ACEI, beta blocker and MRA, consider replacement of ACEI with ARNI. In patients who are tolerating ACEI (or ARB) well, replacement by ARNI may be considered on an individualized basis.

B Beta-blockers: Adding beta-blockers to standard treatment in patients with HF has demonstrated significant risk reduction of up to 30–40% in cardiovascular death, sudden death, hospitalization for worsening HF.[137–139] Based on these data, beta-blockers are now accepted as a standard pharmacological treatment along with ACEI in the management of chronic HFrEF. Three types of beta-blockers (bisoprolol and metoprolol succinate extended release which selectively block beta-1–receptors; and carvedilol, which blocks alpha-1–, beta-1–, and beta-2–receptors) are recommended for use in patients with HFrEF.

- Clinical Use:
  - Initiation of beta-blockers should only be done once the patient is stable and euvolemic (i.e., no pulmonary congestion and no more than minimal edema). In patients with fluid retention, beta-blockers should not be prescribed without diuretics, since exacerbation of volume overload can occur following initiation of beta-blocker therapy. Worsening HF symptoms with a beta-blocker should not be a reason to avoid them permanently.
  - Beta blockers can be safely started pre-discharge even in patients hospitalized for HF, provided patients do not require intravenous inotropic therapy for HF. Even when symptoms are mild or have improved with other therapies, beta-blockers are imperative and their initiation should not be delayed.
  - Beta-blockers should be introduced in lowest possible doses and titrated gradually with periodic assessment of heart rate, blood pressure, and clinical status. The usual recommended schedule is doubling of the dose at 2-week intervals in ambulatory patients until the target dose is reached or the maximally tolerated dose is achieved. Patients should be counselled to monitor weight and report weight gain or worsening signs/symptoms of HF following initiation or up-titration of therapy. If patients are unable to tolerate target doses, lower doses should still be given, in view of the mortality benefit across all dose ranges.
  - Common adverse effects of beta-blockers include fluid retention, bradycardia, hypotension, conduction disturbances and fatigue. Exacerbation of fluid retention or worsening HF usually responds to intensification of conventional therapy (eg. diuretics) and does not necessitate permanent drug withdrawal. Effects of beta-blockers on heart rate and conduction when asymptomatic require no treatment, while in symptomatic cases reduction in dose or stoppage may be needed. It is important to remember that abrupt discontinuation should be avoided due to increased mortality risk.
  - The risk of hypotension can be minimized by administering the beta blocker and ACEI at different times. Most patients with chronic obstructive pulmonary disease tolerate beta-blockers well, although they should not be initiated in those with active bronchospasm. These patients tolerate beta-1 selective agents (metoprolol and bisoprolol) better than carvedilol, which is non-selective. However, beta receptor selectivity is often lost at higher doses which are used in patients with HF.
- Recommendations: Use of any one of the three mentioned beta-blockers is recommended for all patients with current or prior symptoms of HFrEF in absence of contraindications.

C1 What first: ACEI or beta-blocker? There is uniform agreement that beta-blockers and ACEIs are complementary, and can be initiated together as soon as the diagnosis of HFrEF is made. When initiating ACEIs (or ARBs) and beta-blockers, clinical

judgment should be exercised as to which drug to start first, although they can be started concurrently, unless there is a contra-indication to do so. For example, beta-blockers may be preferable in HF patients with angina or underlying arrhythmias while ACEI may be useful in those with diabetes or chronic kidney disease. In stable patients, it is reasonable to add beta-blockers before full target doses of either ACEI or ARBs are reached. In patients with relevant concerns (eg: hypotension), it is recommended that the patient should receive a lower dose of a combination of an ACEI (or ARB) and beta-blocker, rather than either drug as monotherapy, highlighting the importance of a synergistic effect among these drugs.

C Mineralocorticoid receptor antagonists (MRA's): Additive RAS blockade in HF patients by adding a MRA (spironolactone, eplerenone) has demonstrated ~ 20-25% reduction in cardiovascular mortality in patients taking a background of standard therapy (ACEI/ARB's and/or beta-blocker).[140–142] A recent meta-analysis (14 trials, n = 1575 patients) reported a mean improvement in LVEF of 3.2% and significant improvement in NYHA class following treatment with MRA's in patients with HFrEF.[143] The difference between eplerenone and spironolactone is not the effectiveness of anti-mineralocorticoid activity but the selectivity of aldosterone receptor antagonism (spironolactone is a non-selective blocker while eplerenone is a selective blocker).

- Clinical Use:
  - Baseline SCr should be <2.5 mg/dL (males) and <2.0 mg/dL (females), eGFR >30 mL/min/1.73 m2), and potassium should be less than 5.0 mEq/L, prior to drug initiation. It is important to measure renal function and electrolytes at initiation, after 2–3 days, 1 week later and at regular intervals thereafter (eg. at least monthly for the first 3 months and every 3 months thereafter). For those with concerns of renal dysfunction or hyperkalemia, an initial regimen of every-other-day dosing is advised.
  - Patients on MRA's should avoid potassium supplementation, NSAID's and foods rich in potassium. The major risk associated with use of MRA's is hyperkalemia (reported incidence 2–5%). Appx 10% of male patients may develop breast tenderness or gynaecomastia with spironolactone and in these patients eplerenone is a useful alternative.
- Recommendations: Patients of HFrEF (NYHA II–IV, LVEF <35%) who remain symptomatic on optimal tolerated doses of an ACEI (or ARB) and beta-blocker should be offered addition of either spironolactone or eplerenone. MRA's may also be used following an acute MI in patients who have LVEF <40% who develop symptoms of HF or who have a history of diabetes mellitus. Triple combination of an ACEI, ARB and MRA's should be avoided.

D Diuretics: While diuretics improve fluid retention, symptoms and exercise tolerance, no significant mortality reduction is reported in patients with HFrEF. Loop diuretics which act at the loop of Henle (eg. bumetanide, furosemide, and torsemide) are the preferred agents for most patients with HFrEF due to their potency and rapidity of action. In those with gut edema, torsemide is preferred over furosemide. The usual dosing schedule is twice daily with the second dose being administered in the late afternoon to minimize nocturnal dieresis. Thiazide diuretics (hydrochlorothiazide, chlorothiazide, metolazone) and potassium-sparing agents (eg, spironolactone) act at the distal portion of the tubule. Thiazides are weaker diuretics when used alone, and are often considered for patients with milder degree of fluid retention, especially in those with underlying hypertension. Except for metolazone, thiazide-like diuretics are less effective when creatinine clearance (CrCl) is <30 ml/min.

- Clinical use:
  - In an out-patient setting, diuretic therapy should be initiated at low doses, with incremental dosing till urine output increases and there is a weight reduction (usually in the range of 0.5–1.0 kg/day). Further dose adjustments (along with dietary sodium restriction) may subsequently be needed to maintain target weight and sustained dieresis, with a final aim to eliminate clinical evidence of fluid retention.
  - The aim of maintenance diuretic therapy is to achieve and maintain euvolemia with the lowest possible dose and stable patients may be trained to self-adjust their diuretic dose based on monitoring of signs/symptoms of congestion and weight charting. Patients who exhibit resistance (poor diuresis despite high doses of oral diuretics), often respond to intravenous administration (including the use of continuous infusions) or combination of different classes of diuretics (eg, metolazone or a MRA with a loop diuretic).
  - Usual side effects of therapy include fluid and electrolyte depletion, hypotension and azotemia. These effects are exaggerated when diuretics are used in high doses or in combinations.
- Recommendations: Diuretics should be used in patients with HFrEF who have evidence of fluid retention. They are usually combined with an ACEI (or ARB's), beta blocker, and MRA's.

E Ivabradine: This is a selective inhibitor of the I*f* current in the sinoatrial node, and provides heart rate reduction with neutral effects on BP and cardiac conduction. Studies have demonstrated the efficacy of ivabradine in reducing the endpoint of cardiovascular death or HF hospitalization in patients with HFrEF, primarily driven by a reduction in HF hospitalization.[144,145]

- Clinical Use:
  - Usual initiating and maintenance doses are listed in Table 1. Dose adjustments can be made every 5–7 days or over 2 weeks to a maximum dose of 7.5 mg bd (according to heart rate response, to a target rate of < 60 bpm). If resting heart rate is < 50 bpm or patients develop symptoms related to bradycardia, the dose may be reduced to 2·5 mg bd. Side effects include bradycardia, development of AF and rarely torsade's. Visual symptoms (phosphenes) are by far the most common side effect, especially in those on 7.5 mg bd.
- Recommendations: Ivabradine should be considered in symptomatic HF patients who are in sinus rhythm and have a resting heart rate ≥70 bpm despite treatment with maximally tolerated doses of beta-blocker, ACE-I (or ARB), and an MRA. It should also be considered for patients unable to tolerate a beta-blocker or those who have contra-indications for a beta-blocker. It should not be used as substitute for beta-blockers.

F Digoxin: Digoxin reduces hospitalization due to HF but does not improve survival in patients with HFrEF.[146–148] Benefits are reported irrespective of rhythm (sinus rhythm or AF), etiology of HF (ischemic or non-ischemic) or with/without ACEI.

- Clinical Use:
  - Typical initiation doses are 0.125 to 0.25 mg daily; lower doses should be used in elderly (>70 years), females, renal dysfunction and those with lean body mass. In most cases of HF, there is no need to use loading doses of digoxin to initiate therapy. Maintenance dose is 125–250 mcg per day with one or two days of drug holiday each week; in patients with renal impairment, digoxin is given as half doses or alternate daily.
  - Usual adverse effects include arrhythmias (especially ectopic and re-entrant tachycardias with AV block), gastrointestinal symptoms (eg, anorexia, nausea, and vomiting), and

neurological complaints (eg, visual disturbances, disorientation, and confusion).
  - Concomitant use of propafenone, verapamil, quinidine and amiodarone can increase serum digoxin levels and increase the likelihood of digoxin toxicity.
- Recommendations: Digoxin is beneficial in patients with HFrEF to reduce HF hospitalizations. Digoxin is generally used as add-on therapy in persistently symptomatic patients, despite optimal medical therapy. In patients of HFrEF and AF, beta blockers (rather than digoxin) are usually more effective for rate control, especially during exercise.

G Hydralazine and isosorbide di nitrate: The rationale of this combination is that both preload and afterload are reduced while hydralazine also prevents nitrate tolerance obviating the need for a nitrate-free interval. Although previous trials have demonstrated benefit of this vasodilator combination better efficacy is reported in African American patients.[149–152]

- Clinical Use:
  - Therapy should be started at low doses (12.5–25 mg hydralazine and 10–20 mg isosorbide di nitrate tid) and titrated every 1–2 weeks (or every 1–2 days in hospitalized patients according to tolerability). The target dose is 225 mg of hydralazine hydrochloride and 120 mg of isosorbide di nitrate daily.
  - Side effects include headache, dizziness, and non-specific gastrointestinal complaints; patient compliance is also an issue because of the large number of tablets required and thrice a day dosing.
- Recommendations: Although recommended for African Americans patients, it remains to be investigated whether this benefit is evident in patients of other racial or ethnic origins. It may be used in patients with HF who remain symptomatic despite optimal therapy with ACEI and beta blockers or those who are not candidates for ACEI (or ARB's).

H **Pharmaco-economic aspects of HF in India**

- Economics of HF care: The impact of HF has resulted in huge economic burden on health care across the world. The overall global economic cost of HF in 2012 was estimated at $108 billion per annum.[153] Costs incurred in HF care include:
  - Direct costs: expenditure on hospital and physician services, drugs, follow-up etc.
  - Indirect costs: due to lost productivity, sickness benefit and welfare support.

While in high-income countries, direct costs are 2 times more predominant than the indirect costs, in middle and low-income countries like India, indirect costs outweigh direct costs by nearly 9 times. Pharmacotherapy of HF is very resource consuming and the developed world spends a substantial part of its health budget to manage these patients. In terms of overall contribution to global HF spending, USA ranks at the top, accounting for 28.4% of global costs while South Asia accounts for 1.1%, ranking below Europe (6.83%), Oceania (2.65%) and Latin America (1.46%). This is due to different epidemiological and etiological landscape of HF and variations in health infrastructure across the world. India with an overall GDP of 1,841,717 $ million (of which 3.9% is spent on health) had an estimated HF cost of ~1186 $ million (direct costs: 80 $ million, indirect cost 1105 $ million) in 2012.[153]

- Gross under-usage of guideline-directed medical therapy (GDMT) in India: There is only scant data on use of GDMT in patients with HFrEF in India. In-hospital data from the Trivandrum Heart Failure Registry reported use of GDMT in only 19% and 25% of in-patients with HF (n = 1205) during hospital admission and at hospital discharge, respectively.[3] The Practice Innovation and Clinical Excellence (PINNACLE) India Quality Improvement Program (PIQIP) is a registry for cardiovascular quality improvement in India supported by the ACC Foundation. Amongst 15,870 out-patients with HF, this registry observed use of ACEIs/ARBs, beta-blockers, and both in only 33.5%, 34.9%, and 29.6% respectively.[154] Hence despite a huge clinical burden of HF, prescription and use of GDMT is poor in India. Large patient numbers, sub-optimal doctor-patient ratios, poor accessibility to health care and affordability of the population are important reasons for this.

In developing economies like India with limited healthcare provision and social welfare, where majority of the people meet medical expenses on their own (OOP: out-of-pocket health spending), HF has wide reaching economic implications at the individual, societal and national levels. The following measures can be useful in providing cost-effective HF care to Indian patients:

Dedicated HF services with defined national protocols to diagnose, investigate and mange patients with HF.

Structured telephonic support programs run by trained nurses to advise patients about simple measures like weight monitoring and adjusting fluid intake have been found to be useful in reducing recurrent hospital admissions and limiting health care costs.

Focus on early identification of non-responders to reduce morbidity and mortality of HF.

Closer networking with the industry and government to facilitate availability of quality-controlled generic medicines for HF in order to bring down the cost of therapy is necessary.

Similar to the lines for treating coronary artery disease, further research needs to be done in developing "Polypills" for patients with chronic HF incorporating various low cost generic ingredients.

Summary of pharmacotherapy for HFrEF: vide Fig. 8

Other drugs

a. Oral anticoagulants should be prescribed in patients with chronic HF with permanent/persistent/paroxysmal AF, additional risk factors for stroke or those with intracardiac thrombus. The choice of the agent (vitamin K antagonist or newer oral anticoagulants) should be individualized.
b. There is no role of adjunctive statin therapy in HF in the absence of other indications for their use
c. Long-term intravenous infusion of positive inotropic drugs is potentially harmful for patients with HFrEF, except as palliative therapy for those with end-stage HF who cannot be stabilized with standard medical treatment.
d. Amongst calcium channel blockers, verapamil and diltiazem are contraindicated in patients with HFrEF because of their negative inotropic effects. Newer generation agents (felodipine and amlodipine) may be used safely in patients with HFrEF and associated refractory angina or hypertension not responding to guideline recommended HF therapies.
e. With the exception of amiodarone and dofetilide, most Class I and Class III antiarrhythmic drugs should be avoided in patients with HFrEF.

2.4. *Management of heart failure with preserved ejection fraction*

The Trivandrum HF Registry (THER) reported a prevalence of 26% for HFpEF in a patient population whose mean age was 61.2 years.[155] In another study from AIIMS comprising of rural population in Northern India, overall prevalence of heart failure

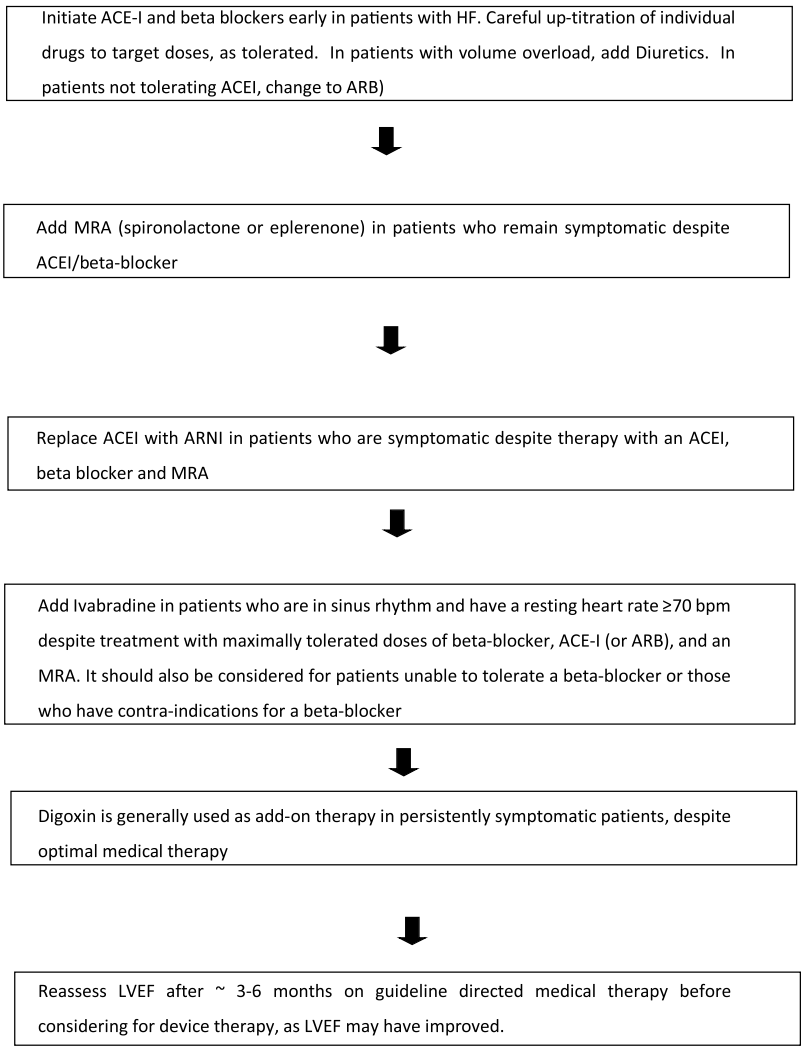

Fig. 8. Flow Chart of Pharmacotherapy for HFrEF.

was 1.2/1000 and two-thirds had HFpEF and all of them had uncontrolled hypertension.[12]

Non-cardiac comorbidities such as chronic kidney disease, anaemia, malignancy and thyroid dysfunction are common in HFpEF; chronic kidney disease in particular may play a dual role in that it contributes to extracardiac volume overload and the development of the cardiorenal syndrome.[156,157] Obesity is a predictor for HFpEF but not for HFrEF.[158,159]

Diagnostic Criteria for HFPEF(Fig. 9)

- Presence of symptoms and signs typical of heart failure
- A preserved ejection fraction (LVEF $\geq$ 50%)
- Elevated levels of natriuretic peptides

  ↙BNP level $\geq$35 pg/mL
  ↙NT-proBNP level $\geq$125 pg/mL

- Objective evidence of other cardiac structural or functional alteration

  ↙either left ventricular hypertrophy (increased left ventricular mass index) or left atrial enlargement
  ↙diastolic dysfunction on echo (increased E/e' or decreased e') or cardiac catheterization (increased LVEFP or PCWP, particularly with exercise)

2.4.1. Treatment

Principles of Management in Patients with HFPEF

A. . Avoid tachycardia:
   Use digoxin or beta-blockers in patients with atrial fibrillation
B. Control Blood Pressure:
   ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists may be of greatest benefit due to the physiological benefits seen in HFREF; further studies are required
C. Treat comorbid conditions:
   Optimise cardiac and non-cardiac conditions (commonly atrial fibrillation, pulmonary disease, anaemia and obesity)
D. Relieve congestion with diuretics Judicious use of loop diuretic with careful monitoring of renal function
E. Encourage Exercise Training:
   Improves exercise capacity and physical function

2.4.2. Fluid retention

Diuretics are necessary to overcome Total blood volume (TBV) expansion and congestion in both forms of HF. Torsemide, in contrast to furosemide, may have additional positive effects on collagen metabolism by inhibition of procollagen type I (PIP).[161] The vasopressin antagonist tolvaptan can be effective in severe cases accompanied by hyponatraemia.[162]

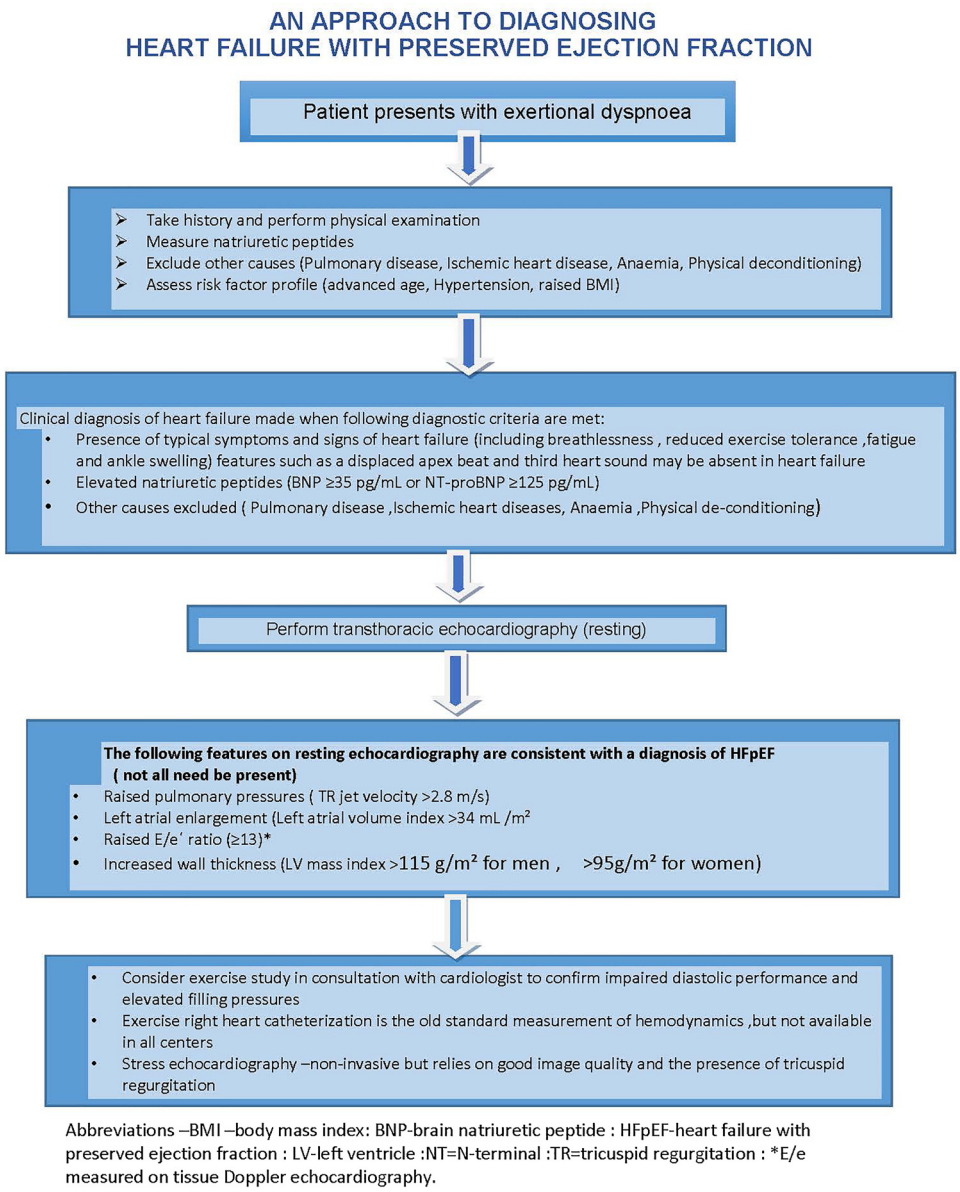

Fig. 9. An approach to Diagnosis Heart Failure with Preserved Ejection Fraction[165].

2.4.3. Atrial contraction

Patients with HFpEF tolerate atrial fibrillation poorly, especially when ventricular heart rate is high.[163] Restoration of sinus rhythm may improve clinical symptoms. If this is not possible, ventricular rate should be lowered using beta-blockers or heart rate lowering calcium antagonists.[164]

2.4.4. RAAS blockade

One study of perindopril in HFpEF has shown benefits on HF hospitalisation within the first year, but did not achieve its primary endpoint.[165] Two large trials have examined the role of angiotensin receptor blockade in patients with HFpEF. I-PRESERVE showed no impact of irbesartan on death, hospitalisation or quality of life.[166] CHARM-Preserved demonstrated a modest impact of candesartan on hospitalization in HFpEF, but it included patients with an ejection fraction down to 40%.[167]

Spironolactone was neutral regarding mortality and hospitalization.[168]

Angiotensin receptor neprilysin inhibition is under investigation in patients with HFpEF in the ongoing PARAGON trial.[136,169]

2.4.5. Heart rate modification

Diastole is shortened during tachycardia, and a reduction in heart rate would be presumed to improve symptoms in patients with HFpEF. Trials of beta blockers have been negative in this regard.[170,171] Trials of heart rate modification with ivabradine have shown early positive results, but not consistently across all studies.[172,173]

2.4.6. Device therapy

To offset left atrial pressure, an inter atrial shunt can be inserted percutaneously, with recent trial results suggesting significant improvements in quality of life and functional capacity.[174] Early trials targeted to offset chronotropic incompetence and improve dyssynchrony with atrial pacing, with larger trials yet to be completed.[175]

2.5. *Device therapy in the management of heart failure patients in India*

2.5.1. Introduction

Unlike western countries where heart failure is predominantly a disease of the elderly, in India it affects a younger age group. The

actual burden of the problem is unknown but as per projections there are at least 8–10 million patients with HF in India with a prevalence of about 1% adult population with a high in-hospital mortality rate of 30.8% and with high post-discharge 6 month re-hospitalization and mortality rates of 40% and 26%, respectively.[2,3] Many patients remain symptomatic despite guideline-directed medical therapy (GDMT).

Device therapy in heart failure includes the implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT). Beyond improving the quality of life and reducing the morbidity, CRT has also shown mortality benefit in selected patients. However, the cost burden it imparts to a developing economy remains its Achilles heel. Also many patients who currently fall within the guidelines were not represented in the clinical trials. The morbidity associated with ICD implant is also overlooked and the cost-benefit analyses are exaggerated in favour of ICD implant. The optimal use of this therapy will require better risk stratification methods or lowering of initial device cost. Hence we need to develop our own guidelines for device based therapy in HF in a resource limited setting taking into account ethnic, socio-economic and geological factors.

