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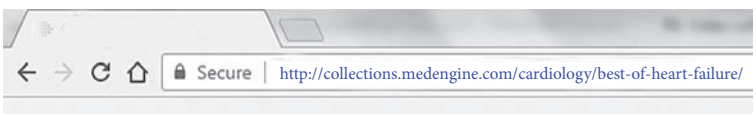

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Management of Advanced Heart Failure: An Overview

Ghulam Murtaza and William G. Cotts

Introduction

With current estimates of heart failure (HF) prevalence at 25 million, HF presents itself globally as both a significant healthcare challenge and economic burden. In the USA alone, nearly 6,000,000 people are plagued with HF, and nearly 600,000 new cases are diagnosed each year [1]. HF is the most common Medicare diagnosis and its overall prevalence has increased as the US population ages [2]. It is estimated that nearly 250,000 people in the USA suffer from advanced HF. The annual cost of caring for HF patients in the USA is nearly 39 billion dollars which places a significant burden on our healthcare system. HF carries a significant mortality and is responsible for nearly three million hospitalizations annually [3]. One-year mortality for advanced HF is nearly 50% [4].

Definition and Staging

HF is considered a clinical diagnosis with a broad range of severity of symptoms. Symptoms vary considerably among patients with some who are virtually asymptomatic while others struggle to walk a few steps despite being on multiple medications. As such, criteria have been established to help classify these patients into categories to help with management and follow-up. The American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines categorizes patients into four stages (Table 1). Stage D, in particular, classifies patients into refractory HF with structural disease and progressive worsening of symptoms including dyspnea at rest, inability to carry out daily activities, and multiple hospitalizations for fluid overload while receiving optimal HF therapy. Recurrent hospitalizations portend a poor prognosis, as the European EPICAL registry of more than 2000 patients with advanced HF revealed that patients were admitted to the hospital an average of 2.05 times per year and spent nearly 28 days per year in the hospital [5, 6].

G. Murtaza
Department of Internal Medicine, Advocate Christ Medical Center, Oak Lawn, IL, USA

W. G. Cotts (✉)
Advocate Heart Institute, Advocate Christ Medical Center, Oak Lawn, IL, USA
e-mail: William.cotts@advocatehealth.com

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Stage D patients include those with symptoms at rest despite being on medical therapy. These patients may benefit from intravenous (IV) inotropic therapy, ventricular assists devices (VAD), and heart transplantation. Similarly, New York Heart Association (NYHA) class separates patients into class I–IV based on the severity of symptoms. Class III and IV, in particular, are noted by marked limitation of physical activity and an inability to carry out any physical activity without discomfort, respectively. Advanced HF patients typically fall into NYHA Class III–IV categories and ACC Stage D [7] (Tables 1 and 2).

Etiology

When a patient presents with signs and symptoms of HF, it is imperative to find the underlying precipitant. While the etiology of HF is extensive, some of the common etiologies include the following: viral infections, thyroid dysfunction, ischemia, alcohol, atrial fibrillation, sleep apnea, obesity, and hypertension. Of note, however, is that ischemia accounts for more than 50% of cases [8]. In some studies, 75% of HF cases had antecedent hypertension. An increased ratio of total cholesterol to HDL cholesterol is associated with increased risk of developing HF [9]. In one study, 49% of the subjects who had underlying sleep apnea had HF [10]. Furthermore, noncompliance with HF medications, poor diet including high consumption of salt and fatty foods, can contribute to worsening of HF.

Assessment of the Heart Failure Patient

A number of criteria should be taken into consideration when assessing the patient with advanced HF including the number of previous admissions, presence of hypotension, intolerance to angiotensin converting enzyme (ACE)/angiotensin receptor blockers (ARB), and beta blockers, widening of the QRS complex, unresponsiveness to biventricular pacing, worsening exertional tolerance, worsening renal function, elevated HF biomarkers, and psychosocial factors.

Common symptoms in HF patients include fatigue and dyspnea on exertion. Dyspnea can range from shortness of breath with mild exertion to orthopnea and paroxysmal nocturnal dyspnea. As such, patients report improvement or worsening in dyspnea marked by inability to walk a few blocks or a few flight of stairs as they move through the different classes of NYHA. Other common symptoms include lower extremity swelling, abdominal bloating, decreased appetite, early satiety, drowsiness, and overall lack of energy. Abdominal bloating and peripheral edema are common

Table 1. ACC/AHA classification of HF.

AHA/ACC classification	
Stage A	Patient at high risk for heart failure but no structural disease or symptoms present
Stage B	Structural heart disease present but patient is asymptomatic
Stage C	Structural heart disease present along with symptoms
Stage D	HF refractory to medical therapy and requiring advanced interventions

Table 2. NYHA classification of HF.

NYHA classification	Symptoms
Class 1	Able to perform usual activities of daily living without experiencing any symptoms of HF
Class II	Some limitations in performing activities of daily living
Class III	Comfortable at rest but any activity triggers symptoms of HF
Class IV	Symptoms of HF at rest including fatigue, inability to ambulate

manifestations of fluid overload and are more prevalent in the advanced HF population. Some of the indicators of advanced HF include the following: need for inotropic support, intolerance to medications, persistent hyponatremia, NYHA III–IV symptoms, multiple HF hospitalizations, and worsening renal function [6, 11]. Since HF is a chronic disease, many patients adapt to their symptoms by decreasing the frequency and duration of their activities of daily living. Because this occurs over a long period of time, it is possible for HF patients to have advanced HF in the absence of significant symptoms or signs of HF.

Physical exam findings associated with advanced HF include an S3 gallop, jugular venous distention, rales on auscultation, hypotension, and cardiac cachexia. The presence of jugular venous pressure (JVP) in HF patients is an important finding. Data suggest that JVP is a reasonably good assessment of elevated left-sided pressures in chronic HF patients. Sensitivity and specificity for an elevated JVP to predict a pulmonary capillary wedge pressure >18 approaches nearly 81% and 80%, respectively [12]. JVP is a good prognostic marker as well. In a multivariate analysis, elevated JVP was associated with an increased risk for hospitalization for HF and increased risk of overall mortality. Presence of an S3 heart sound is also associated with worse outcomes [13]. Although the presence of rales in HF patients is suggestive of severe HF and volume overload, the absence of rales does not rule out significantly elevated pulmonary capillary wedge pressures (PCWP). In one study, pulmonary rales were auscultated in only 19% of patients and lower extremity edema was only presented in 23% of the patients with PCWP >22 mmHg [12].

As a result, a patient with advanced HF can present without any evidence of fluid overload on physical examination and yet still have an elevated pulmonary capillary wedge pressure and an elevated central venous pressure. Therefore, it is important to keep in mind the potential role for invasive assessment of hemodynamics in this population.

Although there are limitations to the physical exam, it should not be abandoned in the patient with heart failure. As such, it is useful to classify patients into four quadrants of HF as proposed by Lynne Warner Stevenson to aid in the assessment of advanced HF patients (Fig. 1). This classification takes into account the presence or absence of elevated filling pressures and adequate or limited organ perfusion. Briefly, it is interpreted as follows: warm and dry, indicating adequate perfusion and volume status; warm and wet, indicating adequate perfusion but congestion; cold and dry, indicating inadequate perfusion and normal filling pressures; and, cold and wet, indicating both inadequate perfusion and congestion [14, 15]. For example, a warm and wet patient is unlikely to need any inotropes and may only require diuresis and subsequent escalation of medical therapy. The cold patient, however, may require inotropic support or mechanical support. Therapy can be tailored to each patient's specific hemodynamic profile as well as comorbid conditions and on the severity of HF.

Imaging, Laboratory Evaluation, and Invasive Hemodynamic Monitoring

Some of the common baseline tests ordered to assess HF include blood urea nitrogen and creatinine to assess for renal function in the setting of HF. An electrolyte panel may reveal hyponatremia in the volume overloaded patient and may suggest acid–base disturbances such as an elevated carbon dioxide level due to diuresis. A complete blood count is routinely checked to assess for anemia which is not uncommon with chronic disease and can affect the oxygen carrying capacity of blood. In more critically-ill patients, a lactic acid level may aid in determining end-organ damage as the body switches to anaerobic metabolism in cardiogenic shock. Thyroid function testing is usually done to assess for hyper- or hypothyroid states that may cause or exacerbate HF. Iron studies can be checked if there is a suspicion for an iron overload state like hemochromatosis or to further assess an anemic state. A sleep study can be performed to assess for both central and obstructive sleep apneas. The presence of an infiltrative disease like sarcoidosis or amyloidosis can often be identified with magnetic resonance imaging/ echocardiography or an endomyocardial biopsy. An echocardiogram can point towards an underlying infiltrative disease with the presence of increased ventricular wall thickness, diastolic dysfunction, and restrictive pathology. These echocardiographic findings along with a high clinical suspicion for an infiltrative process would warrant an MRI for further evaluation. Because coronary artery disease (CAD) is a common cause of HF, either noninvasive imaging or coronary angiography can be helpful to diagnose CAD. Elevation of cardiac troponins may correlate with myocyte loss and deterioration of LV systolic function. Persistent elevation of troponins in this patient population likely is related to continuous ventricular remodeling

Fig. 1: Classification of patients presenting with heart failure.

Low perfusion at rest?	Congestion at rest? No	Congestion at rest? Yes
No	I. Warm and dry PCWP normal CI normal *Optimize meds*	III. Warm and wet PCWP elevated CI normal *Consider increasing diuresis*
Yes	II. Dry and cold PCWP normal/flow CI decreased *Consider inotropes*	IV. Wet and cold PCWP elevated CI decreased *Consider vasodilators and inotropic therapy*

PCWP pulmonary capillary wedge pressure, CI cardiac index

along with myocyte degeneration and reduced coronary reserve. The presence of myocardial ischemia in this patient population can also contribute to the presence of elevation in troponin [16]. Nevertheless, persistent elevation of cardiac troponins serves as a worse prognostic marker in these patients [15]. Lastly, B-type natriuretic peptide (BNP), which is secreted by the heart in response to increased wall stress, serves as a prognostic marker. An elevated BNP is often associated with increased congestion and an increase in mortality.

An electrocardiogram is done to check for any arrhythmias, evidence of ischemia, new bundle branch blocks that could have precipitated HF. Vascular congestion on chest x-ray is commonly seen in HF. However, the absence of congestion on x-ray may exist in the presence of significant HF.

An echocardiogram is performed to assess for diastolic and systolic function, wall motion abnormalities, valvular function, ventricular chamber size, and to compare previous echocardiograms to check for response to medical therapy.

Certain patients may benefit from invasive hemodynamic monitoring with a pulmonary artery (PAC) catheter. Although the ESCAPE trial demonstrated no survival advantage with invasive monitoring in patients with acute decompensated HF, there still may be indications for such monitoring [15]. Examples include the patient in cardiogenic shock, or the advanced HF patient with worsening renal function despite optimal medical therapy who may benefit from inotropic therapy, mechanical assistance or heart transplantation. In such situations, hemodynamics can be optimized. At times, differentiating etiologies of hypotension, renal and pulmonary disease may be better assessed by invasive hemodynamic monitoring. Furthermore, patients who are candidates for heart transplant or LVAD require a PAC for evaluation to assess pulmonary vascular resistance and right sided heart function [15].

Cardiorenal Syndrome

Renal dysfunction in HF is very common with prevalence of nearly 30% among patients with acute decompensated HF. The existence of both simultaneously, commonly referred to as "cardiorenal syndrome" (CRS), carries a very poor prognosis. In a study which evaluated outpatients with Class IV HF, 40% of patients had chronic kidney disease (CKD) stage 4 or worse. Renal function in the setting of HF, therefore, is an important prognostic marker [17]. Numerous mechanisms have been implicated in CRS including low cardiac output and elevated central venous pressures. However, the pathophysiology of CRS is complex as worsening renal function has been noted in the presence of normal cardiac output and adequate renal perfusion. Furthermore, it is important to recognize that an elevated creatinine or decreased glomerular filtration rate (GFR) is not always the result of cardiac dysfunction and that the presence of CRS requires that other causes of renal dysfunction are ruled out. When evaluating for CRS, it is important to look at GFR as compared to creatinine because the former is a more sensitive marker and correlates better with prognosis. At times, creatinine can be normal in HF exacerbation in the setting of reduced GFR [18].

Management of the Heart Failure Patient

Nonmedical management: Nonmedical management of the HF patient can be as important as medical management. A low-salt diet of 2 g is recommended for patients at risk for volume overload. Exercise has not been proven to worsen HF and hence should be encouraged. Avoidance of certain medications such as nonsteroidal anti-inflammatory drugs should be routine in

patients with HF to avoid nephrotoxicity and volume overload. Dihydropyridine calcium channel blockers, in particular amlodipine, should be avoided in HF as they have been shown to cause peripheral edema by causing arteriolar dilatation and fluid extravasation [19]. PRAISE II Trial concluded that amlodipine does not exert favorable effects on the clinical course of patients with HF, regardless of the presence or absence of coronary artery disease. Verapamil has a negative inotropic effect and should ideally be avoided in HF with reduced ejection fraction. Diltiazem has a lesser inotropic effect and can be used with caution with patients with HF, particularly when control of supraventricular tachyarrhythmias is required [20, 21]. Weight reduction should be emphasized. Smoking cessation and vaccinations including influenza and pneumococcal should be encouraged. Alcohol should be limited and completely avoided in cases of alcoholic cardiomyopathy [22].

Medical Management

Over the last 30 years, great advances have been taken in the research of appropriate medicines that improve survival and outcomes in HF. In the 1980s and early 1990s several large randomized clinical trials demonstrated a survival benefit with ACE inhibitors in both asymptomatic patients with LV dysfunction and patients with severe HF. The SOLVD prevention and treatment trials demonstrated survival benefits in symptomatic and asymptomatic patients with left ventricular dysfunction treated with enalapril [23]. In 1987, the CONSENSUS trial showed a significant survival benefit of adding enalapril, to conventional medical therapy in patients with severe congestive HF [24]. Careful attention to side effects of ACE inhibitors such as cough and angioedema should be considered. ARBs may considered as substitutes with such side effects.

With regards to ARBs, the CHARM Trial in 2004 showed improved outcomes when candesartan, an ARB, was added to standard medical therapy including a beta blocker, ACE inhibitor, and aldosterone antagonist [25]. However, the benefit was not enough to recommend the use of both ACE inhibitors and ARBs. Combined use can lead to hyperkalemia, worsen renal function and lead to hypotension [26].

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, was recently approved for HF patients with NYHA Class II–IV with an EF of 35%. The Paradigm trial showed a significant reduction in risk of death and hospitalization for HF with sacubitril/valsartan when compared with enalapril. Patients with GFR less than 30 mL/h. were excluded from the study, limiting its use in patients with poor kidney function [27].

A number of randomized multicenter clinical trials evaluating the efficacy of beta-blockers in patients with HF showed significant survival benefits. Trials such as MERIT-HF, CIBIS II, the US Carvedilol Trials and COPERNICUS showed that metoprolol succinate, carvedilol, and bisoprolol improve survival, improve EF and symptoms in HF [28–31]. Carvedilol may have an added advantage of alfa blocking activity which causes peripheral dilation and carvedilol also has an effect on improving insulin sensitivity [32, 33].

Beta blockers should be gradually uptitrated at 2-week intervals with attention paid to hypotension and bradycardia. Beta-blockers should not be initiated or uptitrated with patients with evidence of acute HF. Abrupt discontinuation of beta blocker therapy in HF should be avoided as rebound effects can occur. In such a situation, a decrease in dosage is warranted. However, in cardiogenic shock, beta blockers should be held.

The A-HeFT trial in 2004, which looked at combined hydralazine and isosorbide dinitrate therapy in advanced HF African American patients with low ejection fraction, NYHA class III to IV symptoms, was terminated early when it demonstrated improved survival and reduced hospitalization in the treatment group [34, 35]. Several studies have demonstrated a survival benefit with aldosterone inhibitors. The first was the RALES trial which showed survival benefit with spironolactone in patients with class III and IV HF [36]. The Ephesus trial demonstrated a survival benefit in post myocardial infarction patient receiving eplerenone [37].

In general, all HF patients should be on a beta blocker, ACE inhibitors (ARBs if ACE inhibitors cannot be tolerated). Loop diuretics should be added for symptomatic improvement of dyspnea and relief of congestion. Aldosterone receptor antagonists are recommended in addition to ACE inhibitors, beta blockers and diuretics unless contraindications are present. Nitrates may be added to help improve dyspnea and angina [4] (Table 3).

Diuresis is an important part of therapy as it reduces filling pressures and central and pulmonary vascular congestion. In most patients, diuresis is achieved through the use of a loop diuretics. Loop diuretics are considered first line diuretic therapy because they are effective and retain their effectiveness with worsening of renal function. Usually, patients are on diuretic therapy at home. In hospitalized patients with ADHF, IV furosemide is generally used to target a net negative fluid balance. IV furosemide is preferred because compared to oral, IV has greater bioavailability. The IV dose should be at least equivalent to the home dose when initiating therapy in the hospital, and uptitration can be done depending on the volume status of the patient. Loop diuretics are the recommended diuretics for patients with advanced CKD as other diuretics are less effective with GFR less than 30 mL/h. However, even loop diuretics may lose their efficacy in the setting of hypotension, significant intrinsic renal disease, and as GFR decreases, as only 15–20% of furosemide is delivered to the kidney tubules in CKD stage 5. In the setting of a severe edematous state, increased gut edema impairs absorption of furosemide. In this setting, either switching to IV furosemide or oral bumetanide or torsemide, loop diuretics with predictable bioavailability, can be considered [38]. Generally speaking, of the three loop diuretics, furosemide, bumetanide, and torsemide, torsemide has the

greatest bioavailability, more predictable diuretic response, and the longest half-life [38].

Thiazide diuretics may potentiate the effects of loop diuretics and so are sometimes used in combination to augment diuresis. IV chlorothiazide and oral metolazone are the thiazides often used in combination with loop diuretics. Metolazone has an added effect of acting on the proximal tubule which adds to its efficacy in advanced renal failure [39]. Combination therapy, however, should be used with caution and frequent monitoring as electrolyte abnormalities are common.

