Heart Failure in Young and Elderly – Management Strategies

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ABSTRACT
Cardiovascular disease is one of the leading cause of death today, of which over half is attributable to ischemic heart disease. Congestive heart failure, ischemic heart disease and atrial fibrillation are the three most common cardiac disorders encountered in an elderly population. Heart failure is a life threatening disease and addressing it should be considered a global health priority. At present, approximately 26 million people worldwide are living with heart failure. Despite of burdens that heart failure imposes on society, awareness of the disease is poor. As a result, many premature deaths occur. This is in spite of the fact that most types of heart failure are preventable and that a healthy lifestyle can reduce the risk. Compliance with clinical guidelines is also associated with improved outcomes for patients with heart failure. It is time to ease the strain on healthcare system through clear policy initiatives that prioritize heart failure prevention and champion equality of care for all.

INTRODUCTION
Heart Failure (HF) is 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 edema) 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.

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The guidelines underscore that “it is largely a clinical diagnosis that is based on a careful history and physical examination.” As HF is a syndrome and not a disease, its diagnosis relies on a clinical examination and can be challenging. The prevalence of HF depends on the definition applied, but is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people ≥70 years of age. The lifetime risk of HF at age 55 years is 33% for men and 28% for women. The most common cause of HF remains an ischemic insult. This insult initiates a cascade of events mediated by neuro-hormonal influences that adversely affect the heart.

CLASSIFICATION OF HEART FAILURE
The main terminology used to describe HF is historical and is based on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF (typically considered as ≥50%; HF with preserved EF (HFpEF)) to those with reduced LVEF (typically considered as,>40%; HF with reduced EF (HFrEF)). Patients with an LVEF in the range of 40–49% represent a ‘grey area’, which we now define as HFrEF (Table 1). Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. Most clinical trials published after 1990 selected patients based on LVEF (usually measured using echocardiography, a radionuclide technique or cardiac magnetic resonance (CMR)), and it is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality.

The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. Patients with HFpEF generally do not have a dilated LV, but instead often have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures. Most have additional ‘evidence’ of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (hence the term ‘diastolic HF’). However, most patients with HFrEF (previously referred to as ‘systolic HF’) also have diastolic dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF. Hence the preference for stating preserved or reduced LVEF over preserved or reduced ‘systolic function’. In previous guidelines it was acknowledged that a grey area exists between HFrEF and HFpEF.

These patients have an LVEF that ranges from 40 to 49%, hence the term HFrEF. Identifying HFrEF as a separate group will stimulate research into the underlying characteristics, pathophysiology and treatment of this group of patients. Patients with HFrEF most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction. Patients without detectable LV myocardial disease may have other cardiovascular causes for HF (e.g. pulmonary hypertension, valvular heart disease, etc.). Patients with non-cardiovascular pathologies (e.g. anaemia, pulmonary, renal or hepatic disease) may have symptoms similar or identical to those of HF and each may complicate or exacerbate the HF syndrome.

HEART FAILURE IN YOUNG
The importance of heart failure in young is that there was a striking difference in signs and symptoms during presentation in younger patients versus older patients.
Younger patients presented with less dyspnea, reflected by a lower New York Heart Association functional class, and they less often had peripheral edema and/or rales. In contrast, they frequently presented with signs of paroxysmal nocturnal dyspnea, increased jugular venous pressure, and hepatomegaly. These findings are important for clinicians who have to diagnose HF, because mild dyspnea and absence of peripheral edema and/or rales might easily lead to a missed diagnosis of HF in younger patients, in particular because of its low prevalence.

Children and young adults can have diverse causes of heart failure depending on the age, geographical location, and many other factors. Hence a descriptive epidemiology of heart failure in children is not possible. The causes of HF can be broadly classified into two groups as in Table 2.

One due to volume overload of ventricle with preserved systolic function of the ventricle, the common example is heart failure secondary to a large left to right shunt shown in Table 2.

The second group consists of pressure overload, persistent arrhythmias, dilated cardiomyopathy and certain systemic disorders where the contractile function of ventricle is reduced.