2.5.2. Device therapy in HF- does it save more lives and is it cost effective?

Randomized trials have demonstrated the efficacy of ICD therapy in the reduction of subsequent death among patients who have been resuscitated from a cardiac arrest.[176–178] Meta-analyses of secondary prevention trials for ICD showed that the relative risk reduction of death with the ICD was 28% which was secondary to reduction in arrhythmic death to around 50%. Though this sounds impressive, relative reductions can be misleading; dissection of the results showed extension of life by a mean of only 4·4 months by the ICD over a follow-up period of 6 years.[179] The absolute mortality reduction of 7.9% (number needed to treat = 13) by prophylactic ICDs should be compared with a 6.1% reduction afforded by ACE inhibitors, 4.4% by beta-blockers, 2.3% by aldosterone antagonists in patients with LV systolic dysfunction at intermediate-term follow-up.

DINAMIT and CABG Patch trials clearly showed no mortality advantage of ICD therapy in primary prevention in HF patients with severe LV dysfunction.[180,181] But other primary prevention ICD trials, most notably MADIT II and SCD-HeFT, have shown that prophylactic implantation of an ICD significantly reduced overall mortality.[182,183] Interestingly MADIT II trial was prematurely terminated after 20 months follow up because prophylactic ICD reduced all-cause mortality (14.2% vs. 19.8%; P = 0.016; NNT = 18). A post-hoc analysis demonstrated that the mortality reduction appeared to be entirely attributed to a reduction in SCD (3.8% vs. 10.0%; $P < 0.01$). A major limitation of two major primary prevention trials, MUSTT and MADIT studies is that many subjects did not receive what is now considered standard medical therapy. In particular, only 8% of patients in the control group in the MADIT trial received beta blockers compared to 26% of patients in the ICD group at the one-month follow-up. Similarly, in the MUSTT trial, only 29% of the EPS guided therapy group was prescribed beta-blockers.[184]

In the primary prevention setting ICD implantation has a cost-effectiveness ratio @ $100,000 (@ Rs 70 lakhs!) per QALY gained.[185]

CRT-P therapy in class III/IV HF patients with EF<0.35 and wide QRS>150 ms has been shown to reduce mortality by 10% (absolute risk reduction) in comparison to only medical therapy in CARE-HF trial therapy.[186] CRT-D implantation in such patients has shown to have mortality benefit over and above CRT-P therapy by 6%.[187] In spite of its substantial benefits, CRT is underutilised even in developed countries like US and Europe. The number of CRT implants increased from 13,000 to 55,000 per year from 2002 to 2005 in the USA; after 2005 the number of implants did not increase.[188] Hence even the developed nation citizens are finding it difficult to adopt such a promising but costly therapy. The situation is obviously worse in developing countries like India.

2.5.3. The actual Indian scenario

In a major survey of cardiac implantable electronic devices (CIED) in India,[189] ICDs and CRT-P/D accounted for 10% each out of the total devices implanted. Surprisingly the indication for ICD implantation was almost equal for primary and secondary prevention and single chamber ICD was most commonly implanted (65%). Coronary artery disease was the etiology in 59% of patients with ICD implants. CRT pacemakers were implanted mostly in patients with NYHA III/IV (82%), left ventricular ejection fraction <0.35 (88%) with CRT-P being most commonly used (57%). In another Indian study on pacemaker and complex CIED,[190] among the total patients who underwent implants, CRT and ICD accounted for 14%.

Hence, when this is projected to the HF population in India with prevalence around 8 million, device therapy in HF is still in its infancy in terms of its usage. The main hindrances for optimal use of CIED in HF patients include cost, understanding of the disease from patient and physician perspective, risk involved with implantation procedure, availability of experienced implanters in many areas and the need for long term follow up and management.

2.5.4. Ethnicity- does it matter?

Even within Asian population considerable ethnic differences prevail which was illustrated in a HF outcome study in Singapore,[191] with Indians and Malays incurring a worse prognosis than ethnic Chinese. The greater burden of diabetes and atherosclerotic vascular disease in Indians may explain their worse outcome. When the MADIT-II criteria were applied to a Japanese cohort, patients who were eligible but did not undergo ICD implantation showed significantly lower risk of SCD and even better overall survival than the historical Western MADIT-II population.[192] In contrast, when applied to a Chinese cohort, those satisfying the MADIT-II criteria were found to be at similar risk of SCD compared with the original Western MADIT-II population.[193]

Thus, previous Asian studies have been criticized for their small sample sizes, possible selection bias, and retrospective nature. However, they clearly demonstrate the ambiguity regarding the risk of SCD among Asian patients. Hence these data clearly explains that CIED for primary prevention may not be that encouraging in our setting especially in the background of a strained health care economy.

2.5.5. Proposed Indian consensus recommendation

2.5.5.1. ICD therapy for heart failure.

i) **Secondary prevention:**

ICD implantation is strongly recommended in patients with a history of hemodynamically significant sustained ventricular arrhythmia or resuscitated sudden cardiac arrest survivor in the absence of a reversible medical cause and a minimum life expectancy of more than 2 years. This is in cohesion with the western guidelines and where the benefit of ICD is expected to be the most. Hence appropriate patients falling under this category should undergo ICD therapy. In the case of financial constraints refurbished devices may be strongly considered which have shown equal efficacy and safety rates as compared to the newer devices.[190,194] Patients in terminal HF with multiple co-morbidities or stage IV HF without enrolment in any heart transplantation programs should be refrained from ICD implantation.

ii) **Primary prevention:**
ICD therapy is suggested for primary prevention of sudden cardiac death to reduce total mortality in selected patients with:

- Non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, with LVEF of <0.35 and NYHA Class II or III symptoms, or <0.3 with NYHA Class I.
- With one additional risk factor such as: Frequent ventricular premature complexes or non-sustained ventricular tachycardia on Holter monitoring.

These are recommendations for primary prevention in Western guidelines[195] but for a country like India, these should be individualized and financial resources of the patient and the government reimbursement also needs to be factored in. In clinical practice, not all patients in this subset are getting ICD implants. We think for Indian patients, ICD for primary prevention should be individualized. This needs one-to-one discussion with patient and relatives before undergoing ICD for primary prevention. On the other hand, we feel that it is also not mandatory to implant ICD if the finance of the patient is constrained. This is especially valid when the cardiologist or the electrophysiologist feels the risk of SCD is not considerable.

In borderline cases, ICD implantation should not be based only on scientific trial data. This typically includes

1. Patients with CAD and LV dysfunction with EF 0.35 to 0.40:

Aggressive anti-ischemic therapy including revascularization is recommended whenever necessary. Holter monitoring is advised to check for complex ventricular ectopy and an electrophysiological study (EPS) may be indicated in case of presence of other risk markers

2. Patients with CAD, LVEF <0.35 with NSVT or complex ventricular ectopy:

EP study to determine inducibility of VT can be strongly considered before embarking on to ICD therapy in such patients. If sustained VT is inducible, the patient should receive an ICD. Before implantation of the ICD, it should be ensured that the patient has not had a recent MI (within 1 month) or revascularization procedure within 3 months

- Patients with CAD, LVEF <0.30 and no ambient ventricular ectopy should not be advised an ICD indiscriminately. Further risk stratification in this group should be based on clinical (NYHA class, QRS width and morphology) and electrophysiological risk markers on EP study, non-invasive risk markers such as heart rate variability, micro T wave alternans, signal averaged ECG changes etc.

We recommend an ICD not be prophylactically implanted in

1. NYHA Class IV HF patients who are not expected to improve with any further therapy and who are not candidates for cardiac transplant or mechanical circulatory support
2. Patients with CAD, poor LV function and recurrent hospitalizations for heart failure should probably not receive an ICD in the absence of a heart failure program/cardiac resynchronization therapy. Survival in these patients is poor due to competing risk of pump failure death and significant longevity will not be achieved by addressing arrhythmic risk alone.
3. HF patients with EF 0.35 to 0.40 and in some patients even with EF <0.35 without any high-risk features for SCD.

2.5.6. ICD – single chamber or dual chamber

Unless there is a definite current or future risk of bradycardia needing pacing, a single chamber ICD should be preferred for prevention of sudden cardiac death. This is relevant for Indian population as dual chamber ICDs are significantly more expensive, with less battery life and hence lower warranty period.

2.5.7. Current recommendation for CRT therapy- an Indian perspective

2.5.7.1. Proposed consensus statement. Though the present ACC/AHA guidelines[195] recommend CRT even for class I patients with all appropriate criteria, in the Indian scenario that might be overenthusiastic. We would rather advise to plan mostly for Class III/ambulatory class IV patients, though no bar on Class II patients as per present guidelines, if feasible.

Indications for Cardiac Resynchronization Therapy

- CRT is indicated for patients who have LVEF of <0.35, in sinus rhythm, LBBB with a QRS duration of 150 ms or greater, and NYHA Class III, or select ambulatory IV patients after exhausted or failed maximal guideline directed medical therapy (GDMT) and without extensive scar burden.
- CRT can be considered for patients who have LVEF of <0.35, in sinus rhythm, LBBB with a QRS duration of 120–150 ms with echocardiographic evidence of dyssynchrony and NYHA Class III, or select ambulatory IV patients after exhausted or failed maximal GDMT and without extensive scar burden.
- CRT can be considered for patients who have LVEF of <0.35, in sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, NYHA class II symptoms on GDMT and echocardiographic evidence of dyssynchrony.
- CRT can be considered in patients with AF and LVEF of <0.35 if the patient requires ventricular pacing or otherwise meets CRT criteria. Cardioversion of AF should be attempted aggressively in these patients before or after CRT.
- CRT can be considered for patients who have LVEF of <0.35 and are undergoing placement of a new or replacement pacemaker implantation with anticipated requirement for significant (>50%) ventricular pacing

CRT is not indicated for patients

1. Whose co-morbidities limit expected survival to <1 year
2. HF patients with non-LBBB Pattern with a QRS duration of <150 ms
3. HF patients with QRS duration <120 ms and only echo evidence of dyssynchrony

When CRT is implanted in younger patients, without co-morbid illnesses, the risk of ventricular arrhythmias should be carefully assessed and CRT-D should be considered in patients at high-risk.

2.5.8. Long term follow up of device therapy in HF

Following up HF patients with device implantation incur additional expenditure in the case of device explantation, lead extractions and pulse generator replacement. A recent study has demonstrated when ICD patients are followed up, almost 26% of the patients no longer met guideline-driven indications for an ICD at the time of generator replacement and an additional 34% had not received any appropriate ICD therapies. Patients with an initial LVEF of 0.30-0.35 were less likely to meet indications for ICD therapy at the time of replacement. Patients without ICD indications subsequently received appropriate ICD therapies at a significantly lower rate than patients with indications (2.8% vs. 10.7% annually, $p < 0.001$). If ICD were not replaced in these patients without ICD indications in the first place, the cost savings would be $1.6 million.[196]

2.5.9. Myocardial scar and response to CRT therapy

Myocardial scar burden in patients with ischemic cardiomyopathy is an important determinant of response to CRT. A large

myocardial scar burden assessed by either single-photon emission computed tomography imaging or magnetic resonance imaging (MRI) is associated with a poor response to CRT and a poor prognosis. The association between higher scar burden and poor CRT response may partially explain why patients with non-ischemic cardiomyopathy tend to respond better to CRT than those with ischemic cardiomyopathy. The location of scarring in reference to the LV lead has been shown to be an important factor for the success of CRT. A lead with its tip placed in a scar region is unlikely to pace the left ventricle effectively, if at all

2.5.10. Summary and conclusions

Device therapy is a boon for HF patients as it has got absolute mortality benefit in addition to reduction in HF admissions and improving the quality of life. It should be considered only after exhausting aggressive GDMT. ICD in HF patients is appropriate in secondary prevention of SCD. The role of ICD for prophylactic reduction of arrhythmic deaths in all HF patients with EF < 0.35 is debatable especially in our setting inspite of established western data in the same regard.

CRT therapy is beneficial in i) HF patients with EF <0.35 and in class III, ambulatory class IV and selected class II patients, sinus rhythm, LBBB >150 ms or ii) LBBB of 120–150 ms with echocardiographic evidence of dyssynchrony and with expected survival to be at least 2 years.

End stage decompensated HF patients may be refrained from device therapy due to poor prognosis. But when such patients are enrolled into a heart transplant program which is becoming a reality in India then device therapy can be considered after stabilisation in selected patients. In the needy poor HF patients with appropriate indications for device therapy, refurbished devices can be considered which has shown good efficacy and safety profile compared to new device implants in Indian population. For cost consideration we often only think about the first implantation; the cost of delayed complications and generator replacement should also be considered.

2.6. *Device therapy in heart failure: ventricular assist devices and other circulatory support systems*

Both the incidence and prevalence of end-stage heart failure is increasing alarmingly in India.[197] Optimum medical management and interventional therapy has rapidly improved in the last decade. However, there still are about 1–5% of patients in end stage heart failure who need higher support. Prognosis for advanced heart failure is poor worldwide[197] and especially so in India; the life expectancy for majority of patients being 6 months to 1 year. The availability of donor organ hearts and the current surgical infrastructure in our country is woefully short to tackle the current need for heart transplantation. The modality of mechanical circulatory support was introduced in India about 20 years back; but has gained popularity only in last 5 years. Availability of this improving technology is a significant advance that improves survival and quality of life significantly in patients with advanced heart failure.[198] The following review briefly outlines the current status of assist device therapy specially keeping the Indian scenario in context.

2.6.1. Lvads – basic definition, working and when to use

Ventricular assist devices are pump-flow devices that can temporarily or permanently support a patient's circulatory system to bolster the function of an end-stage/failing heart. The goal is to divert blood away from the failing ventricle, give rest to the ventricle and maintain adequate cardiac output meanwhile.[199]

Main components – The LVADs have an inflow connection to the left ventricle, a pump that produces continuous (current generation devices) blood flow bypassing the ventricle and an outflow tube graft that is connected to the aorta. All these 3 components rest inside the pericardial cavity. There is an electrical driveline that exits from the iliac fossa and connects the pump to an external rechargeable battery. The computerized settings of the pump can be altered with a controller unit and a monitor to optimize pump output with minimal power consumption.

There are well-defined subsets of clinical situations where LVADs are currently used.[200]

1. **As Bridge to transplant (BTT)** – For ESHF patients who are wait-listed for heart transplant.
2. **As Destination therapy (DT)** – For patients who cannot be given the option of heart transplantation because of currently listed contraindication. Increasing number of LVAD implantations are DT implants in current clinical practice.
3. **As Bridge to decision (BTD)/Bridge to candidacy** – Some patients are too sick at the time of admission to hospital and their candidacy for heart transplantation is not established. For them, a period of support with LVAD triages the best course of action to be followed for them. This forms a small group of implants.
4. **Bridge to recovery (BTR)** – In patients with severe acute myocarditis but with possibility of myocardial recovery, VADs help to tide over the crisis period with significant unloading of the supported ventricle. Rarely used in our country.

2.6.2. Commonly used devices in India

Heartmate II, Heart mate III and the Heart ware VADs are in current use.

2.6.3. Indications and contraindications

Broad philosophy of LVAD implantation (Based on European Society of Cardiology and American Heart Association guidelines) for patients in ESHF[201,202] –

Group 1 patients (BTT indication) – Patient suitable for heart transplant; waiting for donor heart. These patients are on transplant waiting list, have met all institutional criteria for heart transplantation and are significantly symptomatic (Stage D or NYHA Class IV). These patients have low peak VO2 (<14 ml/kg/min), are inotrope dependent, may have starting end-organ damage due to chronic low cardiac output, may be CRT non-responders, need increasing diuretics or have intolerance to dilator medicines). In these patients, LVAD is to be implanted (Class I indication) to

– Improve symptoms
– Reduce PVRI
– Reduce episodes of heart failure hospitalizations
– Reduce risk of death in waiting period before transplant

Group 2 patients, (DT indications) – LVAD implantation is an option in patients deemed NOT SUITABLE for heart transplant due to

- Above cutoff age limit
- Diabetes
- Significant pulmonary hypertension
- Established renal dysfunction
- Recent malignancy

This subset constitutes the destination therapy group of indications.

Patients having ESHF and being considered for device implantation should undergo complete multidisciplinary team evaluation

Table 17
Classification, Clinical Profile and Management strategies of patients based on INTERMACS study.[206]

S. No	INTERMACS Profile	Clinical picture and description	Treatment strategy advised
1.	Profile I	Crash and burn. Patient with acute severe hypotension, cardiovascular crash, on very heavy inotropic support. Prognosis poor	Short term circulatory/ECMO support. Long term VAD not advisable because patient prognosis unclear
2	Profile 2	Progressive decline; sliding fast inspite of significant dose of inotropes	Similar strategy as in INTERMACS
3	Profile 3	Stable but dependent on continuous intravenous inotropes (dependent stability)	Most suitable candidate for LVAD
4	Profile 4	Resting symptoms of congestion at rest or during daily activities on oral therapy at home	LVAD is a good option
5	Profile 5	Patient comfortable at rest and in activities of daily living; but dyspneic on any other activity (exertion intolerant)	VAD is an option to be carefully considered. May be watched closely
6	Profile 6	Exertion limited – Patient gets fatigued AFTER the first few minutes of any meaningful activity (exertion intolerant)	Optimize medical therapy, ICD
7	Profile 7	Patient Advanced NYHA Class III. Patient lives comfortably with self-imposed restriction on meaningful activity (placeholder)	Medicines, ICD for the time being. LVAD Use is controversial.

to determine their ejection fraction, reversibility of medical condition, presence of other life-limiting comorbidities and latest heart failure status (NYHA Class). This evaluation should be done by a multidisciplinary team of cardiac surgeon, cardiologists, nephrologist, hepatologist, physiotherapists, psychiatry personnel, nurse care providers social worker, rehabilitation physician among others.[203] Patients should also be classified into one of the established INTERMACS profiles (Table 17, Ref. [206]); because different levels of INTERMACS profile merit different treatment strategies based on available worldwide clinical practice evidence.[204]

2.6.4. CONTRAINDICATIONS TO VADs

In Indian set up, the following group of patients should NOT be considered for VAD implantation[198]

1. Patients with irreversible renal or hepatic disease
2. Established severe RV dysfunction
3. History of/possible future noncompliance to prescribed medicines
4. Debilitating neurological disease with deficits
5. Poor self-motivation, inadequate family support, poor English-reading ability
6. Inadequate understanding of basic concepts of alarms, charging and hygiene
7. Poor geographical access to a well-equipped tertiary health care center
8. Patient from remote areas where availability of electricity 24×7 is suspect
9. Surgical situations – (relative contraindication) Congenital heart anomalies, small ventricles, multiple reoperations, morbid obesity

2.6.5. Cost implications in India

The high cost is essentially due to the cost of the device.
Heartmate II INR 40–60lakhs
Heartware INR 60–80 lakhs
Heartmate III INR 90–100 lakhs

2.6.6. Preoperative evaluation

Suitability of a patient for LVAD implantation is to be decided after thorough investigations.[198] These include –

Routine blood investigations (Hemogram, liver and kidney profile, HbA1C)
Cultures – Blood, Axilla, groin, nasal swab
Pulmonary function assessment
Neurological assessment
Psychological assessment
Nutritional assessment
Chest CT scan (Ascending aorta calcification, redo surgery, Congenital anomalies)
Echo assessment for RV function, aortic regurgitation, mitral and Tricuspid valves, ASD Assessment for cardiac arrhythmias and peripheral vascular disease
Exclude undetected malignancy

2.6.7. Technique of implantation and early postoperative management[203]

Appropriate cannulas (large intravenous, peripheral arterial and pulmonary arterial lines) are placed for complete hemodynamic monitoring. Broad spectrum antibiotic is given covering gram – positive and gram-negative bacteria. Midline sternotomy incision is given. Pericardium is opened. Aorta and Right atrium are cannulated and cardiopulmonary bypass is instituted. VAD sewing ring is sewn on the LV apex. LV apex is incised and the pump is connected to the outflow graft securely. The outflow graft is sutured to the ascending aorta. The driveline is tunneled out through the right iliac fossa. TEE guidance is used to check inflow lie (parallel to IVS) and adequacy of de airing. The desired pump flow at shifting is 2800 rpms and acceptable cardiac index is 2.2 l/min/m2 or more.

If moderate or more TR is present, tricuspid annuloplasty is to be added. If a PFO is present, that must be closed. Only severe mitral regurgitation needs to be corrected. More than mild aortic regurgitation should be addressed usually by performing bioprosthetic aortic valve replacement.[203]

Aspirin therapy is initiated in first 24 h. Warfarin is started after 24 h; heparin cover is removed after 48–72 h.

During the convalescence period, patient and family members are educated about alarms, wound precautions, device complications and safety measures including travel advisory.[203]

2.6.8. Outcomes, common complications and management (indianperspective)

Compared to optimum medical management alone for ESHF IV (12–15% survival), the survival with LVADs has improved to 65–85%.[205] In addition, there is a significant and perceptible increase in the quality of life in these patients, their activity levels, feeling of wellbeing and psychological makeup all improve. Some patients who initially were ineligible become transplant eligible after a significant rest to the LV and consequent reduction in PVRI.[206]

Good data on common post implant problems is available even for the latest continuous flow devices based on detailed follow-up[205] of more than 18000 VADs worldwide. With rapidly enhancing technology, the efficiency of VAD pumps is increasing and device sizes are decreasing. However, VAD implants are still associated with significant morbidity. In India, the total number of

VADs implanted till date is less than 100. However, the follow up indicates a similar set of problems as seen worldwide.

2.6.9. VAD thrombosis

It is a usually insidious but a devastating complication and is life threatening. Most patient deaths after VAD implants (especially previous generation VADs) are due to this. Blood clot develops usually within the pump or in inflow/outflow conduits. Reports have indicated approximately 8% thrombosis rate with Heartmate II model.[207] The newer models are supposedly less thrombosis prone; however, mid – long term follow-up is awaited.

VAD thrombosis may present in various ways including increase in watts consumed, lower flow rates, vague discomfort and anorexia, giddiness or even sudden fatal cardiogenic shock. Routine antiplatelet and anticoagulation are mandatory after VAD implant and here patient compliance with medicines becomes of utmost importance. INR ratio is to be maintained as per the device implanted; usual desirable INR ratio is 2.0–3.0.[203]

Diagnosis includes assay of lactate dehydrogenase (LDH), indirect bilirubin levels and plasma free hemoglobin levels, assessment of monitor parameters including previous log files.

Management – Immediate admission in critical care, start with intravenous heparin and thrombolytic therapy (if no contraindication) with tirofiban or r-TPA. If thrombolysis is not successful after a reasonable trial, pump replacement is the preferred option.[203]

2.6.10. Right ventricular failure

This occurs very frequently, in almost 20-50% patients[203] following LVAD implantation; either immediately post-op or after variable periods of upto 2 years (patients present as recurrent heart failure). It may cause significantly reduced cardiac output (cardiogenic shock) because the output of the LVAD pump is preload (RV output) dependent. Milrinone, Dobutamine, Sildenafil, optimal preload and RVAD insertion are the management options. Inotrope weaning is to be attempted with daily echocardiography and strict VAD parameter – monitoring.[203]

2.6.11. Gastrointestinal bleeding

Incidence is 20–30% and both upper and lower GI bleeds are common.[203] The causative factor is development of arteriovenous malformations and gastric stress ulcers. Other important factors responsible are consumption of von Willebrand factor and platelet dysfunction due to high shear stress to blood elements in the pump.

Management involves identification of site of bleeding, alteration of antiplatelet and anticoagulation regimes and supportive measures.

Infection

Driveline infections at the site of exit in iliac fossa are common (15-20%). These cause morbidity and even death (20% deaths). Common organisms cultured are Staphylococcus/Pseudomonas or fungi.[203] Common presentation is fever, lethargy and wound discharge. Management consists of hospitalization, daily dressings, sensitivity specific antibiotics and management of septic complications.

2.6.12. Neurological deficits

Strokes may present acutely within 30 days of device implant or over long term.[208] Ischemic, hemorrhagic strokes or TIAs are all possible. Newer generation devices show similar rates of TIAs and strokes. Clot emboli, atherosclerotic debris from aorta or infective vegetations from outflow conduits are possible causes of stroke.

Neurologist's examination OINR estimation and CT evaluation are first line of management. Optimization of anticoagulation status, radiologic intervention for thrombotic strokes and controlling recurrent emboli from potential source are the principles in management.

2.6.13. Outpatient management guidelines for lvad patients

Management of VAD patients, especially of DT group over long term (5–15 years even) involves multidisciplinary vigilant approach and is challenging. At least weekly follow up is advised and all-important parameters are assessed at each visit. (Pump flow parameters, Blood investigations, INR, Hemolysis markers, cardiologist and cardiac surgeon's assessment, psychological and nutritional assessment etc.). CT scans may be needed to determine problems like outflow graft kinking or obstruction at aortic anastomosis. Role of allied medical staff like physiotherapists, counsellors, heart failure nurses is crucial. After 2 months of discharge, longer intervals between follow up visits are acceptable.

Before discharge, a physician/VAD coordinator nurse should inspect the living quarters of the patient and ensure that the premises are device friendly and safe. During OPD visits, the patient should be accompanied by a constant family member/associate so that he/she may be explained all nuances of registering alterations in VAD parameters and patient behavior; thus, building up his fluency with device management. Even the primary care physician of the patient should be trained to detect device parameter alterations and pump malfunction. There should be a 24 h open communication line between the patient and atleast 3 members of the VAD implantation team to rapidly advise (trouble shooting device malfunction) in case of any sudden deterioration.

2.6.14. Temporary support systems

Critical cardiogenic shock in patients with acute or chronic heart failure does not merit DT LVAD in all cases. These situations (INTERMACS profiles 1 and 2) are good indications for use of temporary mechanical support systems like portable ECMO (example Centrimag/Cardiohelp/Hemovent) or Impella devices. This allows partial recovery of critical end-organs, efficient stabilization of hemodynamics and neurological assessment.

They may also be used to provide RV support (cardiogenic shock due to acute RV failure) The duration of support accorded may vary from 6 h to 30 days.[209] Some clinical situations for their use include-

- Acute RV failure following LVAD implant,
- Failure to wean off CPB following heart transplant operation,
- Cardiogenic shock following cardiotomy operation,
- Transferring patients from one centre by surface or air,
- Bridge to decision (whether a patient is a candidate for heart transplant)

2.6.15. Summary

For increasing number of patients with ESHF stage IV, mechanical circulatory support devices are the best option. The number of VAD implants all over the world are constantly increasing. Follow up data convincingly show remarkably good quality of life, reversal of end-organ damage and increased survival.[210]

Constant vigilance, robust followup and awareness about possible device complications is essential for successful VAD programs. The low numbers of device implants in India are related to lack of health insurance and steep costs of the available devices. Other factors like proximity to a tertiary care centre and education level of patients also limit candidacy of patients for VAD implantation in India.