When HF becomes refractory to loop diuretics, it is necessary to look for potential factors including medications which could be limiting their effect on the renal tubules. Uptitration of loop diuretics should then be pursued and switching from IV to a continuous infusion may be considered. Although the DOSE trial in 2011 showed that intermittent infusion of diuretics was not superior to continuous infusion, some clinicians prefer continuous infusion of loop diuretics as this may allow for more effective titration [40].

When ADHF patients are refractory to diuretics, ultrafiltration may be considered. This modality results in greater fluid removal and weight loss. The UNLOAD trial in 2007, which randomized hospitalized HF patients to IV diuretics or ultrafiltration, showed that ultrafiltration produced greater fluid removal, weight loss and reduced 90-day readmissions for HF [41]. However, in the setting of CRS and acute decompensated HF, the CARRESS-HF trial showed that ultrafiltration compared to medical therapy was associated with more adverse events and worsening of renal function. Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy [42].

Once optimal volume status is achieved and patients are optimized on ACE inhibitors and beta-blockers, vasodilators such as the combination of hydralazine and nitrates may be beneficial in reducing afterload. While vasodilators provide symptomatic relief and reduce filling pressures, the two drugs that may slow or reverse cardiac remodeling and disease progression are beta blockers and ACE inhibitors. ACE inhibitors are recommended for all stages of HF while beta blockers should be attempted.

Table 3. Medications used for HFrEF.

Drug	Initial dose(s)	Maximum dose(s)	Side effects
ACE inhibitors			
Captopril	6.25 mg TID	50 mg TID	Cough, hyperkalemia, angioedema, impaired renal function
Enalapril	2.5 mg BID	10–20 mg BID	
Lisinopril	2.5–5 mg QD	20–40 mg QD	
Beta blockers			
Bisoprolol	1.25 mg QD	10 mg QD	Bradycardia, hypotension
Carvedilol	3.125 mg BID	50 mg QD	
Carvedilol CR	10 mg QD	80 mg QD	
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg QD	200 mg QD	
Angiotensin Receptor Blockers (ARBs)			
Candesartan	4–8 mg QD	32 mg QD	Hyperkalemia, angioedema, impaired renal
Losartan	25–50 mg QD	50–150 mg QD	
Valsartan	20–40 mg BID	160 mg BID	
ARNI			
Sacubitril/valsartan	49/51 mg BID (sacubitril/ valsartan) (may consider 24/26 mg BID as initial dose)	97/103 mg BID (sacubitril/ valsartan)	Angioedema, hypotension, impaired renal function, hyperkalemia
Aldosterone antagonists			
Spironolactone	12.5–25 mg QD	25 mg QD or BID	Hyperkalemia, gynecomastia (spironolactone)
Eplerenone	25 mg QD	50 mg QD	
I channel inhibitor			
Ivabradine	5 mg BID	7.5 mg BID	Bradycardia, vision changes
Isosorbide dinitrate and hydralazine			
Fixed-dose	20 mg isosorbide dinitrate/37.5 mg hydralazine TID	40 mg isosorbide dinitrate/ 75 mg hydralazine TID	Headache, hypotension
Isosorbide dinitrate and hydralazine separately	20–30 mg isosorbide dinitrate/25–50 mg hydralazine TID or QD	40 mg isosorbide dinitrate TID with 100 mg hydralazine TID	

ARBs are not as effective ACE inhibitors in the HF population and should be used when intolerance to ACE inhibitors is present.

The V2 receptor antagonist, tolvaptan, can be considered in the setting of hyponatremia in HF exacerbation to improve sodium levels, decrease edema, and promote weight reduction in the short-term. Long term benefits have not been seen with V2 antagonists as per the EVEREST trial [43].

Nesiritide, a recombinant BNP with vasodilatory properties, gained popularity in the early 2000s when it showed improvement in dyspnea and lowering of PCWP in the HF population. ASCEND-HF trial in 2011 concluded nesiritide had a small, nonsignificant effect on dyspnea when used in combination with other medical therapies and that it was also associated with hypotension, limiting its use. This led to a decrease in popularity [44].

In HF patients with either ischemic or nonischemic cardiomyopathy with NYHA III–IV symptoms who are on optimal medical therapy, have poor LV function with EF <35%, QRS duration >120 ms, and are in sinus rhythm, cardiac resynchronization therapy has shown to be beneficial in decreasing mortality and hospitalizations [45].

Inotropes

In patients with refractory HF who are not candidates for LVAD or transplantation, the continuous infusion of inotropes may be considered. The two commonly used inotropes used in the US include milrinone and dobutamine. It is important to note, however, that the mortality rate for patients who receive inotropes is more than 50% at 6 months [46]. The main two ways inotropes are used are either as palliative therapy in patients without another advanced HF option or as bridge to advanced therapies.

Milrinone increases cyclic adenosine monophosphate within the cell, resulting in increased calcium levels and increased contractility. Milrinone also has the advantage of reducing afterload by causing peripheral vasodilation. However, vasodilation could be a problem if the patient is borderline hypotensive and potentially limit its use.

However, symptomatic relief and improvement in dyspnea comes at a price. For example, The PROMISE trial, which randomized advanced HF patients to oral milrinone therapy vs. placebo, was stopped early due to a 28% increase in all-cause mortality and 34% increase in cardiovascular mortality in the oral milrinone group. Similarly, in the OPTIME-CHF trial, advanced HF patients were randomized to either IV milrinone or placebo. The milrinone group had a higher incidence of atrial arrhythmias and hypotension [47].

Dobutamine is a B1 and B2-adrenergic receptor agonist and helps improve myocardial contractility. Due to its B2 properties, it can induce hypotension by peripheral vasodilation. It has a relatively short half-life of 3 min. Due to an increase in mortality associated with dobutamine, it is only used for acute decompensated systolic failure and for improvement in symptoms. It is also used for palliative purposes. Like milrinone, dobutamine is pro-arrhythmic [47] (Table 4).

Digoxin inhibits the Na-K ATPase pump which prevents the efflux of calcium out of the cell, causing an inotropic effect. Digoxin has been used widely for symptomatic relief and to decrease the frequency of HF admissions. Use of digoxin is a Class IIa indication in HF with reduced EF patients who are symptomatic despite optimal medical therapy. Digoxin does not cause hypotension and is commonly used in chronic HF patients who have underlying atrial fibrillation for rate control. However, despite its widespread use, digoxin has no survival benefit [47].

As prognosis for patients, going home on inotropes is very poor and they are not candidates for advanced therapies including transplantation or ventricular assist devices, thorough evaluation should be made taking into account patient preferences and whether they prefer hospice care, palliative support. It is also not unreasonable to have discussion about resuscitation [48].

Table 4. Parenteral drugs used for HFREF.

Drug	Initial dose(s)	Maximum dose(s)	Side effects
Loop diuretics			
Furosemide	20–40 mg	160 mg 3–4×/day 40 mg/h	Hypovolemia, hypokalemia, hypersensitivity, ototoxicity, contraction alkalosis
Torsemide	10–20 mg	200 mg BID 20 mg/h	
Bumetanide	0.5–1 mg	4–8 mg 3–4×/day, 1–2 mg/h	
Thiazide diuretics			
Chlorothiazide	250 mg QD	250–500 mg 3–4×/day	Hypotension, hypokalemia
Inotropes			
Milrinone	0.125–0.75 mcg/kg/min	0.75/mcg/kg/min	Arrhythmias, hypotension
Dobutamine	0.5–20 µg/kg/min Typically 2.5–5 µg/kg/min	40 mcg/kg/min	

Palliative Care

Despite significant advancement in medical therapy to improve survival and quality of life, advanced HF still carries a poor prognosis. These patients usually are older and have underlying comorbidities, poor quality of life, and common complaints like dyspnea, depression, pain, and fatigue. Since many healthcare providers are seeing advanced HF patients, these patients often have a sense of uncertainty about prognosis and feel left out due to lack of communication. End of life transition and the whole process dealing with it is an unfamiliar territory for most. Furthermore, there is significant psychosocial burden on the family when a loved one is inflicted with HF. Palliative care strives to provide an improved quality of life and focuses on symptoms rather than therapy to prolong life. It takes into account the patient and family as a whole and looks to alleviate suffering. Palliative care is underutilized in this patient population [49].

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Evidence-Based Management of the Patient with Congestive Heart Failure

Nicolas W. Shammas

24.1 Epidemiology of Congestive Heart Failure

Congestive heart failure (CHF) is the result of either a weak heart muscle (systolic failure) or a stiff ventricle (diastolic failure). Systolic and diastolic failure may coexist in the same patient [1]. Irrespective of the etiology, it leads to an inadequate amount of oxygenated blood to meet cellular demand.

CHF is a growing problem in the United States and particularly in the elderly [2]. Over half a million cases are diagnosed on an annual basis with subsequent high mortality [3] and a large cost to our economic system [4].

Although less studied, diastolic failure occurs in approximately 30–35% of all patients and 55% of the elderly with CHF [5, 6]. Recently heart failure with normal left ventricular function (HFNEF) is a term that has been more widely used than "diastolic heart failure" and describes a heterogeneous group of patients with a number of pathological mechanisms [7]. It is estimated that 50% of HF patients have HFNEF and display similar physiologic and neurohormonal phenotypes to patients with HF and reduced systolic function. Unless more effective acute and preventative therapies are implemented in treating CHF patients, the social burden in treating these patients will continue to rise [8].

CHF appears to be on the rise in the United States [4, 9] and is partly due to the high prevalence of the metabolic syndrome, diabetes mellitus, hypertension, and obesity [10]. Although improvement in survival has been noted in the younger heart failure patient over the past two decades, this benefit has not been seen in the elderly and females [11]. Survival has improved however in both genders over the past 50 years [12].

N. W. Shammas
Midwest Cardiovascular Research Foundation,
Davenport, IA, USA

24.2 Pathophysiology of Congestive Heart Failure

There are multiple risk factors that lead to injury to the myocardium including coronary artery disease (CAD), hypertension, valvular heart disease, diabetes mellitus, congenital heart defects, anemia, metabolic syndrome, cardiotoxins, and alcoholism [13, 14]. Left ventricular remodeling with reduction of left ventricular function (as measured by the ejection fraction) and dilatation of the left ventricle subsequently occurs. The remodeling process is initially an adaptation mechanism to reduce wall stress and increase cardiac output by hypertrophy of viable myocytes. Hypertrophy, however, eventually leads to an increase in mass-to-volume ratio and premature myocyte cell death [15]. As the syndrome of heart failure occurs, a patient presents with fatigue, increased weight, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and chest pain. A reduced left ventricular function increases the risk of arrhythmias and sudden cardiac death as well as pump failure [16, 17].

Cardiac remodeling is mediated partly by activation of the renin–angiotensin–aldosterone (RAAS) system and the sympathetic nervous system (SNS) (Fig. 24.1). Activation of the RAAS system leads to a rise in angiotensin II (AII); sodium retention and myocardial fibrosis mediated by angiotensin II and aldosterone; peripheral vasoconstriction; and endothelial injury [18], which lead to programmed cell death (apoptosis), hypertrophy, and fibrosis. AII also promotes aldosterone secretion. In addition, vasoconstrictors such as endothelin-1 and reactive oxygen species (ROS) are increased, and nitric oxide (NO) synthesis and release are reduced, all contributing to vasoconstriction [18–20]. Furthermore, endothelial dysfunction is further impaired by the increase in inflammatory markers and cytokines [19, 21, 22].

Elevated sympathetic tone is part of the syndrome of heart failure with elevation of circulating catecholamines and suppression of adrenergic receptors [23]. Adrenaline has direct toxic effect on the myocardium [24]. Also, it induces cellular

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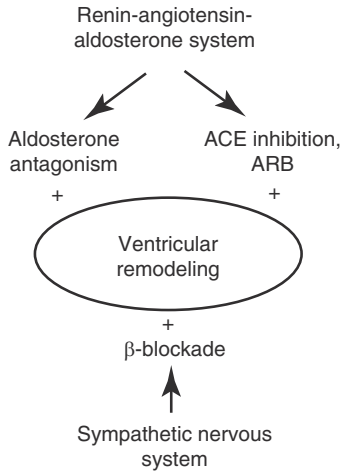


Fig. 24.1 The renin–angiotensin–aldosterone system and the sympathetic nervous system promote ventricular remodeling, a process that can be reversed with aldosterone antagonism, ACEI, or ARB and beta blockade

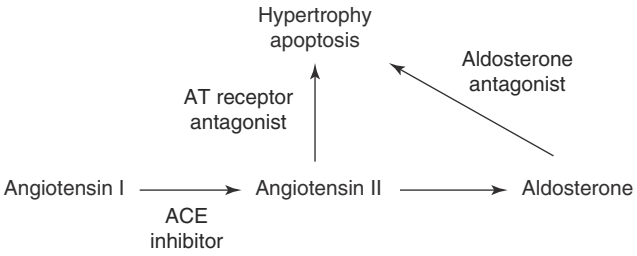


Fig. 24.2 Interventions to block the renin–angiotensin–aldosterone system

calcium overload [25], decreases myocardial mechanical efficiency, precipitates arrhythmias, increases myocardial oxygen consumption and coronary blood flow requirements, and induces left ventricular hypertrophy [26].

The SNS and the RAAS systems are therapeutic targets, and blocking their activation has been shown to reduce mortality and morbidity in patients with CHF. Aldosterone is only partially produced as a result of angiotensin activation, and therefore, AII suppression [27] is not adequate to block its secretion. The addition of aldosterone blockers is, therefore, needed for optimal suppression of aldosterone, and it has been shown to provide additional reductions in mortality and morbidity in patients with CHF [28, 29] (Fig. 24.2). Finally, beta adrenergic blockade also contributes in reducing the activity of the RAAS [30].

The activation of the RAAS and the SNS is generally partially counter-regulated by the production of vasoactive peptides including the natriuretic peptide (NP) system. These vasoactive peptides, particularly, brain natriuretic peptides (BNP) lead to vasodilation and increase sodium/water excretion. Also they inhibit aldosterone release and prevent cardiac and vascular fibrosis. In patients with heart failure, NP renal effects are blunted for unclear reasons, and they are also degraded by the neprilysin system. Recently, the advent of angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan provided a novel pharmacologic approach that is capable of inhibiting the neutral endopeptidase enzyme neprilysin (with sacubitril) and concomitantly blocks the adverse effects of angiotensin II (with valsartan).

In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study [31], a double-blind, randomized, multicenter trial, 8442 patients with Class II–IV heart failure and an ejection fraction of 40% or less were randomized to receive either sacubitril/valsartan (at a dose of 97/103 mg orally twice daily, respectively) or enalapril (at a dose of 10 mg twice daily). The primary outcome of death from cardiovascular causes or heart failure rehospitalization was significantly reduced in the ARNI arm (21.8%) compared to enalapril (26.5%) ($p < 0.001$). Cardiovascular death was reduced by 20% (HR 0.80 (95% CI, 0.71; 0.89)) and risk of first heart failure hospitalization by 21% (HR 0.79 (95% CI, 0.71; 0.89)). Also total mortality was reduced by 16% (absolute risk reduction 2.8%) (HR 0.84 (95% CI, 0.76; 0.93)). The study was prematurely stopped because of the overwhelming benefit of ARNI when compared to ACEI.

Adverse reactions of ARNI were reported in more than 5% of patients in the double-blind study, and these included hypotension, hyperkalemia, cough, dizziness, and renal failure. The incidence of angioedema was also higher in patients treated with ARNI compared to enalapril (0.5% versus 0.2% respectively; 2.4% in the black population). These adverse events are likely to be encountered more frequently in practice as the double-blind period of PARADIGM-HF was preceded by a single-blind run-in period where patients were excluded if they could not tolerate the high dose of ARNI or ACEI.

Several other therapies have been tested in CHF patients and have shown conflicting results. These include endothelin antagonists, immunomodulating agents, and growth hormone [32]. At the present time, interventions that modulate the SNS and RAAS and inhibit the neprilysin enzyme (in conjunction with ARB) remain the only proven treatment to reduce mortality and morbidity in patients with congestive heart failure.

Another pharmacologic advent in treating patients with reduced EF and heart failure is ivabradine, an HCN channel blocker. It is indicated in patients in normal sinus rhythm and who are intolerant to beta blocker or on maximum tolerable dose of a beta blocker. Ivabradine was tested in The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) [33] which randomized 6505 patients with chronic heart failure and reduced EF to ivabradine versus placebo on top of optimal medical treatment. Patients had to be in normal sinus rhythm with a heart rate of more or equal 70 bpm, NYHC Class II–IV, EF less or equal 35%, and have

been hospitalized with heart failure in the past 12 months. Ivabradine significantly reduced the relative risk of hospitalization for worsening HF or CV death (RRR 18%, $p < 0.0001$); the significance is driven mostly by a reduction of rehospitalization.

HFNEF describes a heterogeneous pool of patients that make about 50% of HF patients with a unique set of pathophysiologic mechanisms. These patients are typically older with hypertension, obesity, renal failure, anemia, and atrial fibrillation and are more likely to be females. There is also a high incidence of diabetes and coronary artery disease in these patients [7]. In contrast to patients with impaired left ventricular EF, HFNEF patients have non-dilated left ventricular cavity size, concentric instead of eccentric left ventricular hypertrophy, and a normal EF [34].

It is controversial whether LV systolic function is truly normal in patients with HFNEF because EF is an imprecise measure of left ventricular systolic function. However, invasive conductance studies suggested from pressure–volume loops that end-systolic pressure–volume relationship is steeper or normal in HFNEF suggesting a normal systolic function. On the other hand, end-diastolic pressure–volume relationship is shifted leftward and upward indicating diastolic dysfunction [35, 36].

Diastolic dysfunction is not uncommon among elderly patients estimated at about 5.6%, but only 1% has HFNEF [37]. In one study, the product of left ventricular mass index and left atrial volume has the highest predictive accuracy for HFNEF [38]. In addition to ventricular stiffness, arterial stiffness has also been suggested to contribute to HFNEF, and the combined ventricular–arterial stiffness leads to an exaggerated hypertensive response after small increases in LV end-diastolic volume [7].

24.3 ACC/AHA Classification of Congestive Heart Failure

The current ACC/AHA classification for CHF [3] is complementary to the New York Heart Classification (NYHC) [39] and helps define the evolution of symptoms of patients with CHF. In addition, the ACC/AHA classification focuses on the risk factors for CHF by identifying patients who have risk factors for CHF.