Symptoms and signs of heart failure can be confusing or fairly non-specific in children. HF presenting on the first day of life are commonly due to metabolic abnormalities. Structural diseases that cause HF in neonates usually do not manifest on 1st day of life; rather it is the causes of fetal HF like Ebstein’s or abnormal heart rate/rhythm that predominate. About 90% of all cases of HF in children occur before the end of first year of life and reflect the preponderance of congenital heart disease (CHD) as a cause of HF. In the first week of life, obstructive and duct-dependent lesions can present with HF or acute circulatory shock. Development of HF due to left-to-right shunts usually waits the fall in pulmonary vascular resistance at 4-6 weeks, though large VSD, PDA and aorto-pulmonary window can cause HF by 2nd week of life. Isolated ASD are mostly asymptomatic in children and if an infant is diagnosed to have ASD and is in failure, the likely diagnosis is TAPVC.

The myocardium perse is normal in most CHD and the heart failure, if not presenting in the first year, is unlikely to develop for the next 10 years unless complicated by infective endocarditis, anemia, infections or arrhythmias. Thus older children (usually beyond two years) are likely to have other causes for HF like acute rheumatic fever with carditis, decompensated chronic rheumatic heart disease, myocarditis, cardiomyopathies and palliated CHD (post Senning operation for transposition of great arteries or Fontan group of surgeries for univentricular hearts).

Dilated cardiomyopathy remains the principal indication for cardiac transplantation in children worldwide throughout childhood, apart from infancy when congenital heart disease is a more common indication. The prognosis for dilated cardiomyopathy is around 60% at five years from presentation with a high attrition within six months of presentation.

Supraventricular tachycardia (SVT) causing heart failure and tachycardia-induced cardiomyopathy (TIC) are often used interchangeably. Although SVT is the most common cause of TIC, it is a broad term that also includes heart failure caused by ventricular arrhythmias. Chronic tachycardia has long been linked to the development of congestive cardiomyopathy through chamber dilatation and ventricular dysfunction resulting from structural and cellular changes that occur as a result of the rapid heart rates. SVT-related TIC is a treatable and often reversible cardiomyopathy that is usually a diagnosis of exclusion, evaluation, and management of SVT causing heart failure.

The most common supraventricular arrhythmias causing TIC are atrial fibrillation and atrial flutter. Standard workup for cardiomyopathies should include a thorough history and physical, laboratory assessment, echocardiogram, and ischemic evaluation. If initial workup is negative,
then TIC should be considered. Many patients with SVT-related TIC present with signs and symptoms of heart failure, including exertional dyspnea, orthopnea, and edema. It can often be difficult to determine whether the tachycardia is the cause or the result of cardiomyopathy. The goal of treatment is to control the tachycardia through rate or rhythm control, thereby improving a patient’s symptoms, reversing ventricular dysfunction, and preventing future cardiomyopathy. Despite the apparent normalization of systolic function with control of the tachycardia, cellular and structural abnormalities of the myocardium may persist and cause early recurrence of cardiac dysfunction when optimal medical therapy of cardiomyopathy and heart failure is stopped. A small subset of treated SVT-related TIC patients had sudden cardiac death after resolution of ventricular dysfunction, supporting the observation of enduring cellular and molecular abnormalities.

Lymphocytic myocarditis accounts for around 10% of recent onset cardiomyopathy. Viruses are the main causes in developed countries, coxsackie B and adenovirus accounting for most cases; Chagas disease is the most common cause in Central and South America, and other infectious causes should be considered. The treatment of heart failure caused by myocarditis in children is supportive and not essentially different from dilated cardiomyopathy, although patients with fulminant myocarditis are more likely to be supported to recovery rather than transplantation.

About half of all young adults who survive childhood cancer have received anthracyclines, particularly daunorubicin or doxorubicin. The number of young adult patients with potential heart muscle disease is therefore going to be larger than, for example, young adult survivors of tetralogy of Fallot, or transposition. Cardiotoxicity is dose related, and myocyte damage on biopsy has a linear relation with cumulative dose. The myocyte necrosis is irreversible, although echocardiographic improvement in systolic function and recovery from symptomatic heart failure can be seen with treatment in most cases. In children there is progressive, dose related impairment of afterload in asymptomatic individuals.