2.7. *Management of heart failure: role of surgical revascularisation and other surgeries*

Despite enormous strides made in pharmacotherapy, a large number of patients reach end stage HF and 30–40% dies, refractory to any form of medical therapy, especially if associated with structural heart disease. Fortunately a variety of surgical procedures (Fig. 10) are now available to address these advanced HF patients.[211]

2.7.1. CABG in heart failure

There is a great paucity of data of myocardial revascularization in LV dysfunction with land mark studies like the European Surgical Study, VA Cooperative Study, CASS Study, MASS II, Courage, and ISCHAEMIA all excluding patients with severe LV dysfunction. Even SYNTAX Trial had LVEF <30% in 2% of patients and in FREEDOM Trial, barely 2.5% of patients had LVEF <30%.

The landmark STICH I failed to demonstrate any benefit of CABG over medical therapy in five year primary end points, there were some benefits in five years secondary end points, of cardiovascular mortality (28% vs 33%, p-0.05), composite of cardiovascular hospitalization plus mortality (58% vs 68%, $p < 0.001$) and composite of repeat revascularization plus mortality (39 Vs 55%, $p < 0.001$). However, the ten year follow up showed unequivocal superiority of CABG. The STICH Extension (STICHES) trial showed improvement even in primary end point of all-cause mortality with number needed to treat (NNT) to save one life of 14, which was highly significant. These improved results of CABG were magnified with increasing severity of CAD (better results in triple vessel CAD) and were attenuated with increasing age.[212]

With judicious use of Intra-Aortic Balloon Pump (IABP) and careful patient selection, as also with improvement in intra and post-operative care, results of CABG in this subset of patients have been gratifying. Salutary results of Off Pump-CABG in patients with significant LV dysfunction and HF in Indian context were demonstrated.[213–215]

Though presence of hibernating or stunned myocardium contributing to viability improves long term survival,[216] the STICH Trial has conclusively shown that if the distal targets are suitable for bypass, then viability demonstration is not a pre-requisite for myocardial revascularization.[217] However, both European and ACC/AHA guidelines[218] give Class IIa recommendation to viability testing in moderate to severe ischaemic LV systolic dysfunction.

Besides direct myocardial viability assessment using Dobutamine Stress Echocardiography (DSE), PET, Magnetic Resonance Imaging (MRI) or Single Photon Emission Computed Tomography (SPECT), such other parameters like ventricular wall thickness >8 mm[219] and good sized distal coronary targets are reliable indicators of short and long term survival. Insertion of IABP, incomplete revascularization, wall motion scores on DSE and post operative low cardiac output syndrome are significant predictors of adverse outcomes after CABG in patients with impaired LV systolic function.[220] Recently, Global longitudinal strain, systolic dys-synchrony index and septal-lateral delay have been validated as echocardiographic predictors of early adverse outcomes of CABG in patients with severe LV dysfunction as also biomarkers.[29,221]

2.7.2. Ischaemic mitral regurgitation

Various pathogenetic mechanisms leading to MR in ischaemic cardiomyopathy may be annular dilatation, tethering of posterior mitral leaflet due to apical and lateral displacement of the papillary muscle and LV dys-synchrony.

The debate of repair/replacement in ischaemic MR has not been sorted out, with Acker et al[222] finding repair not durable and therefore recommending replacement for ischemic MR.[211] Probably percutaneous therapies like mitra clip may be the way forward and are being investigated in the RESHAPE-HF trial in Europe and COAPT Trial in USA.

2.7.3. LV aneurysm

Over 5000 patients in small trials and registries demonstrated that reduction of LV volume through SVR improved LVEF and ventricular function.[223–227] Even neuro-hormonal responses to LV reconstruction were salutary with a 34% fall in Norepinephrine levels, 64.7% fall in plasma Renin activity, 68.3% in Angiotensin2 and 46.3% reduction in BNP levels.[228] However, Society of Thoracic Surgeons national database propounded a contrarian view point with 30 days mortality of 9.3% and no benefit of SVR in these patients.

STICH 2 Trial[229] too failed in terms of primary outcomes and though there was reduction in mean LV end systolic volume index (LVESVI) of 19% in CABG + SVR versus only 6% in CABG (p-0.001),

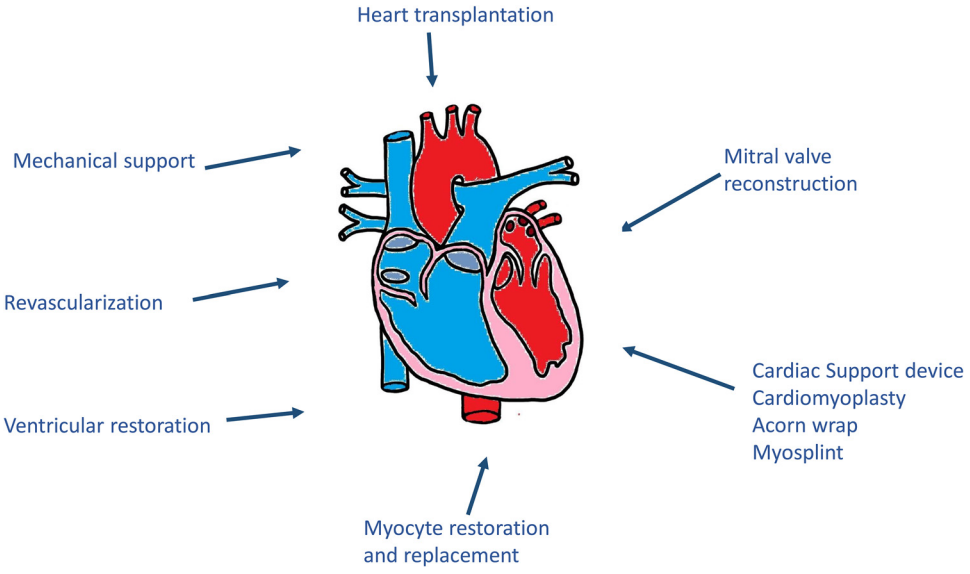

Fig. 10. Surgical Strategies in Heart Failure[213].

there was no improvement in angina class, HF class, six minute walk test or all cause death and hospitalization from cardiac causes.

Various postulations as to why STICH failed are wrong patient selection, SVR induced reduced diastolic distensibility, short axis remodelling in non viable segments after SVR, no pre-operative core lab analysis,[230] inadequate reduction in the LV size,[231] inadequate experience of the surgeons and the centres.

However, in a retrospective subgroup analysis of core lab measures, Oh et al[232] found that SVR results were good if LVESVI was <60 ml/m^2 and LVEF was >33%.

The basic principles of LV aneurysm surgery include[233]:

1. Relief of ischaemia by concomitant CABG
2. Reduction of LV volume
3. Restoration of ventricular geometry
4. MV intervention to reduce LV volume overload

2.7.4. Stem cells and gene based therapies

These therapies failed to keep the initial promise. Even patient-derived bio-artificial myocardium, through bioengineering of human myocardium on native extra cellular matrix, may provide functional support to a failing LV.[234]

Thymosin Beta 4, a protein, has been tried to reactivate the myocardial cells' embryonic developmental potential and for vascular regeneration[235] with the aim of stimulating angiogenesis and myogenesis. Some studies demonstrated them to be safe and effective.

2.8. *Status of cardiac transplantation in India*

Heart Transplantation in India as a planned procedure started in 1994 once the National Organ Transplant act was passed by Parliament. Computerized Transplant registries like TRANSTAN (Tamil Nadu), KNOS (Kerala) and jeevandhan (Andhra Pradesh), started functioning regularly from 2008 onwards.[236]

2.8.1. Intermacs grading –

Interagency Registry for mechanical assisted circulatory support (INTERMACS) is a very Sophisticated Grading used to assess prognosis and sickness level of patients with advanced Heart failure. This is also widely used to select patients who need Mechanical assist before Heart Transplants or Implantable VAD's.[237] If Patient is in INTERMACS grade 3 or less, he is in cardiogenic shock or advanced Heart failure and may need Mechanical assist (Temporary) or permanent LV Assist device as a Bridge to eventual Heart Transplantation. INTERMACS grades more than 3 can be stabilized on Drugs before taking up for Heart Transplantation.

2.8.2. High risk factors for heart transplant

PVR more than 6 Wood units (Prior to vasodilator Challenge)
Creatinine Clearance less than 40 ml/min
Hepatitis C seropositivity
Age less than 1 year
Panel reactive Antibodies (PRA) more than 40%
Diagnosis of congenital heart disease
Interfaces score of 2 and less
Multiple previous operations.

2.8.3. Classical indications of heart transplant

- Impaired Left or Right Ventricular Systolic Function (LVEF less than 30%) with significant Breathlessness (NYHA Class 3–4) after Optimal combined medical therapy or CRT device
- Evidence of Poor prognosis like Vo2 max less than 14 ml/kg/m2 or NT pro BNP more than 1000 units' pg/ml
- Recurrent Heart failure episodes more than 2 per 6 months
- Intractable Ventricular arrhythmias related to Ventricular dysfunction
- Survival Chances less than 80% at one year by Established Gradings Like Seattle Heart Survival scores and Ventricular dysfunction
- Late Stage Congenital heart disease with Ventricular dysfunction or Failed Congenital Heart Surgery like Failed Fontans operation
- Late stage Hypertrophic cardiomyopathy or restrictive Cardio-myopathy
- Severe Pulmonary Hypertension with RV dysfunction
- Altered Renal or hepatic function secondary to ventricular dysfunction.
- Age less than 70 years

2.8.4. Absolute contraindications

- Age More than 75, Biologically unfit or Frail
- Advanced malignancies
- HIV/AIDS
- Severe Renal dysfunction (candidate for Combined heart Kidney transplant)
- Moderate Liver Cirrhosis
- HIGH RISK CRITERIA FOR DONORS:
- Donor Age more than 50 years
- On multiple Inotropes
- History of Cardiac arrest
- Presence of significant degree of ventricular dysfunction not improving with optimization of Metabolic factors and Inotropes
- female Donors to male recipients
- Donor Body weight lower than 20% of recipient weight
- Donor weight more than twice recipients weight, especially in paediatric transplants

2.8.5. Distinctive clinical features in indian patients

Indian Patients typically present quite late for heart Transplant especially in INTERMACS grades 3 or less, higher creatinine levels more than 2.5, jaundice and other parameters of altered Liver dysfunction, with Increased Frailty Index and poorer Nutritional Status Compared to their western counterparts. Also the Pulmonary vascular resistance (PVR) tends to be higher in Indian patients with end stage Heart failure, Needing special vasodilator drug testing protocols and Special pre and perioperative Drugs regimens to Combat higher Pulmonary vascular resistance (PVR) after HTx.[238,239]

2.8.6. Common infections detected in indian patients

In a series of 164 patients from Chennai – 5 patients had significant CMV Infection from a period of 4 weeks to 1 year after transplant, 3 patients had overwhelming sepsis in the ICU in the first few days after transplant, 2 had pneumonia 3–5 months after transplant, one had severe form of lymph node and GI tuberculosis, 2 had mild candida infection of GI tract. Rest were infection free after they were strictly counselled to follow an infection avoidance life style and periodic monitoring for life threatening infections like CMV.

2.8.7. Surveillance endomyocardial biopsies

Surveillance Endomyocardial (EM) biopsies are routinely advocated every month in the first year after heart Transplant in the Unites States. Since Cost of EM biopsies is prohibitively high and recalling patients from far flung areas is difficult, it is prudent to limit the EM Biopsies to two in the first Year – one at one month and another at one year after Heart Transplant. This policy does not see to impact survival or rejection rates. In a series of 164 cases

clinical and biopsy proved rejection rates have remained very low (only 8 clinical or biopsy proved rejection in 164 in a 3 year period).[240,241]

Extra care is taken during The EM biopsy to make the procedure Low risk by adopting all precautions like using a 6 F Mullins Sheath to introduce the 5 F bioptome and using ECHO guidance to place the Sheath oriented towards the septum. In the 130 EM Biopsy procedures done there were no cases of pericardial tamponade and only 2 cases of increased or new tricuspid regurgitation. The EM Biopsy samples are sent for both cell mediate rejection (CMR) analysis and antibody mediated rejection (AMR) analysis.

2.8.8. Immunological matching before heart transplant

The Immunological Matching prior to Heart Transplant Involves the Following process:

1. ABO Blood group Match
2. To Check Quantitative Anti- HLA Pre-Formed Antibodies (PRA)
3. Complement dependent Cytotoxic assay (CDC assay) between Donor Serum and recipient Lymphocytes.
4. So no HLA Typing or HLA cross March is done as a routine.

2.8.9. Preservation and transport of donor organ

The present standard of care for preservation and transport of the donor organ involves cross clamp and introduction of crystalloid long duration cardioplegia using solutions like htk – custodial solution.

Then the Donor Heart is transported in ice cold saline at temperatures of 1–4 ° centigrade. This cold ischemic non-beating heart survives of anaerobic energy generation but at low levels of metabolism. Since there is loss of tissue ATP levels along with cold injury during transportation. The maximum tolerated cold ischemic time is 4 h – from donor body to removal of cross clamp in recipient.[242]

2.8.10. Organ care systems (OCS) and normothermic donor organ transport

Transmedics Inc has now introduced a Normothermic, Beating heart, Ex-Vivo Organ care system for Donor Heart Transport – which can extend the Ex Vivo Warm ischemic time upto 8–9 h after explanting the Organ.[243]

2.8.11. Non-biopsy markers for rejection surveillance

1. Single Antigen Anti HLA Class 1 or 2 Antibody – Useful in Diagnosis of Antibody mediated rejection – Available in India (SRL Labs Gurgaon)
2. Donor Derived Cell Free DNA – Extremely useful one point blood test for early diagnosis of rejection – Available In USA, Under development in India
3. Cylex (Immuknow) test – Activated ATP levels in Lymphocytes – levels less than
4. 120 unit Suggest over immunesuppression. More than 180 – Under immune suppression
5. ALLOMAP – gene Expression Analysis 15/19 gene panel for rejection surveillance– Available in USA (CAREDx labs).

2.8.12. F. Future directions

In a Large but developing country like India with total Population of 1310 Million and Area of 3.2 million Square kms and limited resources, The Logistics of Creating a Nationwide Cadaveric Organ procurement and Sharing network is Extremely Challenging and daunting by any Criteria.

Hence given the fact that total heart transplants in the country, going by the availability of cadaveric organs will be in the range of only maximum 150–200 per year for the next 2 years, there is bound to be a huge gap between demand from dying patients with heart failure (approximately 2.5 million end stage heart failure patients per year) ands upply of cadaveric organs (Only 150–200 per year).

Also to facilitate Inter Hospital learning Huge Collaborative efforts need to be put in Place between Advanced Heart Transplant centers and Preliminary Heart Transplant programs. Such efforts need to Assisted By National cardiac bodies like Cardiological society of India (CSI), Indian association of cardiac surgeons (IACTS), Heart failure societies and the Newly Planned Indian Society for heart Lung Transplantation.

International Collaboration for improving various special areas of heart transplant is the need of the hour. Such collaborations with International Experts can be in the Form of visiting fellowships, Travel Grants and Annual Conferences or workshops

The other area where more government help is urgently required is for long distance organ transport for the harvested cadaveric organ. Because interstate transport of vital organ like heart with cold ischemic time of 4 h is extremely difficult and expensive (air charter costs above 5 lakh INR), regular Heart Transplants from distances over 200 Kms will need State aid for unaffordable patients. Also the introduction of the new Normothermic Organ transport systems (Transmedics, OCS system) would ensure safe long distance transport of hearts in South Asia.

2.8.13. Conclusion

Heart Transplantation as a standard of care Therapy for end stage Heart Failure has become established in India. The international guidelines for heart transplantation are also now widely known and now being implemented in various Indian centres. Safe Immune suppression and anti-infective measures have also allowed long term survival of Indian patients. But an Indian Heart Transplant registry and long-term data on survival of heart transplants are need of the hour for the country.

3. HF situations specific to India

3.1. *Acute rheumatic fever*

Acute rheumatic fever (ARF) is the result of an autoimmune response to pharyngitis caused by infection with the beta haemolytic group A *Streptococcus* (GAS), *Streptococcus pyogenes*. The carditis of ARF results in valvular regurgitation with the potential for secondary HF failure. ARF still occurs at a relatively younger age in India, affecting children as young as 3 years. The incidence of carditis is also higher during an episode of ARF.

3.1.1. Mechanism of heart failure in acute rheumatic fever

Heart failure had earlier been thought to be due to rheumatic myocarditis as a part of pancarditis of ARF. However, echocardiography has always shown severe valvular regurgitation with almost normal ventricular function in a vast majority of patients presenting with HF[244] and HF gets ameliorated with successful valve surgery.[245,246] Absence of myocarditis is further supported by normal levels of MB fraction of creatinine kinase (CK-MB), troponin I and T and myoglobin.[247,248] Radionuclide studies and myocardial biopsy have also failed to confirm the presence of myocarditis.[249,250] Hence, congestive HF in ARF is due to an acute mitral and/or aortic regurgitation but not due to myocarditis *per se*.

3.1.2. Management of heart failure in acute rheumatic fever

The diagnosis of ARF is made using clinical criteria (the Jones Criteria).[251] Echocardiography is recommended in all patients and subclinical carditis is taken as a major criterion. It shows presence of variable degree of mitral and/or aortic regurgitation and a near

Table 18
Echocardiographic changes in acute Rheumatic Fever.[252]

Valvular regurgitation **(WHO/WHF suggested)**
Regurgitant jet >1 cm in length
Regurgitant jet seen in at least two planes
Mosaic color jet with a peak velocity > 2.5 m/s
Jet persists throughout systole (mitral valve) and diastole (aortic valve)
Valve stenosis – **pre-existing with recurrence of ARF**
Leaflet
Prolapse
Coaptation defect
Thickening
Focal or irregular
Diffuse thickening of AML
Age specific cut offs; >3 mm
Reduced mobility
Excess leaflet motion
Nodules
Annular dilatation
Chordal elongation/rupture
Increased echogenicity of subvalvular apparatus
Pericardial effusion
Ventricular dilatation and dysfunction (almost always with significant regurgitation)

normal LV function. Focal nodular changes at the tips and bodies of the leaflets, mainly in the mitral valve, and with associated annular dilation has been described for the first time from India. The common echocardiographic changes in ARF is summarized in Table 18.

The mainstay of treatment includes diuretics and vasodilators. Intravenous (IV) furosemide may be required initially. ACEi such as captopril, enalapril, Ramipril should be used with diuretics in relatively stable patients with significant valvular regurgitation and/or left ventricular dysfunction.[253] Patients presenting in NYHA class III or IV with severe valvular regurgitation and HF, intravenous infusion of vasodilators is preferred over ACEi. Other measures to control HF include treatment of arrhythmias, if present, bed rest and fluid restriction. Role of digoxin and betablockers is not clear and are best avoided.

Anti-inflammatory drugs, either corticosteroids or salicylates, are the mainstay of therapy and are effective in suppressing the acute signs of inflammation. Corticosteroids have shown a prompter action than salicylates, and can be lifesaving in severe presentations of carditis. Corticosteroids have been widely used in moderate to severe carditis including those in HF as these drugs dramatically reduce inflammatory markers of ARF. Though fever and acute phase reactants show rapid decline but there is no evidence that the anti-inflammatory therapy affects the frequency or severity of the valvar lesions, or prevents the cardiac sequels in the chronic phase.[254,255]

When comparing salicylates and corticosteroids, no treatment has been shown definitely to be superior. Despite this, corticosteroids are frequently used to treat severe carditis around the world.[256] The initial dose of prednisone is given for 2 to 3 weeks depending on the severity of the carditis. After this period, a gradual tapering is required. The drug should be slowly withdrawn, decreasing by one-fifth each week, which means a total duration of the treatment of about 8 to 12 weeks, coinciding with the duration of the acute episode. Rebounds are sometimes associated with rapid withdrawal of corticosteroids. Some authors have recommended an overlapping therapy with the aim to prevent rebounds, with the introduction of salicylates as the dose of corticosteroids is reduced. The advantage of the use of high doses of methylprednisolone as an alternative treatment remains controversial. It has most frequently been administered as a lifesaving therapy for those with severe carditis. Likewise use of intravenous gamma globulin has not shown superiority over other anti-inflammatory agents in patients with carditis.[257,258] Table 19 summarizes the doses of various drugs used for carditis and other major manifestations of ARF.

3.1.2.1. Eradication of the Group A streptococcal infection. The most reliable drug is intramuscular benzathine penicillin (BPG) as a single dose or a full 10 days course of oral penicillin or amoxicillin. Cefadroxyl (oral), and Cephalexin are also useful.

In all patients, eradication should be followed by long term secondary prophylaxis to prevent recurrences.

3.1.3. Role of valve interventions for control of HF

Most patients can be stabilized with HF failure treatment. Wherever possible, cardiac surgery is best delayed until the active inflammation has settled, since the valve repair during active carditis is associated with higher failure rates and less durability.[259] Valve surgery during ARF may be required in select cases. Even in such cases valve repair is to be preferred over valve replacement, especially in younger patients.[260] Those with a flail leaflet due to chordae tendinae rupture may present with acute pulmonary edema due to a rapid rise in left atrial pressure. Emergency surgery in such cases is life saving.[261] Even balloon mitral valvotomy may be done in selected patients with Indian studies reporting a similar acute success rate as compared to that reported in a large series in children.[262,263] Thus, valve

Table 19
Management of Acute Rheumatic Fever.

Drug/Situation	Dose
HF	
Frusemide	IV 1 mg/kg/dose, 2–4 times a day. Then, oral1–3 mg/kg/day in 2 divided doses.
ACE inhibitors	Enalapril – 0.1-0.5 mg/kg/dose twice a day, start at a smaller dose.
Nitroglycerine	0.5mcg/kg/min IV, up-titrated, maximum of 10mcg/kg/min.
Nitroprusside	0.5mcg/kg/min IV infusion. Gradually titrated to a maximum of 10mcg/kg/min.
Anti-inflammatory	
Severe carditis	Prednisone 2 mg/kg/day once daily, maximum dose 80 mg/day
Moderate carditis	Prednisone 1–2 mg/kg/day once dailyor Aspirin 75–100 mg/day divided into 4 doses
Eradication of streptococcal infection	
Penicillin V (oral)	Children: 250 mg TID for 10 days Adults: 500 mg BD for 10 days
Benzathine penicillin G (deep IM injection) Given after sensitivity test	For those >27 kg: 12 lakh units For those <27 kg: 6 lakh units
Erythromycin ethyl succinate (oral)	Children: 20 mg/kg/dose (max: 800 mg) BD for 10 days Adults: 800 mg BD for 10 days

Table 20
Salient features of Acute Rheumatic Fever.

RF and RHD continue to be an undesirable burden in India
RF occurs at a young age resulting in significant morbidity as well as mortality in adolescents and young adults
HF in ARF occurs due to significant valvular regurgitation, with normal or near normal ventricular function
Early recognition and treatment is of paramount importance as patients may improve or even completely recovery
Treatment consists of HF therapy, eradication of streptococcal infection and anti-inflammatory therapy
Urgent valve surgery should be considered in active phase for those who do not stabilize on medical therapy
All patients should be put on secondary prophylaxis to prevent recurrence of ARF.

interventions/surgery during active carditis should also be considered in cases with gross valvular lesions where HF is not improving despite best medical treatment.

The salient features of ARF in our country are detailed in Table 20.

3.2. *Rheumatic heart disease*

Rheumatic heart disease (RHD) is the most common acquired heart disease in children and young adults in many developing countries including India. At least 33 million people are estimated to be currently affected by RHD[264] with a significant number of them requiring repeated hospitalization for HF. Surgery is often required to repair or replace heart valves, the cost of which is very high and a drain on the limited health resources of poor countries.

3.2.1. Epidemiology of RHD

The burden of RHD remains high in India with 1.3 crore cases of RHD estimated in 2015, which is nearly one third of all cases of RHD in the globally. India also accounts for the highest number of RHD-related deaths (1.2 lakh deaths in 2015).[265] These despite a seemingly significant fall in the point prevalence of cases of RHD reported from school surveys in the same region over different time periods.[266] Recently, one of the largest echocardiographic school survey from 4 states reported a prevalence of 7.7/1000 children,[267] which is also lower than the prevalence previously reported from other echocardiographic surveys from India.[268,269] One of the reasons for the high burden of RHD with reducing prevalence rate in India could be the increase in the population at risk of RHD.[27]

3.2.2. RHD & HF

RHD remains one of common causes of HF in India. The proportion of RHD among HF is higher in lesser developed states and government hospitals. For instance, a study from secondary care hospital in central India reported RHD to be responsible for more than half of all admissions for ADHF. However, the proportion of RHD among HF patients was only 8–10% in the other major registries {AFAR &TVMN Registries}. For this publication, the hospital admissions of RHD a 3 months period were analyzed at a major tertiary care hospital. Among the 515, RHD patients admitted, 212 patients were admitted to ICU. Most common indication for admission was HF (78%) and 7.2% expired despite the best treatment {personal communication Dr Vijayalakshmi}.

Two large hospital-based echocardiographic studies from India have shown the contemporary distribution of valve lesions in RHD.[270,271] Mitral valve is the most common valve involved. Most common lesion in patients aged <18 years is mitral regurgitation (MR) and in patients above 18 years is mitral stenosis (MS).[270,272] Multivalvular involvement was seen in a third of all cases. Among the combination lesions, MS and MR was the commonest followed by MS and AR.[271] Females seem to have severe disease and needing more interventions.[272]

3.2.3. Diagnosis

Diagnosis of HF in RHD can be at times challenging. Traditionally, the term HF is used in a patient with RHD with the presence of congestive symptoms. However, any patient with dyspnea with severe valve involvement may be construed to have HF. Heart failure in RHD and in other primary valve diseases may not easily fit in the scheme of HFrEF and HFpEF. Even though biomarkers are shown to be elevated in patients with RHD,[273] they are rarely used in routine practice.