This classification includes four stages of CHF:

Stage A: Asymptomatic patients with no left ventricular dysfunction but are at risk of developing CHF including patients with coronary artery disease, hypertension, diabetes mellitus, family history of cardiomyopathy, and the metabolic syndrome.

Stage A is not represented in the NYHC.

Stage B: Asymptomatic patients with left ventricular dysfunction. This is equivalent to Class I of the NYHC.

Stage C: Symptomatic patients with exertion and with left ventricular dysfunction. This is equivalent to the NYHC Class II and Class III and includes about five million people in the United States.

Stage D: Symptomatic patients at rest. This is equivalent to Class IV of the NYHC and includes about 200,000 people in the United States.

24.4 Pharmacologic Therapy of Congestive Heart Failure

24.4.1 Heart Failure with Normal Ejection Fraction (HFNEF) and Diastolic Dysfunction

As noted above, one of the main pathophysiologic mechanisms of HFNEF is diastolic dysfunction, but not all patients with diastolic dysfunction have heart failure, and not all patients with HF and diastolic dysfunction represent "true" HFNEF. "True" HFNEF does not include those with coronary artery disease, valvular heart disease, restrictive or constrictive cardiomyopathy, obesity, pulmonary hypertension and right-sided failure, high-output failure caused by anemia, thyrotoxicosis or arteriovenous fistula, constrictive pericarditis, or intracardiac shunt.

Diastolic dysfunction has been associated with many conditions including coronary artery disease, hypertension, valvular disease, age [40], elevated triglyceride levels possibly secondary to intracellular lipid accumulation [41], sleep apnea [42], and hypertrophic cardiomyopathy. Treatment with an ARB (losartan) has yielded improvement in diastolic function but did not change left ventricular cavity size or mass [43].

Isolated diastolic dysfunction is uncommon and has been identified in 11.5% of patients with no CAD or valvular disease with the use of echocardiography [44]. Increase in left atrial size and N-terminal pro B-type natriuretic peptide (NT-proBNP) appears to be predictors of LV diastolic dysfunction [45]. Also, varying degrees of diastolic dysfunction are seen with different left ventricular geometric patterns [46].

Recently an algorithm to diagnose HFNEF has been proposed by the working group of the European Society of Cardiology [47]. In general, patients with signs and symptoms of HF, normal EF > 50%, and LVEDVI < 97 mL/m^2 and with evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness will meet the diagnosis of HFNEF if one of the following three criteria is met: mean PCWP > 12 mmHg or LVEDP > 16 mmHg by invasive testing, $E/E' > 15$ by tissue Doppler, or $8 < E/E' < 15$ by tissue Doppler with a BNP > 200 pg/mL and/or NT-proBNP > 220 pg/mL or BNP > 200 pg/mL and/or NT-proBNP > 220 pg/mL and LVH or atrial fibrillation or left atrial dilation or abnormal pulmonary venous return.

Patients with left ventricular diastolic dysfunction need to be treated with aggressive blood pressure control with the use of diuretics, beta blockers, or non-dihydropyridine calcium channel blockers (diltiazem or verapamil) [48]. The *ACC/AHA 2005 Guidelines* recommend blood pressure control as a Class I level A in patients with HFNEF [49].

ACE inhibitors or angiotensin receptor blockers (ARBs) can have long-term value in reducing left ventricular hypertrophy and theoretically may improve left ventricular compliance [50] and improve diastolic function in contrast to hydralazine and hydrochlorothiazide [51]. In the Hong Kong Diastolic Heart Failure Study [52], diuretics in combination with an ACEI (ramipril) or ARB (irbesartan) marginally improved LV systolic and diastolic function and lowered BNP at 1 year.

Aldosterone antagonist appears to have a beneficial effect on diastolic function particularly in the elderly, possibly by reducing myocardial fibrosis [53]. Losartan and amlodipine were compared in the effect of losartan and amlodipine on left ventricular diastolic function in patients with mild-to-moderate hypertension (J-ELAN) to determine their role in improving diastolic function [54, 55]. Fifty-seven patients were randomized to losartan or amlodipine and were followed up for 18 months. Despite similar blood pressure in both regimens, there was no statistical difference between the two drugs in shortening the transmitral E-wave deceleration time or reducing LV mass index; However, mean carotid intima-media thickness (mean IMT) and plaque score significantly increased in the amlodipine group (pre, 1.05 ± 0.26 mm; follow-up, 1.23 ± 0.33 mm, $p = 0.0015$), but not in the losartan group indicating that losartan may reduce against progression of atherosclerosis in these patients.

Diastolic dysfunction also has been described in diabetic patients with impaired glucose tolerance and insulin resistance [56] and is associated with endothelial dysfunction and abnormalities on stress myocardial single-photon emission computed tomography [57]. Glycemic control shows an improvement in diastolic parameters that was inversely correlated with percent changes in glycated hemoglobin [58].

In the Euro Heart Failure Survey I, preserved systolic function is also seen in elderly patients with HF [59]. These patients typically have a high mortality. Measurements of EF and lifesaving therapies are quite often underutilized in this group of patients with multiple comorbidities. The use of beta blockers and ACEI was associated with a better outcome in these patients.

In conclusion, ACEI and ARB are important therapies in reducing left ventricular hypertrophy and improving left ventricular diastolic function. The role of beta blockers and calcium channel blockers remains unclear but of concern is the likelihood of progression of atherosclerosis in patients on amlodipine when compared to ARB. Diuretics reduce left ventricular filling pressures and improve symptoms. Risk factor modification is also important including treatment of hypertension, diabetes, sleep apnea, elevated triglycerides, coronary artery disease, and valvular disease.

24.4.2 Asymptomatic Left Ventricular Systolic Dysfunction

Asymptomatic left ventricular dysfunction (Stage B, ACC/AHA classification) is prevalent and typically identified by echocardiography [60]. Asymptomatic left ventricular systolic dysfunction (ejection fraction ≤50%) was reported in 6.0% of men and 0.8% of women with a hazard ratio for CHF of 4.7 on 12 years follow-up [61]. Neurohormonal activation is present in patients with asymptomatic left ventricular dysfunction and leads to worsening left ventricular function and progression to symptomatic failure [62].

Risk factors modification is also important in these patients including treatment of hypertension, diabetes, sleep apnea, elevated triglycerides, coronary artery disease [63], valvular disease, smoking cessation, reducing alcohol intake or illicit drug use, and routine exercise. Tachycardia-induced cardiomyopathy needs to be recognized and treated. Anemia has been associated with asymptomatic left ventricular dysfunction and progression to heart failure particularly when the hematocrit is ≤40% [64].

Beta blockers and ACEI are important therapies in Stage B CHF including the post-myocardial infarction patients [64, 65] and have been shown to improve left ventricular EF [66] and reduce progression to heart failure [67]. In the SOLVD trial [68], asymptomatic patients with reduced left ventricular function (EF < 35%) were randomized to enalapril ($n = 2117$) versus placebo ($n = 2111$) and followed for an average of 37.4 months. The reduction in cardiovascular mortality was larger in the enalapril group than placebo (risk reduction of 12%, $p = 0.12$). Also, the combined endpoint of death and heart failure was 36% lower in the enalapril group ($p < 0.001$).

ARBs are a reasonable alternative to ACEI [69]. The role of calcium channel blockers or digoxin in Stage B CHF is unclear. Endothelin A/B receptor antagonists (enrasentan) increases resting cardiac index but was associated with more serious adverse events (16.7% and 2.8%, respectively, $p = 0.02$) than enalapril [70].

As per *ACC/AHA Guideline Update 2005*, patients with asymptomatic left ventricular dysfunction post-myocardial infarction and an EF of ≤30% despite optimal medical therapy for at least 40 days post-MI need to be considered for an implantable defibrillator (ICD) without requiring screening for ventricular arrhythmias, whether occurring spontaneously or induced by electrophysiologic testing [71–73]. ICD therapy in this population yielded a 31%

reduction in mortality during an average follow-up of 20 months [73].

Echocardiography or isotope ventriculography has been used for periodic follow-up of patients with asymptomatic left ventricular dysfunction. Patients with familial cardiomyopathy need to have their immediate family members screened for asymptomatic left ventricular dysfunction [74].

24.4.3 Symptomatic Left Ventricular Systolic Dysfunction

Symptomatic left ventricular systolic dysfunction (Stage C, ACC/AHA classification) requires close follow-up and intense pharmacologic treatment (Table 24.1). In addition to risk factor modifications, patients will need to be treated with pharmacologic and mechanical means to improve their morbidity and mortality. Serial monitoring of ejection fraction is also important. A summary of therapies for Stage C CHF is presented below.

Table 24.1 Commonly used drugs in the treatment of congestive heart failure

Angiotensin-converting enzyme inhibitors
Accupril 5–40 mg PO QD, max 40 mg/day, start 5–10 mg PO QD
Captopril 12.5–50 mg PO TID, max 150 mg/day, start 6.25–12.5 mg PO TID
Enalapril 2.5–20 mg PO BID, max 40 mg/day, start at 2.5 mg QD
Lisinopril 5–20 mg PO QD, max 40 mg/day, start 2.5–5 mg PO QD
Monopril 10–40 mg PO QD/BID, max 80 mg/day, start 10 mg PO QD
Perindopril 4–16 mg PO QD, max 16 mg/day, start 2 mg PO QD
Ramipril 5 mg PO BID, max 10 mg/day, start at 2.5 mg PO BID
Angiotensin receptor blockers
Losartan 25–100 mg PO QD, max 100 mg/day, start 25–50 mg PO QD[a]
Candesartan 8–32 mg PO QD, max 32 mg/day, start 16 mg PO QD[a]
Valsartan 40–160 mg PO BID, max 320 mg/day, start 40 mg PO BID
Irbesartan 75–300 mg PO QD, max 300 mg/day, start 75 mg PO QD[a]
Beta blockers
Carvedilol 3.125–25 mg PO BID, max 50 mg PO QD, start 3.125 mg PO BID
Metoprolol succinate 12.5–200 mg PO QD, max 200 mg/day, start 12.5 mg PO QD
Bisoprolol 5–10 mg PO QD, max 10 mg PO QD, start 2.5 mg PO QD[a]
Aldosterone antagonists
Spironolactone 12.5–25 mg PO BID, max 50 mg/day, start 12.5 mg PO BID
Eplerenone 50 mg PO QD, max 50 mg/day, start 25 mg PO QD[b]
Angiotension receptor neprilysin inhibitor (ARNI)
Sacubitril/valsartan 24 mg sacubitril/26 mg valsartan PO BID to be increased to 49 mg/51 mg PO BID and 97 mg/103 mg PO BID as tolerated every 2 weeks[c]
HCN channel blocker
Ivabradine 5 mg PO BID. Can increase to maximum dose of 7.5 mg PO BD

[a]Off-label use
[b]For CHF patients post-myocardial infarction
[c]Sacubitril/valsartan should not be used with ACEI

24.4.4 Angiotensin-Converting Enzyme Inhibitors (ACEI)

ACEIs reduce mortality by 15–20% and rehospitalizations by 30–35% in patients with left ventricular systolic dysfunction (ejection fraction of <40%). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) compared the effects of enalapril versus placebo on mortality in patients with severe CHF. Enalapril reduced mortality by 31% at 1 year ($p = 0.001$) as well as congestive heart failure hospitalization [75]. The SOLVD trial also confirmed the same findings. Patients receiving conventional treatment for Class II and III heart failure were randomly assigned to receive either placebo ($n = 1284$) or enalapril ($n = 1285$). Enalapril reduced mortality by 16% ($p = 0.0036$) and congestive heart failure by 26% ($p < 0.0001$) at an average follow-up of 41.4 months [76]. Furthermore, SOLVD showed that enalapril attenuates progressive increases in left ventricular dilatation and hypertrophy in patients with reduced left ventricular function [77]. Finally, Pitt and colleagues also has shown that enalapril reduced development of heart failure by 37% and hospitalization from heart failure by 36% ($p < 0.001$) [78].

ACEI post-MI has also shown a significant mortality benefit. The Acute Infarction Ramipril Efficacy (AIRE) study [79] showed a 27% ($p = 0.002$) reduction in the 30-month cumulative mortality with ramipril over placebo in post-MI CHF patients. Also, in the Survival and Ventricular Enlargement (SAVE) trial [80], captopril was administered 3–16 days after myocardial infarction in patients with asymptomatic left ventricular dysfunction (EF < 40%) and followed for an average of 42 months. Captopril improved survival (risk reduction was 19%, $p = 0.019$) and morbidity. In addition, in the Trandolapril Cardiac Evaluation (TRACE) study, trandolapril reduced mortality by 22% ($p = 0.01$) in patients with reduced left ventricular function after an MI. Trandolapril reduced overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure [81]. Finally, in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study [82], zofenopril reduced the risk of death or severe congestive heart failure by 34% ($p = 0.018$) at 6 weeks when initiated early after MI. At 1 year, the reduction in mortality risk was 29% ($p = 0.011$).

Early initiation of ACEI in hospital leads to a higher use of ACEI on an outpatient basis, and, therefore, initiating ACEI early is important in all patients with CHF.

24.4.5 Angiotensin Receptor Blockers (ARB)

ARB is an effective treatment in patients with CHF. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study [27], 768 patients in NYHC II–IV and EF <40% received candesartan, candesartan plus enalapril, or enalapril alone for 43 weeks. Left ventricular cavity size increased less, and BNP levels decreased more with combination therapy compared to ARB or ACEI alone [69].

In the Evaluation of Losartan in the Elderly (ELITE) trial [83], 722 patients with EF ≤ 40%, ≥65 years of age, and in NYHC Class II–IV were included. The primary endpoint was death and/or hospital admission for heart failure and occurred at a rate of 9.4% in the losartan group compared to 13.2% in the captopril group (risk reduction 32%, $p = 0.075$). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% versus 8.7%; risk reduction 46%, $p = 0.035$) with similar rates of hospital admissions in both groups (5.7%). ELITE II [84] randomized 3152 patients aged 60 years or older with NYHC II–IV and ejection fraction of <40% to losartan ($n = 1578$) titrated to 50 mg once daily or captopril ($n = 1574$) titrated to 50 mg three times daily. ELITE II showed no differences in mortality between losartan and captopril and confirmed that ARB therapy can be a potential substitute to ACEI.

The Valsartan in Heart Failure Trial (Val-HeFT) [85] randomized 5010 patients with heart failure of New York Heart Association (NYHA) Class II, III, or IV to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined endpoint of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 h. Mortality was similar in both groups, but the combined endpoint of morbidity and mortality was reduced by 13.2% with valsartan ($p = 0.009$), predominantly driven by a reduction in heart failure hospitalizations (13.8% versus 18.2%, $p < 0.001$). In patients intolerant to ACEI, valsartan (titrated to 160 mg twice daily) reduced both all-cause mortality and combined mortality and morbidity compared with placebo (17.3% versus 27.1%, $p = 0.017$ and 24.9% versus 42.5%, $p < 0.001$, respectively) [86]. In a substudy of this trial, valsartan taken with either ACEI or beta blockers reversed left ventricular remodeling [87]. Of interest, in the Val-HeFT, valsartan with either a beta blocker or ACEIs showed a positive effect on outcome [88], but an adverse effect in patients receiving both types of drugs [85]. This concern of adding an ARB to patients on both ACEI and beta blockers was not confirmed in the CHARM trial.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) [86] was a randomized, double-blind, placebo-controlled, multicenter study in patients with NYHC Class II–IV. This trial had three complementary arms: CHARM-added, candesartan (titrated to 32 mg once daily) is added to an ACEI; CHARM-alternative, candesartan administered to patients who cannot tolerate ACEIs; and CHARM-preserved, candesartan is administered to patients with preserved left ventricular function irrespective of whether they are on ACEI or not. In the CHARM-added and CHARM-alternative arms, patients with EF ≤ 40% were included. In the "overall program" of this study [87], which included both preserved and reduced left ventricular function, total mortality was not reduced compared to placebo. However, in a subgroup analysis of patients with symptomatic heart failure and reduced left ventricular function, candesartan significantly reduced all-cause mortality (28% versus 31%, $p = 0.0018$), cardiovascular death (22.8% versus 26.2%, $p = 0.005$), and CHF hospitalizations (22.5% versus 28.1%, $p < 0.001$) when added to standard therapies including ACEI, beta blockers, and aldosterone antagonists [88]. Candesartan also reduced progression to diabetes [89], sudden cardiac death, and death from worsening heart failure in patients with symptomatic failure [86].

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) [90] randomized patients 0.5–10 days after an acute MI with reduced left ventricular function to valsartan (4909 patients) titrated to 160 mg twice a day, valsartan (80 mg twice a day) plus captopril (50 mg three times a day) (4885 patients), or captopril (4909 patients) alone titrated to 50 mg three times a day in addition to standard therapy. The primary endpoint of the study was all-cause mortality at a median follow-up of 24.7 months. Valsartan was equally effective compared to captopril in reducing all-cause mortality. Also combining valsartan with captopril increased the rate of adverse events without improving survival.

In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), patients after an acute myocardial infarction were randomized to losartan versus captopril. The primary endpoint was reduction in all-cause mortality at a mean follow-up of 2.7 years. A nonsignificant difference was seen in total mortality in favor of captopril (18% versus 16% in the losartan versus captopril, respectively, $p = 0.07$). However, there were significantly more cardiovascular deaths with losartan (15%) than with captopril (13%) ($p = 0.03$) [91]. Losartan was better tolerated than captopril with fewer patients discontinuing their medications (17% versus 23%, $p < 0.0001$) [92]. An echocardiographic substudy of the OPTIMAAL trial has shown that both losartan and captopril improve systolic function after an acute MI, but the benefit is greater for captopril [93].

A growing body of evidence suggests that an ARB can be an alternative to an ACEI in patients with CHF [74].

24.4.6 Aldosterone Blockers

Angiotensin II is a dominant stimulus of aldosterone secretion [94]. Aldosterone secretion, however, continues to escape ACEI or ARB [27, 95, 96]. A reduction, however, in aldosterone plasma level is seen with angiotensin blockers [97]. Recent data confirms that aldosterone blockers are important to improve morbidity and mortality in patients with CHF and reduced left ventricular systolic function. Aldosterone blockade reduces myocardial fibrosis and ventricular remodeling and has important effects on autonomic balance, fibrinolysis, oxidative stress, and activation of the NF-kappaB and AP-1 signaling pathways [98].