**Investigations - Heart Failure in Young**

- Echocardiography (including check for anomalous coronary)
- ECG
- Myocarditis: Tracheal aspirate for viral PCR, paired serology (including coxsackie, adenovirus, echo, influenza, para-influenza, varicella, RSV, rubella, CMV, EBV, HIV, parvovirus, mycoplasma, and endemic infections depending on geography — for example, Chagas’ disease, dengue, diphtheria, Coxella burnetti; many organisms cause myocarditis ), troponin T, blood count for lymphocytosis. Myocardial biopsy for histology and PCR. Consider toxins if suggested by history, and illegal drugs (for example, cocaine)
- Autoimmune: Anti-Ro and Anti-La, full SLE screen including antinuclear antibody, double stranded DNA, rheumatoid factor, ESR. Autoantibody screen (availability varies)—for example, anti-mysosin β receptor antibodies
- Mitochondrial: Carnitine, acyl carnitine, lactate, glucose, white cell count for neutropenia, urine amino acids for methylglutaconic aciduria, muscle biopsy if clinical suspicion of mitochondrial disease. Molecular genetic diagnosis of Barth syndrome is available in some centres

**HEART FAILURE IN THE YOUNG: KEY POINTS**

**Myocarditis**

- Coxsackie and adenovirus account for the majority of cases of viral myocarditis
- Fulminant infections have a better prognosis than non-fulminant infections
- Children can be bridged to recovery using mechanical support
- Randomized studies have not shown any benefit from immune suppression
- Immunoglobulin may reduce cytokines in heart failure and short term echo improvement may be attributable to this, not resolution of myocarditis

**Apoptosis, cytokines, and regeneration**

- Apoptosis occurs in myocytes
- The nucleus is affected later in myocyte apoptosis and this may allow recovery with bridging
- New myocytes can develop as shown by chimeric studies
- Circulating cytokines such as tumour necrosis factor α are increased in heart failure

**Heart failure treatment in children**

- ACE inhibitors are widely used in children
- Carvedilol is helpful in stable patients
- Aspirin may oppose the action of ACE inhibitors and carvedilol

**Treatment of Heart Failure in Young**

Heart failure treatment in children is very similar to that of adults. However, because of lack of resources and a reluctance of the pharmaceutical industry to undertake trials, few of the proven treatments in adults are licensed in children and paediatric preparations are not available, leaving parents to grind and dissolve adult tablets.

A principle of paediatric drug usage is that the therapeutic effect in children is likely to be similar to what it is in adults, but pharmacokinetics are different. For example, phosphodiesterase III inhibitors have been shown to have a deleterious effect on long term survival, milrinone having a 28% increase in mortality compared to placebo, yet oral phosphodiesterase inhibitors such as enoximone are still used by paediatric cardiologists.
ACE inhibitors are widely used in children, but β blockers are less commonly used even though the adult evidence base is strong; carvedilol has been successfully used in New York Heart Association functional class III and IV patients, and it has also been used in children. They should only be introduced in stable patients and the dose increased slowly. β Blockers must be stopped if inotropes are needed. Spironolactone has been shown to be beneficial in heart failure. Digoxin use remains controversial in adults and children, and although therapeutic benefits have been seen in adults with a reduced hospitalization rate, overall mortality is not reduced. Digoxin may not be helpful in acute myocarditis. Anticoagulation with warfarin is difficult in children, but those with severe heart failure are at risk of mural thrombus. There is now evidence that aspirin and other non-steroidal anti-inflammatory agents can exacerbate heart failure and may reduce the effect of the diuretics, ACE inhibitors, and β blockers. The mechanism probably involves the inhibition of prostaglandin synthesis, increasing peripheral resistance and decreasing renal perfusion. Angiotensin II receptor blockers may have a role in replacing ACE inhibitors when there is an unwanted effect such as a severe cough, but they do not convey a survival benefit in adults and experience of their use in children has been very limited.