Chest radiograph may show chamber enlargement, pulmonary venous hypertension and pulmonary arterial hypertension. ECG may show evidence of chamber enlargement and abnormalities of rhythm. Echocardiogram is the mainstay in diagnosis and planning therapy. Echocardiogram is a useful tool to assess the ventricular function and underlying structural abnormality. It is a valuable tool in measuring LV volumes, assessment of severity of regurgitation and stenosis, understand hemodynamics and estimate pulmonary artery pressures.

3.2.4. Management of HF in RHD (Table 21)

Management is to improve symptoms and enhance survival. Diuretics are important in relieving symptoms. The therapy for RHD related HF is summarized in Table below. The pharmacotherapy of HF related to RHD is different than those recommended for HFrEF. The principles of treatment for valve disease in RHD are similar to those recommended for other valve diseases.[274,275]

Table 21
Management of HF in RHD.

Common Measures
- Diuretics – all patients with dyspnea and clinical HF
- Atrial Fibrillation
  - Rate control
    - Digoxin (if HF present)
    - Beta blockers (reduces both resting/exercise heart rates)
    - CCB – Verapamil/Diltiazem
    - Amiodarone in selected cases
  - Oral anticoagulation – Vitamin K antagonists preferred to NOACS
- Secondary prevention
  - Recommended in all patients aged <40 years
  - Benzathine penicillin
    - 1.2 MU every 21 days (if patient weighs >27 kg)
    - 0.6 MU every 14 days (if patient weighs <27 kg)
  - Penicillin V 250 mg BD (in states where injectable Penicillin not used)
  - Erythromycin 250 mg BD (if penicillin allergy is present)

Specific Therapies for Valve Lesions
- Mitral stenosis
  - Increase filling time – Betablokcer/Ivabradine[276]
  - Balloon mitral valvoplasty
  - OMC/MVR (if not suitable for BMV)
- Valve Regurgitation
  - ACE Inhibitors (ARB if ACEi not tolerated)
  - Valve repair in MR if possible
  - Valve replacement
- Tricuspid valve disease
  - TV repair

HF – Heart failure, CCB – Calcium channel blockers, NOACS – Novel oral anticoagulants, MU – million units, BMV – balloon mitral valvoplasty, OMC – open mitral commissurotomy, MVR – mitral valve regurgitation, ACE – Angiotensin converting enzyme, ARB – Angiotensin receptor blocker, MR – mitral regurgitation, TV – Tricuspid valve.

Table 22
Major studies of Infective endocarditis from India;* Native valve disease (not RHD).

	Chandigarh 1981–1991[278]	Lucknow 1992–2001[279]	New Delhi 2004–2006[280]	Vellore 2005–2015[281]	Ahmedabad 2011–13[282]	Western Series 2000–06[283]
N	186	198	104	172	75	2781
Mean age (years)	25.0	27.6	23.5	41.8	27.5	57.9
% Male	71.5	73.4	71.1	78.4	69.3	68.0
RHD related (%)	42%	46.9%	29.8%*	40.6%	41.3%	3%
Culture positive (%)	47%	67.7%	41%	83.7%	40%	90%
Surgery (%)	1%	23.1%	15%	15.7%	16%	48.4%
In hospital mortality (%)	25%	21%	26%	24%	29%	18%

3.2.5. Infective endocarditis

India has a dual burden of infective endocarditis (IE); modern IE like dialysis and medical care related IE is being increasing recognized yet, the traditional Oslerian IE involving previous RHD is still widely prevalent.[277] The major studies of IE from India are compared to a Western series in the Table 22 below.

Infective endocarditis in India has several unique features and are summarized in Table 23 below.

It is recommended to make special efforts to increase culture positivity, adhere to guidelines of IE in choosing pharmacotherapy and perform early surgery when indicated. Current guidelines recommend IE prophylaxis for a limited group of patients with heart disease.[284] In India, it is also recommended to extend IE prophylaxis to all patients with severe valve disease as the outcome of IE in India is also suboptimal.

3.2.6. Ischemic cardiomyopathy

Ischemic cardiomyopathy is defined as onset of LV Systolic dysfunction which results from significant CAD.[285] The incidence of HF, after an ischemic insult steadily increases with time after an index event ranging from around 10% after 2 years to more than 40% after 6.5 years.[286] Ischemic cardiomyopathy results from loss of cardiac myocytes leading to adverse remodelling of heart secondary to ischemic insult resulting in LV systolic dysfunction.[287]

3.2.7. Indian data

A prospective study on ADHF in Indian patients[288] from a tertiary care center revealed that ischemic cardiomyopathy was the leading cause for HF (53.9%) and the mean age of presentation was 53 years. "CREATEECLA study[289]" which enrolled 8060 Indian patients out of a total of 20,201 participants, reported a prevalence of HF at 30 days of 17%. Late and suboptimal reperfusion therapy in STEMI in India may lead to more patients ending up with HF. IA cross-sectional study involving 120 patients with STEMI reported a prevalence of HF at 30 days of 11%.[290] Thus, the data from various studies from India suggest that ischemic cardiomyopathy occurs more commonly and at an earlier age compared to western population. Additionally, the burden of this problem is quite high.

3.2.8. Diagnostic approach to ischemic cardiomyopathy

Coronary angiogram is the gold standard investigation in establishing diagnosis of significant CAD in a patient presenting with HFrEF. Coronary angiogram should always be done in patients with previous MI or >40 years of age for establishing the diagnosis of CAD. Stress echocardiography/nuclear studies with exercise or dobutamine will assess stress-induced ischemia and will give vital information regarding need for future revascularization. Positron emission tomography (PET) is regarded as the gold standard test for assessment of myocardial metabolism and viability. CMRI helps in assessing viable myocardium and differentiating it from scared myocardium.[291,292] Among the biomarkers, hs-troponin and BNP are good predicators for diagnosing and guiding therapy in ischemic cardiomyopathy. High sensitive troponin levels are directly proportional to the amount of myocardium under jeopardy. The various non-invasive methods for evaluating HF are discussed in previous sections.

Table 23
Salient features of IE in India.

- IE occurs among younger patients in India
- RHD is the most common predisposing heart lesion
- Culture positivity rate is lower
- Streptococcus species still the dominant organism
- Surgery is less often performed
- Outcomes are suboptimal

3.2.9. Management

Patients with ischemic cardiomyopathy should be treated with optimal medication sticking to guidelines of HF. The pharmacological therapy, devices including ICD, CRT have the same indications in ischemic cardiomyopathy as eluded to in previous sections. Patients with ischemic heart disease also need additional anti platelet drugs and Statins in appropriate doses.

3.2.10. Coronary artery revascularization

Revascularization of dysfunctional but viable myocardium may lead to reverse LV remodelling and confer prognostic benefits in patients with post ischemic HF. About 20 to 50 percent or more of chronic ischemic LV dysfunction patients have significant viable myocardium to improve LV function following revascularisation.[216,293,294] Several studies have shown that LVEF improved significantly (i.e. >5%) after revascularization in more than 60% of patients (range, 38–88%).[295–306] However, in the substudy of STITCH trial, presence of myocardial viability was associated with reduced mortality but did not predict a benefit from revascularization, which raises the question of whether viability assessment is needed prior to surgical revascularization. The merits and demerits of coronary revascularization with CABG are discussed in detail in previous sections.

Data are limited on the relative efficacy of PCI in patients with ischemic cardiomyopathy. An on-going trial, estimated to be completed in 2019, is comparing the effects of PCI with medical therapy alone in patients with HF.[307] The best available observational data comparing PCI with CABG in HF comes from the New York State registries among 2126 propensity score matched patients.[294] At a median follow-up of 2.9 years, there was no significant difference in death between contemporary PCI and CABG. PCI was associated with a greater risk of MI and need for repeat revascularization, but a significantly lower risk of stroke as compared with CABG. Patients with ischemic cardiomyopathy, as well as patients with an LVEF <35 percent in the nonrandomized AWESOME registry, there was no difference in mortality with CABG or PCI.[307]

Despite lack of randomized controlled trials, PCI may be performed in selected patients with CAD and HFrEF (in the absence of angina) with a coronary anatomy suitable for PCI, if the benefits of PCI are likely to outweigh the risks as assessed by a heart team.

3.3. *Dilated cardiomyopathy in Indian patients*

Dilated Cardiomyopathy (DCM) is a genetic disorder and is characterized by ventricular dilatation, impaired systolic function, reduced myocardial contractility with LVEF less than 40% that is not caused by ischemic or valvular heart disease. DCM is next to ischemia among the causes of HFrEF from the reported studies in India. DCM was seen in 13% of study population in a series of chronic HF and 19% in a series of ADHF patients.[3]

Some studies indicate that 30–35% of idiopathic DCM may have a positive family history.[308] Most of the familial DCMs have an autosomal dominant inheritance, but autosomal recessive, X-linked and mitochondrial inheritance are also noted in some cases.[309]

Diagnosis: A through clinical history, general physical and cardiovascular examination, relevant investigations and imaging modalities are cornerstone for diagnosis of DCM. A thorough evaluation for reversible causes is needed (table below). These conditions are extremely rare, yet a positive diagnosis and treatment may result in complete recovery of LV function (Table 24).

Treatment: There is no specific therapy for DCM. All the proven Non-pharmacological & pharmacological therapies of HFrEF are indicated in all patients with DCM. Indication for devices are the same as in HFrEF. However, for primary prevention of SCD in DCM, this position statement recommends ICD in only those DCM patients with LVEF <30% with family history of SCD (as discussed in earlier sections).

Table 24
Curable causes of DCM like echocardiographic picture.

- Obstructions
  - Low gradient AS
  - Coarctation of aorta
  - Aortoarteritis – Aorta/renal artery narrowing
- Electrophysiological
  - Tachycardiomyopathy
  - Dyssynchrony – WPW syndrome
  - Complete heart block
- Metabolic/Endocrine
  - Hypocalcemia
  - Vitamin D deficiency
  - Hyperthyroidism
  - Hypopituitarism
  - Deficiency of Carnitine/thiamine/magnesium or Selenium **(Keshan disease)**
- Coronary artery abnormalities
  - ALCAPA/ARCAPA
  - Kawasaki disease
- Inflammatory diseases
  - Myocarditis
  - Cardiac Sarcoidosis
- Others
  - Peripartum CMP
  - Drug/toxin induced
  - Alcoholic CMP

3.4. *Non-specific aorto arteritis*

Non-Specific Aorto Arteritis (NSAA) commonly known as Takayasu arteritis (TA) is a chronic inflammatory panarteritis affecting large vessels, predominantly the aorta and its main branches. Vessel inflammation leads to wall thickening, fibrosis, stenosis, dilatation, aneurysm formation and thrombus formation.[310–312] Women are affected in 80 to 90 percent of cases, with an age of onset between 10 and 40 years.[313] The onset may be earlier in childhood but rare in infancy.[314,315]

There appears to be a wide variation in the prevalence of TA in different geographical regions of the world. Takayasu arteritis is most commonly seen in Japan, South East Asia, India, and Mexico.[316–319]

The female: male ratio has lot of variation ranging from 9: 1 in Japan to 1.3: 1 in India.[320,321] It is the commonest cause of renovascular hypertension in Asian children.[315] Its long term prognosis is studies in few series and the mortality ranges from 3 to 15%.[322–324]

Clinical manifestations range from asymptomatic disease found as a result of diminished or impalpable pulses or bruits, to more serious neurological or cardiac emergencies. The common symptoms are constitutional symptoms, carotidynia, arthralgias, absent or weak peripheral pulses, limb claudication, gastrointestinal symptoms, skin lesions, symptoms because of involvement of pulmonary arteries or coronary arteries and neurological symptoms. Sometimes patient present as hypertension, angina, heart failure, cerebrovascular events, retinopathy, glomerulonephritis, renal failure, cardiomyopathy, aortic regurgitation, pulmonary artery hypertension or aneurysm rupture.

Angiographic manifestations is very heterogeneous in different geographical areas with predilection for stenotic versus dilative and thoracic versus abdominal aortic involvement in different geographic locations.[325–330]

In Indian series, most common clinical presentation was claudication (74%) followed by musculoskeletal symptoms (48%), fatigue (46%), weight loss (22%), headache (22%), visual disturbances (16%), syncope (10%). Dyspnea was present in (20%) of the cases. Absent or diminished pulses were present in 80–82%, hypertension in 61 – 75%, congestive cardiac failure in 8–38% and claudication in 13–74% of the cases.[329–332]

3.4.1. Diagnosis of TA

No well-defined criteria for the clinical diagnosis of TA were available till Ishikawa proposed his criteria in 1988.[333] The American College of Rheumatology (ACR) classification criteria were basically developed to distinguish one form of vasculitis from another.[334] Sharma et al., 1995 proposed Modified diagnostic criteria for Takayasu arteritis.[335] Classification according to angiographic findings of TA was also proposed. This classification was on the basis of the distribution of lesions detected by angiography.[332]

Heart failure (HF) in TA

This is not a very uncommon presentation in India, especially in children. Up to 60% children can present with heart failure.[314]

Common Causes of heart failure in TA are

- Hypertension,
- Renal Artery Stenosis,
- Myocarditis,
- Aortic Regurgitation,
- Mitral Regurgitation,
- Pulmonary Artery Involvement,
- Coronary Artery Involvement,
- Aortic Stenosis (Thoracic, Abdominal).

TA can rarely present as postpartum cardiomyopathy,[336] Acute Myocardial Infarction with Left Ventricular Failure,[337] Ruptured Right Sinus of Valsalva Aneurysms.[338]

3.4.2. Treatment

The primary objectives of treatment include the control of disease activity by drug therapy, pharmacologic control of blood pressure (BP), supportive management and revascularization (surgical or endovascular) of the symptomatic ischemic territory.

The disease activity can be assessed by clinical, biochemical, or radiological markers.[339] Presence of new vascular signs and symptoms like bruits, absent pulses, blood pressure differences in limbs. Raised ESR and CRP levels, Increased IMT in USG, moving bright spots and linear flow of microbubbles within the vascular lesions with carotid contrast enhanced ultrasonography, Enhancement of the thickened aortic wall in CT Angiography, vessel wall thickness, oedema, and contrast enhancement in MRA, 18-F-FDG-PET uptake in wall of large vessels, PET might be able to distinguish vessel thickening that is due to active inflammation from that due to scar formation.

Treatment should aim to control disease activity, preserve vascular competence with minimal long-term side effects.

Beside standard treatment of HF these patients may benefit from immunosuppressive therapy which has shown promise in short term and long term in patient with myocarditis.[340,341]

Steroids are the mainstay of treatment for TA. Approximately half of the patients respond to steroids. The dose should be adjusted according to the age and constitution of the patient. As soon as clinical and laboratory findings showed continue improvement for 2 weeks, the dose should be tapered gradually. The typical maintenance dose is 5 to 10 mg/day. Regular assessment of disease activity and progression should be performed. Complete glucocorticoid therapy withdrawal should be attempted as soon as possible.

The patient who does not show satisfactory response to steroid or resistant or having adverse drug reaction with steroid can be treated with cytotoxic drugs like cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate.[342–344]

Tocilizumab (IL-6 receptor inhibitor),[345,346] Etanercept (Anti-tumor necrosis factor)[347] and Rituximab (a chimeric IgG1 antibody that binds to CD20 expressed on the surface of B cells)[348] has shown promising results.

Surgical treatment is challenging due to the diffuse nature of the disease and involvement of adjacent aortic walls. It has a high incidence of anastomotic aneurysm formation (12 to 14%) and graft failure (20 to 40%) over time.[349–351] In case of focal stenotic lesions percutaneous procedure can be performed with good long term results, however stenting all lesions is debatable if good result can be achieved by plane balloon angioplasty.[352–355]

Any intervention in acute setting and in patients with severe signs and symptoms should be performed after a sedimentation rate of <30 mm/h and CRP of <1.0 mg/dL have been achieved with treatment, until it is an emergency and patient cannot be stabilized on medication. If aortic regurgitation is severe and need aortic valve replacement both mechanical and bio prosthesis valve can be given. Need for Aortic root replacement depend on the size of aorta but in some cases when inflammation cannot be controlled, affected vessels should be replaced with a valve conduit (Bentall surgery) even with our root dilatation.[356,357]

Some patient who has severe pulmonary artery hypertension due pulmonary artery stenosis pericardial patch angioplasty or reconstruction with vascular prostheses should be performed. When angina pain and Significant coronary stenosis are present, coronary revascularization can be performed with good long term results.[358,359]

Heart failure because of renal artery stenosis (RAS), respond very well with either percutaneous intervention or surgical treatment. However vascular surgery is associated with high prevalence of graft occlusion.[360,361] The favored treatment for RAS in TA, particularly for inactive lesions, is percutaneous transluminal angioplasty (PTA).[362] Percutaneous intervention of aorta in TA is associated with some technical problem but has good short and long term results (Table 25).[362–366]

3.5. *Peripartum cardiomyopathy*

Initially recognized in the 19th century by Virchow, heart failure following pregnancy was formally described by Hull and Hafkesbring in the 1930s.The term “peripartum cardiomyopathy” (PPCM) was coined by Demakis et al. in the seminal publication of 1971. PPCM presents as unexplained left ventricular systolic dysfunction towards the end of pregnancy or early postpartum period in previously healthy women.

3.5.1. Etiology and pathogenesis

The etiology and pathogenesis of the illness still remain unclear. Since it is a diagnosis of exclusion, clinical heterogeneity is inherent to any patient population of this disease. The most common risk factors are summarized in Table 26. In view of the similar clinical, echocardiographic and nonspecific histological features, considerable interest revolves around a common basis for dilated cardiomyopathy (DCM) and PPCM. The prevalence of PPCM in familial DCM is about 6% and a family history of DCM is elicited in 10% of PPCM patients.

3.5.2. Diagnosis

The current clinical definition of PPCM includes 4 criteria Table 27.[367]

The commonest symptom of heart failure, dyspnea, is predominantly physiological in pregnancy (60%) with PPCM accounting for only 0.23% of cases presenting with dyspnea. Antepartum presentation of PPCM is seen in only 10%.Cardiomegaly may not be present as PPCM can occur without LV dilatation.96% of the patients have an abnormal ECG. A risk score of ≥2, developed by scoring 1 for each of the three ECG disturbances (tachycardia, ST–T-wave abnormalities and QRS

Table 25
Salient features of takayasu arteritis in India.

- Takayasu arteritis is rare, affects mainly women, and is most commonly seen in Japan, South East Asia, India, and Mexico, where it usually presents in the 2nd or 3rd decade of life.
- Its clinical Manifestations range from asymptomatic disease, to catastrophic complications.
- Disease symptoms, signs varies between different populations.
- Hart failure is common in Indian patients especially in children.
- Hypertension remain the commonest cause of heart failure.
- Treatment should aim to control heart failure with standard therapy for heart failure and also to control disease activity and preserve vascular competence, with minimal long term side effects.
- Inactive disease carries a good prognosis and these patients should not be put at risk by treatment that is more harmful than the disease itself
- Majority of the patients treated with steroids will respond, but steroid unresponsive patients respond to methotrexate; mycophenolate mofetil or aziothiprim.
- Surgical intervention and percutaneous intervention in selected patient should be performed whenever it is needed and can be very useful.

Table 26
Common Risk factors for development of Peri partum cardiomyopathy.

Twin pregnancy
Preeclampsia
Advanced maternal age
Multiparity
Long term oral tocolytic therapy with β-agonists
PPCM in previous pregnancy

Table 27
Clinical criteria used for definition of PPCM.[a]

Development of HF in the last month of pregnancy or within 5 months after delivery
LV systolic dysfunction (LV EF <45% by echocardiography)
No identifiable cause for HF
No recognized heart disease before the last month of pregnancy

[a] All four criteria must be fulfilled to diagnose PPCM thus preventing overdiagnosis as well as excluding cases of preexisting DCM.

duration), had a sensitivity of 85.2%, specificity of 64.9%, negative predictive value of 86.2% for potentially predicting PPCM.

3.5.3. Prognosis

A mortality rate of 5–10% is found in PPCM and about 4% of cardiac transplantations in the US are performed for PPCM.A Danish study found a MACE of 14.8% with 3.3% mortality, 8.2% mechanical circulatory support requirement and/or heart transplantation and 4.9% persistent severe heart failure. The concept of PPCM as a unique entity distinct from DCM is strengthened by a significantly worse prognosis for DCM compared to PPCM both at 1 and 3 year follow up. After 1 year, the HF readmission rate did not significantly differ between the two diseases, suggesting that HF medications should be aggressively instituted in patients with PPCM.

3.5.4. Indian data

Various Indian series published are summarized in Table 28

3.5.5. Management of ppcm

The non-pharmacological management of stable patients of PPCM includes salt and fluid restriction and restricted physical activity. **ACEI and ARBs are contraindicated in pregnancy** and are substituted by a combination of hydralazine and nitrates. Benazepril, captopril and Enalapril are safe in lactating women. In spite of an increased risk of fetal growth restriction, **β blockers** are recommended in all stable patients for at least 6 months following diagnosis with Metoprolol Succinate the preferred agent. Diuretics in the form of thiazides or frusemide are indicated in patients with pulmonary congestion but they may lead to placental hypoperfusion. **Spironolactone should be avoided in pregnancy**. Digoxin is an add-on drug in patients with low EF and persistent symptoms. Both pregnancy as well as PPCM are prothrombotic conditions.

Bromocriptine, a dopamine antagonist, inhibits prolactin secretion and has been tried in addition to conventional therapy.[377] In the retrospective non-randomized German PPCM Registry, treatment with beta-blockers, ACE inhibitors, and Bromocriptine (2.5 mg twice daily for 2 weeks followed by 2.5 mg per day for 6 weeks) was associated with favorable outcomes. The effectiveness of this drug is greater in patients whose symptoms onset occurred before delivery or in the first month postpartum. The suppression of lactation by bromocriptine

Table 28
Summary of major studies of Peripartum cardiomyopathy from India.

Study	Follow up (yrs)	Mean Age (years)	Presenting Features	Outcomes
Elkayam et al[368] (n = 123)	NA	31 ± 6	Mean LVEF – 29 ± 11%	• Complete Recovery of EF in 54% • Mortality in 9%
TK Mishra et al[369] (n = 56)	6.1	31± 5	Mean LVEF –31% ± 7.2	• LVEF improved to 43% ± 8% • 16% reconceived out of which 55% died during pregnancy and 23% during follow up
Patil et al[370] (n = 65)	7.5	27.5	Mean LVEF- 21% Mean PA pressure = 37 mmHg	• Breathlessness, palpitation and cough at presentation in all. • 50% complained of hemoptysis. 50% had pedal edema and 25% gave history of syncope.
PGIMER study[371] (*n*-38)	NA	NA	Mean gestational age – 35 weeks	• Maternal mortality was 16%, all of whom presented with NYHA class IV symptoms. • Poor obstetric outcome manifested as 8 stillbirths, 40% prematurity and a mean birth weight of 2 kg
M. Tergestina et al[372] (n = 8760)	6 months	23.8	Mean LVEF –31.4%	• 80% of patients had significantly improved LVEF (mean 50.5% at 6 months). • Low EF <30% at baseline significantly correlated with poor recovery
Sion Hospital[373] (n = 22)	6 weeks	26.8	Mean LVEF –25.3%	1 patient (4.8%) showed an improvement in LVEF to >60% and 1 died.
Hubli Study[374] (n = 24)	6 months	29	Mean Parity- 2.1 87% presented in post partum preiod	• 25% succumbed in the first week after diagnosis. • 83% of the survivors recovered completely and the rest had residual LV dysfunction after 6 months.
Gujrat Study[375]	4 years	NA	55% – NYHA class III/IV 50% – LVEF < 30%.	• 80% required ICU admission • Maternal mortality was impressively low (5.5%). • Preterm delivery occurred in 50% and stillborn in a substantial 17%
Nagpur study[376] (n = 11)			81% multipara	• 18% developed persistent cardiomyopathy • Clinical recovery occurred in 37% but LVEF improved in 27%. • Maternal mortality was a substantial 27%. • 6 out of 11 babies had IUGR. 2 intrauterine and 1 neonatal death was reported

is of crucial importance to the newborn especially in developing countries where there may be no practically feasible alternative. Bromocriptine may be considered in patient of PPCM over and above conventional therapy.

Delivery should be conducted in a specialized care setting under multidisciplinary supervision. Mode of delivery is dictated by hemodynamic status as well as obstetric indications. In patients with stable hemodynamics, vaginal delivery is preferred due to less blood loss, less thromboembolism and faster recovery. Moreover, regional anesthesia is not associated with depression of LV function. With unstable hemodynamics, Cesarian section is recommended preferably under spinal anesthesia.

3.5.6. Subsequent pregnancy

There is a substantial risk of relapse of PPCM in subsequent pregnancies with its attendant risks. A multi-centric study of 34 patients found a relapse rate of 56% with 12% mortality. A reduced LVEF before next pregnancy is associated with higher mortality and lower rate of full recovery on follow-up. Addition of Bromocriptine to standard HF therapy after delivery resulted in better outcome in subsequent pregnancy. Counseling regarding contraception is imperative and as exemplified by the fact that 1 in 4 PPCM patients are sexually active and not using contraception.

3.6. *Diabetic cardiomyopathy*

Diabetes is rapidly emerging as an epidemic in the modern era, affecting about 300 million people worldwide, and the number is likely to cross 450 million by 2030.[378] India, sometimes referred to as “the diabetic capital” was estimated to have about 69.2 million people living with diabetes in 2015, overall prevalence being 8.7%.[379] Diabetes may affect the heart in three different ways:[378] coronary artery disease due to accelerated atherosclerosis;[379] cardiac autonomic neuropathy and[380] diabetic cardiomyopathy, a relatively newly recognized entity.

Diabetic cardiomyopathy is defined as “a distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension, and significant valvular disease”.[381] Hence, diabetic cardiomyopathy affects the myocyte at the cellular levels, culminating in structural and functional abnormalities in the heart.

3.6.1. Prevalence

Exact prevalence is not known, as a diagnostic criterion for this entity does not exist. Studies have shown that after adjusting for other conventional cardiovascular risk factors, heart failure is 2–3 times more common among diabetics.[382] According to a study by Bertoni et al., the prevalence of diabetic cardiomyopathy was 12% and reached 22% in people aged greater than 64 years.[383] Prevalence of diastolic dysfunction, thought to be an early marker of diabetic cardiomyopathy, was about 30% in some studies, and up to 60% in others.[384,385]

Indian studies till date, have focused on prevalence of diastolic dysfunction in diabetes. The estimated prevalence ranges from 30 to more than 70% of all diabetic patients.