The Randomized Aldactone Evaluation Study (RALES) [28] randomized patients ($n = 1663$) with advanced CHF and EF $\leq$ 35% to spironolactone 25 mg daily ($n = 822$) or placebo ($n = 841$) including ACEI, digoxin, and diuretics. After a mean follow-up of 24 months, the trial was stopped early. Spironolactone reduced the primary endpoint of mortality by 30% (46% versus 35%, $p < 0.001$) primarily due to reduction of progression of CHF and sudden cardiac death. In addition, spironolactone significantly improved New York Heart Association functional class ($p < 0.001$) and reduced rehospitalization due to worsening CHF by 35% ($p < 0.001$). Spironolactone also increases the risk of hyperkalemia [99], which accounted for an increase in hospitalization from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001 ($p < 0.001$) and a mortality increase from 0.3 per 1000 to 2.0 per 1000 patients ($p < 0.001$). Therefore, close follow-up of patients for serum potassium levels is needed when spironolactone is initiated. Avoiding spironolactone in patients with elevated potassium levels (>5 mEq/L) and high baseline creatinine (>2.0) is advised to avoid serious hyperkalemia problem.

Another recent trial, Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) [29], randomized patients with CHF and an EF < 40%, 3–14 days post-MI, to eplerenone (25–50 mg daily) or placebo. At a mean follow-up of 27 months, eplerenone reduced total mortality by 15% ($p = 0.008$), cardiovascular mortality or cardiovascular hospitalizations by 13% ($p = 0.002$), and sudden cardiac death by 21% ($p = 0.03$). The EPHESUS established the importance of aldosterone antagonism in post-MI patients with reduced left ventricular function irrespective of the degree of heart failure.

24.4.7 β(Beta) Blockade in Heart Failure

Multiple β(beta) blockers have been shown to reduce mortality and morbidity in patients with heart failure and reduced left ventricular systolic function. Current guidelines support the use of carvedilol, metoprolol, and bisoprolol to treat

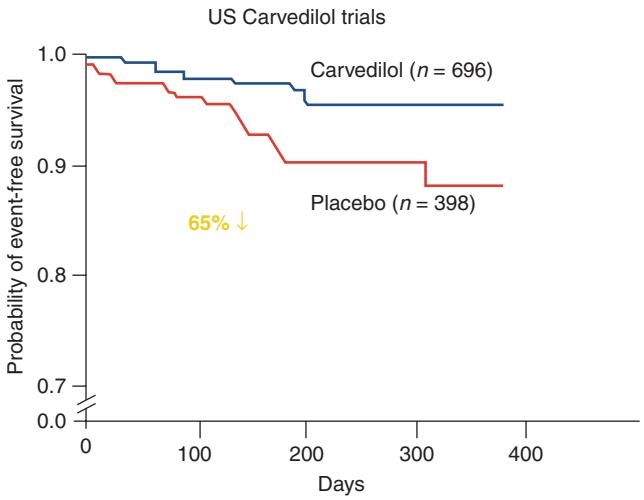


Fig. 24.3 US Carvedilol trials showing a significant reduction in mortality with carvedilol compared to placebo in patients with left ventricular systolic dysfunction

patients with CHF. Beta blockers reduce mortality by approximately 35% when added to standard therapy in mild-to-moderate [100–102] or advanced CHF [103] and reduced hospitalizations by 33–38% [100, 101, 104]. Beta blockers have a positive impact on positive remodeling by reducing cavity size and improving ejection fraction [105].

In the US Carvedilol Heart Failure Study [100] (Fig. 24.3), 1094 patients were enrolled in a double-blind, placebo-controlled, stratified program in which they received one of four treatment protocols based on their exercise capacity. Patients with heart failure were randomized to placebo ($n = 398$) or carvedilol ($n = 696$) in addition to conventional therapy. The overall mortality at 6-month follow-up was reduced by 65% ($p < 0.001$) and rehospitalization by 27% with carvedilol ($p = 0.036$). This effect was seen in both black and non-black patients [106]. Carvedilol also reduced length of hospital stay and length of stay in the intensive care unit leading to a 57% reduction in inpatient care costs for cardiovascular admissions ($p = 0.016$) and 81% lower for heart failure admissions ($p = 0.022$) [104]. Finally, severe heart failure (EF < 22%, markedly reduced 6-min corridor walk test, and severe impairment of quality of life) had an improvement in EF with carvedilol ($p = 0.004$) [107]. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study group [108], 2289 patients with severe heart failure symptoms were randomly assigned to receive carvedilol ($n = 1156$) or placebo ($n = 1133$). The carvedilol group experienced no increase in cardiovascular risk and had fewer patients who died (19 versus 25; hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.41–1.35) and were hospitalized (134 versus 153; HR 0.85; 95% CI 0.67–1.07). Carvedilol was well tolerated in euvolemic patients with fewer patients withdrawn from treatment than placebo.

In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study 991 patients with chronic heart failure in NYHC II–IV and EF ≤ 40% were enrolled in a double-blind, randomized, placebo-controlled study of metoprolol CR/XL versus placebo [101]. All-cause mortality and sudden death were reduced by 34% ($p = 0.00009$) and 41% ($p = 0.0002$) in the metoprolol group. Also, metoprolol CR/XL reduced the number of hospitalizations due to worsening heart failure ($p < 0.001$) and number of days in hospital due to worsening heart failure ($p < 0.001$). In post-MI patients with symptomatic CHF and an EF ≤ 40% and receiving contemporary management, metoprolol CR/XL reduced total mortality by 40% ($p = 0.0004$) and sudden death by 50% ($p = 0.0004$) [109].

The Cardiac Insufficiency Bisoprolol II (CIBS-II) study was a double-blind, placebo-controlled trial in Europe that enrolled 2647 symptomatic patient with Class III or IV heart failure and an EF ≤ 35% randomized to bisoprolol or placebo. At 1.3 years, all-cause mortality and sudden death were reduced by 34% ($p < 0.0001$) and 44% ($p = 0.0011$), respectively, with bisoprolol. Also, bisoprolol resulted in fewer hospital admissions per patient hospitalized, fewer hospital admissions overall, and fewer days spent in hospital or intensive care unit leading to a reduction in the cost of care by 5–10% compared to placebo [110].

The Carvedilol Or Metoprolol European Trial (COMET) [111, 112] is the only randomized trial that compared two beta blockers in a randomized, double-blind study in the management of CHF patients. 3029 patients with Class II–IV heart failure were recruited at 317 centers in 15 European countries. At 58 months, there was a 17% reduction in mortality with carvedilol compared to metoprolol tartrate ($p = 0.0017$). Recently, carvedilol (6.25–25 mg twice daily) was also shown in The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study not to alter glycemic control in diabetics when compared to metoprolol tartrate (50–200 mg twice a day). Furthermore, it did improve some components of the metabolic syndrome such as improving insulin sensitivity [113].

Currently recommended beta blockers in the management of CHF are carvedilol, metoprolol succinate, and bisoprolol [74]. Adherence to the use of beta blockade is of paramount importance to reduce the economic burden of CHF. Beta blockers are currently underutilized in patients with CHF [114], and continued educational efforts are needed to promote guidelines in heart failure management.

Aggressive titration of beta blockers is needed in patients with CHF. Higher levels of beta blockade and ACEI are associated with better improvement of ejection fraction and greater reductions in cardiovascular hospitalizations [115–117]. In a substudy of the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, the composite endpoint of mortality or hospitalization decreased incrementally with the use of high-dose ACE inhibitors ($n = 475$) (adjusted odds ratio (aOR) 0.93; p = NS), high-dose ACE inhibitors plus beta blockers ($n = 72$) (aOR 0.89; p = NS), and high-dose ACE inhibitors plus beta blockers plus digoxin ($n = 77$) (aOR 0.47; $p = 0.006$) compared with low-dose ACE inhibitors ($n = 471$) [117]. A stepwise approach in titration of beta blockade is generally followed with an increase in the dose every 2 weeks as tolerated until achieving the maximum tolerable dose.

24.4.8 Angiotensin Receptor Neprilysin Inhibitor (ARNI) in Heart Failure

The natriuretic peptide (NP) system counter-regulates the activation of the RAAS and the SNS. Recently, the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was introduced to inhibit the neutral endopeptidase enzyme neprilysin (with sacubitril) and concomitantly blocks the adverse effects of angiotensin II (with valsartan). In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study [31], ARNI reduced the primary outcome of death from cardiovascular causes or heart failure rehospitalization (21.8%) when compared to ACEI (26.5%) ($p < 0.001$). The individual endpoint of cardiovascular death was reduced by 20% (HR 0.80 (95% CI, 0.71; 0.89)), the risk of first heart failure hospitalization by 21% (HR 0.79 (95% CI, 0.71; 0.89)), and total mortality by 16% (absolute risk reduction 2.8%) (HR 0.84 (95% CI, 0.76; 0.93)). Current ACC/AHA/HFSA guidelines [118] consider ARNI as a Class I indication for treating patients with congestive heart failure and are preferred over an ACEI to further reduce mortality.

24.4.9 HCN Channel Blocker in Heart Failure

Ivabradine, an HCN channel blocker was recently introduced to reduce heart failure hospitalization. It is indicated in patients in normal sinus rhythm and who are intolerant to beta blocker or on maximum tolerable dose of a beta blocker. Ivabradine was tested in The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) [33]. It included patients in normal sinus rhythm with a heart rate of more or equal to 70 bpm, NYHC Class II–IV, EF less or equal to 35%, and have been hospitalized with heart failure in the past 12 months. Ivabradine significantly reduced the relative risk of hospitalization for worsening HF or CV death (RRR 18%, $p < 0.0001$); the significance is driven mostly by a reduction of rehospitalization.

24.4.10 Digoxin Therapy in Congestive Heart Failure

Digoxin was introduced by William Withering and has been used therapeutically for more than 250 years [119]. It has been widely used in the treatment of atrial fibrillation as a rate control agent, but its utility in CHF has been debated.

The Digitalis Investigation Group (DIG) [120] is a randomized, double-blind clinical trial that studied the effects of digoxin on mortality and hospitalization in patients with congestive heart failure. DIG showed no advantage of digoxin on mortality at 37 months follow-up. Digoxin, however, reduced the rate of hospitalization for worsening heart failure. A comprehensive post hoc analysis, however, of the DIG showed that digoxin at a serum concentration of 0.5–0.9 ng/mL did reduce mortality (29% versus 33%, adjusted hazard ratio (AHR) of 0.77) and heart failure hospitalizations (23% versus 33%, AHR of 0.68) in all heart failure patients with no interaction with EF > 45% ($p = 0.834$) or gender ($p = 0.917$) [121]. In another substudy of the DIG trial, perceived health, quality of life measures, and the 6-min walk test were not statistically different between digoxin and placebo in patients in normal sinus rhythm at 12-month follow-up [122]. Furthermore, digoxin efficacy was not altered by renal glomerular filtration, but renal dysfunction was a predictor of mortality in patients with GFR < 50 mL/min [123].

Patients on digoxin and receiving standard treatment for congestive heart failure might experience a slight reduction in EF [124–127], worsening maximal exercise capacity, and increased incidence of treatment failure upon withdrawal of this drug [125, 127].

Currently, digoxin is indicated for the treatment of chronic heart failure in patients with left ventricular dysfunction and NYHC Class II–III despite optimal medical treatment with ACEI, beta blockers, and diuretics (ACC/AHA Class IIa indication). Digoxin is not indicated for the acute treatment of CHF, and serial measurements of digoxin levels are currently considered unnecessary. Digoxin dose needs to be reduced when administered with amiodarone.

24.4.11 Mechanical Treatment of Stage C Heart Failure

24.4.11.1 Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is indicated in patients with advanced heart failure symptoms (Class III or IV) despite optimal medical management, an EF ≤ 35%, sinus rhythm, and cardiac dyssynchrony defined as a wide QRS complex >120 ms. The outcomes of CRT system implantation in 2078 patients from a multicenter study program showed that the procedure is safe, well-tolerated, and has a high success rate [128].

In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial [128], 369 patients with EF ≤ 35%, QRS duration ≥130 ms, and Class III–IV NYHC, despite optimal medical treatment, were randomized to controls ($n = 182$, ICD activated, CRT off) and the CRT group ($n = 187$, ICD activated, CRT on). CRT improved quality of life, functional status, and exercise capacity without adversely influencing ICD function. In addition, in the InSyncIII study [129], a multicenter, prospective, non-randomized, 6-month trial of 422 patients with wide QRS complex and a Class III or IV heart failure, sequential CRT therapy provided a modest increase in stroke volume and improved exercise capacity but had no change in functional status or quality of life compared to a historic control from the MIRACLE trial. Furthermore, improvement in left ventricular function that occurs with CRT is more prominent in patients with nonischemic heart failure and less severe mitral insufficiency [130]. Finally, in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, the risk of the combined endpoint of death from, or hospitalization for, heart failure was reduced by 34% ($p < 0.002$). In the same trial, death from any cause was reduced by 24% ($p = 0.059$) in the pacemaker group compared to the medical therapy alone [131]. In this trial, the addition of a defibrillator reduced mortality beyond that achieved with CRT therapy alone.

Current guidelines recommend CRT therapy in patients with advanced heart failure symptoms and wide QRS complex who are already optimized on medical treatment with the goal to improve exercise capacity, functional status, and quality of life and to help reverse left ventricular remodeling [74].

24.4.11.2 Implantable Cardioverter Defibrillators

Sudden death is a major cause of mortality in patients with left ventricular dysfunction. Implantable cardioverter defibrillators (ICD) are currently indicated in patients with moderate CHF and reduced EF < 30% on optimal medical therapy who have a reasonable expectation of survival for more than 1 year who are at least 40 days post-myocardial infarction, have nonischemic cardiomyopathy, or have had a serious arrhythmia such as ventricular fibrillation, ventricular tachycardia, or cardiac arrest [73, 132].

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 2521 patients with moderate heart failure and an EF ≤ 35% were randomized to conventional therapy for CHF plus placebo, conventional therapy plus amiodarone, or conventional therapy plus ICD. Amiodarone had no

favorable effect on survival, whereas ICD reduced overall mortality by 23% at 45.5 months mean follow-up [132]. In addition, the COMPANION [131] trial showed that ICD therapy can reduce death by 36% ($p = 0.003$) in patients with advanced heart failure due to ischemic or nonischemic cardiomyopathy and a QRS $\geq$ 120 ms when compared to optimal medical therapy. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) randomized 1232 patients with EF $\leq$ 30% to ICD or conventional medical therapy. Death was the primary endpoint, and the average follow-up was 20 months. The mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group (hazard ratio for the risk of death in the ICD group was 0.69, $p = 0.016$) [133]. A long-term follow-up study from MADIT-II showed that the probability of survival after successful therapy with an ICD for ventricular fibrillation or tachycardia was 80% at 1 year [134]. The MADIT-II also indicated that benefit from ICD therapy is similar among all the different heart failure subgroups [71]. Currently the MADIT-CRT is ongoing and is testing whether CRT-D will reduce the risk of mortality in patients with reduced EF ($\leq$30%) and prolonged QRS $\geq$ 130 ms and NYHC Class I–II [135].

24.4.12 Miscellaneous Therapy

CHF patients need to be instructed on dietary salt restriction (2 g sodium/day), fluid restriction, daily weight monitoring, smoking cessation, regular exercise, avoidance of alcohol intake, and aggressive treatment of high blood pressure and dyslipidemia. Aggressive treatment of sleep apnea is also indicated [136]. In general CHF patients need to avoid nonsteroidal anti-inflammatory drugs (NSAIDS), most calcium channel blockers, and antiarrhythmic agents. Finally, exercise testing and enrolment in an exercise structured program are advised in these patients.

24.4.13 Management of the ACC/AHA Stage D Congestive Heart Failure Patient

Acutely decompensated CHF patients with severe left ventricular dysfunction require intense pharmacologic and mechanical management. Patients with advanced decompensated failure have a poor short-term prognosis. In the Initiation Management Pre-discharge Assessment of Carvedilol Heart Failure (IMPACT-HF) registry [137], mortality and rehospitalization rate was 31% at 60-day follow-up.

Positive inotropic agents such as dopamine and milrinone might be utilized for palliative reasons because they improve symptoms and increase functional capacity, but they could worsen arrhythmias and possibly increase the risk of mortality [138, 139]. In a randomized trial of milrinone versus placebo in 951 patients with decompensated CHF, milrinone caused more sustained hypotension and atrial arrhythmias compared to placebo with no positive impact on mortality [140]. An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE), a large retrospective registry of patients with acute decompensated CHF, patients who received milrinone and dobutamine had a higher in-hospital mortality than those who received nitroglycerin and nesiritide. Both nesiritide and nitroglycerin had similar in-hospital mortality [141].

Current *ACC/AHA Guidelines* consider the use of intermittent positive inotropic agents for the management of decompensated heart failure as a Class III indication, indicating that their use should be discouraged.

Data on IV nesiritide suggest that this drug is effective in lowering wedge pressure and improving patient's symptoms [142]. In the Vasodilatation in the Management of Acute CHF (VMAC) trial, 489 inpatients with decompensated CHF were enrolled in a randomized trial of nesiritide versus nitroglycerin or placebo for 3 h followed by nesiritide or nitroglycerin for 24 h. The primary and secondary outcomes of the study are pulmonary capillary wedge pressure (PCWP) at 3 and 24 h, respectively. IV nesiritide was administered as a bolus of 2 μg/kg followed by continuous infusion of 0.01 μg/kg/min. At 3 h, dyspnea improved with nesiritide compared with placebo ($p = 0.03$), but there was no difference compared to nitroglycerin. At 24 h, the reduction in PCWP was greater in the nesiritide group (−8.2 mmHg) than the nitroglycerin group (−6.3 mmHg) with a modest improvement in clinical status (VMAC investigators). In VMAC, there was no significant difference between nesiritide and nitroglycerin subjects in 6-month mortality. The hemodynamic benefits and safety of nesiritide in patients with acutely decompensated CHF are maintained in patients receiving chronic beta blockers [143].