**Diagnosis and Initial Prognostic Evaluation of Heart Failure**

The diagnostic workup needs to be started in the pre-hospital setting and continued in the emergency department (ED) in order to establish the diagnosis in a timely manner and initiate appropriate management. The greater benefit of early treatment is well established in ACS and now needs to be considered in the setting of HF. In parallel, coexisting life-threatening clinical conditions and/or precipitants that require urgent treatment/correction need to be immediately identified and managed (Figure 1).

Typically, an initial step in the diagnostic workup of AHF is to rule out alternative causes for the patient's symptoms and signs (i.e. pulmonary infection, severe anaemia, acute renal failure).

When AHF is confirmed clinical evaluation is mandatory to select further management. It is recommended that initial diagnosis of AHF should be based on a thorough history assessing symptoms, prior cardiovascular history and potential cardiac and non-cardiac precipitants, as well as on the assessment of signs/symptoms of congestion and/or hypoperfusion by physical examination and further confirmed by appropriate additional investigations such as ECG, chest X-ray, laboratory assessment (with specific biomarkers) and echocardiography.

Typically, symptoms and signs of Acute Heart Failure reflect fluid overload (pulmonary congestion and/or peripheral hypoperfusion) or, less often, reduced cardiac output with peripheral hypoperfusion (Figure 2).

Since the sensitivity and specificity of symptoms and signs are often not satisfactory, careful clinical evaluation needs to be followed by these additional investigations.

**Management Strategies of Heart Failure in Elderly**

Understanding the pathophysiology of heart failure allows one to achieve the goals of treatment, which are to relieve symptoms, avoid hospital admissions, and prolong life. The fact that several drugs for HF have shown detrimental effects on long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers, has led regulatory bodies and clinical practice guidelines to seek mortality/morbidity data for approving/recommending therapeutic interventions for HF. However, it is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.

The goals of treatment in patients with HF are

- to improve their clinical status
- functional capacity
- quality of life
- prevent hospital admission
- reduce mortality
• Non-pharmacological management:
  1. Lifestyle modifications
  2. Salt & water restriction
  3. Weight reduction
  4. Physical activity as per tolerance of patient
• Pharmacotherapy -
  1. B- Blocker
  2. ACEI/ARBs
  3. MRA
  4. Diuretics
  5. Digoxin
• Novel Treatment -
  1. LCZ-696 - ARNI
  2. IF-Channel Inhibitor - Ivabradine
• Interventional Modalities -
  1. CRT-P / D
  2. LVAD
  3. Cardiac transplantation

NON-PHARMACOLOGICAL TREATMENT /LIFE-STYLE MODIFICATION

Diet
All patients need support and dietary advice regarding maintenance of optimal weight. Obesity increases the workload on the heart, especially during physical activity. Weight reduction, through restriction of dietary fat and calories is imperative for those who are obese, and is advised for those who are overweight. In patients with coronary heart disease and raised lipids, a low fat diet may delay recurrence of significant cardiovascular events.

Salt intake should be restricted as this may aggravate a patient’s condition. Salt should not be added during cooking or at the table. A reduction in dietary sodium intake of 2,000 mg per day alone may provide substantial hemodynamic and clinical benefits for heart failure patients. Patients should be referred to a registered diettitian if there are repeat episodes of edema or for comorbid conditions such as diabetes, dyslipidemia and renal failure. It is important to help patients prioritize dietary modifications.

Formerly called herbals, any over-the-counter dietary supplement or vitamin product should be discussed with a health care clinician to make sure there is not an interaction with the disease condition or other medications.

Fluid intake
Patients with heart failure often have an intense thirst, which can lead to excessive fluid intake and hyponatremia. Fluid intake should be limited where possible, to about 1 liter a day for most patients. During periods of hot weather, diarrhea, vomiting or fever, fluid intake may be increased or the dose of diuretic reduced.

Alcohol intake
Since even moderate usage may be associated with decreasing ventricular systolic function, alcohol use should be discouraged, or at the least, saved for special occasions. One drink is considered 10 oz. of beer, 5 oz. of wine or 1.5 oz. of hard liquor. In severe heart failure or those with alcoholic cardiomyopathy, complete abstinence is recommended.