3.6.2. Risk factors

Diabetic cardiomyopathy can occur in both type 1 and type 2 diabetes. Studies have shown female sex, poor glycemic control, High BMI, advanced age, use of insulin, proteinuria, coexistence of retinopathy and nephropathy to be risk factors associated with development of heart failure/cardiomyopathy in diabetic patients.[386,387]

However, none of the above is a well-established risk factor for the condition.

3.6.3. Management:-

Standard therapy for HF is applicable to Diabetic Cardiomyopathy however a good glycemic control and choice of Oral Hypoglycemic Agents also have a bearing on the progression and outcomes of HF

- Lifestyle modification: Smoking cessation, exercise, healthy food habits and weight reduction can be helpful.
- Glycemic control: Adequate glycemic control might be helpful to retard the progression of diabetic cardiomyopathy in early stages. Metformin has been found to be particularly helpful, as it provides mortality benefit, and also can up regulate cardiomyocyte autophagy, which contributes to prevention of diabetic cardiomyopathy in animal models.[388] (Fig. 11,[371]) Incretin-based therapies (DPP4 inhibitors and GLP 1 agonists) are newer drugs which may offer cardio-protection and may also improve systolic function.[389,390] Some non-randomized studies indicate a harmful effect of insulin, though it was not demonstrated in subsequent studies.[391]
- ACE inhibitors, ARBs and aldosterone antagonists: Myocardial fibrosis and hypertrophy may be prevented by this class of drugs.
- Beta blockers: Might prove to be beneficial, but randomized trials in diabetic cardiomyopathy patients is missing.
- Statins: Independent of their lipid lowering effect, atorvastatin and fluvastatin have been found to reduce intra-myocardial inflammation, myocardial fibrosis, and cardiac dysfunction.[392,393]

3.6.4. G. diabetic cardiomyopathy: Indian perspective

Large population-based studies focused on diabetic cardiomyopathy are lacking in the Indian scientific literature. Extensive search revealed a handful of studies, most of which assessed diastolic dysfunction among diabetic people of different ethnicities. The following table summarizes the findings from various Indian studies (Table 29 & Fig. 12).

3.7. *Right sided heart failure*

Right heart failure (RHF) is a complex clinical syndrome that can result from any structural or functional cardiovascular disorder that impairs the ability of the RV to fill or to eject blood. Causes of RHF are listed below in Fig. 13.

The cardinal clinical manifestations are because of fluid retention; decreased systolic reserve or low cardiac output &atrial

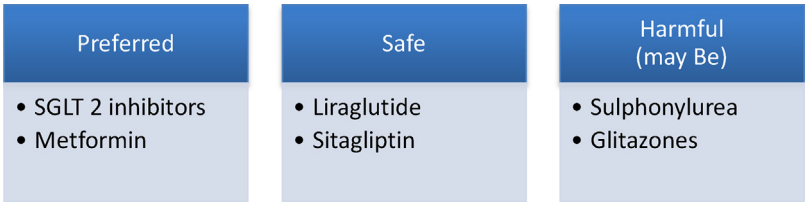

Fig. 11. Choice of Antidiabetic agent in patient with Heart failure.

Table 29
Summary of major studies on Diabetic cardiomyopathy from India.

Authors (Year)	Place of study	Sample size	Key findings
Rothangpui et al. (2011)[394]	Manipur	100 type 2DM patients	Prevalence of Diabetic CM was 40% No relation with duration of diabetes and glycemic control Majority (67%) had diastolic dysfunction LV mass was more in females with cardiomyopathy Cardiomyopathy patients had higher LDL, TG and lower HDL
Patil VC et al. (2011)[395]	Satara, Maharashtra	127 type 2 DM patients	54.33% had diastolic dysfunction Correlation with disease duration, obesity, glycemic control and microangiopathies was noted
Chaudhary et al (2015)[396]	Meerut (UP)	100 newly diagnosed normotensive diabetics	41% had LVDD Correlated with HbA1c and age
Senthil N et al (2015)[397]	Chennai	100 young normotensive (<40 yrs.) diabetics	Overall prevalence of DD was 30% Distinct female preponderance No relation with disease duration, type of diabetes or glycemic control
Dikshit NM et al (2013)[398]	Surat	50 normotensive diabetics, 50 matched controls	Prevalence of DD was 66% LV mass and wall thickness was more in diabetics compared to controls
Patil MB et al (2010)[399]	Mysore	50 normotensive diabetics	64% had DD More in females and increasing age Positive correlation with HbA1c, disease duration and treatment with both OHA and insulin.
Sridevi et al (2015)[400]	Pune	100 patients, 50 non-diabetic controls	79% prevalence of DD Correlation with coexistent CAD and hypertension
Shekhda et al (2017)[401]	Western India	100 normotensive asymptomatic diabetics	Prevalence of DD was 64% Strong association with disease duration and glycemic control No relation to age, gender, lipid parameters and type of treatment

- **All these studies had relatively small sample size.**
- **Prevalence of diabetic cardiomyopathy was based on echocardiographic estimation of diastolic and systolic dysfunction only.**
- **Prevalence of diastolic dysfunction in diabetic Indians appear to be higher than western population.**
- **Inconsistent association with glycemic control and diabetes duration is observed. Some studies described a strong correlation, while others failed to establish any association between diabetes duration and glycemic status.**
- **Females with diabetes were at greater risk of developing diastolic dysfunction, hence cardiomyopathy, a finding in accordance with other parts of the world.**

Fig. 12. Key findings of Indian studies on Diabetic Cardiomyopathy.

or ventricular arrhythmias. RHF due to pressure-overload may report dyspnea, light headedness, and syncope. In both RV infarction and PE, chest discomfort, tachycardia and elevated jugular venous pressure are important features. Patients with acute-on-chronic RVF have hepatic congestion, and lower-extremity swelling. Physical examination may show parasternal heave, an RV third-heart sound, and tricuspid regurgitation. Other findings of coexisting LV failure or valvular lesions may be present.[402,403]

The Right Ventricle adapts better to volume-overload than to pressure-overload. In atrial septal defect (ASD) and tricuspid regurgitation (TR), the RV may tolerate volume-overload for a long time. In contrast, pH in the adult often leads to RV dilatation and failure.

In acute pressure-overload states such as pulmonary embolism (PE), a previously normal RV is incapable of acutely generating a mean pulmonary artery pressure (mPAP) >40 mm Hg, and RV failure occurs early.

Atrial flutter and atrial fibrillation are the most common arrhythmias in severe RV dysfunction, often lead to hemodynamic instability and are associated with an increased risk of morbidity or mortality.[404–408]

RHF may progress from RV dysfunction to symptomatic RV failure to refractory RV failure. Decreased exercise tolerance represents most important prognostic factors for death or hospitalization.[409–411]

The clinical syndrome of RVMI characterized by the triad of hypotension, elevated jugular veins, and clear lung fields in a patient with minimal LV involvement. Hemodynamically significant RVMI with hypotension occurs in less than10% of IWMI patients.[404]

3.7.1. Management

The evidence that guides the management of isolated RV failure is not nearly as well established as the evidence that guides the management of chronic HF resulting from LV systolic dysfunction. Most recommendations are based on either retrospective or small randomized studies.

3.7.2. General measures

Moderate sodium restriction (<2 g/d), daily measurements of weight, and judicious use of diuretics are recommended. Moderate exercise training may significantly improve functional capacity and quality of life. Isometric activities may be associated with syncope and should be avoided. Pregnancy in patients with severe RV failure is associated with high maternal and fetal mortality rate.[412,413]

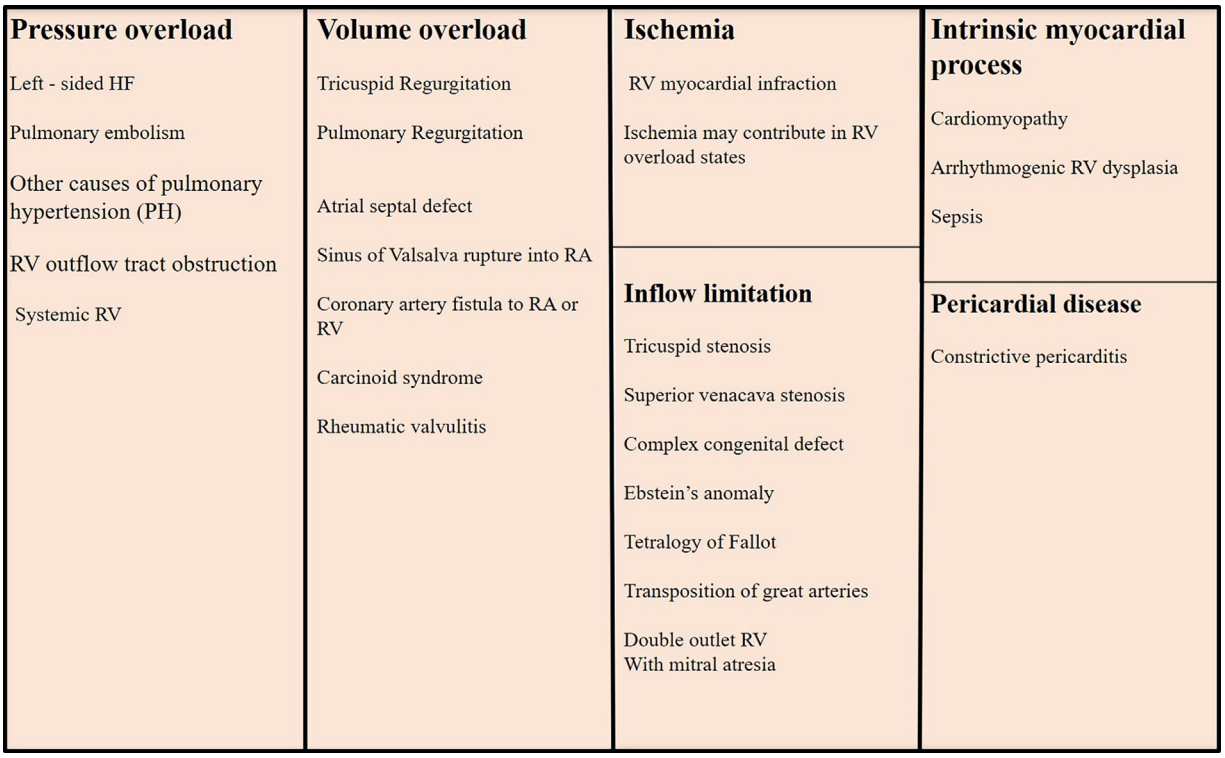

Fig. 13. Common causes of right sided heart failure.

3.7.3. Preload optimization

In conditions where RV output is impaired due to contractile dysfunction but the afterload is normal, a higher preload is needed to maintain forward flow. It is generally agreed that maintaining a moderately high RV diastolic filling pressure of 8–12 mmHg is optimal in RHF.[414]

3.7.4. Afterload reduction

General measures include lung protective ventilation, avoiding hypoxaemia and hypercarbia. Pulmonary vasodilators are currently not approved for use in critically ill patients with RV failure not due to PAH. However, inhaled nitric oxide (iNO) with its rapid onset of action and short half-life is the pulmonary vasodilator of choice in the critically ill and improves pulmonary haemodynamics in RHF. Inhaled prostacyclin analogues have been shown to be safe and effective in cardiothoracic surgical patients with pulmonary hypertension, refractory hypoxaemia. Phosphodiesterase 5(PDE5) inhibitors decrease PAP and increase cardiac output in both acute and chronic pulmonary hypertension.[412–418]

3.7.5. Improving contractility

General measures targets maintaining RV perfusion by reducing wall tension and increasing coronary artery diastolic pressure and maintaining acellular milieu conducive to myocyte contractility. The general principles of inotrope use for LVF are applicable for RVF also.

3.7.6. Rhythm management and resynchronization

Maintenance of sinus rhythm and heart rate control are important in RV failure. Sequential AV pacing and cardioversion of unstable tachyarrhythmias should be considered promptly when appropriate.

The study of RV resynchronization is at its initial stages.[419,420]

3.7.7. Anticoagulation

The risk of thromboembolic events in patients with RV failure has not been well established. Although anticoagulation is usually recommended in patients with evidence of intracardiac thrombus, documented thromboembolic events, paroxysmal or persistent atrial flutter or fibrillation in the presence of PAH and significant RV dysfunction.[407,412]

3.7.8. Neurohormonal modulation of RV failure

ACE inhibitors have been shown to increase RVEF and to reduce RV end-diastolic volume and filling pressures. Small studies also have demonstrated that β blockade with carvedilol or bisoprolol improves RV systolic function.

3.7.9. Supplemental oxygen therapy and ventilation

Hypoxemia may lead to pulmonary vasoconstriction and contribute to PH. Supplemental oxygen is recommended in patients with evidence of resting or exercise-induced hypoxemia. Patients with hypoxemia associated with pulmonary-to-systemic shunting usually do not benefit from supplemental oxygen therapy.[415]

3.7.10. Atrial septostomy

The observation of improved survival of patients with pulmonary hypertension (PH) and patent foramen ovale has led to the hypothesis that atrial septostomy, which "decompresses" the RV and increases right-to-left shunting, may be helpful in severe RV failure. At this time, atrial septostomy should be considered palliative.[421]

3.7.11. Transplantation

Originally, it was believed that patients with advanced RV failure secondary to PH could be candidates only for heart-lung transplantation. However, lung transplantation has been tried and has been successful in many patients.[412]

3.7.12. RV assist device

In acute RV failure refractory to medical treatment, mechanical support with an RV assist device maybe used as a bridge to transplantation or to recovery.[422]

3.8. *Constrictive pericarditis*

Chronic Constrictive pericarditis (CCP) represents the end stage of various pericardial inflammatory processes causing thickening and fibrosis of pericardium which limits diastolic ventricular filling. This is described more than 300 years ago but in spite of socioeconomic development, surprisingly the burden of constrictive pericarditis has not declined.[423]

In the majority of cases of CCP the etiology remains unclear. In India majority of the patients with CCP are suspected to have tuberculosis in past. The common causes of constrictive pericarditis include infectious diseases like tuberculosis, neoplasms, cardiac surgery, and irradiation. Less important causes are idiopathic pericarditis, sarcoidosis, uremia, autoimmune (connective tissue) disorders and trauma.[424,425] In developing countries, tuberculosis is still the leading cause of CCP with a reported incidence of 38%–89%.[426–430] however developed world has seen rapid decline in the cases resulting from tuberculosis (only 0%–1%)[431,432] and relative rise in the incidence of post-operative constrictive pericarditis.[433–435]

The risk of progression is especially related to the etiology: low (<1%) in viral and idiopathic pericarditis, intermediate (2–5%) in immune-mediated pericarditis and neoplastic pericardial diseases and high (20–30%) in bacterial pericarditis, especially purulent pericarditis.[436]

In hospital series from India constrictive pericarditis used to account for 0.24% to 0.41% of all medical admissions and 0.77% to 3.0% of all cardiac cases admitted.[437–439]

The disease is most prevalent from the second to fourth decades of life and is seldom seen at the extremes of age.[426] It has been found to be more common in men than women in India as compare to western world.[426,440,441] The duration of symptoms before the diagnosis is ranges from 1 to 15 years (mean 6 years) due to late diagnosis of the disease.[426,442] The pathophysiological hallmark of pericardial constriction is equalization of the end diastolic pressure in all 4 cardiac chambers which is because of restricted ventricular filling due to loss of pericardial compliance.[443]

The most striking presenting clinical features were ascites, exertional dyspnea and easy fatigability across all series. Exertional dyspnea and ascites are seen in three fourths of patients. Pedal edema is seen in nearly half while fatigue is the presenting symptom in one fourth of patients. Less commonly, gastrointestinal symptoms like anorexia, abdominal fullness, or abdominal pain may develop secondary to ascites.

A mechanical constriction around the heart produces gross signs of right heart failure without severe dyspnea. The jugular venous pressure is elevated with a deep, steep y descent. Positive Kussmaul sign and a pericardial knock favor the diagnosis of constrictive pericarditis. Pulsus paradoxus is uncommon in constrictive pericarditis.

ECG usually shows nonspecific ST segment and T wave changes. Atrial fibrillation (AF) has been reported in 25%-30% of patients with CCP.[444] X Ray evidence of pericardial calcification is less in Indian patients (15%) compared to the reported figures of 30%-50% in the western literature.[442] Echocardiography is usually the choice of imaging in patients with suspected constrictive pericarditis.[424] CT is useful in diagnosing constrictive pericarditis and can demonstrate increased pericardial thickness (>4 mm) and calcification.[445] If diagnosis is in doubt then invasive hemodynamic study can be useful.[446]

3.8.1. Management

Although the mainstay of treatment of chronic permanent cases is surgery, medical therapy may have a role in some conditions. Medical therapy of specific etiologies (i.e. tuberculous) is useful to prevent the progression to constriction. Antituberculosis antibiotics may significantly reduce the risk of constriction from >80% to <10%.[447,448] Medical therapy (generally based on anti-inflammatory drugs) may solve the transient constriction occurring in 10–20% of cases within a few months, generally as a temporary phenomenon during the resolution of pericarditis. Medical therapy is supportive and aimed at controlling symptoms of congestion in advanced cases and when surgery is contraindicated or delayed.

Pericardiectomy is the definitive treatment for constrictive pericarditis.[430] There is an improvement in mortality rates in series published after 1985. The actuarial survival was ~84% in patients undergoing total pericardiectomy compared to ~74% in patients undergoing partial pericardiectomy at a mean follow-up of 18 years.[426]

In the western studies, the operative mortality is about 6%.[431,449] Survival at 5- and 10-years is reported to be $78 \pm 5\%$ and $57 \pm 8\%$, respectively, which is inferior to that reported from India. This has been proposed to be due to older age group of patients and the higher incidence of post irradiation constrictive pericarditis which leads to myocardial dysfunction as well. Predictors of late events include 3 baseline variables: age, NYHA class, and a radiation cause for constrictive pericarditis.[431] Idiopathic CP had the best prognosis (7-year Kaplan-Meier survival: 88%, followed by postsurgical (66%) and post radiation CP (27%).[449]

3.9. *Restrictive cardiomyopathy*

Restrictive cardiomyopathy (RCM) is the least common type of cardiomyopathy. RCM is characterised by *diastolic dysfunction that results in impaired ventricular filling, normal or decreased diastolic volume of either or both ventricles, and increased left ventricular wall thickness*.[450] Unlike DCM and HCM, where the definition is morphological, the definition of restrictive cardiomyopathy requires hemodynamic distinctions. Myocardial relaxation abnormality with interstitial fibrosis and calcifications compose the fundamental abnormalities of restrictive cardiomyopathies. RCM constitutes 10–15% of all cases of HFpEF.[451]

Etiology (Table 30) –

3.9.1. Idiopathic (Primary) RCM

Idiopathic RCM is a rare condition that may present in both children and adults.[452,453] Both familial and sporadic cases have been described.[454,455] Familial cases are usually characterized by autosomal dominant inheritance with incomplete penetrance. The condition warrants earliest recognition as development of pulmonary hypertension precludes heart transplantation.[456]

3.9.2. Amyloidosis

Cardiac amyloidosis is an infiltrative disorder caused by deposition of insoluble fibrillar protein in the interstitial space.[457] It typically presents as a systemic disorder, with multi organ infiltration. Primary or systemic amyloid light-chain (AL) amyloidosis is the most common form of amyloidosis and is associated with blood dyscrasias, such as multiple myeloma. Cardiac involvement is associated with a poor prognosis, with a median survival from diagnosis of 1 year.[458] The diagnosis of AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome; nonischemic cardiomyopathy with “hypertrophy” on echocardiography.[459]

A detailed description of other conditions causing RCM is beyond the scope of this document and details can be found elsewhere.

3.9.3. Diagnosis of RCM

The ECG often shows low voltage, nonspecific ST-T wave changes, various arrhythmias and conduction blocks. Most patients have normal or near-normal cardiac size on examination

Table 30
Causes of Restrictive cardiomyopathy.

Primary
Familial Cardiomyopathy
Endomyocardial fibrosis
Loeffler endocarditis
Idiopathic cardiomyopathy
Secondary
Infiltrative
Amyloidosis
Sarcoidosis
Non-infiltrative
Myocardial
Scleroderma
Diabetic cardiomyopathy
Pseudoxanthoma elasticum
Endomyocardial
Carcinoid heart disease
Metastatic cancers
Radiation
Toxic effects of anthracycline
Drugs causing fibrous endocarditis (Serotonin, methysergide, ergotamine, mercurial agents and busulfan)
Storage disorders
Fabry's disease
Gaucher's disease
Haemochromatosis
Hurler's disease
Fatty infiltration
Storage diseases
Glycogen storage disease

and chest x-ray. In advanced cases there is cardiomegaly. Echocardiographic findings in RCM include biatrial dilatation, hypertrophied ventricles with decreased compliance, initially small cavities of the left ventricle, and normal-to-depressed systolic function (Table 31).[460]

Other classical features of RCM can be studied using Tissue Doppler,&Strain rate imaging and Myocardial contraction function

Cardiac magnetic resonance (CMR) is a versatile technique providing anatomical, morphological and functional information in suspected RCM. In recent years, it has been shown to provide important information regarding disease mechanisms, and also been found useful to guide treatment, assess its outcome and predict patient prognosis.[461] It confirms the existence of thrombi or calcifications, allows an exact delineation of hypoperfused areas that correspond to fibrosis, and provides hemodynamic information.[462] Myocardial suppression scans, acquired after injection of gadolinium, allow exact appreciation of the disease extension of fibrosis by delayed hyperenhancement of the pathologic areas.[463]

Cardiac catheterization is rarely used for the diagnosis of RCM, since complete noninvasive assessment is possible in most patients. Endomyocardial biopsy is rarely used in India to diagnose RCM. It may be done when specific treatable etiologies are suspected.

3.9.4. Outcomes

The course of RCM varies depending on the pathology, and the treatment is often unsatisfactory. The prognosis for children with IRCM is especially poor. In adult presentation, patients often have extensive disease; therefore, survival after diagnosis is relatively brief, averaging approximately two years after symptom onset.[464] Gupta and colleagues,[465] showed a 10 year survival of only 37% in patients of EMF.

3.9.5. Treatment

Unlike the overwhelming evidence for guideline based treatment for dilated and hypertrophic cardiomyopathy, there has been less direction on the best treatment of RCM. The goal of treatment in RCM is to reduce symptoms by lowering elevated filling pressures without significantly reducing cardiac output.

The general principles are summarized below-

- Principles of Non-pharmacological management are similar to that applied in HF of other etiologies
- Diuretics (aldosterone antagonists and loop diuretics) – are the mainstay
- Midodrine* may be helpful when symptomatic hypotension (*Not available in India)
- **Beta blockers and ACEI:**
  - Reasonable if the patient has hypertension
  - Often advanced RCM have low baseline blood pressures
  - Prudent to titrate these drug classes with extreme caution.
- **Calcium Channel blockers**:
  - Verapamil/diltiazem useful in RCM
    - Increased LV filling time and improving LV relaxation
    - Relatively contraindicated in amyloidosis – high sensitivity to high-degree heart block and profound negative inotropic effects.[466]
- **Digoxin**:
  - Amyloidosis – highly sensitive to digoxin may cause sudden death[467,468]
  - Should be avoided.

3.9.5.1. Management of atrial fibrillation. Patients with restrictive physiology rely more heavily on atria's contribution to stroke volume. Hence, AF needs to be treated with amiodarone and beta blockers promptly. Patients with AF warrant standard anticoagulation therapy.

3.9.6. Specific management

RCM has no specific treatment. However, therapies directed at individual causes of RCM have been proven to be effective (Table 32).

Cardiac transplantation or mechanicals support therapy can be considered in select patients of RCM with refractory symptoms who have idiopathic RCM, amyloidosis or EMF. Cardiac transplantation may be effective in patients with m-TTR amyloid if there is limited hepatic and nerve involvement. Liver and combined liver–cardiac transplantation may improve survival in these patients when there is significant liver involvement.

3.10. *Endomyocardial fibrosis*

EMF is a disease of the tropics and widely prevalent and was then reported from India, Uganda, Nigeria, Ivory Coast and Brazil.

Table 31
Distinguishing Echocardiographic features in different causes of RCM.

Disease	Echocardiographic features
EMF	Cavity obliteration and right ventricular outflow tract dilatation with varying degrees of atrioventricular valve regurgitation
Cardiac Amyloidosis	Increased thickening of the ventricular wall, mitral and tricuspid leaflets, and interatrial septum. decreased global longitudinal strain
Friedrich's ataxia	Hypertrophic cardiomyopathy, including symmetric LV hypertrophy, abnormal myocardial relaxation, and LV outflow obstruction
Drug induced	Valvular thickening

Table 32
Treatment of the Restrictive Cardiomyopathies

	Treatment
Idiopathic RCM	Heart transplant
EMF	Endocardiectomy, Heart transplant
Amyloidosis	
• Primary (AL)	Bortezomib-based chemotherapy, stem cell transplant, ICD
• Secondary (AA)	Treat the underlying condition
• Hereditary (m-TTR)	Heart and/or liver transplant, ICD
Hemochromatosis	Phlebotomy, iron-chelating agents
Anderson-Fabry	Phlebotomy, iron-chelating agents

AA = amyloid A; AL = amyloid light-chain; ICD = implantable cardioverter-defibrillator; m-TTR = mutant transthyretin; wt-TTR = wild-type transthyretin; other

EMF in India

As per hospital statistics, incidence and prevalence of EMF peaked during 1960–1990 in Kerala and subsequently there has been a marked decrease in newly diagnosed cases of EMF. In the registry of over 400 cases of EMF during 1978–1990,[469,470] RVEMF was seen in 30%, LVEMF in 20% and biventricular EMF (BVEMF) in 50%. Mortality at 2 years in those presenting with NYHA class 3–4 was 50% on optimal medical therapy. During a five year period from 1998 to 2003, there were only 50 new cases of EMF with mostly older patients. The patients were less symptomatic; most of the cases were diagnosed consequent to evaluation of abnormal electrocardiograms and non-specific symptoms. The mortality of the patients who presented in this period was less than 10 percent at two years after diagnosis.