In the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT), 255 patients were randomized to dobutamine or nesiritide in

Table 24.2 Percent 30-day mortality in seven nesiritide trials

Trial	Natrecor (%)	Control (%)	Hazard ratio	Confidence interval
Mills et al.	2.70	7.50	0.38	(0.05–2.67)
PRECEDENT	3.70	6.10	0.6	(0.18–1.97)
Efficacy	5.90	5.80	1.25	(0.24–6.45)
Comparative	6.90	4.90	1.43	(0.53–3.97)
VMAC	8.10	5.10	1.56	(0.75–3.24)
PROACTION	4.2	0.90	4.99	(0.58–42.73)
FUSION I	1.40	2.90	0.49	(0.07–3.47)
Pooled (all)	5.30	4.30	1.27	(0.81–2.01)

the management of decompensated congestive heart failure. Dobutamine was associated with arrhythmia and tachycardia, whereas nesiritide reduced ventricular ectopy and did not increase heart rate suggesting a safer profile of nesiritide over dobutamine [144].

The 30-day mortality from pooled data from seven clinical trials (Table 24.2) [142, 144–148] was 5.3% for Natrecor and 4.3% for control (hazard ratio 1.27 [0.81–2.01]). In a recent pooled analysis of three randomized studies [149], 485 patients were randomized to nesiritide and 377 to control therapy. Death at 30 days occurred more frequently in patients treated with nesiritide than placebo at 30 days of follow-up (7.2% versus 4%, $p = 0.059$).

24.4.14 Mechanical Support of the Failing Heart

The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial [150, 151] randomized 129 patients with end-stage heart failure who were ineligible for cardiac transplantation to receive a left ventricular assist device ($n = 68$) or optimal medical management ($n = 61$). Survival (52% versus 25%, $p = 0.002$) and quality of life were significantly improved with the device compared to medical therapy at 1 year. Serious adverse events did occur in the group when compared to medical therapy and included infection, bleeding, and device malfunction. In this trial, patients undergoing inotropic support derived major mortality and quality of life benefits from the assist device compared to patients receiving medical therapy. Also, patients not undergoing inotropic support had an overall better survival rates both with and without the assist device, but differences did not reach significance.

Recent improvements in the HeartMate VE left ventricular assist device (LVAD) to the HeartMate XVE LVAD have recently led to significant improvements in outcomes [152] indicating that as technology and experience with LVAD evolve this therapy might become more accessible to the Class IV heart failure patient who is ineligible for cardiac transplantation.

24.5 Case Studies

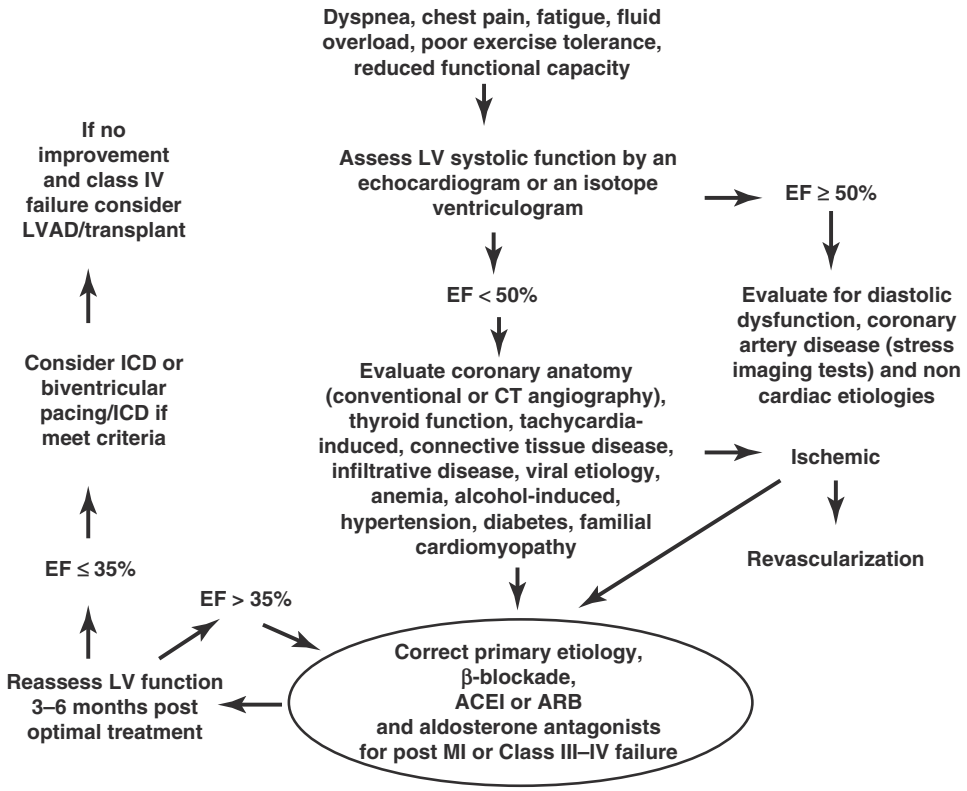
24.5.1 Case Study 1

P.S. is a 57-year-old male with history of old myocardial infarction, ischemic cardiomyopathy, and an ejection fraction of 32%. He has been short of breath with minimal home activity, placing him in a Class III New York Heart Classification for failure. Patient has been on carvedilol 25 mg PO BID, lisinopril 20 mg PO daily, furosemide 60 mg PO daily, and spironolactone 25 mg PO BID. Patient is euvolemic on his current medical regimen. His electrocardiogram showed a normal sinus rhythm with a left bundle branch block and a QRS complex duration of 140 ms. Patient was referred for biventricular pacing defibrillator placement. Two weeks post-procedure, the patient's symptoms improved, and he was in Class II NYHC. Lisinopril was then discontinued, and 36 h after, he was started on sacubitril/valsartan 24 mg/26 mg PO BID for 2 weeks. This was well tolerated, and in 2 weeks ARNI dose was increased to 97 mg/103 mg PO BID.

24.5.2 Case Study 2

M.S. is a 35-year-old female with a recent viral infection and subsequent congestive heart failure. Echocardiography showed an ejection fraction of 25% and no evidence of significant valvular disease. Blood testing showed normal thyroid function tests, negative antinuclear antibody, normal iron and iron saturation, normal liver function tests, and electrolytes. Computed tomography of the coronaries showed a calcium score of 0 and normal coronaries in a right dominant system. Patient was started on carvedilol 3.125 mg PO BID and titrated to 25 mg PO BID over a period of 2 months. She was also started on lisinopril 5 mg PO daily and increased to 20 mg PO QD. After 6 months, patient's ejection fraction

Fig. 24.4 Algorithm



normalized to 56%, and she was completely asymptomatic. She was maintained on her carvedilol and lisinopril, and at 2-year follow-up, she continued to have stable left ventricular function. Patient was presumed to have a viral cardiomyopathy and experienced excellent recovery of cardiac function (Fig. 24.4).

24.6 Conclusion

Treatment of heart failure starts with controlling risk factors, management of asymptomatic systolic dysfunction, and aggressive treatment of symptomatic failure with diuretics, beta blockers, ACEI (or ARB or ARNI), and aldosterone antagonists. The use of IV inotropes should be discouraged except for hemodynamic stability. Eligible patients need to receive biventricular pacing, ICD, or LVAD. Diastolic dysfunction is often a neglected cause of CHF, and diagnosis needs to be considered when CHF is present in the setting of normal left ventricular systolic function. HFNEF diagnosis is a relatively new entity that needs to be considered in the symptomatic heart failure patient.

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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Revascularization in Cardiogenic Shock and Advanced Heart Failure

Youssef Rahban, MD
Carlos D. Davila, MD
Peter S. Natov, BS
Navin K. Kapur, MD[*]

Address
[*]The Cardiovascular Center, Tufts Medical Center, Boston, MA, 02111, USA
Email: Nkapur@tuftsmedicalcenter.org

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Youssef Rahban and Carlos D. Davila contributed equally to this work.
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Abstract

Purpose of review Ischemic heart disease is the most common cause of heart failure with systolic dysfunction. The progressive course of heart failure characterized by increasing levels of care and worsening quality of life often indicates an advanced stage. Similarly, cardiogenic shock remains a major clinical problem with prohibitively high mortality rates despite major advances in clinical care. Here, we review the current treatment options and available data for revascularization in patients with ischemic cardiomyopathy, advanced heart failure, and cardiogenic shock. We also explore the emerging role of Interventional Heart Failure specialist within the Heart Team.

Recent findings Although guideline-directed medical therapy remains the cornerstone treatment strategy for patients with advanced heart failure, coronary revascularization is sometimes indicated. There is a relatively paucity of evidence regarding different revascularization strategies and the use of acute mechanical circulatory support in patients with advanced heart failure and in those presenting with cardiogenic shock. A deep understating of the physiologic and hemodynamic effects of different acute mechanical support platforms is of paramount importance in preparation for revascularization in these patients.

Summary The decision regarding revascularization in patients with coronary artery disease in the setting of left ventricular dysfunction remains challenging. Clinical decision-making in these cases requires interdisciplinary discussion and assessment of the potential long-term survival derived from surgical revascularization against its higher perioperative risk.

Introduction

Heart failure (HF) is a growing public health issue worldwide as the incidence and prevalence of HF continue to steadily increase over the last decades. This trend is in part due to improved survival of patients with cardiovascular diseases and an aging general population [1]. Coronary artery disease (CAD) represents the predominant etiology of HF and left ventricular (LV) dysfunction [2]. In fact, almost 60% of the patients enrolled in the Acute Decompensated Heart Failure National Registry had a history significant for CAD [3]. Moreover, ongoing ischemia is a common precipitant of acute decompensated HF [4]. While guideline-directed medical therapy remains the cornerstone treatment strategy for these patients, coronary revascularization is sometimes indicated in HF patients with CAD [5]. Although revascularization by coronary artery bypass grafting (CABG) and/or percutaneous coronary interventions (PCI) has been studied in different settings, there is relatively little evidence for such strategies in patients with HF and CAD, particularly in cases with advanced HF and cardiogenic shock (CS). Lastly, the use of acute mechanical circulatory devices (AMCS), durable mechanical circulatory devices, and bridge strategies must be considered in these patients undergoing revascularization by a multidisciplinary team. Here, we review the current treatment options and available data for revascularization in patients with ischemic cardiomyopathy (ICM), advanced HF, and CS.

The Heart Failure Association (HFA), American College of Cardiology/American Heart Association, and Heart Failure Society of America have used various criteria to define advanced HF [6, 7]. Furthermore, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has designated different clinical profiles dictating the need for advanced therapies [8•]. In 2018, the HFA of the European Society of Cardiology published a position statement with an updated definition of advanced HF (Table 1) to include patients with clinical features of HF with preserved ejection fraction and with unplanned outpatient visits for HF [10, 11]. An understanding of the severity, complexity, and diversity of the HF syndrome is needed for patients planned to undergo revascularization.

Revascularization strategies in heart failure with reduced ejection fraction secondary to coronary artery disease: CABG versus PCI

Left ventricular dysfunction and CAD frequently coexist with comorbidities that translate into higher risk for invasive or surgical procedures. Although new technologies and tools have been designed and introduced, revascularization strategies in the setting of LV dysfunction remain an area of interest and debate.

The Surgical Treatment for Ischemic Heart Failure (STICH) trial compared optimal medical therapy (OMT) plus CABG with OMT in 1212 patients with ICM and LV ejection fraction of ≤ 35% [12••]. Mortality within the first 30 days was significantly higher in the surgical group (4% vs. 1%; HR 3.12; 95% CI 1.33 to 7.32; $p = 0.009$). At a median of 4.6 years, OMT plus CABG did not result in a significant reduction in the primary outcome of all-cause mortality compared with those assigned to OMT alone (36% vs. 41%; HR 0.86; 95% CI 0.72 to 1.04; $p = 0.12$). More recently, however, the STICH Extension Study did find a significant extended effect of CABG on top of OMT in this cohort of patients. Here, after a median follow-up of 9.8 years, all-cause mortality was significantly reduced in the CABG group compared to that in OMT alone (59% vs. 66%; HR 0.84; 95% CI 0.73–0.97; $p = 0.02$) (Fig. 1). Moreover, the CABG group had significant reductions in the prespecified secondary outcomes of cardiovascular

Table 1. Updated HFA-ESC criteria for defining advanced heart failure

Updated HFA-ESC criteria for defining advanced heart failure
All the following criteria must be present despite optimal guideline directed treatment:
Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
Severe cardiac dysfunction defined by a reduced LVEF ≤ 30%, isolated RV failure (e.g., ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF [9].
Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing > 1 unplanned visit or hospitalization in the last 12 months.
Severe impairment of exercise capacity with inability to exercise or low 6MWTD (< 300 m) or pVO_2 (< 12–14 mL/kg/min), estimated to be of cardiac origin.
In addition to the above, extracardiac organ dysfunction due to heart failure (e.g., cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present but are not required.
Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g., severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

ARVC, arrhythmogenic right ventricular cardiomyopathy; *BNP*, brain-type natriuretic peptide; *ESC*, European Society of Cardiology; *HFA*, Heart Failure Association; *HFmrEF*, heart failure with mid-range ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *NYHA*, New York Heart Association; *pVO_2*, peak exercise oxygen consumption; *RV*, right ventricular, *6MWTD*, 6-min walk test distance

mortality and the combination of all-cause mortality with cardiovascular hospitalization [13••].

Given the early mortality hazard associated with CABG, the advances made in PCI and mechanical circulatory support devices have led some to propose revascularization with PCI as an alternative to CABG for patients with ICM. Although numerous studies have compared surgical and percutaneous revascularization, most of these randomized trials focused on symptomatic coronary artery disease and excluded patients with congestive heart failure and/or reduced LV function. Available data directly comparing PCI and surgical revascularization in the setting of LV dysfunction is limited to observational studies. A recent analysis of the New York state registries used propensity score matching to compare PCI and CABG in 1063 matched pairs with multivessel disease (excluding significant left main disease) and left ventricular ejection fraction (LVEF) of ≤ 35% over a period of 4 years. At a median follow-up of 2.9 years, there was no significant difference in all-cause mortality between the two groups (HR 1.01; 95% CI 0.81–1.28). PCI was associated with fewer strokes but more myocardial infarctions and repeat revascularizations [14].

The Ischemic Cardiomyopathy Percutaneous Revascularization for Ischemic Ventricular Dysfunction (the REVIVED-BCIS2) is an ongoing prospective multicenter randomized controlled trial comparing percutaneous revascularization plus OMT with OMT alone in patients with LVEF of ≤ 35% and viable myocardium [9] (Fig. 2). Since August 2013, more than 400 patients have been randomized. Follow-up continues for at least 2 years following randomization. The primary outcome is a composite endpoint of all-cause death or

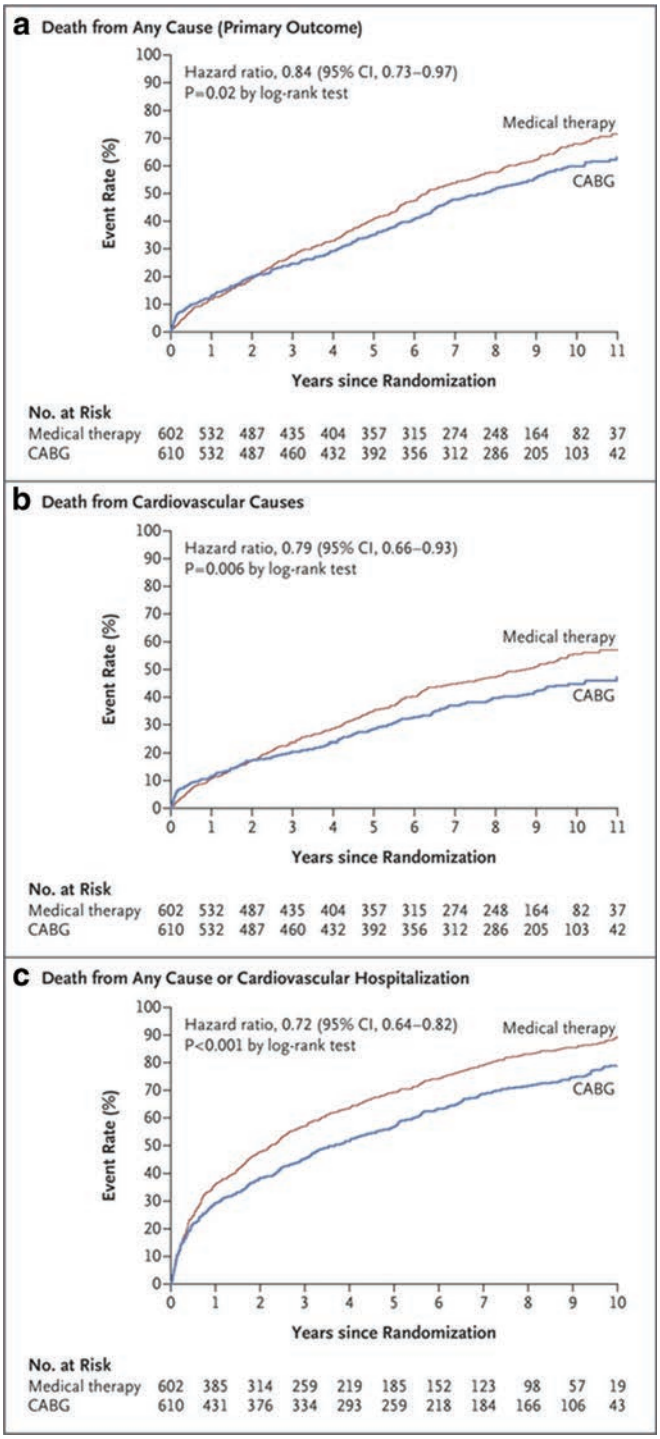

Fig. 1. Kaplan–Meier estimates of the primary and secondary outcomes of the STICHES trial. Panel **a** shows the rates of death from any cause; panel **b** shows the rate of death from cardiovascular causes; panel **c** shows the rate of death from any cause or hospitalization for cardiovascular causes.

hospitalization due to HF. Secondary outcomes include LVEF assessment at 6 and 12 months from randomization, quality of life scores, appropriate implantable cardioverter defibrillator therapy, and acute MI. Results are expected to be released in 2022.