Smoking
Smoking increases the risk of many cardiovascular, pulmonary and other problems, including cancers, and must be avoided at all costs.

Exercise
Bed rest is an important part of the treatment of acute heart failure or decompensated chronic heart failure, though early mobilization is important. Otherwise regular, and moderate physical activity for the condition of the patient, should be encouraged. This has significant symptomatic and other benefits in patients with heart failure. Dynamic exercise activities such as walking, cycling, swimming, bowling, gardening, etc. should be continued at a pace that is comfortable for the patient.

Exercise instruction should be included as a part of a comprehensive heart failure program. Referral to a cardiac rehabilitation program is recommended for exercise prescription and modeling and will contribute to patients’ compliance with exercise, functional improvement and quality of life. Participation in a formal program may also contain education and compliance monitoring of lifestyle management components for heart failure.

Vaccination
Heart failure may predispose to and be exacerbated by pulmonary infection, which is a common cause of hospitalization. Therefore, influenza and pneumococcal vaccinations are recommended.

PHARMAACOLOGICAL TREATMENT

Beta blocker
Beta-blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic. There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made.

There is no evidence favoring the initiation of treatment with a beta-blocker before an ACEI has been started. Beta blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose. In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized.

Beta-blockers should be considered for rate control in patients with HFrEF and AF, especially in those with high heart rate Beta-blockers are recommended in patients...
with a history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce the risk of death.

The MERIT HF study\textsuperscript{13} of metoprolol succinate compared to placebo showed a mortality reduction at one year in patients with NYHA Class II-IV heart failure and, recently, the COMET trial\textsuperscript{14} has shown carvedilol to produce an additional 17\% risk reduction in mortality versus metoprolol tartrate.

**Angiotensin-converting enzyme inhibitors**

ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF and are recommended unless contraindicated or not tolerated in all symptomatic patients\textsuperscript{15,16}. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS).

ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death. The equivalence of angiotensin receptor blockers to ACE inhibitors in reducing mortality from CHF remains to be confirmed. The addition of valsartan to an ACE-inhibitor may reduce heart failure hospitalizations particularly in those not on a beta-blocker.

**Mineralocorticoid/aldosterone receptor antagonists**

MRAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors. Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35\%, to reduce mortality and HF hospitalization\textsuperscript{17,18}. Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels high. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

Spironolactone in low doses (mean 26 mg/day) was investigated in the RALES Trial\textsuperscript{17} which enrolled a population of patients (mean age 65 yrs) with advanced (NYHA III-IV, LVEF 220 micromoles/l) or other significant co-morbidities. Spironolactone significantly reduced mortality by 30\% and hospitalizations for worsening heart failure by 35\%, and significantly improved NYHA functional class.

**Diuretics**

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects on mortality and morbidity have not been studied in RCTs. Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant edema. However, adverse effects are more likely and these combinations should only be used with care.

The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose. The dose of the diuretic must be adjusted according to the individual needs over time. In selected asymptomatic euvolaemic/hypovolemic patients, the use of a diuretic drug might be (temporarily) discontinued.

**Principles of using diuretics for heart failure** –

- Use in moderation; avoid excessive doses of any single drug
- Make use of synergy between different classes of drugs, especially in cases of diuretic resistance (the principle of sequential nephron blockade)
- Monitoring of blood chemistry may help to avoid uremia, hypokalemia, and hyponatremia
- Use in combination with an angiotensin converting enzyme (ACE) inhibitor and/or digoxin unless this is not tolerated

**Angiotensin II receptor blockers**

ARBs are recommended only as an alternative in patients intolerant of an ACEI. Candesartan has been shown to reduce cardiovascular mortality. Valsartan showed an effect on hospitalization for HF in patients with HFrEF receiving background ACEIs\textsuperscript{19}. Therefore, ARBs are indicated for the treatment of HFrEF only in patients who cannot tolerate an ACEI because of serious side effects. The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.

**Combination of hydralazine and isosorbide dinitrate**

There is no clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF. A subsequent RCT conducted in self-identified black patients (defined as being of African descent) showed that addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (ACEI, beta-blocker and MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA Classes III–IV\textsuperscript{20}. The results of this study are difficult to translate to patients of other racial or ethnic origins.