3.10.1. Anatomical/structural involvement in EMF

As the name suggests, and as clinically recognized, endomyocardial fibrosis is primarily a fibrotic disease process involving predominantly the endocardium of either or both ventricles and conspicuous by sparing the atria of clinically important involvement. There is a predilection for the pathologic process to involve the apices of the ventricles and spare the outflows of the right and left ventricles though an occasional case of RV outflow involvement with the fibrotic process has been described. The endocardial fibrotic process extends to adjacent myocardium to variable degree and can rarely cause in addition, systolic ventricular dysfunction. Superimposed thrombus on the fibrotic endocardial surface can lead to systemic as well as pulmonary thromboembolism and organized clots are postulated to be an additional reason for ventricular cavity obliteration. The fibrotic process can involve the papillary muscles of either of the ventricle and this leads to loss of function of the chordo-papillary structure often leading to fixity and plastering of the leaflets with reduced mobility and inadequate coaptation causing atrio-ventricular (AV) valve regurgitation, though primary involvement of the valve leaflets is not described.

3.10.2. Clinical presentation:

The extent of obliterative endocardial involvement and AV valve incompetence affecting either or both ventricles will determine the clinical symptomatology. Isolated RVEMF with obliterative changes and no tricuspid incompetence, are mildly symptomatic and the only abnormal clinical finding may be prominent 'a' wave in JVP. At the other extreme, patients with isolated RVEMF with severe TR present with features of chronic right HF with markedly elevated JVP and expansile large 'v' waves, pulsatile liver, hepatomegaly, ascites precox, edema, cyanosis, cachexia, and malnutrition. They may also have pericardial effusion, marked cardiomegaly, RV third heart sound, and inconspicuous systolic murmur of TR. The severity of TR rather than the presence of RV diastolic dysfunction is the determining factor for the outcome of patients with RVEMF.

Isolated LVEMF, in the absence of AV valve incompetence, is often minimally symptomatic. Hemodynamic study may reveal a prominent 'a' wave in the pulmonary artery wedge pressure and LV end diastolic pressure may be elevated. Patients with LVEMF usually have features of mitral incompetence with grade 1 to 3/6 intensity systolic murmur. A systolic thrill is rare, so also is a fourth heart sound. LV third heart sound is common. Patients with LVEMF and significant mitral incompetence, present similar to patients with valvular incompetence from rheumatic heart disease. Left atrial and pulmonary venous hypertension is followed by pulmonary arterial hypertension and RV failure. Features of PAH will depend on the presence of pulmonary venous hypertension resulting from mitral incompetence as well as diastolic LV dysfunction. Symptomatic patients with LVEMF usually have significant AV valve incompetence and symptoms correlate well with severity of mitral incompetence, suggesting that mitral incompetence is the dominant factor in determining the clinical disease progression.

Biventricular involvement is seen in at least 50% of patients and clinical presentation depends upon the severity of mitral incompetence, tricuspid incompetence and diastolic dysfunction due to obliterative changes in both the ventricles. These patients are hemodynamically more compromised and deteriorate rapidly and have a poor prognosis. Though large RA thrombi are occasionally seen, it is rare to see massive pulmonary embolism and pulmonary infarcts are rarely recognized clinically or at autopsy. Large pericardial effusion with isolated severe RV EMF rarely contribute to hemodynamic deterioration and is an indicator of severe disease, re-accumulates rapidly and is not drained as a routine.

3.10.3. Investigations:

Electrocardiogram and Chest skiagram are useful to assess chamber enlargement, pulmonary venous hypertension, and pericardial effusion. LA enlargement is common finding. RVEMF is often characterized by qR pattern in V1 with a diminutive 'R' and hypothesized as due to RA enlargement displacing a diminutive RV (Figs. 13 and 14)

Echocardiography with Doppler study, and hemodynamic study with ventricular angiography are essential tools for assessment of the morphological and hemodynamic derangement in EMF to decide on need for therapeutic interventions (Figs. 15–18).[460,471]

Cardiac MRI has the potential to be the choice imaging mode for better delineation of ventricular morphology, shape, function as well as endocardial thickening, thrombosis, myocardial characterization for fibrosis and AV valve incompetence. (Fig. 19)

3.10.4. Management of HF in EMF

For clinical simplicity, 3 scenarios of EMF which will encompass the majority of clinical spectrum of EMF are summarized in Table below

1. Isolated RVEMF:
   - Medical management is as for isolated right HF with diuretics for preload reduction
   - Chronic low pressure TR has a better prognosis with patients often surviving many years, though the majority may succumb to HF and inter-current illness due to malnutrition
   - Surgical options: TV replacement, TV replacement with Glenn shunt (one and half ventricle repair) and Fontan type surgery
2. Isolated LVEMF:
   - Mildly symptomatic patients – small dose diuretics as needed and rhythm management and anticoagulation when indicated for AF.

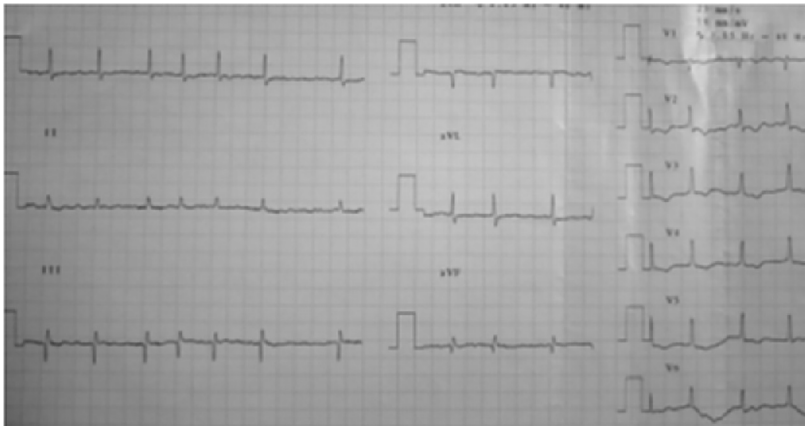

Fig. 14. ECG of a patient with LVEMF, showing LVH with strain pattern.

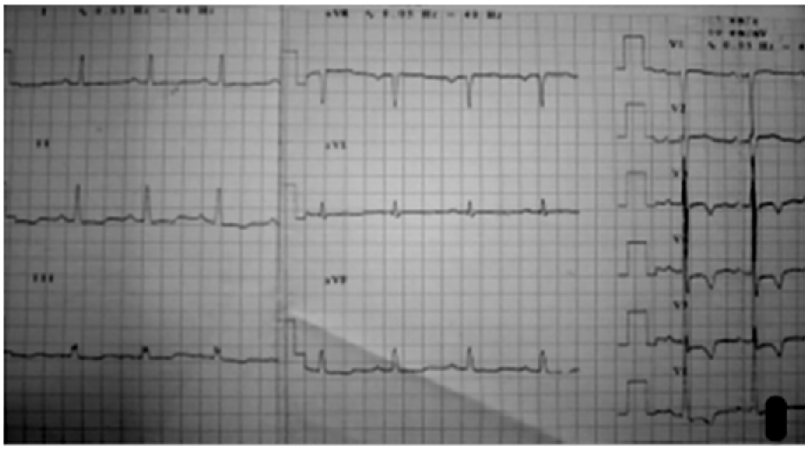

Fig. 15. Fluoroscopy showing, the presence of LV apical calcium.

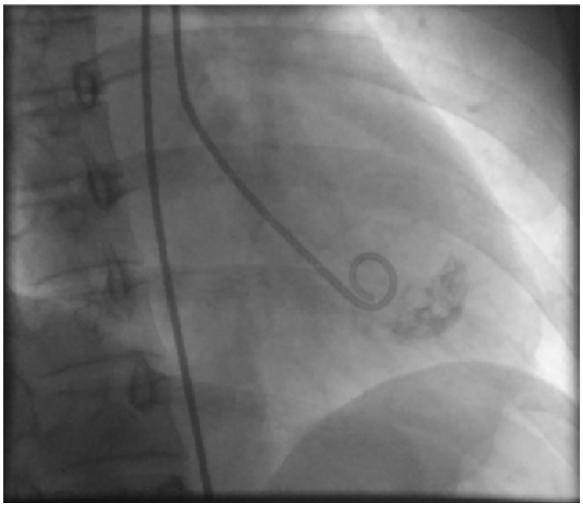

Fig. 16. LV angiogram in a patient with LVEMF, showing the obliteration of the LV apex, transverse diameter more than the longitudinal diameter and no MR (Primary diastolic HF).

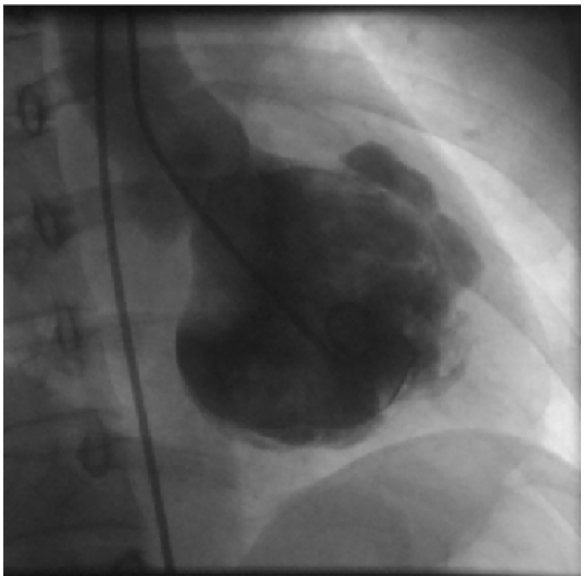

Fig. 17. RV angiogram in a patient with RVEMF, showing obliteration of the RV apex and body, RVOF dilatation and significant TR.

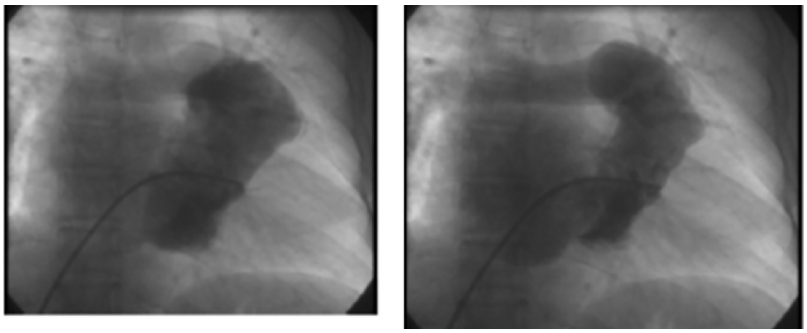

Fig. 18. Echocardiogram, Apical 4 chamber view, showing the presence of calcium at the LV apex.

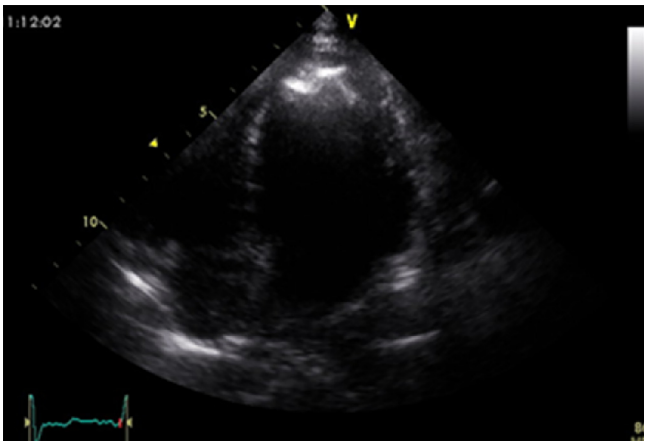

Fig. 19. Perfusion MRI, 4 chamber view in diastole showing fibrosis and obliteration of RV apex (white arrow) [RV – right ventricle, RA – Right atrium, LA – left atrium].

- Ventricular arrhythmias are infrequent and prophylactic ICD/CRT not indicated in view of preserved LVEF in the vast majority.
- Severely symptomatic patients – surgery with mitral valve replacement and LV endocardiectomy
- The short term, intermediate and long term outcome is excellent, though underlying myocardial dysfunction, extend of restoration of LV cavity and LV compliance at surgery are confounding factors.

3. BVEMF with hemodynamically significant biventricular involvement:
   - Most difficult subset of patients to manage medically as well as surgically
   - Medical therapy is supportive with optimal diuretic use, ventricular rate control and anticoagulation for AF
   - Decision on feasibility of surgery is largely dependent on the extent of RV involvement and adequacy of RV to support the entire cardiac output by its structure and function. A hypertensive RV (RV pressure more than 50 mmHg is a useful yardstick) indicates adequate systolic function to support the systemic circulation and these patients can undergo MV replacement with LV endocardectomy and TV repair ensuring adequacy of RV cavity volume and systolic RV function. These patients cannot have Glenn/one and half ventricle repair/Fontan type surgery along with MV surgery. In the absence of significant obliterative and contracted volume deficient RV, these patients have a fair long term surgical outcome.

Severe LV involvement with severe RV involvement characterized by severe TR and severe RV cavity obliteration are not offered surgical options in view of high surgical risk and uncertain long term outcome. They are managed as chronic HF and can be listed for cardiac transplant as there is little risk of recurrence of EMF.

Eosinophilic systemic disease with EMF: Hypereosinophilic syndrome with tissue infiltration and endo myocardial involvement (Loeffler's syndrome) can closely mimic tropical EF.

Experience at the Sree Chitra Tirunal Institute for Medical Sciences and Technology showed 54% survival among 210 medically followed up patients. However those in class 3–4 had 50% mortality at 2 years. 89 patients underwent various surgical procedures from 1980- 1990.[471] Operative mortality at one month was 30% and additional late mortality of 12%. Late mortality and morbidity were related to prosthetic valve dysfunction more so in the tricuspid position with bioprosthesis degeneration and mechanical prosthesis thrombosis. 27 patients with isolated RVEMF had TV replacement with RV endocardectomy with early mortality 30%. 13 patients with LVEMF had LV endocardectomy and MV replacement including 2 TV annuloplasty, with early mortality 23%. 49 patients with significant BVEMF, had MVR + TVR+ BV endocardectomy in 12, MVR + LVE+ TVA in 15, MVR+ LV endocardectomy in 11 and TVR + RV endocardectomy in13 (patients with hemodynamically insignificant LV involvement) with early mortality 30%. Mortality in patients less than 15 years was 58% compared to 22% in those above 15 years. 3 patients showed recurrent fibrosis of endocardium at follow up of which, one had significant cavity obliteration. In view of the unsatisfactory surgical outcome, only 7 patients out of 11 patients presenting in 1990–2000 period were offered surgery and none was offered TV replacement. 3 had LV endocardectomy with MVR, one LV endocardectomy alone, 1 biventricular endocardectomy, 2 bidirectional Glenn shunt. There was no early or intermediate term mortality, essentially because of case selection, avoiding patients with severe biventricular disease and resorting to RV bypass avoiding TV replacement (Table 33).

3.11. *Nutritional and metabolic causes of HF*

Metabolic derangements are rare but important cause of HF. In developing countries like India, this becomes even more important due to higher prevalence of malnutrition and poor general health care leading to delayed diagnosis and ineffective management of potentially reversible causes of HF.

Metabolic derangements leading to HF can be divided into Nutritional causes and Hormonal causes (Table 34).[26]

3.11.1. Nutritional causes

3.11.1.1. Thiamine deficiency (Beriberi). Asians have higher incidence of beriberi because the diet consists of a high intake of polished rice which is deficient in thiamine. Thiamine is required as a cofactor for energy production via the Krebs cycle at two steps: oxidative decarboxylation of pyruvate to acetyl

Table 33
Salient features of EMF in India.

- Endomyocardial fibrosis is presently reported sporadically from many parts of India
- There is a remarkable reduction in newly diagnosed cases
- 3 Phases – Thrombotic (acute) phase, sub acute phase and chronic fibrotic phase
- Management – predominantly addressing pulmonary and systemic venous congestion with diuretics, arrhythmia management and anticoagulation
- Various surgical interventions have been attempted, and MV replacement and or LV endocardectomy for isolated LV EMF have similar results to MV replacement in rheumatic valvular heart disease. Surgical outcome for primary RV involvement is less satisfactory with high surgical mortality and early prosthetic valve thrombosis.

Table 34
Metabolic causes of heart failure.

Nutritional Causes	Hormonal causes
Deficiency of micronutrients	Thyroid diseases
Thiamine	Parathyroid disease
L-carnitine	Acromegaly
Selenium	GH deficiency
Coenzyme Q10	Hypercortisolemia
Iron	Primary hyperaldosteronism
Phosphates	Addison's Disease
Calcium	Diabetes mellitus
Complex malnutrition	Metabolic Syndrome
Malignancy	Pheochromocytoma
AIDS	Related to pregnancy and peripartum
Anorexia nervosa	
Obesity	

coenzyme A and of alpha ketoglutarate to succinyl coenzyme A. Thiamine deficiency initially presents as a high-output state secondary to vasodilation and an increase in blood volume this is followed by eventual depression of myocardial function and the development of a low output state. Direct impairment of myocardial energy production has been proposed as one possible mechanism of the heart failure seen in beriberi. Exact mechanism responsible for vasodilation is not clearly understood.[472–475]

Classically, beriberi has been divided into two major types: a "dry" form, in which features of peripheral neuropathy predominate, and a "wet" form, in which signs and symptoms of right-sided heart failure with normal or high cardiac output are the presenting features. Rarely, a fulminant or "pernicious" variant, termed Shoshinberiberi, may occur with severe biventricular failure, metabolic acidosis, and variable cardiac output with vascular collapse, peripheral cyanosis and death. Laboratory diagnosis of thiamine deficiency can be made on the basis of an increase in thiamine pyrophosphate effect (TPPE), decrease in blood thiamine concentration, or a decrease in red cell transketolase activity.

Thiamine supplementation may be initiated depending on the severity of HF. In mild deficiency states including lactating women at risk of inadequate thiamine intake, a daily oral dose of 10 mg thiamine should be given during the first week, followed by 3–5 mg for at least six weeks. In critically ill child if severe heart failure, convulsions or coma occur, 25–50 mg of thiamine should be given very slowly intravenously, followed by a daily intramuscular dose of 10 mg for about a week. This should then be followed by 3–5 mg of thiamine per day orally for at least 6 weeks. In adults with severe heart failure 50–100 mg thiamine should be administered very slowly intravenously, followed by the same oral doses as for children. With appropriate treatment, the cardiac index and heart rate are reduced and there is an increase in systemic vascular resistance. Magnesium may have to be co-administered with thiamine, particularly in magnesium-depleted patients as magnesium depletion alone leads to a blunted response to thiamine supplementation and loss of thiamine from tissues. Beneficial effects of thiamine have been demonstrated in Indian population in some small studies.[476,477]

3.11.2. L- carnitine deficiency

Carnitine is a naturally occurring hydrophilic amino acid derivative, produced endogenously in the kidneys and liver and derived from meat and dairy products in the diet. It plays an essential role in the transfer of long-chain fatty acids into the mitochondria for beta-oxidation.

The three areas of involvement include[26] the cardiac muscle, which is affected by progressive cardiomyopathy (by far, the most common form of presentation),[472] the central nervous system, which is affected by encephalopathy caused by hypoketotic hypoglycemia, and[473] the skeletal muscle, which is affected by myopathy. Cardiomyopathy (affecting older children) may occur with rapidly progressive heart failure. Pericardial effusion has also been observed in association with primary carnitine deficiency. In patients with carnitine deficiency, the carnitine level in plasma is usually less than 5% of normal.

Medical therapy with oral carnitine in primary carnitine deficiency improves fasting ketogenesis, cardiac function, growth, and cognitive performance. The usual dose of oral L-carnitine in children is 100 mg/kg per day in four divided doses. The dose of L-carnitine in adults is 2 to 6 g daily. For life-threatening events, intravenous therapy of 100 to 400 mg/kg per day should be used.[478]

3.11.3. Selenium deficiency

Selenium (Se) is a trace mineral with a role in multiple biologic functions. Seafood, kidney and liver, and meat are good sources of selenium. Drinking water usually contains very little selenium.[479,480] The selenium content of grains and seeds is variable and depends on the selenium content of the soil and the form in which selenium is present

Severe selenium deficiency is associated with skeletal muscle dysfunction and cardiomyopathy and may also cause mood disorders and impaired immune function macrocytosis, and whitened nailbeds. Keshan disease, an endemic cardiomyopathy that affects children and women of childbearing age in areas of China, has been linked to selenium deficiency.[481] Several cases of selenium deficiency in chronic total parenteral nutrition users have been reported with cardiomyopathy and skeletal muscle dysfunction.[482]

The Recommended dietary allowance for selenium is 20 mcg daily for young children, rising to 55 mcg daily for adults.

3.11.4. Coenzyme Q10 deficiency

Coenzyme Q10 (CoQ10) is a natural antioxidant synthesized and diet-supplied lipid-soluble cofactor that acts in the mitochondrial membrane. Coenzyme Q10 (CoQ10) or ubiquinone can potentially enhance cardiac function through a variety of mechanisms.[483]

Coenzyme Q10 deficiency is associated with HF. In patients with HF, the reduced intake of CoQ10 is correlated with New York Heart Association (NYHA) functional class, lower left ventricular ejection fraction (LVEF) and increased NT-proBNP levels.[484] Measurement of total CoQ10 represents the sum of the reduced form (Ubiquinol-10) and the oxidized form (Ubiqinone-10).

Two meta-analyses[485,486] that have examined pooled data from 13 trials demonstrated an improvement in LVEF of 3.67% (95% CI, 1.6%–5.74%) in those receiving CoQ10 versus placebo. The majority of benefit of LVEF improvement was in trials published before 1993 (7/13). Lack of contemporary cardiovascular drugs and devices, and use of more subjective outcomes (such as hospitalizations and symptoms) limit the strength of these findings. Recent Q-SYMBIO trial completed in 2014 which enrolled 420 patients demonstrated that compared with placebo, CoQ10 at 100 mg orally thrice a day reduced the primary two year end point of cardiovascular death, hospital stays for HF, or mechanical support or cardiac transplant (30 versus 57, P = 0.005).[487] Cochrane Database review **n**o conclusions can be drawn on the benefits or harms of coenzyme Q10 in heart failure at this time as trials published to date lack information on clinically relevant endpoints. Furthermore, the existing data are derived from small, heterogeneous trials that concentrate on physiological measures: their results are inconclusive. Until further evidence emerges to support the use of coenzyme Q10 in heart failure, there might be a need to re-evaluate whether further trials testing coenzyme Q10 in heart failure are desirable.

3.11.5. Iron deficiency

Iron deficiency contributes to cardiac and peripheral dysfunction and is associated with increased risk of death, independent of the hemoglobin level.[488] Iron deficiency affects nearly 40% of HF patients.[489] Jankowska et al. demonstrated that iron deficiency is a strong and independent predictor of prognosis in HF, with a 1.58 increased risk of death or heart transplant.[490] In recent INDIC study, iron deficiency was seen in 67.5% patients with systolic heart failure and was associated with advanced NYHA class.[491]

In HF patients, iron deficiency can be defined as ferritin <100 mg/L (absolute iron deficiency, related to depletion of iron stores), or 100–300 mg/L with transferrin saturation <20%. CONFIRM-HF trial demonstrated a 61% relative decrease in HF hospitalization for worsening HF and an improvement in functional capacity, symptoms, and quality of life in patients receiving intravenous ferric carboxymaltose.[492] A meta-analysis of five randomized clinical trials suggested that intravenous iron supplementation reduces cardiovascular hospitalization (OR 0.44), cardiovascular death or hospitalization for worsening HF (OR 0.39), while improving quality of life, functional capacity and other symptoms.[23]Recent ESC guidelines recommend Intravenous ferric carboxymaltose in symptomatic patients with Heart failure with reduced ejection fraction and iron deficiency (serum ferritin <100 μg/L, or ferritin between 100 and 299 μg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.[26]

Advantages of IV iron therapy include the small number of injections required, rapid improvement in iron parameters and the cost-effectiveness. Preparation of iv iron like ferric carboxymaltose (FCM), ferric hydroxide sucrose, ferric gluconate, and ferric hydroxide dextran are available. The recommended dose for FCM (750 mg) is higher than that for ferric sucrose (100–400 mg) or ferric gluconate (125 mg), so fewer injections of FCM are needed to replenish iron stores.

3.11.6. Hormonal causes

3.11.6.1. Thyroid dysfunction. Thyroid hormone regulates cardiac performance by acting on the heart and vascular system. Several important cardiac structural and functional proteins are transcriptionally regulated by T3, namely, sarcoplasmic reticulum calcium ATPase (SERCA2), α-myosin heavy chain (αMHC), β1 adrenergic receptors, sodium/potassium ATPase, voltage-gated potassium channels, malic enzyme and atrial and brain natriuretic hormone.[493]

Short-term hyperthyroidism is characterized by a high cardiac output state with a remarkable increase in heart rate and cardiac preload and a reduction in peripheral vascular resistance, resulting in a hyperdynamic circulation. T3 promotes relaxation of the peripheral vasculature and decreases systemic vascular resistance indirectly by affecting tissue thermogenesis and directly by acting on vascular smooth muscle cells and endothelial nitric oxide production. Patients with overt and subclinical hyperthyroidism are at increased risk of cardiac death. The increased risk of cardiac mortality might be a consequence of the increased risk of atrial arrhythmias and of the risk of HF in these individuals. The development of high-output HF in thyrotoxicosis may be due to 'tachycardia-mediated cardiomyopathy'.[494] The symptoms and signs of HF occur in the setting of an increased cardiac output with normal systolic function and low systemic vascular resistance, whereas blood volume is increased due to the chronic activation of the RAS and, consequently, cardiac preload is enhanced. Impaired exercise tolerance can be interpreted as the first symptom of HF in hyperthyroid patients subsequently patient may complain breathlessness at rest, fatigue and fluid retention with peripheral oedema, pleural effusion, hepatic congestion and increased pulmonary arterial hypertension. Several case reports suggest that treatment with β-blockers and diuretics may improve the congestive circulatory symptoms in these patients.[492] Euthyroidism results in a rapid clinical improvement of cardiac function and symptoms of congestive HF. However, HF may become irreversible in some cases. Approximately, one-third of patients may develop hyperthyroid cardiomyopathy.[495]

Hypothyroidism causes cardiac atrophy due to decreased αMHC expression and increased βMHC expression. Moreover, hypothyroidism leads to chamber dilatation and impaired myocardial blood flow. Even patients with subclinical hypothyroidism are increased risk of heart failure. The Health Aging and Body Composition population-based study showed that patients (aged 70–79 years) with TSH level 7 mU/l or greater, who were monitored for 4 years, had a higher risk of HF events than euthyroid patients.[496] Thyroid function should be evaluated in patients with HF and non-ischaemic dilated cardiomyopathy to determine whether hypothyroidism and low T3 syndrome caused the cardiac disease. The American College of Cardiology guidelines for HF recommend screening of serum thyrotrophin levels for all cases of newly diagnosed HF.[100] The administration of replacement doses of L-T4 reduces myocyte apoptosis and improves cardiovascular performance and ventricular remodeling. Diastolic dysfunction due to slowed myocardial relaxation and impaired ventricular filling is reversible after replacement therapy. Patients with TSH >10 mU/l had an increased risk of HF during the periods of L-T4 withdrawal than during its use[497] and replacement doses of L-T4 should be considered in patients with Subclinical Hypothyroidism and TSH > 10 mU/l to prevent the risk of HF events.