Revascularization strategies in patients with cardiogenic shock: from door-to-balloon to door-to-support

Cardiogenic shock secondary to ICM results in hemodynamic disarray characterized by a loss of cardiac output leading to reduced end-organ perfusion and promoting pulmonary and venous congestion. When identified early, achieving several key hemodynamic objectives can reverse the shock state and prevent the onset of end-organ failure. One of these objectives is rapid restoration of coronary blood flow along with supporting systemic circulation and unloading the LV and/or right ventricle [4]. In acute myocardial infarction complicated by cardiogenic shock (AMI-CS), the landmark Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial identified that early revascularization improves long-term survival when compared to initial medical stabilization [15]. Revascularization was accomplished by either CABG or angioplasty. Since then, three decades have passed with little improvement in clinical outcomes for patients with CS. Patients with CS represent a minority of those undergoing CABG; yet, they have persistently high operative risks, accounting for 14% of deaths in CABG patients [16]. Recently, Thiele et al. showed that culprit-vessel-only revascularization as opposed to multivessel PCI during AMI-CS was associated with better clinical outcomes.

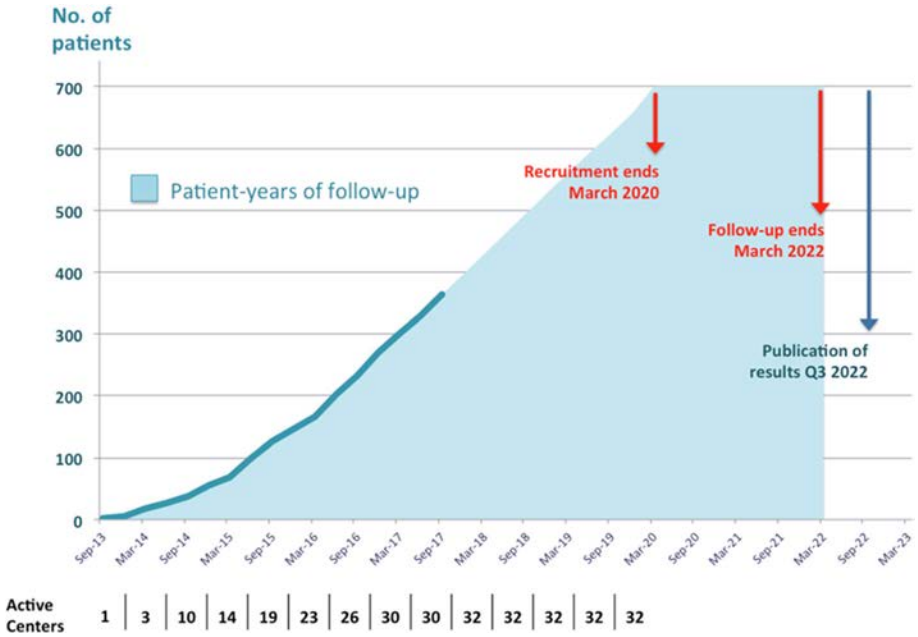

Fig. 2. Study timeline of the REVIVED-BCIS2 trial sowing approximately 400 patients with left ventricular dysfunction randomized since August 2013 with 1:1 allocation between the percutaneous coronary intervention and optimal medical treatment arms.

Here, investigators randomly assigned 706 patients who had multivessel disease, acute myocardial infarction, and CS to one of two initial revascularization strategies: either culprit-lesion-only PCI with the option of staged revascularization of non-culprit lesions or immediate multivessel PCI. The primary endpoint was a composite of death or renal failure leading to renal-replacement therapy within 30 days after randomization. Safety endpoints included bleeding and stroke. At 30 days, the composite primary endpoint occurred in 45.9% of subjects in the culprit-lesion-only PCI group and 55.4% in the multivessel PCI group (relative risk [RR], 0.83; 95% CI, 0.71 to 0.96; $p = 0.01$). The RR of death in the culprit-lesion-only PCI group as compared with the multivessel PCI group was 0.84 (95% CI, 0.72 to 0.98; $p = 0.03$) and for renal replacement therapy was 0.71 (95% CI, 0.49 to 1.03; $p = 0.07$) [17••]. Furthermore, data on 1-year follow-up were recently published by the same investigators, affirming the benefits of culprit-vessel-only PCI in patients presenting with AMI-CS. At 1 year, death had occurred in 50.0% of patients in the culprit-lesion-only PCI group compared to 56.9% in the multivessel PCI group (RR, 0.88; 95% CI, 0.76 to 1.01) (Fig. 3). The rate of recurrent infarction was 1.7% with culprit-lesion-only PCI and 2.1% with multivessel PCI (RR, 0.85; 95% CI, 0.29 to 2.50), and the rate of a composite of death or recurrent infarction was 50.9% and 58.4%, respectively (RR, 0.87; 95% CI, 0.76 to 1.00). Importantly, repeat revascularization occurred more frequently in patients initially randomized to culprit-lesion-only PCI than in patients with multivessel PCI (32.3% vs. 9.4%; RR, 3.44; 95% CI, 2.39 to 4.95), as did rehospitalization for heart failure (5.2% vs. 1.2%; RR, 4.46; 95% CI, 1.53 to 13.04) [18••].

With percutaneously delivered AMCS increasingly available, this paradigm may begin to change in patients with CS. Ventricular unloading and systemic circulatory support may be initiated by experienced operators even before achieving effective restoration of coronary flow. While the door-to-balloon time continues to be important for ST-elevation MI not complicated by CS, optimizing systemic circulation and organ perfusion in patients with CS appears to be as or more important than immediately opening an occluded vessel in order to avoid hemo-metabolic shock [19]. Timely initiation of AMCS, or the "door-to-unload time" (DTU), may be a key determinant of outcomes in patient presenting with CS [20]. Preliminary data from the Detroit Shock Initiative to treat AMI-CS has shown improving survival rates by up to 65%. Here, clinicians utilized a standardized protocol for patients presenting with AMI-CS, including but not limited to mechanical unloading using the Impella CP, a catheter-mounted trans-valvular axial flow pump, prior to primary PCI [21]. Although more appropriately powered and randomized data are required, our current level of knowledge seems to support prompt and proper initiation of AMCS in patients presenting with AMI-CS.

Revascularization in patients with advanced heart failure and patients on durable mechanical circulatory support devices

It is important to differentiate patients who are "crashing, burning, or sliding fast" (INTERMACS 1–2) as discussed above from patients with HF who are

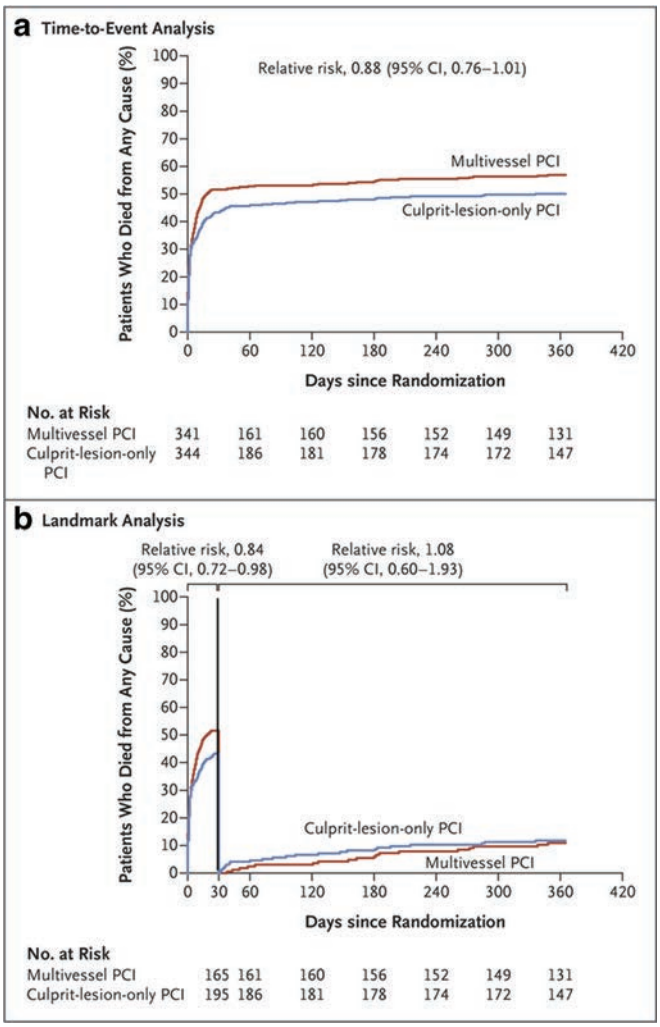

Fig. 3. Time-to-event and landmark analyses for death from any cause through 1 year of the CULPRIT-SHOCK trial. Panel **a** shows Kaplan–Meier estimates of the rate of death from any cause through 1 year. Panel **b** shows the rate of death from any cause through 30 days, as well as the rate between 30 days and 1 year.

relatively stable (INTERMACS 3–7) (Table 1) when planning for revascularization. Moreover, a deep understanding of temporary AMCS platforms is critical since they may be indicated in these cases. Devices that are used to provide hemodynamic support during revascularization include the intra-aortic balloon pump (IABP), trans-valvular axial flow pumps, and veno-arterial extracorporeal membrane oxygenator (VA-ECMO).

Although IABP augments coronary perfusion, overall reduction in myocardial ischemia is limited by the fact that this device provides little or no reduction in native LV work and thus myocardial oxygen demand [22]. IABP works by diastolic augmentation and volume displacement mainly driven by the native heart's pulsatility. In failing hearts, this effect is particularly modest because native pulsation is needed to achieve effective counterpulsation. For this and other reasons in patients with LV dysfunction undergoing IABP-assisted

revascularization, adjunct pharmacologic support with inotropes or vasopressors may be required which in fact can worsen myocardial ischemia. In cases of severe CAD with high "Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery" (SYNTAX) score, LV dysfunction and/or planned for surgical revascularization, timely initiation of IABP support prior to CABG has been associated with better outcomes including perioperative mortality and all-cause 30-day mortality [23].

The Impella is an axial flow catheter placed into the LV in retrograde fashion across the aortic valve. The Impella transfers kinetic energy from a circulating impeller to the blood stream, which results in continuous blood flow from the left ventricle to the ascending aorta. The PROTECT II trial randomized 452 patients referred for non-emergent high-risk PCI to insertion of an Impella 2.5 or IABP before PCI. High-risk PCI was defined as a LVEF ≤ 35% and unprotected left main or last patent coronary conduit or LVEF < 30% with three-vessel coronary disease. Heart failure severity was based on LVEF and functional class (NYHA class III/IV 67% of the Impella group and 64% of the IABP group). The Impella 2.5 demonstrated superior hemodynamic support compared to IABP therapy. No difference in the primary endpoint (composite rate of intra- or post-procedural major adverse events at discharge or 30-day follow-up) was observed between groups (35% vs. 40%, Impella 2.5 vs. IABP, $p = 0.227$). At 90-day follow-up, a trend towards reduced MACE was observed in the Impella arm but not in the IABP arm (40.6% vs. 49.3%, $p = 0.066$) in the intention-to-treat population and (40% vs. 51%, $p = 0.02$) in the per-protocol population [24]. Since the completion of that trial, newer generation axial flow pumps with higher performance power have been developed, namely, the Impella CP and Impella 5.0. Data on assisted revascularization with these platforms are limited to case series, but it has been shown to be a feasible concept in patients with severe LV dysfunction.

Lastly, VA-ECMO withdraws deoxygenated venous blood from the body and delivers it to a centrifugal pump. The pump then delivers this deoxygenated blood through an oxygenator and back into the arterial circulation. VA-ECMO can be initiated using central (surgical) or peripheral (percutaneous or surgical) access [25]. It provides circulatory support by displacing blood volume from the venous to the arterial circulation, which increases aortic systolic, diastolic, and mean arterial pressures. VA-ECMO, however, does not provide effective ventricular unloading. By pressurizing the arterial circulation, LV afterload is increased, and depending on native LV function, VA-ECMO may in fact be associated with increased LV end-diastolic pressures, potentially leading to or worsening pulmonary edema. To date, revascularization while on VA-ECMO has been reported in patients with LV dysfunction suffering from cardiopulmonary collapse or intractable arrhythmias.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Trial demonstrated that durable, surgically implanted left ventricular assist devices (LVADs) improved survival in patients with end-stage HF compared to medical therapy alone. Moreover, in 2009, continuous flow LVADs (CF-LVADs) showed significantly improved 2-year survival compared to pulsatile LVADS. Since then, the use of permanent CF-LVADs has grown exponentially to more than 2500 implants per year. In these patients, revascularization is practically an unknown topic given the paucity of available data. Chest pain on LVAD support is a complex

presentation that is most commonly due to non-cardiac causes. The true incidence of ischemic chest pain during LVAD support remains undefined, but ischemia may nevertheless be a possible cause of pain in these patients. Acute MI can occur in LVAD patients and may be due to coronary plaque rupture, paradoxical thromboembolism, LV or aortic root thromboembolism, and impaired myocardial perfusion due to elevated LV filling pressures secondary to LVAD failure. Left heart catheterization should be performed only after carefully weighing the risks and potential benefits and by operators with experience in durable mechanical support. Potential benefits of coronary intervention for patients with LVAD include symptom relief, prevention of arrhythmogenesis, reduction of ongoing myocardial damage, and support of RV function. Future studies are necessary to evaluate the benefit of revascularization in the setting of LVAD support, especially as the number of patients receiving LVADs as "bridge to decision" and "destination therapy" continue to grow. Whether coronary revascularization in LVAD patients with severely depressed LV systolic function who demonstrate myocardial viability impacts clinical outcomes remains unknown.

Heart-team approach in patients with advanced heart failure undergoing revascularization

Growth in three major cardiac device domains has helped to shape contemporary practice around advanced HF. A landmark study identified that the Heartmate II (Thoratec, Pleasanton, CA) rotary flow LVAD demonstrated superior clinical outcomes compared with pulsatile LVADs for patients with advanced HF, triggering immense growth in the use of LVADs amongst HF specialists and cardiac surgeons. Around the same time, AMCS device and newer generation stents used within the interventional cardiology community were growing mainly for high-risk percutaneous coronary intervention. Finally, there has been improvement in "off-pump" surgical techniques and increasing use of arterial conduits for CABG. Ever-expanding device development and improving surgical and percutaneous techniques have led to the creation of heart teams at tertiary medical centers. This unique collaboration should be applied universally to patients with advanced HF undergoing revascularization procedures. Communication and collaboration amongst a team consisting of HF and cardiac transplantation specialists, interventional cardiologists, cardiac surgeons, intensivists, and others are fundamental to optimizing clinical outcomes in this challenging patient population [26]. The interventionalist offers invasive hemodynamic assessment, coronary revascularization, and possibly AMCS for LV, RV, or biventricular failure. The cardiac surgeon manages post-MI mechanical complications and surgical coronary revascularization if PCI is not an option, to assist with initiation of AMCS or VA-ECMO and to provide input regarding candidacy for LVAD or orthotopic heart transplantation (OHTx). The advanced HF specialist also assists with evaluating a patient's candidacy for LVAD or OHTx in addition to optimizing hemodynamics, managing AMCS or VA-ECMO, and providing input regarding end-of-life decision-making, palliation, and medical futility. The cardiac intensivist further assists with hemodynamic optimization and AMCS device management and provides input on the

management of non-cardiac organ systems, the prevention and treatment of infectious complications, and the importance of nutrition, early mobilization, and prophylaxis against deep venous thrombosis, gastric ulcers, and cutaneous ulcers. Indeed, recent data suggests that incorporation of a cardiac intensivist into the team approach improves short- and long-term mortality in CS. In addition, laying out the end goal, exit plan, and bail-out strategies is a fundamental aspect when planning revascularization in HF patients. Moreover, defining medical futility is a critical part of the management of these patients. A team-based approach in these complex contexts may facilitate the decision-making process.

Conclusion

Given the complexity of the patient population in contemporary clinical practice, the decision regarding revascularization in patients with CAD in the setting of LV dysfunction remains challenging. Clinical decision-making in these cases requires interdisciplinary discussion and assessment of the potential long-term survival derived from CABG against its higher perioperative risk. In accordance with the available data, we believe that surgical revascularization offers improved survival, particularly in those with more extensive multivessel disease and the greatest degree of LV systolic dysfunction and remodeling. These patients, it must be noted, are also at the greatest short-term risk of mortality with CABG. When necessary, PCI is feasible and safe. Data from large randomized clinical trial testing newer generation stents and the use of mechanical circulatory support is needed to further aid these decisions. A heart-team approach including but not limited to a general cardiologist, heart failure specialist, interventional cardiologist, cardiothoracic surgeon, palliative care provider, and critical care specialist is of paramount importance. Indeed, interventional heart failure is an emerging field within cardiology. Trainees become proficient in interventional cardiology, advanced heart failure, and the use of MCS devices. This new breed of cardiologist may narrow the gap between these two important sub-specialties with an increasingly overlapping patient population with the goal of improving outcomes.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Novel drugs for heart rate control in heart failure

Agata Bielecka-Dabrowa[1] · Stephan von Haehling[2] · Jacek Rysz[3] · Maciej Banach[1]

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Abstract
In patients with heart failure, increased sympathetic activity is associated with a positive chronotropic stimulation leading to accelerated resting heart rate. Elevated heart rate (HR) is a risk factor for cardiovascular events, both in the general population and in patients with heart failure. Ivabradine is a pure HR-lowering agent, and it does not affect myocardial contractility, blood pressure, intracardiac conduction, or ventricular repolarization. In clinical trials such as BEAUTIFUL, CARVIVA HF, SHIFT, and INTENSIFY in patients with systolic left ventricular dysfunction, heart rate reduction with ivabradine brought positive outcomes. However, the results of the recent meta-analysis are rather neutral. In a diabetes mouse model of heart failure with preserved ejection fraction (HFpEF), selective heart rate reduction by I_f inhibition improved vascular stiffness, left ventricular (LV) contractility, and diastolic function. However, EDIFY (Effect of ivabradine in patients with heart rate with preserved ejection fraction) trial show that the use of ivabradine in patients with HFpEF is not supported. The further clinical trials investigating the use of ivabradine in heart failure should be carried out.

Keywords Heart failure · Ivabradine · Heart rate

Heart failure burden

Chronic heart failure (HF) is highly prevalent and affects roughly 2–3% of the population in industrialized countries. It is associated with significant morbidity and mortality. HF progresses even in the setting of current evidenced-based therapies with many patients ultimately requiring mechanical support and/or heart transplantation for survival [1, 2]. Patients with HF are categorized on the basis of underlying left ventricular ejection fraction (LVEF) into HF with preserved ejection fraction (HFpEF), reduced LVEF (HFrEF), and mid-range LVEF (HFmrEF) [3].