**Digoxin and other digitalis glycosides**

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization\textsuperscript{21}. In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued.

**Renin inhibitors**

Aliskiren (direct renin inhibitor) is not presently recommended as an alternative to an ACEI or ARB.

**Oral anticoagulants and antiplatelet therapy**

Other than in patients with AF (both HFrEF and HFP EF), there is no evidence that an oral anticoagulant reduces mortality/morbidity compared with placebo or aspirin\textsuperscript{13}. Studies testing the (NOACs) in patients with HFrEF are currently ongoing. Patients with HFrEF receiving oral
anticoagulation because of concurrent AF or risk of venous thromboembolism should continue anticoagulation.

**n-3 polyunsaturated fatty acids**

n-3 polyunsaturated fatty acids (n-3 PUFAs) have shown a small treatment effect in a large RCT as an effect on the cumulative endpoint of cardiovascular death and hospitalization.

**Calcium-channel blockers**

Non-dihydropyridine calcium-channel blockers (CCBs) are not indicated for the treatment of patients with HFREF. Diltiazem and verapamil have been shown to be unsafe in patients with HFREF.

**NOVEL THERAPY**

**Development of the ARNI/LCZ696**

A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)] 22. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy23.

The >8000-person-strong PARADIGM-HF trial showed that patients with chronic HF treated with LCZ696 had a 20% decrease in Cardiovascular death or HF hospitalizations vs those treated with the ACE inhibitor enalapril, as well as a significant reduction in all-cause mortality24.

**If-channel inhibitor (Ivabradine)**

Ivabradine slows the heart rate through inhibition of the If channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality and hospitalization for HF in patients with symptomatic HFrEF and LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 beats per minute (bpm) who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA25.

**TREAT SECONDARY CAUSES OF HEART FAILURE AND SIGNIFICANT COMORBID CONDITIONS AND RISK FACTORS**

**Atrial fibrillation in heart failure**

Patients with heart failure are at increased risk for atrial fibrillation and constitute an important subgroup of all patients with this arrhythmia. Atrial fibrillation affects 10-30% of patients with chronic heart failure. Atrial fibrillation may be a marker of poor prognosis, in which the primary problem is poor ventricular function, neurohormonal activation, or inflammation, with no independent effect of atrial fibrillation on outcome.

The control of ventricular rate and the prevention of thromboembolic events are essential elements of treatment of heart failure in patients with an underlying supraventricular arrhythmia. Beta-blockers and digoxin used either alone or in combination are the drugs of choice for achieving rate control.

**Cardiorenal Syndrome**

Cardiorenal syndrome can be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other. The characterization and classification of this syndrome may provide ideas for the testing of hypotheses regarding the pathogenesis of this syndrome and help in designing interventions for the management of cardiorenal syndrome. No interventions based on proposed mechanisms of the development of cardiorenal syndrome (CRS) have shown consistent advantage, and the work group does not have any specific recommendations. However, developing awareness, the ability to identify and define, and physiological understanding will help improve the outcome of these complex patients.

**Anemia: Workup and Treatment for Iron Deficiency in Patients with Heart Failure**

The prevalence of iron deficiency in congestive heart failure ranges from 5-21% and may be related to malabsorption, long-term aspirin, uremic gastritis, or reduced iron recycled in the reticuloendothelial system. The Ferric Iron Sucrose in Heart Failure (FERRIC-HF) trial of 35 heart failure patients with iron deficiency witnessed an improved global assessment score and significantly increased peak oxygen uptake in patients with anemia. Overall, IV iron in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity and quality of life. The side effect profile is acceptable.

**RECOMMENDATIONS**

- Beta-blockers and digoxin should be used either alone or in combination for achieving rate control in atrial fibrillation in heart failure.
- Blood transfusions are not recommended to treat anemia in heart failure.
- Intravenous iron replacement may improve anemia symptoms specifically the six-minute walk test.