Other less common hormonal causes of heart failure are summarized in Table 35.

3.12. *HIV cardiomyopathy*

With the advent of anti-retroviral therapy and better opportunistic infection control, chronic complications of Human Immunodeficiency Virus (HIV) infection, like HIV cardiomyopathy is gaining prominence. The cause is multi-factorial, including myocarditis secondary to HIV itself or other infectious agents, nutritional deficiencies (selenium, carnitine, and vitamins B1 and B12), autonomic insufficiency, and autoimmune factors (cytokine imbalances), effects of anti-retroviral drugs etc. Patients living with HIV/AIDS should be carefully evaluated and screened for

Table 35
Other hormonal disorders causing heart failure.

Disorder	Characteristics	Treatment
Parathyroid diseases	• Autonomous adenoma or secondary hyperparathyroidism secondary to chronic renal disease or vitamin D deficiency • hypertension, obesity, glucose intolerance, and insulin resistance • myocyte hypertrophy, diastolic dysfunction, calcification of aortic valve, mitral valve and myocardium	• Surgical removal of adenoma
Acromegaly	• Benign adenoma in >98% cases, • Hypertension, systolic and diastolic dysfunction, increased myocardial mass, interstitial fibrosis, ventricular cavity dilatation, and increased systemic vascular resistance, atrial and ventricular arrhythmias,	• Surgical resection of adenoma, somatostatin analogies • May reverse hypertrophy, improve diastolic filling and systolic performance
GH deficiency	• Atherosclerosis, decreases in LV mass index, impaired LV performance at peak exercise, and exercise intolerance	• GH replacement therapy improves cardiac performance and increases LV mass, LV end diastolic volume, and stroke volume
Cushing's Syndrome	• Due to pituitary adenoma or ectopic ACTH syndrome • Increased septal and free wall thickness, diastolic dysfunction, subclinical systolic dysfunction	• Transphenoidal surgery or bilateral adrenalectomy, radiotherapy • Reversible with normalisation
Primary hyperaldosteronism	• Unilateral adrenal adenoma or bilateral adrenal hyperplasia • Hypertension, potassium depletion, • Maladaptive cardiac remodelling, diastolic dysfunction	• Laparoscopic adrenalectomy for unilateral adenoma, • MRAs for bilateral hyperplasia
Pheochromocytoma	• Catecholamine-producing tumours that originate from chromaffin cells of the adrenal medulla and the sympathetic ganglia • Hypertension (episodic or sustained) and paroxysmal symptoms such as dizziness, headache, flushing, diaphoresis, and palpitations may lead to dilated cardiomyopathy or hypertrophic cardiomyopathy.	• Surgical resection, with preoperative medical optimization to obtain adequate blood pressure control and volume expansion • reversal of cardiomyopathy in early stages after surgery

GH – Growth Hormone, MRAs – Mineralocorticoid Receptor Antagonists.

presence of HIV cardiomyopathy. Indian data regarding the prevalence of this condition is inadequate.

In the pre highly active antiretroviral therapy (HAART) era, the heart failure in HIV-infected individuals was mainly due to myocarditis, related to direct effects of HIV, opportunistic infections, autoimmunity, nutritional deficiencies, or severe immune deficiency.[498] After HAART introduction, it has been proposed that incidence of coronary artery disease is more in HIV affected individuals, probably due to metabolic derangements caused by protease inhibitors.

Pre-HAART era: HIV-associated cardiomyopathy was broadly defined as a decreased left ventricular (LV) ejection fraction or dilated LV by imaging studies, with or without symptoms of heart failure and mainly prevalent in the developing countries.

After introduction of HAART, definition of HIV-associated cardiomyopathy now includes diastolic dysfunction.[499–502]

3.12.1. Pathological features of HIV-associated cardiomyopathy

Gross examination reveals endocardial fibrosis and mural thrombus. Histologically, there is evidence of myocyte hypertrophy and degeneration, with increased interstitial and endocardial fibrillar collagen often associated with evidence of previous myocarditis.

3.12.2. Treatment[503–512]

No randomized trials of heart failure medications have been performed in HIV cardiomyopathy, and therapy is based on consensus statements and standard guideline directed medical treatment for non-HIV heart failure.

3.12.3. The Indian perspective

Studies on cardiovascular manifestations of HIV are sparse in India, as the clinical picture is still dominated by opportunistic infections, and cardiological symptoms in these patients are frequently ascribed to non-cardiac causes by the treating physicians due to lack of awareness. However, after initiation of HAART and better infection control, there has been a prolongation of life span of HIV patients, and more and more patients are being diagnosed with cardiomyopathy. According to some case reports, HAART may prolong life expectancy in HIV cardiomyopathy.[513] Echocardiography remains the mainstay of diagnosis in India, and its use in HIV patients needs to be encouraged. The ensuing table summarizes the findings of various authors who have studied HIV related cardiovascular manifestations in the Indian subcontinent (Table 36).

3.13. *Management of heart failure in specific situations: alcohol induced cardiomyopathy*

Alcohol consumption is common modifiable risk factor for development of Cardiac dysfunction and symptomatic HF. The diagnosis of Alcohol induced Cardiomyopathy (ACM) is usually one of exclusion in a patient with DCM with no identified cause and a long history of heavy alcohol abuse.

Alcohol consumption is very common in the developed world due to easy availability and low cost In India the prevalence of alcohol consumption is increasing and has shown 100% rise from 1970 to 1995 and 38% rise from 2003 to 2006

3.13.1. Mechanisms of alcohol toxicity

There are various possible/proposed ways Alcohol can have deleterious effects on cardiac structure and function and exact pathogenesis is not fully understood. The cardiac adverse effects could be due to direct toxicity of ethanol or its metabolites,toxicity of additives (Arsenic, Cobalt), dietary deficiencies (Thiamine, Selenium), electrolyte imbalance and associated malnutrition. Increased prevalence of various co morbid conditions, RAAS activation and due to genetic factors may also be responsible.

Table 36
Major studies on HIV associated cardiomyopathy from India.

Author	Year of publication	Summary of findings
B P Chattopadhyay, et al[514]	2009	150 patients, Male Female ratio 3:1; Mean age 29.2 years; 50 patients had echo abnormalities. Pericardial effusion in 22.6%, DCM in 11.3%, PAH in 8.6%, diastolic dysfunction in 3.3%, QT prolongation in 11.3%. Significant relation with CD4 count.
Santanu Guha et al[515]	2010	45 asymptomatic HIV ART naive patients; diastolic dysfunction (18%), pericardial effusion (13%) and systolic dysfunction (7%). Low CD4 count was significantly associated with pericardial effusion
Sakthi Vadivel, V. et al[516]	2014	150 patients; 16 had abnormal echo. Pericardial effusion (56.25%), dilated cardiomyopathy (31.25%), interventricular septal hypokinesia (6.25%) and infective endocarditis (6.25%)
Joshi et al[517]	1998	74 patients; DCM in 10.6%, pericardial effusion 8.5%, vegetation 4.2%, constrictive pericarditis 2.1% and 10.6% had incidental valvular HD, LVH, IHD
Mishra et al (AIIMS)[518]	2003	36.7% had diastolic dysfunction and 23.3% had systolic dysfunction
P Kannan et al[519]	2003	200 patients, LV dysfunction in 28 patients, pericardial effusion in 20, PAH in 6 patients, DCM 1 patient
R. B. Sudagar Singh et al[520]	2015	100 patients; 30 moderate risk category and 8 high risk category for Framingham 10 year absolute risk. Echocardiographic abnormalities in 24 patients. Pulmonary hypertension (12%), Pericardial effusion (7%), LV systolic dysfunction (6%), Diastolic dysfunction (23%), RV dysfunction (1%) and Chamber dilatation in 14%

3.13.2. Treatment

There are no separate guidelines or recommendations for ACM so these patients are to be treated as chronic heart failure patients. ACM patients should be managed with guidelines based therapies as other patients with HFrEF. Replacement of nutritional deficiencies such as B12 and folate, correction of malnutrition and treatment of electrolyte imbalance is very important. Non pharmacologic measures such as reduced salt and water intake, regular exercise, vaccinations and treatment of co morbidities should be followed as per the guidelines.

The most important part of the treatment of ACM is total and sustained abstinence from alcohol intake and that should be strictly enforced.

3.14. *Heart failure in the elderly*

3.14.1. Introduction

Heart Failure (HF) in the elderly is a complex outcome of the interactions between age related physiologic changes, prolonged exposure to the cardiovascular risk factors and co existent comorbidities. India is witnessing an epidemiological transition wherein we are increasingly confronted with degenerative diseases in the older population.

3.14.2. Epidemiology

The definition of the age of the elderly and a chronological age above 65 years are defined as 'elderly' by the World Health Organization. Patients aged >65 years are disproportionately affected and more than 80% of HF patients are 65 years of age or older.[521] The prevalence of HF doubles for every decade after 40 years and is <1% for age <40 years, and >10% for age >80 years.[522] The prevalence of systolic and solitary diastolic dysfunction in this group is 5.5% and 36%, respectively.[523] The mortality and the average length of hospitalisation for acute heart failure increases by 2–4 days in this group. The diagnosis of HF portends a prognosis worse than most cancers.[524]

3.14.3. The pathobiology of aging and heart failure

Aging is associated with a myriad of changes in cellular composition and function in the organ systems of the body. These changes enhance the susceptibility, alter the clinical profile, influence management and prognosis of HF in the elderly. The alterations with a significant impact with respect aging and HF affect the cardio-vascular system, the body composition, pro-inflammatory state and co-morbid conditions.

3.14.4. The treatment of HF in the elderly

HF in the elderly is a distinctive syndrome and on account of the age associated decline in organ functions, psycho-social issues, subtle presentations and comorbidities is a challenge warrants a multidisciplinary, specialty intensive and prompts approach. The recommendations for the treatment of HF emanate from trials which often excluded the elderly as a consequence of age, associated comorbidities and limited life expectancy.[525,526]

The cornerstone of management of HF is drug therapy and this in the elderly is less predictable on account of the changes in body composition and slow metabolism. There is increase in body fat, a reduction in the muscle mass and body water which results in lower volume of distribution. The levels of hydrophilic drugs increase whereas the levels of lipophilic drugs decrease.[527] This coupled with the decline the renal and hepatic function alters the pharmacokinetics, bioavailability and drug interactions.[528–530]

3.14.5. Recommendations

The treatment of HF in the elderly is a growing concern on account of the increasing age of the population and a challenge (Fig. 20). The multitude of issues range from lack of data on optimal therapy, atypical presentations, coexistent comorbidities, polypharmacy, poorer prognosis, psychosocial isolation and penetration of health care. There is an urgent need to have multidisciplinary and joint effort at all levels to address the preventive aspects, increase awareness, increase the reach of health care delivery, adopt a cohesive evidence based management, an increasing representation in research and a need to develop dedicated program at all levels of healthcare.

3.15. *Management of heart failure in pulmonary hypertension*

Management of patients with pulmonary hypertension developing right ventricular failure is a common challenge encountered

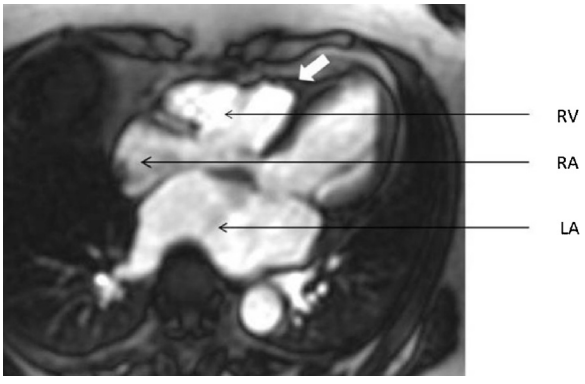

Fig. 20. HF in Elderly.

in the daily practice. A combination of a low central venous O2 saturation (≤60%) with increasing levels of lactate and low or absent urine production in patients with pulmonary hypertension are indicator of imminent right heart failure.[531] Both right ventricular dysfunction and pulmonary hypertension portend a poor prognosis and are associated with significant morbidity and mortality.

3.15.1. Pathophysiology of Right Ventricular Failure

In pulmonary hypertension, the compensatory RV hypertrophy results in supply-demand mismatch. Patients with advanced pH can develop acute RV failure as a result of disease progression despite appropriate therapy but more commonly it develops following an triggering event such as medication non- compliance, systemic infection, upper respiratory infection, anemia, arrhythmias, pulmonary embolism, or changes in overall volume status.[532]

3.15.2. Principles of management: (Table 37)

Treatment of triggering factors: In patients presenting with decompensated right ventricular failure and hemodynamic compromise, infection and anemia must be actively searched and adequately treated.[533] In patients with Eisenmenger syndrome and cor pulmonale, hyperviscocity and erythrocytosis be watched and managed accordingly.[534] Pulmonary embolism should be ruled out as it precipitates RV failure. Digoxin, amiodarone, or diltiazem should be used to control heart in atrial arrhythmias.[535] Beta blockers and calcium channel blockers should be avoided in acute RV failure as they impair ventricular contraction. Amiodarone, electrical cardioversion and radiofrequency ablation is often required for rhythm control .[536]

Optimization of fluid balance: Volume loading is useful only in patients with underfilled right ventricles with low central venous pressures.[537] In patients with fluid overload state, loop diuretics with or without thiazide diuretics targeting a CVP of 6–12 mmHg is often sufficient.[538]

Reduction of RV afterload: Pulmonary vasodilators should be used only after optimization of RV perfusion and cardiac output. Caution however in needed to avoid systemic hypotension and pulmonary oedema.[539] Inhaled NO has proven beneficial in improving RV performance in varied scenarios and should be considered upfront.[540] Prostacyclins, including epoprostenol, treprostinil, and iloprost can improve RV performance by reducing pulmonary vascular resistance. Because of a global reduction in systemic vascular resistance and consequent worsening of hypoxia secondary to ventilatory-perfusion mismatch, intravenous prostacyclins are not preferred. Once stabilized, consideration must be given for a switch to oral therapy. Though limited, data on their use in acute setting, has shown promise in facilitating NO weaning and minimizing rebound pulmonary hypertension following discontinuation of inhaled agents.

Improvement of cardiac output and maintenance of systemic blood pressure with vasopressors: Dobutamine is preferred inotrope for management of RV failure but should be avoided in hypotension. Limitation of catecholamine vasopressors (eg: noradrenaline) is that they tend to increase pulmonary vascular resistance at higher doses. Other vasopressors like Milrinone, vasopressin and Phenylephrine can be used.

Mechanical RV support: Mechanical support can be utilized as a bridge to recovery or bridge to transplant. Centrifugal pumps can be surgically implanted (CentriMag, Thoratec Corporation, Pleasanton, CA) or percutaneously inserted (TandemHeart, Cardiac Assist, Pittsburg, PA) in selected patients with pH and RV failure. The Impella RP (Abiomed Inc, Danvers, MA) is another novel percutaneous, axial flow pump offering support with a single vascular access. Veno-arterial extracorporeal membrane oxygenation (ECMO) is preferred approach because of additional benefit of unloading the RV.

Ventilatory Support and Tissue Oxygenation: Supplemental oxygen should be given to maintain near-normal systemic oxygen saturations and adequate hemoglobin level should be maintained to prevent tissue hypoxia. Endotracheal intubation can cause systemic hypoperfusion and hemodynamic collapse secondary to the sedatives administered during intubation. Induction agents that maintain vascular tone and contractility such as etomidate are often preferred.

Balloon atrial septostomy (BAS): It is currently reserved for patients who are in WHO-FC IV with right heart failure refractory to medical therapy or with severe syncopal symptoms and in patients awaiting lung transplantation.

Transplantation: Both heart–lung and double-lung transplantation have been performed for PAH, although the threshold for unrecoverable RV systolic dysfunction and/or LV diastolic dysfunction is unknown.

Table 37
General Principles of Management.

Treatment of triggering factors
Reduction of RV afterload
Maintenance of systemic blood pressure with vasopressors.
Improvement of cardiac output
Ventilatory Support and Tissue Oxygenation
Mechanical RV support
Balloon atrial septostomy (BAS)
Heart lung or Lung-Lung Transplantation

3.16. *HF in GUCH (Grown up congenital heart disease)*

3.16.1. Introduction

Prior to the advent of specialized cardiac surgery and interventional catheterization techniques, less than one fifth of children born with congenital heart disease (CHD) reached adulthood.[541] Most patients who did survive were those who had mild lesions and only a minority of those with complex lesions survived to adulthood. With earlier diagnosis and better management facilities being available (especially in the West), the adult survival rates have increased from ~10-15% in the 1960s to >85–90% in the current era.[542,543] The term "***grownups with congenital heart disease***" (GUCH) is now often used as a standard terminology for these patients as it best describes the transition of the pediatric patient through adolescence to adulthood. Unlike Western countries, unoperated surviving patients still form a significant proportion of patients with GUCH in India.

With more and more patients with CHD now reaching adulthood, most deaths from CHD now occur in adults.[544] Frequent reasons for hospital admissions in operated patients with GUCH include management of atrial and ventricular arrhythmias, infective endocarditis, diagnostic or interventional cardiac catheterization procedures and HF (HF), with the latter accounting for ~20% of hospital admissions in these patients.[545] Presently advanced HF, is the leading cause of death in patients with GUCH.

India specific GUCH data: Of all neonates born with CHD in India, 30–50% have critical disease that requiring early interventions. ***Since only a minority of these receive requisite therapy, the number GUCH patients in India is also steadily increasing****. Prevalence estimates of GUCH in India are reported to be 2.4/1000,* which compares with 2.2/1000 in the UK, 3.2/1000 in the Netherlands and 4.09/1000 in Canada.[546–548]

Composition of patients presenting to GUCH clinics: The type of underlying CHD in patients with GUCH is significantly different from that presenting to a specialist pediatric cardiology unit. ***The GUCH clinic is likely to include the following three kinds of patients***:

- Those with complex CHD which was either not diagnosed or not treated, representing the more severe end of the CHD spectrum.
- Some patients may have had a palliative surgery in childhood (a situation especially likely in developing countries like India) or may be survivors of "definitive surgery" for complex defects.
- Some patients on the other hand are ***"natural survivors"*** who often reach adulthood without having had or needed surgery. These include
  - Those with minor abnormalities (small ASD, VSD or PDA)
  - Those with complex CHD with a balanced physiology (eg. univentricular heart without PS)
  - Those with established pulmonary vascular disease.

Recent studies have reported that although patients with simple defects still predominate in GUCH clinics, there has been an appx. 6–7 fold increase in the number of patients with moderate or complex CHD highlighting the fact that more number of these patients are surviving to adulthood.[549]

3.16.2. Pathophysiology of HF in the GUCH population

Causes of HF failure in GUCH patients can be divided into the following groups:

- ***Systolic dysfunction of either ventricle (systemic or subpulmonary)***
  - Systolic dysfunction of the morphological systemic left or subpulmonary right ventricle or morphological systemic right ventricle or systemic single ventricle
- ***Acquired heart disease due to*** coronary artery disease,hypertension, dyslipidaemia, diabetes mellitus, smoking), Congenital coronary artery abnormalities (anomalous origin and/or course, extrinsic compression by a dilated pulmonary artery, coronary kinking after re-implantation of coronary arteries), include the following mechanisms
- ***Altered genetic mechanism***s

3.16.3. Principles of management of GUCH-HF

As the pathophysiology of cardiorespiratory function in GUCH with HF is different from that of non-GUCH patients, extrapolation of published data to GUCH patients may be difficult. The current guidelines for HF suggest that diuretics, renin–angiotensin–aldosterone system (RAAS) blockers, b-blockers, and mineralocorticoid receptor antagonists can be safely used in the CHD/GUCH population. Hence, clinicians taking care of GUCH patients in general, should follow current treatment recommendations for HF.

Cardiac resynchronization therapy (CRT) in GUCH-HF: Unlike data for CRT in standard HF population which is based on multiple randomized clinical trials, evidence for CRT in GUCH-HF is limited to small studies or anecdotal reports. In general, patients with NYHA class II–IV symptoms, impaired ***systemic*** ventricular EF and prolonged QRS duration are candidates for CRT. ***Studies have shown that presence of a systemic LV predicted a better CRT response*** than a systemic RV and those with single ventricle morphology can achieve further benefit from optimized pacing sites.[550,551] **Implantable cardioverter defibrillator (ICD) in GUCH-HF**: Although the overall incidence of sudden cardiac death (SCD) in patients with CHD is low (<0.1% per year), SCD accounts for nearly 20–25% of late deaths in GUCH patients. An ICD is recommended for ***secondary prevention of SCD*** in survivors of SCD due to ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) without any apparent reversible cause, patients with spontaneous sustained VT not amenable to ablation or surgery, syncope with inducible sustained VT/VF at EP study electrophysiology.

- **Ventricular assist devices (VADs) and Cardiac Transplantation**: In acute decompensated HF patients, if despite maximal medical treatment haemodynamics remain unstable, consideration should be given to extra-corporal membrane oxygenation (ECMO) and/or ventricular assist device (VAD) or cardiac transplantation. Adult CHD accounts for only 5–10% of all CT indications in patients aged 18–30 years, according to the 2014 International Society for Heart Transplantation (ISHLT) Registry and the Scientific Registry of Transplant Recipients.[552,553]

4. Heart failure situations important in Indian settings – II, prevention and future perspectives

4.1. *Role of the heart failure programs*

Management of heart failure is complex and evolving. It has been established that a dedicated heart failure management programs can improve the delivery of care to the patients and result in better outcomes. Running of a good heart failure program depends upon the availability of resources in different centres in our country.

Over the last 2 decades many important drug and device clinical trials have been completed in heart failure population. These have formed the basis of various guidelines that have been published and regularly updated.[26,29] The appropriate application of these guidelines however, continues to be inadequate in general practice, resulting in worse outcomes than those reported in clinical trials.[554] This is where the role of specialised Heart Failure clinic comes. A recent review of 29 randomised control trial of organised versus usual care showed that heart failure hospitalization reduced by 26% and mortality reduced by 25% in organised care setting.[555–557] Heart failure setup is an organized way to assess, educate, treat and monitor patients with heart failure. The program can be developed in any clinical setting however there are essential components, which have to be considered while planning such a facility.

While conceptualizing a heart failure management program the following areas need focus.

1. Goals and Objectives
2. Infrastructure required
3. Personnel Needed
4. Activities and processes
5. Audits and feedbacks

Goal and Objective of a heart failure setup is primarily to provide state of the art care to patients diagnosed to have heart failure in order to minimise the mortality and morbidity. The program should be flexible and be able to accommodate increasing number of patients. **Infrastructure required** to create a good heart failure setup depends upon the availability of hospital resources. Provision of adequate manpower to conduct the heart failure service is of paramount importance for the success of the setup.

The heart failure program has to be tailor-made in our country keeping in mind the paucity of resources. A hub and spoke model appears to be suitable for country, where the peripheral centres should be able to provide at least a guideline mandated pharmacological treatment and suggestions for lifestyle modification to the patients. The medium level centres, where at least echocardiography is available, can function in further refinement of the diagnosis. Several hubs can be established at district level hospitals, which would further establish the etiology and long term management strategies for these patients with heart failure. The higher centres could also take the responsibility of training the peripheral centres through workshops and symposia regarding the

latest guidelines and the "Do's and Don'ts in a patient with heart failure.

Such centres would serve as centres for referral of patients from primary or secondary care physicians. These centres should have availability of biomarker estimation, detailed echocardiography, cardiac catheterization, electrophysiology service and cardiac surgery. The role of cardiac MRI in diagnosis and management of heart failure is being increasingly realised, thus the availability of cardiac MRI along with a trained radiologist in such centres is the need of the hour.

Personnel for heart failure setup include medical and paramedical staff trained in the nuances of heart failure along with technical staff required to provide audits and generate periodic reports.

Medical staff: Studies have demonstrated better outcomes for heart failure patients once they are admitted under Heart failure cardiologists.[557–559] During this crucial period the diagnosis must be clarified or revisited, reversible factors looked for and therapies reviewed. Co-morbidities should be treated appropriately and post discharged management should be planned. Especially important is up-titration of therapies or initiation of therapies which could not be started earlier for some reasons even if a patient was asymptomatic. The cardiologist needs to be aware of newer drugs and devices which can further improve outcomes and use them judiciously keeping the cost issues in mind.

Nursing Staff: The value of a heart failure specialist nurse in reducing subsequent hospitalisation and improving outcomes has been shown in a number of studies.[560–562] The calibre and training of these nurses determines the impact on outcomes. The role of a heart failure nurse is primarily to spend time in educating the patient, answer their queries in detail, act as a bridge between the patient and the cardiologist and follow up with the patient after their discharge from the hospital via a telephone call or an email. A regular enquiry about pulse rate, blood pressure and weight change, presence of swelling over legs, breathlessness and unusual weakness can help the nurse to ascertain if the patient is doing well or otherwise. The training to carry out these activities can easily be conducted even in a primary care facility.

Multi-disciplinary team: Heart failure management is essentially a multidisciplinary management and its appropriate application has been slow. This is so because heart failure in itself is a syndrome, which besides impacting various system organs due to altered circulatory dynamics, has a significant bearing on social and physical being of the patient. Inclusion of a nutritionist and physiotherapist in the heart failure management team is important as many of the patients are malnourished and do not have adequate counselling regarding DO's and Don'ts in their diet. Both these strategies have been shown to be beneficial for the wellbeing of the patients. As the knowledge of guarded prognosis seeps in depression is a common result in heart failure patients. Appropriate psychological assessment and counselling is needed for these patients. Psychologist's role is even more important in centres where there is a program for LVAD or heart transplant, where assessment has to be made for capability of a patient to accept these procedures and their capacity to deal with the problems that may arise out of them.

Activities and Processes: There are various activities to be conducted in a heart failure setup, which include running of a specialized outpatient clinic for heart failure, diagnostic services, educating patients and monitoring of their progress, conducting training and teaching sessions, establishing institutional guidelines of heart failure management besides conducting and learning from periodic data audits.