✉ Agata Bielecka-Dabrowa
agatbiel7@poczta.onet.pl

Maciej Banach
maciejbanach@aol.co.uk

[1] Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland

[2] Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany

[3] Department of Nephrology, Hypertension and Family Medicine, Chair of Nephrology and Hypertension, Medical University of Lodz, Zeromskiego St. 113, 90-549 Lodz, Poland

While LVEF is the most commonly used surrogate marker of left ventricular (LV) systolic function, the implementation of two-dimensional echocardiography in estimating this parameter imposes certain caveats on current HF classification [1–3]. In HFrEF, pharmacotherapy with inhibitors of the renin–angiotensin aldosterone system (RAAS) and sympathetic nervous system improves survival, reduces morbidity, and has been the mainstay of medical management [4, 5]. Beta-blockers have reduced morbidity and mortality beyond what is achieved with RAAS antagonists alone. Additional benefits of these drugs in the management of chronic HF include improved left ventricular remodeling and reduction in sudden deaths. These benefits seem to be linked, at least in part, to their heart rate-lowering properties [4, 5].

Heart rate as a therapeutic target

Resting heart rate (HR) is central to cardiac output and is influenced by changes occurring in numerous diseases. Resting HR is the heart rate with the subject being quiet or inactive. HR can be viewed as an overall reflection of the status of the cardiovascular system, and it is an indicator of autonomic nervous system activity and body metabolic rate. HR can be affected by many factors, for example, physical fitness, psychological status, diet, drugs, co-morbidities, and

the interaction of genetics and the environment [6]. In patients with HF, increased sympathetic activity is associated with a positive chronotropic stimulation leading to accelerated resting HR [7]. Indeed, resting HR is a major determinant of myocardial oxygen demand, coronary blood flow, and overall myocardial performance. It acts along with myocardial wall stress and LV contractility [8, 9].

It is well known that coronary arterial perfusion mainly occurs during isovolumetric relaxation, especially in the left coronary artery: for this reason, a reduction in diastole duration reduces myocardial perfusion time. Coronary blood flow decreases at higher HR values physiologically, but the full amount of flow per minute rises as a result of metabolic vasodilatation of coronary resistance vessels. Indeed, an increase in HR in the presence of stable coronary artery stenosis causes an imbalance between myocardial oxygen requirement and perfusion, enhances coronary shear stress, and can also predispose to arrhythmias [10, 11]. This mechanism, in synergy with β_2-adrenergic-mediated vasodilatation, adjusts the quantity of blood supply depending on the level of myocardial oxygen consumption when tachycardia reduces the diastolic time available for coronary perfusion [10, 11]. Resting HR is known to predict longevity and cardiovascular diseases, and current evidence suggests that it is also an important marker of outcome in cardiovascular disease, including HF [12].

Increased HR has been associated with reduced myocardial function, progressive mechanical dyssynchrony, and reduced inotropy [13–16]. Chronic elevations in HR cause a reversible syndrome of LV dysfunction known as tachycardia-mediated cardiomyopathy, and even pacing at progressively increased but non-tachycardic rates are associated with worsening LV function and depressed exercise capacity [17].

Part of the ability of the HR to predict risk is related to the forces driving it, namely, neurohormonal activation, which is also associated with increased mortality. However, there is substantial evidence that high HR is a mediator and not simply a marker of risk, a phenomenon that has been also observed in illnesses outside of cardiology, for example in cancer [18]. Teodorescu et al. performed a study to evaluate the relationship between HR, LV systolic dysfunction (LVSD), HR-modulating drugs, and sudden cardiac death (SCD) in the community by using a case-control approach [19]. Mean resting HR was significantly higher among 378 SCD cases compared to that among 378 controls from the Oregon Sudden Unexpected Death Study (7.5 beats per minute (bpm difference; $p < 0.0001$). HR was a significant determinant of SCD after adjustment for significant co-morbidities and medications (odds ratio for 10 bpm increase 1.26; 95% confidence interval 1.14–1.38; $p < 0.0001$). After considering LVSD, resting HR was slightly attenuated but remained significantly associated with SCD ($p = 0.005$). Contrary to expectations, the significant relationship between increased resting HR and SCD persisted even after adjustment for LVSD and HR-modulating drugs [19]. In patients with coronary artery disease (CAD) and left ventricular dysfunction, a heart rate of 70 bpm or higher was associated with a 34% increased risk of cardiovascular death and a 53% increase in admission to hospital for heart failure compared with heart rate lower than 70 bpm [20].

The association between HR and survival has also been observed among 1520 patients discharged after an episode of acute HF, in which the highest stratum of HR (> 80 bpm) was associated with a 41% increase in the risk of death versus the first quartile (HR, 1.41; 95% CI, 1.08–1.84) [21]. The association of increased HR with morbidity and mortality outcomes was well documented in many other studies [14, 22–27]. These data suggest that for patients with HF, high residual HR indicates high residual risk and an opportunity for treatment. Therapies that reduce HR in patients in sinus rhythm, such as beta-blockers, improve outcomes in HF, and the extent of HR reduction predicts the magnitude of this benefit. However, these medicines also have effects on contractility, remodeling, autonomic tone, and arrhythmia burden that importantly contribute to their benefit. Besides, patients who were receiving beta-blockers but had the highest HR were at highest risk, indicating that there are patients resistant to beta-blocker therapy and that these patients are at even higher risk [28].

There are data indicating improper HR control in HF patients resulting from both: resistance to therapy and unawareness of and adherence to guidelines for HR control among physicians. Pourdjabbar et al. performed a retrospective chart review of 300 patients being followed in a heart function clinic for a minimum of 1 year to identify the prevalence of suboptimal HR control among real-life patients and to identify the potential role for further HR reducing therapy. In this analysis, over one third (36.5%) of analyzed patients had suboptimal HR control, of which 75% had sinus rhythm, in spite of a very high usage of beta-blocker use (~ 95% on a beta-blocker and over 25% at target doses) and other available guideline recommended agents [29]. The survey of HR in patients with HF in Sweden (HR-HF survey) was an investigator-initiated, prospective, multicenter, observational longitudinal study designed to investigate the state of the art in the control of HR in HF and to explore potential underlying mechanisms for suboptimal HR control with focus on awareness of and adherence to guidelines for HR control among physicians who focus on the contributing role of beta-blockers. The 734 patients with HF enrolled into the registry had a mean HR of 68 ± 12 bpm (37.2% of the patients had a HR > 70 bpm). The authors concluded that suboptimal control of HR was noted in HFrEF with sinus rhythm, which appeared to be attributable to physician decision-making rather than to the use of beta-blockers. Their results underline the need for greater attention to HR control in patients with HFrEF and sinus rhythm and thus a potential for improved HF care [30]. However, the proportion of patients in

contemporary clinical practice (featuring multiple background drugs) who can be titrated to target beta-blocker doses seems to be in the range of 20 to 40% [31].

Hyperpolarization-activated cyclic nucleotide-gated channel inhibitors

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play important roles both in the control of HR and neuronal excitability. HCN channels open on hyperpolarization voltage, permeate to potassium and sodium, and generate an inward current, which is modulated by intracellular cyclic adenosine monophosphate (cAMP). In different cardiac pathologies, dysfunctional HCN channels have been suggested to be a direct cause of rhythm disorders. HCN channel gain-of-function in atrial fibrillation, ventricular hypertrophy, and failure might help enhance ectopic electrical activity and promote arrhythmogenesis [32].

Novel compounds with enhanced selectivity for cardiac HCN channel isoforms are being studied as potential candidates for new drug development. Ivabradine is the first HCN channel inhibitor being clinically approved in 2005 for the treatment of chronic stable angina pectoris and HF. Ivabradine is a selective HR-reducing drug that works only in sinus rhythm. It acts by inhibiting the so-called funny current (I_f) in sinus node cells through the blockade of the I_f channel (Fig. 1).

The current across the I_f channel is a mixed sodium–potassium current, and the I_f channel is activated by hyperpolarization and regulated by direct binding of cAMP [33]. The cAMP directly modulates the HCN channel by increasing the likelihood of channel opening during diastole; in this way, the diastolic depolarization slope becomes steeper and faster, leading to an increase in HR [34, 35]. I_f inhibition by ivabradine not only induces a selective reduction of resting HR but also attenuates tachycardia due to sympathetic stimulation [35]. Ivabradine is a pure resting HR-lowering agent, and it does not affect myocardial contractility, blood pressure, intracardiac conduction, or ventricular repolarization [36–38]. Notably, ivabradine is more active as the HR increases (when channels are more often open). When the HR is lower, ivabradine has minimal effects, because it is not able to effectively penetrate the hyperpolarization-activated cyclic nucleotide-gated channel responsible for I_f [37, 38]. Ivabradine has no effects on blood pressure, coronary and peripheral vascular resistance, and myocardial activity because I_f expression is highly specific to the sinoatrial node. Compared to beta-blockers and calcium channel antagonists, ivabradine does not have any negative inotropic effect on myocardial tissue [39]. Other substances with a similar mechanism of action are being investigated. YM758 investigated and owned by Astellas Pharma is a novel I_f channel inhibitor that has an inhibitory action for I_f current and shows a strong and specific activity, selectively lowering HR and decreasing oxygen consumption by cardiac muscle. As such, it is useful as a preventive and/or treating agent for diseases of the circulatory system, such as ischemic heart diseases, HF, and arrhythmia. In clinical trials, it has been reported that the I_f channel inhibitors zatebradine and ivabradine reduce HR without concomitant negative inotropic or hypotensive effects [40–43].

Ivabradine in clinical trials in patients with left ventricular systolic dysfunction

In recent years, a large number of trials have been performed to evaluate the benefits of ivabradine as a selective HR-reducing

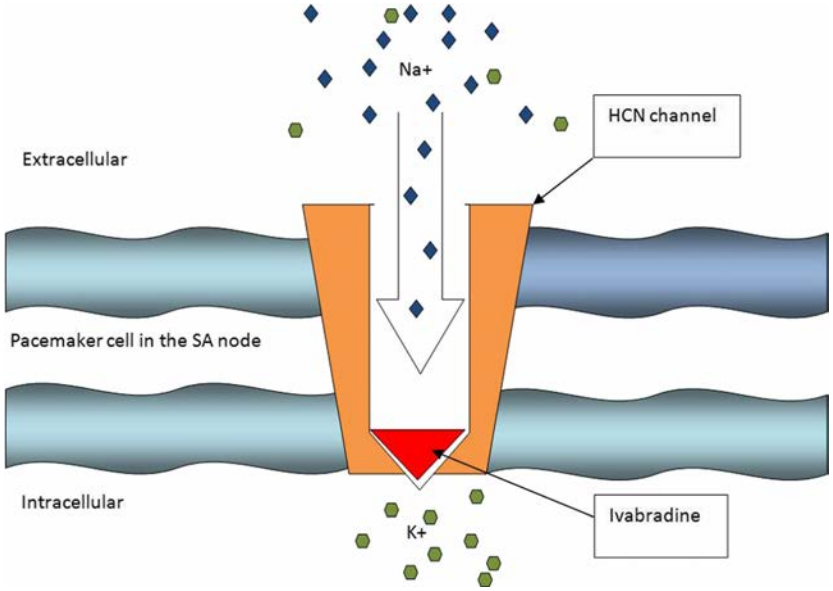

Fig. 1 The mechanism of action of ivabradine. Ivabradine within SA node selectively blocks the HCN channel, inhibits the If current, slows diastolic depolarization, and lowers heart rate. HCN channel hyperpolarization-activated cyclic nucleotide-gated; If current inward flow of positively charged ions that initiates the spontaneous diastolic depolarization phase, modulating heart rate; SA node sinoatrial node

drug [44–49]. In the BEAUTIFUL trial, more than 10,000 patients with CAD and LV systolic dysfunction were randomly assigned to receive ivabradine or placebo in addition to first choice cardiovascular medication, including beta-blockers. Ivabradine reduced the incidence of admission to hospital for myocardial infarction and coronary revascularization in a subgroup of patients with HR of 70 bpm or greater [20]. In the CARVIVA HF trial, the effect of HR reduction with carvedilol, ivabradine, and their combination on exercise capacity was assessed in HF patients [50]. The distance walked on the 6-min walking test and the exercise time on mixed venous oxygen saturation test significantly improved in the ivabradine and the combination (ivabradine plus carvedilol) groups (both $p < 0.01$ vs baseline), as did peak oxygen uptake and ventilatory anaerobic threshold ($p < 0.01$ for ivabradine and $p < 0.03$ for combination vs carvedilol, respectively). Patients receiving ivabradine or the combination had better quality of life ($p < 0.01$ vs baseline for ivabradine and $p < 0.02$ for combination) versus no change with carvedilol [50].

The pivotal clinical trial for ivabradine was the Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial (SHIFT) study, which included 6558 patients. Patients were eligible for participation in this randomized, double-blind, placebo-controlled, parallel-group study if they had symptomatic HF and a left ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 bpm or higher, had been admitted to hospital for HF within the previous year, and were on stable background treatment including a beta-blocker if tolerated [51]. Subjects were randomized to ivabradine (titrated to a maximum of 7.5 mg twice daily) or placebo and followed for a median of 22.9 months. For the primary endpoint of cardiovascular death or hospital admission for worsening HF, the relative risk reduction was 18% (hazard ratio, 0.82; 95% CI, 0.75–0.90). The effects were driven mainly by hospital admissions for worsening HF (672 [21%] placebo vs 514 [16%] ivabradine; hazard ratio 0.74, 0.66–0.83; $p < 0.0001$) and deaths due to HF (151 [5%] vs 113 [3%]; hazard ratio 0.74, 0.58–0.94, $p = 0.014$) [51]. Some of this effect might be explained by reduced myocyte ischemia and increased available energy for myocyte maintenance and repair. In the SHIFT study, LV end-systolic volume index was reduced by 5.5 mL/m^2, representing an approximate 10% reverse remodeling in addition to angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARB), or beta-blocker therapy [52]. Reduction of HR has also been associated with reduced LV end-diastolic pressure, improved LV relaxation, endothelial cell proliferation, prevention of HF-related LV capillary rarefaction, and increased endothelial nitric oxide synthase expression (leading to improved nitric oxide-dependent coronary vasodilatation) [53]. In the prospective, open-label multicenter INTENSIFY study, the effectiveness and tolerability of ivabradine as well as its impact on quality of life (QOL) in systolic HF patients were evaluated over a 4-month period. A total of 1956 patients with chronic HF were included. After 4 months of treatment with ivabradine, HR was reduced to 67 ± 9 bpm. Furthermore, the proportion of patients presenting with signs of decompensation decreased to 5.4%, and the proportion of patients with brain natriuretic peptide levels > 400 pg/mL dropped to 26.7%, accompanied by a shift in New York Heart Association (NYHA) classification towards lower grading (24.0 and 60.5% in NYHA I and II, respectively). These benefits were accompanied by improved QOL and good general tolerability [52]. The main clinical trials investigating ivabradine in patients with HFrEF are presented in Table 1.

The potential mechanisms of ivabradine benefits

The benefits of HR reduction with ivabradine were directly related to the magnitude of HR reduction achieved by the drug and to the absolute value to which HR was maximally reduced [53]. A subsequent echocardiographic study from SHIFT trial provided further insight regarding the mechanism of benefit, showing that ivabradine use was associated with reverse LV remodeling [52]. Subjects with the largest reduction in LV volumes derived the greatest benefit in terms of clinical endpoints [52].

Reil et al. [54] present data from another SHIFT echocardiographic substudy that HR reduction with ivabradine may also directly benefit the vasculature. In this study, the arterial elastance (Ea), total arterial compliance (TAC), and end-systolic elastance (Ees) were calculated at baseline and after 8 months of treatment. After follow-up, HR was significantly reduced in the ivabradine group ($p < 0.0001$) and was accompanied by marked reduction in Ea ($p < 0.0001$) and improved TAC (measured as the ratio of stroke volume to pulse pressure) ($p < 0.004$) compared with placebo. Although contractility remained unchanged, ventricular–arterial coupling was markedly improved ($p < 0.002$), resulting in a higher stroke volume (SV) ($p < 0.0001$) in the ivabradine-treated patients. Because Ees was unaltered, improved ventricular–arterial coupling is responsible for increased SV [54]. This indicates that long-term treatment with ivabradine may improve pulsatile components of LV afterload and potentially offer additive or even synergistic effects with conventional vasodilators that primarily target arteriolar resistance and/or venous tone [54].

The presence of concomitant erectile dysfunction (ED) with HF is connected with endothelial dysfunction [55]. It was demonstrated that ivabradine treatment can improve endothelial function and ED in experimental models. Mert et al. assessed the effect of ivabradine treatment on ED in patients with HF via International Index of Erectile Function (II EF-5) questionnaire. In 24 patients, between 18 and 70 years of age, male with chronic HF known for at least 1 year, New York Heart Association functional class I–II, LVEF less than 40%, in sinus rhythm with a resting HR of at least 70 bpm, IEFF-5

Table 1 Clinical trials investigating ivabradine in patients with left ventricular systolic dysfunction

Study	Design	Efficacy outcomes
BEAUTIFUL [20]	Randomized, double-blind, placebo-controlled, parallel-group trial; ivabradine ($n = 5479$) and placebo ($n = 5438$); median follow-up—19 months	Ivabradine did not affect the primary endpoint (composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening heart failure), but it did reduce secondary endpoints: admission to hospital for fatal and non-fatal myocardial infarction (0.64, 95% CI 0.49–0.84, $p = 0.001$) and coronary revascularization (0.70, 95% CI 0.52–0.93, $p = 0.016$)
CARVIVA HF [50]	Randomized open-blinded endpoint study; carvedilol ($n = 38$) versus ivabradine ($n = 47$) versus carvedilol plus ivabradine ($n = 42$), follow-up—3 months	Improvement in 6-min walking test, the exercise time on mixed venous oxygen saturation test ($p < 0.01$), peak oxygen uptake, and ventilatory anaerobic threshold ($p < 0.03$) in the ivabradine and combination (ivabradine plus carvedilol) groups; better quality of life ($p < 0.01$ vs baseline for ivabradine and $p < 0.02$ for combination) versus no change with carvedilol
SHIFT [51]	Double-blind placebo-controlled study, $n = 6558$; placebo group ($n = 3264$) and ivabradine group ($n = 3241$); median follow-up—22.9 months	24% patients in the ivabradine group and 29% in placebo group had a primary endpoint event (the composite of cardiovascular death or hospital admission for worsening heart failure) (hazard ratio 0.82, 95% CI 0.75–0.90, $p < 0.0001$) The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; hazard ratio 0.74, 0.66–0.83; $p < 0.0001$) and deaths due to heart failure (151 [5%] vs 113 [3%]; hazard ratio 0.74, 0.58–0.94, $p = 0.014$)
INTENSIFY [52]	Prospective, open-label multicenter study, follow-up—4 month, ($n = 1956$)	Heart rate reduction to 67 ± 8.9 bpm; signs of decompensation decreased to 5.4%; patients with BNP levels > 400 pg/mL dropped to 26.7%, a shift in NYHA classification towards lower grading (24.0 and 60.5% in NYHA I and II, respectively); improvement of EQ5D to 0.79 ± 0.21

CI confidence interval, *BNP* brain natriuretic peptide, *NYHA* New York Heart Association, *EQ5D* EuroQol-5 Dimension

questionnaire scores increased significantly ($p = 0.003$) after the ivabradine treatment; on the contrary, significant decrease in HR was revealed as expected. These initial results seem promising that ivabradine has favorable effects on ED. These findings were postulated to be dependent exclusively on HR reduction [55].