**PRIMARY PREVENTION**

Compared with amiodorone treatment, ICDs reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias. An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should take into account the patient’s view and their quality of life, the LVEF (survival benefit is uncertain
when the LVEF is <35%) and the absence of other diseases likely to cause death within the following year²⁶.

An ICD is recommended¹ to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF < 35% despite of 3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:

- IHD (unless they have had an MI in the prior 40 days
- DCM.

ICD implantation is recommended only after a sufficient trial (minimum 3 months) of optimal medical therapy (OMT) has failed to increase the LVEF to 35%. Patients with a QRS duration ≥130 ms should be considered for a defibrillator with CRT (CRT-D) rather than ICD.

CRT improves cardiac performance in appropriately selected patients and improves symptoms²⁷ and well-being and reduces morbidity and mortality. Of the improvement in quality-adjusted life-years (QALYs) with CRT among patients with moderate to severe HF, two-thirds may be attributed to improved quality of life and one-third to increased longevity²⁸.

CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration >150 msec and LBBB QRS morphology and with LVEF < 35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality¹.

Cardiac contractility modulation (CCM) is similar in its mode of insertion to CRT, but it involves non-excitatory electrical stimulation of the ventricle during the absolute refractory period to enhance contractile performance without activating extra systolic contractions. CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (120 msec).

Ventricular assist devices are mechanical devices that help improve pumping actions. They are used as a bridge to transplant for patients who are on medications but still have severe symptoms and are awaiting a donor heart. In some cases, they may delay the need for a transplant.

**HEART TRANSPLANTATION**

Heart transplantation is an accepted treatment for end-stage HF²⁹. Apart from the shortage of donor hearts, the main challenges in transplantation are the consequences of the limited effectiveness and complications of immunosuppressive therapy in the long term (i.e. antibody-mediated rejection, infection, hypertension, renal failure, malignancy and coronary artery vasculopathy). The most important factor for heart transplant eligibility is overall health. Chronological age is less important. Most heart transplant candidates are between the ages of 50 - 64 years.

While the risks of this procedure are high, the 1-year survival rate is about 88% for men and 77% for women. Five years after a heart transplant, about 73% of men and 67% of women remain alive.

**PREVENTION AND SCREENING**

Screening for heart failure and treatment of patients at increased risk of developing heart failure are useful if interventions can modify the natural history of the condition and are safe and evidence-based. Control of systolic hypertension in the elderly is important in the prevention of heart failure, especially in patients with a past history of myocardial infarction.

The SHEP Trial³⁰ demonstrated that the risk of heart failure could be significantly attenuated in such patients by blood pressure lowering with a thiazide diuretic as first line therapy and similar findings were obtained recently in ALLHAT³¹.

The SOLVD Prevention Trial demonstrated that treatment of asymptomatic left ventricular systolic dysfunction (LVEF<35%) with an angiotensin-converting enzyme inhibitor (enalapril 10 mg BID) could delay the expression of symptoms of heart failure by an average of eighteen months, but patients over the age of eighty were not randomized into this study.³²

**REHABILITATION**

Programs that offer intensive follow-up to ensure that the patient complies with lifestyle changes and medication regimens at home can reduce rehospitalization and improve survival. Patients without available rehabilitation programs should seek support from local and national heart associations and groups. A strong emotional support network is also important.

**CONCLUSION**

The incidence of heart failure is increasing. It is therefore incumbent on healthcare providers to evaluate their heart failure practices and to incorporate the most current knowledge of the pathophysiology, assessment, and treatment modalities for heart failure into their patient care. Current practice guidelines provide a basis for the treatment of patients with heart failure. Critical to the success of heart failure management is the discharge planning process and follow-up in the outpatient setting. Integration of medical care and patient education with close communication between inpatient and outpatient care providers is essential. Monitoring and enhancement of patient compliance are the responsibility of both in-hospital and outpatient heart failure team members. An integrated and innovative approach to the management of heart failure patients based on consensus recommendations can contribute to improved patient outcomes, including reduced morbidity rates, improved functional status and quality of life, enhanced compliance, reduced rates of rehospitalization, reduced costs, and prolonged survival.

**REFERENCES**


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