Outpatient clinic: The primary physician should refer the patient to a heart failure specialist early in the course of management. The responsibility of the specialist is to confirm the diagnosis, establish the etiology, carry out appropriate investigations, look of reversible causes and aggravating factors and ensure that appropriate pharmacologic therapy has been instituted. The referral back to the GP should include instruction regarding up titrating the drugs and particular precautions relevant to that patient. A multidisciplinary approach to HF may reduce costs,[563] decrease length of stay[564,565] curtail readmissions,[566,567] improve compliance, and reduce mortality. The facility should advise on appropriate use of advanced heart failure therapies such as cardiac resynchronization therapy, ICD, heart transplant or Ventricular assist devices and other newer medical and surgical therapies about which the primary or secondary care physician may still be in the dark. Periodic small group CME's conducted by the heart failure specialists for primary and secondary care physicians of their region are very useful for establishing a rapport between the teams and updating knowledge. These clinics also provide an access to patients who may have worsening of their clinical status, which may or may not require hospitalisation.

Who needs to attend heart failure Clinic: Since heart failure management programs were aimed at reducing morbidity and mortality the focus generally has been on sicker patients. An important set of patients are those who have recently been discharged from the hospital following an episode of acute heart failure. They have a high incidence of rehospitalisation in first 6–8 weeks and a high mortality in the first month and one year. Telemonitoring in many of these patients is useful in identifying patients at higher risk of sudden cardiac death.

Appropriate application of guidelines in heart failure clinics has been shown to reduce rehospitalisation, mortality and improve the quality of life in patients with advanced heart failure.

Formulate and adhere to guidelines: There are well established guidelines for heart failure from various international societies. These include European society of cardiology, American heart association and American college of cardiology etc. These guidelines thus need to be modified and optimised for our country and region.

Diagnostic services: At various levels various diagnostic services may be required.

Primary centre level: Apart from a good history and clinical examination, ECG, Chest X-Ray, routine haematology and biochemistry should be available.

Secondary Centre level: Apart from the above facilities these centres should have Echocardiography, NT Pro BNP and CCU with basic hospitalisation facility.

Tertiary care centre level: If possible they should have state of art Echo, Cardiac catheterization facilities, nuclear cardiology, facilities of Cardiac biopsy and Cardio-Pulmonary excise testing. They should also have facility for cardiac surgery, Electrophysiology lab for CRT/D implantation and advanced intensive care unit. A few selected centres should have transplantation and LV Asset device available.

Periodic Audits: For improvement of services a periodic audit is necessary. This can help identify gaps in care which may be missed knowingly or unknowingly. Evaluation of the program should focus on the organisational as well as patient perspective.

4.1.1. Conclusion

Heart Failure clinics in our country are few. Keeping specific problems of resources and personnel in India in mind it is suggested that a three layer program to be made available. At a very basic level an MD Physician with interest in heart failure should be identified and his knowledge upgraded to enable him/her to read ECG's, Chest X-Ray an institute guideline mandated, basic investigation and pharmacological treatment. This should be supplemented by a nurse or a paramedic. The second level centres should have facilities for good

Echocardiography, biomarkers, cardiac catheterisation laboratories and ICU facilities. They may have cardiac surgery backup. The tertiary care centre should have in addition advanced therapies including device based therapy, heart transplant cardiac biopsy and advanced surgical set up with state of the art ICU's. This three layered approach will ensure a good basic care for heart failure patients even at the primary levels and incremental investigative and therapeutic facilities at central level.

4.2. *Stem cell and gene therapy for heart failure*

Stem cell therapy and gene therapy has been studied in heart failure.[568]

- In the REPAIR-AMI trial, the combined end point of death, myocardial infarction, need for revascularisation was reduced in the bone marrow stem cell group.
- In the BALANCE study, at five years follow up, there was a reduction in mortality.
- Studies from India have also found modest benefits in patients with chronic ischemic heart disease, dilated cardiomyopathy, and myocardial infarction.[569]
- A Cochrane review included 38 randomised controlled trials involving almost[570] 2000 patients. Stem Cell therapy reduced long-term mortality. It was also associated with a long-term reduction in the incidence of non-fatal myocardial infarction. The authors found no evidence of reduction in risk of rehospitalisation for heart failure or composite incidence of mortality or left ventricular ejection fraction. The Cochrane review concluded that treatment with bone marrow-derived stem/progenitor cells reduced mortality and improved left ventricular ejection fraction and could reduce the incidence of non-fatal myocardial infarction and improve New York Heart Association (NYHA) Functional Classification in people with heart failure. The authors specified that event rates were generally low, leading to a lack of precision.
- Gene therapy using various virus vectors have been tried in clinical trials but as yet have not been found to be useful.

Stem cell therapy guidelines for India are based on the ICMR guidelines and stem cell therapy has been to be given under Research Protocols with ICMR approval and with ethics approval. They cannot be used for commercial purposes. The following are the current patient groups who are likely to benefit and where trials are going on worldwide:

1. Cell therapy patients: Ischemic HF/dilated cardiomyopathy. Myocardial infarction may not be an optimal target, as benefit has not been seen.
2. Attempts to improve cell therapy results are ongoing with more specific cell types (i.e., mesenchymal stem cells, cardiac progenitor cells) or *ex vivo* modified cells.
3. No gene therapy trials are ongoing in India.

4.3. *Prevention of heart failure*

Preventing or delaying the onset of HF is a feasible task and a priority for our country because of the cost effectiveness. HF prevention can be achieved either by targeting those at high risk (Stage A & B) or by promoting healthy lifestyle for the entire population.

4.3.1. Population strategy

The measures that need to be taken at population level, to prevent HF and heart diseases as a whole include. Healthy eating and safe cooking: Calorie restriction, Eating in time without skipping a meal, Choosing whole grains & legumes and variety of vegetable oils but not exceeding 5 tsp/day, Consuming 4–6 cups of fruits & vegetables, Limiting red meat, Avoiding processed meat and transfat and using low fat dairy and 1 tblp of nuts. Avoiding tobacco, recreational drugs, sugary drinks and excessive salt. Limiting alcohol (Not to exceed 1 drink for women & 2 drinks for men. Maintaining ideal BMI (~23 kg/m2). Exercising at least 150 m/week. Minimizing exposure to indoor and atmospheric air pollution & Coping up with psychosocial stress.

4.3.2. Targeting stage a

(Above heading - Targeting Stage A) Stage A denotes high risk for HF but without structural heart disease and it includes those with known risk factors for HF. Major Clinical risk factors for HF include age, male gender, hypertension, left ventricular hypertrophy (LVH), myocardial infarction, valvular heart diseases, obesity, increased heart rate, arrhythmias (SVT, AF, VPDs) and toxic factors like alcohol, chemotherapeutic agents, cocaine, glitazones and NSAIDs. Minor Clinical risk factors are sleep disordered breathing, CKD including albuminuria, anemia, sedentary lifestyle and low socioeconomic status. Morphological risk factors consist of LVH, asymptomatic LV dilatation/dysfunction and LV diastolic dysfunction. Polymorphisms of alpha 2 adrenergic receptors, beta 1 adrenergic receptors, ACE and AT1 Receptors constitute Genetic risk factors.

Hypertension is widely prevalent affecting nearly 30% of adults and it increases the risk of HF by 2–3 fold, either directly or by acting as a CAD risk factor. LVH or albuminuria add to the risk requiring aggressive management. In a systematic review,[575] every 10 mm Hg reduction in systolic blood pressure yielded 28% risk reduction of HF. Calcium blockers were inferior, diuretics were superior and ACEI/ARBs are neutral for HF prevention. Intensive BP lowering resulted in 38% relative risk reduction (RRR) in HF in SPRINT trial, but In a meta-analysis[571] only a modest effect was achieved (15% RRR). Early diagnosis, ensuring drug adherence and achieving the goal value (<130/80) are more important than the choice of the drug.

Atherosclerotic Coronary Artery Disease is the commonest cause of heart failure. Nearly 60% of HFrEF is due to CAD, occurring mostly after MI and rarely due to hibernation caused by chronic myocardial ischemia. STEMI increases the risk of HF by 2–3 fold due to adverse LV remodeling. Reducing the time delay in achieving rapid, effective and sustained reperfusion is important to salvage the ischemic myocardium. Adequate post reperfusion pharmacotherapy that includes early administration of optimal doses of beta blockers, ACEI, Mineralocorticoid receptor antagonists and statins are equally important. In our country, where the resources are limited, the spoke and hub model with the hub hospitals providing the 'round the clock' primary PCI and spoke hospitals providing rapid thrombolysis followed by timely transfer to the nearest hub hospitals for the timely angiography and PCI yield better outcomes.[576] Data from STEMI INDIA programme suggests non inferiority of pharmaco invasive approach when compared to primary PCI. Actually heart failure (6.1 vs 7.6%) and cardiogenic shock (4.4 vs 5.9%) occurred to a lesser extent in them. Similarly optimal usage of Beta blockers, ACEIs, Statins and Antiplatelets could help in preventing HF in stable IHD patients. Pooled data from HOPE, EUROPA and PEACE trials confirmed the benefit of ACEI in reducing HF admissions by 23% even in those with normal LV function. Hence ACEI should be given for all those atherosclerotic CVD. Aspirin or any other antiplatelet drug has not been proved to decrease HF, though effective in reducing death and nonfatal MI.

Dyslipidemia is associated with increased risk of HF but it is not known whether this association is independent of its

predisposition to atherosclerosis and MI. Among the dyslipidemic drugs, statins remain the cornerstone of therapy because of robust data. Statin use for more than 4 years offered a modest benefit (10% RRR) on HF hospitalizations but without benefit on HF related mortality. Moreover, intensive statin therapy (atorvastatin 80 mg) significantly reduced the rate of HF hospitalization by 45% when compared to moderate dose. However, in those with manifest HF, statins did not improve outcomes as confirmed by trials like GISSI HF and CORONA. Moreover there is a theoretical risk of adverse effect of statins in heart failure in the form of inhibition of CoQ synthesis and interference with lipoprotein mediated inhibition of bacterial lipopolysaccharide endotoxins. Thus, unless indicated for CAD protection (ischemic HF, those with multiple CVD risk factors), routine use of statins in HF or asymptomatic LV dysfunction is not justified.

Diabetes mellitus is associated with 2–5 fold increase in risk of HF. For every 1% increase in HbA1C there is an 8–16% increase in the risk of hospitalization for HF and for every 1 mmol increase in fasting blood glucose levels, there is a 5% increase in the risk of HF admissions. Apart from being a major risk factor for CAD, diabetes may cause cardiomyopathy as a result of micro vessel disease and metabolic insult to myocardium. Diabetes is also risk factor for HFpEF, as LVH and diastolic dysfunction are quite prevalent among them. In a meta-analysis[572] of Turnbull in which the data from ACCORD, UKPDS, ADVANCE and VADT trials have been pooled, there was 15% RRR for MI with intensive glucose lowering but no protection against death or HF hospitalization (HR 1.0). In the RENALL study, losartan reduced the occurrence of HF in diabetics manifesting LVH. In HOPE study, Ramipril given for diabetics with an additional risk factor, heart failure occurrence was reduced by 20% though hospitalization for heart failure did not reduce significantly. Both the studies underscore the importance of administering ACEI or ARB in those with diabetes and additional risk factor particularly those with hypertension, LVH or albuminuria, to reduce incident HF.

With respect to the drugs used in managing diabetes, glitazones have been found to increase the occurrence of HF and are contraindicated in class II & IV HF. In a meta-analysis of 14 trials (95502 patients, median follow up for 4.3 years), the risk of incident HF increased by 42% with glitazones, 25% with Gliptins and neutral with Insulin Glargine.[577] It looked as if the weight gain with therapies play a role – for every 1 kg weight gain, there was a 7.1% relative increase in the risk of HF. In TECOS trial, Sitagliptin was not found to increase heart failure (HR 1.00) while other Gliptin trials have shown mixed results. SGL2 inhibitor, namely Empagliflozin was found to significantly reduce HF (HR 0.65). Liraglutide, a GLP-1 analogue reduces HF by 13%. Early detection, optimal control of dysglycemia, concomitant management of clustering risk factors and appropriate choice of diabetic drugs are the measures found to be useful to prevent HF in diabetics.

Chronic Kidney Disease (CKD) is a strong predictor of HF with Diabetes and Hypertension being the commonest causes of CKD. Incidence of HF is 3 fold in those with eGFR of < 60 ml/min/m2. 1/3 of dialyzed patients have HF. Though supportive data are not available, optimal control of BP & DM, early use of beta blockers, ACEI/ARB, correction of Ca-P metabolism and Vit D3 deficiency, optimization of diuretic/dialytic therapy and correction of anemia could prevent or delay HF in CKD patients.

Obesity is an important risk factor for heart failure. For every 1 kg/m^2 increment in BMI, the HF risk increases by 5% in men and 7% in women. But prognosis appears to be better in obese patients with HF and limited data suggest that weight loss predict worse prognosis in heart failure. In spite of such contradictory findings, prevention and treatment of obesity can reduce the HF burden and heart disease in general. Sleep disordered breathing may be a risk factor for HF. An apnea-hypopnea index of > 11, increases HF by 2.4 fold. Despite lack of data, promoting weight loss and nocturnal CPAP therapy may prevent HF.

Valvular heart diseases (VHD) contribute to nearly 20% of heart failure in our country. Effective primary and secondary prophylaxis for rheumatic fever is the most cost effective method of reducing heart failure due to RHD. Among those with chronic VHD of various causes, HF can be prevented by prompt surgical or transcatheter management, once the symptoms manifest or when any of the following high risk features is encountered in asymptomatic individuals – LV dysfunction in all VHD, rapid progression or dense calcification in aortic stenosis; pulmonary hypertension, atrial fibrillation or LVESD >40 mm in mitral regurgitation, LVEDD >65 mm or LVESD >50 mm in aortic regurgitation. It is reasonable to offer surgery to asymptomatic VHD patients if biomarkers (BNP) are high or when long axis function of LV declines. Prevention or aggressive treatment of infective endocarditis could also reduce HF. Though optimal treatment of co-existing hypertension is definitely indicated, routine vasodilator therapy in chronic regurgitant lesions is not justified.

Alcohol consumption has a J or U shaped relationship to heart failure as it has with hypertension, diabetes and MI.[578] Epidemiologic data suggest that consuming less than 14 drinks per week lowers the risk of HF by 34 to 59% when compared to abstainers. In contrast, heavy drinking increases the risk of HF by 1.7 fold. Among individuals with ischemic LV dysfunction, moderate consumption was associated with 23% lower risk of mortality compared with abstainers. However, because of lack of adequate data, it is prudent to advise abstinence for those with LV dysfunction. Obviously abstinence is strongly indicated in alcoholic cardiomyopathy and clinically manifest HF.

Apart from being a major risk factor for CAD including MI and death related to it, Cigarette smoking is also a strong predictor for the development of HF, sudden death in patients with HF and of mortality in idiopathic dilated cardiomyopathy. Nonsmokers have 30% lower mortality, which underscores the importance of achieving abstinence in smokers.

Physical inactivity is risk factor for HF and there is an inverse dose response relationship between physical activity and the HF risk. In a pooled analysis of 12 prospective cohort studies with a median follow up of 13 years,[574] guideline recommended minimum activity (500 MET-min/week) was found to have a modest reduction of HF risk (10%). Higher levels of activity resulted in much better outcomes – hazard ratio for 1000 MET-min/week was 0.81 and 0.65 for 2000 MET-min/week. Apart from favorably modifying the conventional risk factors, exercise may have direct beneficial action on LV compliance, skeletal muscle performance, peripheral vasculature, heart rate and lung function all of which could be responsible for reduction of HF risk.

Drugs like NSAIDs, anti-arrhythmic drugs and tricyclic antidepressants may cause or exacerbate HF. Appetite suppressants, ergot alkaloids and dopaminergic agonists used for Parkinsonism (cabergoline, pergolide) may cause valve diseases which are preventable by surveillance. Cancer chemotherapeutic agents, particularly anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and Transtuzumab may cause cardiomyopathy and heart failure.[579] Anthracycline mediated LV dysfunction is either irreversible or partially reversible and dose related (Type I) while transtuzumab causes reversible LV dysfunction and not cumulative dose related (Type II). Prevention of heart failure may be achieved by avoiding their use and choosing an alternative agent in those with baseline LVEF <50%, Limiting the cumulative dose of doxorubicin to <450 mg/m2, administration by infusion rather than bolus, by using liposomal formulation, reducing or stopping the drug if EF falls by >10% or decrease in global longitudinal strain by >15% or if troponin gets elevated. Baseline echo should be done for all those who receive potentially cardiotoxic drugs and it should

be repeated after completion and 3–6 months later. For type I agents, echo should be repeated when the dose exceeds 240 mg/m2 and before each subsequent dose of 50 mg/m2. Limited data suggest that beta blockers particularly Carvedilol, ACEI/ARB and statins when given prophylactically, could minimize the decline in LVEF and occurrence of HF. Dexrazoxane, a cytoprotective agent has also been approved for this purpose.

Incessant tachycardias particularly ectopic atrial tachycardia, permanent form of junctional reciprocating tachycardia, atrial flutter/fibrillation, ventricular tachycardia etc. may lead to a reversible form of cardiomyopathy and HF. Prompt restoration of sinus rhythm or control of ventricular rate either by drugs or catheter ablation is an effective method of preventing HF in such individuals. Emerging data indicate that frequent ventricular premature beats (>10% of overall beats) could also lead to LV dysfunction and HF.[580] Apart from frequency, broader QRS and epicardial origin may imply an increased risk of LV dysfunction. Despite lack of randomized studies, it is worthwhile to consider catheter ablation in such patients to prevent HF.

Since as many as 20–50% of dilated cardiomyopathies are familial, first degree relatives should be screened to identify those with asymptomatic LV dysfunction, who will benefit from early therapy with neurohormonal agents. Moreover the inheritance pattern and genetic testing may help the clinician to provide genetic counseling. By avoiding late pregnancy and multiple pregnancies and prompt treatment of hypertension/pre-eclampsia, incidence of peripartum cardiomyopathy can be reduced. Prevention of recurrence is possible by appropriate advice on subsequent pregnancies based on recovery of LV function after the index pregnancy.

4.3.3. Targeting stage B

Stage B includes those who have structural heart disease but no current or prior symptoms of HF. The patients with asymptomatic LV dysfunction (ALVD – systolic & diastolic, ischemic or non-ischemic) form the majority of such patients and the other structural changes that precede HF include LVH, Post MI remodeling and asymptomatic VHD. As much as 3–6% of adults in the community have asymptomatic LVSD and outnumber symptomatic HF by fourfold. 13–30% of such individuals develop HF sooner and 5–7% die suddenly. In a meta-analysis of 11 studies of ALVD[581] (25369 patients followed up for 7.9 years), the absolute risk of progression to HF was 8.4 per 100 person years in those with systolic dysfunction, 2.8 person years in those with diastolic dysfunction and 1.04 person years in those without any dysfunction. The relative risk of HF per 1 standard deviation of lower EF was 1.4. Multiple RCTs including SOLVD, SAVE and TRACE have shown benefit of ACEIs and ARBs in these subset of patient. Beta blockers provide additional benefit in lowering mortality, slowing progression to Heart failure along with better reverse remodeling.

4.4. *FUTURE DIRECTIONS IN HEART FAILURE – INDIAN PRESPECTIVE*

Heart failure is reaching epidemic proportions and is a public health challenge in India. Since it affects Indians a decade earlier, it Impacts on the productivity and Disability adjusted life years lost (DALYs). The limited Indian data shows that we have a higher mortality, which lead to huge social and economic costs.

We also know that the therapy of HF is resource intensive. Since 80–90% of Indians spend out-of-pocket for their health, the available therapies are unaffordable to the vast majority of the population. Considering the vastness of the country and the concentration of healthcare facilities in the cities, there are issues of accessibility and availability.

So there is an urgent need to intervene at every stage of the disease right from understanding the disease burden to early identification to better management.

4.4.1. Need for generation of data

Country-wide data on HF is sparse and hence the difficulty to quantify the real burden which might be much higher than the projections estimated currently in various studies, mostly based on western figures. This data is critical for planning strategies focused on relevant parameters, which enable managing this burden more effectively with proper allocation of funds and resources. Hence, the need of the hour is a national HF registry which is a mammoth task considering the population and the clinical burden on doctors.

With the Indian governments' decision to introduce a standard based system for creation and maintenance of electronic health records (EHRs) by healthcare providers, data collection may become easier.[582]

4.4.2. Primary prevention of HF

We know that the therapy to manage HF, once the disease has already set in, is unaffordable to the vast majority of Indian. Governments cannot prioritize treatment of such end stage diseases over strategies like immunization in children and maternal health.

So primary and primordial prevention assumes prime importance. This is of paramount importance as damage to the heart can only be controlled and not reversed. Identifying risk factors early enough and appropriate modification strategies to reduce the same can go a long way in reducing the HF burden. Various stakeholders (government, health care professionals, patients, general public) will need to be involved, educated and supported to implement preventive strategies.

Salt restriction and tobacco control are cost effective strategies to initiate. Increasing taxation on tobacco (cigarettes and bidis) has been used to help reduce consumption. Increasing education of the optimum salt intake and highlighting the salt content in various foods, especially processed foods is important. Packaged foods should have labels indicating the salt and trans-fat content to help people make the right choices.

The importance of regular physical activity and the benefits of vegetable and fruit intake should be emphasised.

Implementing regular screening program scan identify important HF risk factors like hypertension, diabetes, coronary artery disease and rheumatic heart disease. These programs can be implemented in high-risk individuals which can be a more effective targeted approach to identify patients likely to develop HF and thereby intervene at an early stage. We have data from the west which emphasizes that HF can be prevented and that the progression of HF can be interrupted.

The Western guidelines recommend focusing on stage A patients, those without symptoms or detectable LV dysfunction. Hypertension was considered as the most powerful risk factor, and their recommendation was to think of hypertension as pre-heart failure situation. Increasing education and awareness regarding the importance of regular screening tests and regular follow-up to ensure control of risk factors can improve detection and control. Enforcing a mandatory annual HF risk factor screening program in the corporate sector, Industrial workers and government employees could be a strategy to increase detection and improve awareness of this condition.

Increasing awareness amongst the entire community is also an important lever. Media campaigns can help increase disease awareness about HF amongst the general population. Social media is also an important tool. Technology can be an effective way to reach our youth and to access remote areas.

Healthcare professionals (HCP) across all clinical disciplines should be educated to identify patients with risk factors for HF and intervene appropriately to screen, refer or treat as needed. Often the general practitioner is the first point of contact followed by general physicians. Patients present earlier in the course of disease to these physicians providing an opportunity to prevent disease progression. So increasing the awareness about HF among primary care physicians is very important.

4.4.3. Impacting HF diagnosis

Clinical approach is the mainstay of heart failure diagnosis and a detailed clinical examination should be a priority over laboratory and imaging modalities of diagnosis. The primary care physicians and the general medical specialists should be given adequate training to detect cases of HF.

ECHO is an extremely important tool to diagnose heart failure and should be ideally done in all patients. In India, it is an easily available tool and not too expensive. Biomarkers like NT-proBNP help differentiate HF from chronic obstructive pulmonary disease (COPD) and should be done wherever feasible. With the availability of point-of-care devices, which are cost-effective, authorities can make this equipment available in all PHCs. The Awareness regarding the usefulness of biomarkers needs to be increased to help improve to diagnosis when somebody is in doubt after clinical examination.

4.4.4. Encouraging guidelines recommended therapy

However, the challenge is that despite clear recommendations and proven mortality benefits, evidence based guideline recommended therapies are not implemented in majority of the patients as seen in the Trivandrum registry. The lack of GDMT increases mortality. Various factors impact this ranging from lack of education to an incorrect prescription to poor compliance due to various factors, an important one being cost of therapy.

Training programs (planned and conducted by national societies) focusing on clinical quality for general physicians/consulting physicians is a clear mandate to make them understand the need for guideline directed therapy and its impact in mortality reduction. They also should understand the need for appropriate and timely referrals to cardiologists or heart failure clinics when the need arises for more specialized interventions. Timely referral is critical in ensuring best treatment for the patients' condition.

Quality improvement programs are very important in Indian settings. The ACS = QUIK initiative in Kerala which improved the compliance to therapy is such an initiative. It should be mandatory for physicians managing HF patients to participate in quality improvement programs like PIQIP.[154]

The cost of various devices and therapies is a limiting factor in implementation of guideline-based therapy in the Indian healthcare system as these therapies are beyond the reach of many patients. To overcome this barrier there is a need for the government, insurance sector and industry to develop programs to address this affordability challenge and help more patients to get guideline-based therapies. Government mandated price controls as done for coronary stents recently, may allow a greater application of device use in HF in India.

Affordability to drugs is a very important problem in management of HF as these patients require lifelong therapy. Generic drugs can solve the issue to some extent. Authorities should ensure quality of generics and should ensure availability in PHCs.

4.4.5. Role of physician associations

The role physician associations in increasing the awareness and decimation of HF problems and good practice management in the care of these patients is very important. Now we have CME programs dedicated to heart failure which is attracting a large number of delegates thereby increasing the quality of HF management in our country. These associations should get affiliated with various world HF bodies allowing our physicians to interact with world authorities on HF. It is likely that in the near future, HF will emerge as a separate sub specialty in cardiology in India and this will further enhance the management this growing problem.

4.4.6. Heart failure clinics

The role of dedicated HF clinics is very important in the specialized management of HF. WE have already described this in a previous section (Vide Supra)

Vision for reducing HF mortality.

1. **Treatment of HF once the disease has set in, is non-affordable to the patients and the already constrained Indian health system. So primary prevention is the key, which is focussing on the control of risk factors.** – Concentrating on stage A of HF will prevent progression and probably lead to far greater reductions in mortality than more sophisticated and expensive therapies applied at a much later stage.
2. **To emphasize that heart failure can be prevented** – To focus on risk factors that lead to HF and concentrate on aggressive management of these factors even when the patient feels and looks good.
3. **To get the most out of known effective interventions within the limitations of available resources** – Within the constraints of limited health care budgets and infrastructure, we need to focus on proven effective interventions suited to our population rather than all the recommended interventions by global societies.
4. **To ensure HF healthcare access for all patients** – Overcoming the challenge of affordability with better insurance programs can help patients access guideline based therapy thereby improving their quality of life and reducing mortality.

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