Ivabradine in heart failure with preserved ejection fraction

HF with preserved ejection fraction (HFpEF) accounts for up to 50% of all incident cases of HF, and its prevalence is rising as a result of the aging population [56]. An elevated HR is a predictive factor of worse outcomes and increased mortality in patients with HF, including HFpEF [56]. In HFpEF animal models, ivabradine was shown to reduce cardiac fibrosis and improve vascular stiffness and LV systolic and diastolic function [56, 57]. Patients with LV diastolic dysfunction are characterized by exertional dyspnea. HR reduction by beta-blockers can improve exercise tolerance by prolonging LV filling, but their negative inotropic and lusitropic properties can be detrimental in this disease. In the pilot study of Fischer-Rasokat et al., 24 patients with CAD and normal LVEF on chronic beta-blocker therapy were included. Beta-blockers were replaced by ivabradine and patients were re-tested after 6 weeks [58]. E/e' significantly decreased during ivabradine therapy in patients with high E/e' (10.7 ± 2.9 vs 8.9 ± 1.7; $p < 0.01$), whereas no difference occurred in patients with low E/e' (6.4 ± 0.7 vs 6.5 ± 1.1; $p =$ ns). With ivabradine, patients with high E/e' had an increased oxygen uptake at the anaerobic threshold (from 10.8 ± 1.4 to 11.8 ± 1.9 mL/min/kg; $p < 0.05$) and a steeper slope of the initial oxygen pulse curve (from 293 ± 109 to 359 ± 117 μL/beat/kg/W; $p < 0.05$). Moreover, patients with high E/e' had lower N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels at rest (169 ± 207 vs 126 ± 146 pg/mL; $p < 0.05$) and after exercise (190 ± 256 vs 136 ± 162 pg/mL, $p < 0.05$) during ivabradine therapy [58]. The results of this study suggest that ivabradine may be a suitable alternative in patients with CAD and a greater than normal LV filling index who do not tolerate beta-blockade. Moreover, switching therapy from beta-blockers

to ivabradine may have beneficial effects in these patients, as lower levels of E/e' and NT-proBNP suggest reduced LV filling pressures and parameters of submaximal exercise capacity were improved compared with those of beta-blockade [58].

In another randomized study in 61 patients with HFpEF, short-term treatment with ivabradine increased exercise capacity, with a contribution from improved LV filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity [59].

However, the results of the studies were ambiguous. In the study of Pal et al., ivabradine compared with placebo significantly worsened the change in peak $V0_2$ in the HFpEF cohort (− 2.1 vs 0.9 mL kg^{-1} min^{-1}; $p = 0.003$) and significantly reduced submaximal exercise capacity, as determined by the oxygen uptake efficiency slope [60]. The proof-of-concept EDIFY study (prEserveD left ventricular ejection fraction chronic HF with ivabradine studY) examined whether HR reduction with ivabradine improves diastolic function and exercise capacity and reduces NT-proBNP concentration in patients with HFpEF [61]. After 8 months of treatment, no evidence of improvement was found in any of the three co-primary endpoints. HR reduction with ivabradine did not show a beneficial effect on cardiac filling pressures (E/e′), exercise capacity (6 min walk test—6MWT), and plasma NT-proBNP concentrations. The study showed that a decrease in HR (of about 13 bpm in the ivabradine group) was associated with longer LV filling time with significant increases in peak early filling velocity. However, these changes were not associated with improvements in LV relaxation (no significant increase in mean e′). Therefore, E/e′ was not reduced, reflecting no improvement in LV filling [61].

There was no change in LV mass or in arterial–ventricular coupling assessed by the Ea/Ees ratio. The authors explained the failure to demonstrate any benefit of ivabradine in HFpEF patients by the fact that the population enrolled had rather advanced HFpEF with extensive myocardial fibrosis that allowed only a poor response to pharmacological intervention (subjects were too sick to benefit) [61]. In cases of extensive fibrosis with predominant restriction and no or minimal stroke volume reserve, cardiac output is entirely dependent on HR. Also, the hypothesis that lowering HR would facilitate an increase in filling time in stiff ventricles and as a result induce a reverse remodeling was not verified. EDIFY does not support the concept that HR reduction is beneficial in HFpEF. This differs from findings in HFrEF, in which the SHIFT study demonstrated significant improvements in cardiovascular outcomes and an anti-remodeling effect as a result of ivabradine treatment, including when HFrEF was associated with severe diastolic dysfunction [51, 52, 62]. One of several potential explanations of this difference might be connected to different patterns of myocardial remodeling arising from their different pathophysiological mechanisms in HFpEF and HFrEF [54, 63].

Meta-analysis with ivabradine in patients with heart failure

Recently, Kang et al. performed a meta-analysis of eight randomized controlled clinical studies (with 40,357 participants); three of which used ivabradine versus placebo (36,069 participants), and five other studies ivabradine versus beta-blockers (4288 participants). The authors aimed to investigate whether ivabradine reduces resting HR, cardiovascular disease (CVD) mortality, and all-cause mortality than placebo or beta-blockers in randomized controlled trials [64]. The change of resting HR from baseline to endpoint was 8 to 16 bpm in the ivabradine groups, 1 to 8 bpm in the placebo groups, and 4 to 24 bpm in the beta-blockers groups. In ivabradine versus placebo, the reduced risks of CVD mortality and all-cause morbidity were not significant (risk ratio [RR] 1.02; 95% confidence interval [CI] 0.91–1.14, $p = 0.737$; RR 1.00, 95% CI 0.92–1.09, $p = 0.992$, respectively). CVD and all-cause morbidity were similar for ivabradine versus beta-blockers (RR 1.04; 95% CI 0.80–1.37, $p = 0.752$; RR 1.17, 95% CI 0.53–2.60, $p = 0.697$, respectively) [64]. In this meta-analysis, ivabradine had a neutral effect suggesting that a pure resting HR-lowering agent does not reduce CVD and all-cause mortality. These meta-analysis data were based on published studies and reports in different CVD populations, and the authors could not provide detailed analysis to show that ivabradine would provide a possible trend of improved survival in the HF population with the cutoff of HR > 70/min. The authors noticed that ivabradine improved HF mortality with placebo (3 vs 5%), but it did not further decrease CVD mortality and all-cause mortality compared to placebo in the same HF population [64]. Considering that ivabradine in this meta-analysis reduced only 2% HF death rate as compared to placebo, it is necessary in several large sample trials to prove the 2% value and significant in real world. The primary endpoint of the SHIFT trial was the composite of cardiovascular death or hospital admission for worsening HF, and the effect was driven mainly by hospital admissions for worsening HF. In that situation, when patients are admitted to the hospital, follow-up is ended, so we can only know the effects of ivabradine on cardiovascular mortality when the patients die before the first hospitalization for worsening HF. It remains unknown how the increase in the risk of atrial fibrillation occurrence in patients treated with ivabradine influences the course of HF [65–67].

Ivabradine in critically ill patients

Critical care patients are prone to develop stress-induced cardiac impairment and consequently an increase in sympathetic tone. This, in turn, increases HR. In this setting, however, HR lowering might be difficult because the effects of inotropic drugs could be hindered by HR-reducing drugs like beta-

blockers. Beta-blockers possess strong negative inotropic effect, and they can unfavorably modify the hemodynamic profile of inotropic agents [37, 68–70]; thus, they seem not to be suitable as rate-controlling agents in multiple organ dysfunction (MODS) patients. Ivabradine lowers HR, reduces diastolic depolarization slope, and is not active on sympathetic pathways, thus avoiding any interference with inotropic amines. Ivabradine could counteract the adverse effects of elevated HR in MODS lowering myocardial oxygen consumption, increasing diastolic coronary perfusion, and acting on the negative force–frequency relationship of the failing heart.

Hoke and colleagues [71] in a prospective observational study in 89 patients with MODS found that HR at the time of MODS diagnosis is an independent risk factor for mortality. Twenty-eight-day mortality was 32 and 61% in patients with HR < 90 bpm and HR > 90 bpm, respectively. However, in the study by Nuding et al., the number of critically ill patients with MODS and a sinus rhythm of at least 90 bpm that experienced a HR reduction of at least 10 bpm did not differ significantly between the ivabradine and the control groups [72]. The moderate but significant reduction in HR by 7 bpm did not affect hemodynamics or disease severity [72]. The results of the MODI(f)Y trial are needed to assess the utility of ivabradine in MODS.

Summary

Among patients with systolic HF, the dose to which a beta-blocker can be titrated is dependent on patient co-morbidities and other demographics. Based on actual data, if an increase of the dose of the beta-blocker in patients with HFrEF can be achieved and results in lowering the heart rate below 70 bpm, therapy with beta-blocker alone is appropriate. If this goal is not achievable clinically, the addition of ivabradine will result in a reduction in the risk of future cardiovascular events. At present, there is insufficient evidence to justify the use of ivabradine in HFpEF. Based on the results of EDIFY study, perhaps, it should be assessed the potential utility of ivabradine in HFpEF patients with a mitral valve flow velocity pattern of impaired LV relaxation, pseudo-normalization not in restriction [73]. There are also groups of patients in which ivabradine is a drug of choice like people with psoriasis where beta-blockers are contraindicated. In our opinion, ivabradine could be also the best option as rate-controlling agent in patients who need inotropic amine therapy. We have positive experience with ivabradine in management of patients with cardiogenic shock. We also see a perspective for ivabradine use in conditions where it is important to reduce heart rate without blood pressure lowering like for example inappropriate sinus tachycardia or postural orthostatic tachycardia syndrome. Further clinical trial investigating the use of ivabradine in HF should be carried out with optimal treatment of the patient population in order to identify the subgroup of patients who respond to ivabradine. Besides, it is necessary to explore head to head comparisons of ivabradine and beta-blockers in large-scale trials with longer follow-up periods.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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SHORT COMMUNICATION

Ivabradine in Postural Orthostatic Tachycardia Syndrome: Preliminary Experience in Children

Grazia Delle Donne[1] · Ferran Rosés Noguer[1,3] · Jan Till[1] · Tushar Salukhe[1] · Sanjay K. Prasad[1,2] · Piers E. F. Daubeney[1,2]

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Abstract
Objective Ivabradine is a selective and specific inhibitor of the I(f) current in the sinoatrial and atrioventricular nodes. It decreases heart rate and myocardial oxygen consumption at rest and during exercise. It is used in adults for management of heart failure and angina, but promising results have been obtained in postural orthostatic tachycardia syndrome (POTS). There is little experience of ivabradine in childhood, although it is used on a compassionate basis. Our aim was to review our experience of ivabradine in a retrospective evaluation of pediatric patients with POTS.
Methods We evaluated all patients younger than 18 years for whom ivabradine had been prescribed for this indication, from February 2008 to June 2014.
Results Twenty-two patients were identified (15 female). Median age was 14.5 years (11–17 years). The ivabradine dosage after up-titration was 0.1 mg/kg per dose twice daily. In 15 (68%) symptoms improved. Ivabradine was suspended in five, but only in one for worsening of symptoms. There was a reduction in heart rate on resting electrocardiogram (EKG) from a mean (standard deviation) of 82.5 (13.6) bpm to a mean of 71 (16.5) bpm ($p = 0.007$). No patient had increased duration of QTc ($p = 0.44$). One (4.5%) experienced phosphenes.
Conclusions From this initial experience, ivabradine is safe in patients younger than 18 years with POTS. We observed improvement of symptoms in 68% and phosphenes in less than 5%. Further studies are needed to assess the safety in a randomized control setting.

Key Points

Ivabradine is safe in the pediatric population.

Ivabradine improves symptoms in patients with postural orthostatic tachycardia syndrome.

1 Introduction

Ivabradine is a selective and specific inhibitor of the I(f) current in the sinoatrial node and atrioventricular node. The I(f) current controls the spontaneous electrical pacemaker activity in the sinoatrial node. Ivabradine decreases the heart rate and thereby the myocardial oxygen consumption at rest and during exercise. It is used in the adult population for management of heart failure and angina [1, 2]. Ivabradine has also been used in patients with postural orthostatic tachycardia syndrome (POTS), showing good results in improving symptoms [3, 4].

Whereas ivabradine is used in the adult population, little is known about it in the pediatric population. Recently, Bonnet et al. [5] published a multicenter study establishing the efficacy of ivabradine in reducing heart rate in children with dilated cardiomyopathy. The aim of this descriptive retrospective study was to review the efficacy and safety of ivabradine in children with POTS. This was an observational study and no attempt was made to influence the

✉ Piers E. F. Daubeney
p.daubeney@rbht.nhs.uk

[1] Royal Brompton Hospital, Sydney St, London SW3 6NP, UK

[2] Imperial College, London, UK

[3] Vall d'Hebron University Hospital, Barcelona, Spain

management of the patients or the clinicians' decision-making. The patients had all been prescribed the drug on a compassionate basis by their clinician and after potential benefits and side effects had been discussed with them and their parents.

2 Methods

We evaluated patients younger than 18 years in our institution for whom ivabradine had been prescribed, from February 2008 to June 2014. We used our institutional pharmacy database. We ascertained the indication for starting the medication and in particular those where POTS was specified. POTS was defined as a sustained heart rate increase of 30 bpm or increase of heart rate to 120 bpm within the first 10 min of orthostasis associated with symptoms of orthostatic intolerance and without significant orthostatic hypotension [6]. Gender, weight, age at commencement, dose at commencement and after up-titration, reason for discontinuation, follow-up, days of treatment, medication prior to starting ivabradine, and medications with ivabradine, outcome (improvement, worsening of symptoms), heart rate and QTc at baseline and at follow-up were evaluated. Heart rate and electrocardiogram (EKG) were recorded before starting ivabradine and at follow-up.

2.1 Statistical Analysis

Normally distributed data were described with the mean and standard deviation (SD), whereas non-parametric data were described with median and range. Student's independent *t* test was used as appropriate. A statistically significant level was set at $p < 0.05$.

3 Results

From the pharmacy database, ivabradine was prescribed to 28 children < 18 years; POTS was the indication to start ivabradine in 22. Their demographics are shown in Table 1.

All patients included in this study had adopted non-pharmacological therapies (e.g., increase in salt and fluid intake, counter pressure maneuvers, avoidance of precipitating factors). One (4.5%) had hypermobility syndrome and three (13.6%) confirmed Ehlers–Danlos syndrome. A tilt test was performed in all of these 22 patients.

All 22 had an echocardiogram to exclude cardiac structural abnormalities. Twenty-four hour Holter monitoring was performed in 17 of the 22 patients (77%) showing no arrhythmia. Fourteen of the 22 patients (63.6%) were on at least one other medication for POTS prior to the introduction of ivabradine (Table 2). In four of 22 (18%), ivabradine was added to one other drug: fludrocortisone in two patients and midodrine in two patients.

Ivabradine was prescribed at the initial dosage of 5 mg/day in two divided doses. It was titrated up to 15 mg/day according to the control of symptoms.

Ivabradine was up-titrated in 11 patients (50%). Mean (SD) dose of ivabradine after up-titration was 9.5 (4.1) mg, corresponding to 0.1 mg/kg/dose twice a day. EKGs after commencing ivabradine were available for retrospective analysis in 19 patients.

3.1 Follow-Up and Outcome

Median follow-up was 4.6 (0.9–17) months. Six patients were followed up for less than 3 months. In four of them, ivabradine was discontinued: two for complete resolution of symptoms, one for worsening of the symptoms of syncope and palpitation (after 55 days). In one patient,

Table 1 Demographics and the clinician's stated indications for starting ivabradine

POTS	22 patients
Gender	Female 15, male 7
Age at commencement, median (range) and mean (SD)	14.5 (11–17) years, 14.8 (1.6) years
Dose after up-titration mean (SD), absolute and per kg	9.5 (4.1) mg, 0.1 mg/kg
Follow-up median (range)	4.6 (0.9–17) months
Duration of treatment median (range)	3.7 (0.9–17) months
EKG available for retrospective analysis (number of patients)	19
Holter 24-h monitoring (number of patients)	17
Echocardiogram (number of patients)	22
Tilt test (number of patients)	22
Baseline heart rate, mean (SD)	82.5 (13.6) bpm
Baseline QTc, mean (SD)	397.6 (20.2) ms

EKG electrocardiogram, *POTS* postural orthostatic tachycardia syndrome, *SD* standard deviation

Table 2 Medications taken prior to starting ivabradine. Some were discontinued when it was started

Number of medications prior to ivabradine	Medication	Number of patients
1	Fludrocortisone	7
	Beta-blocker	2
	Midodrine	4
	Sodium supplement	0
2	Fludrocortisone	1
	Beta-blocker	0
	Midodrine	0
	Sodium supplement	1

Table 3 Follow-up (total patients, $n = 22$)

	Number of patients	Ivabradine discontinued
Follow-up < 3 month	6	4
Follow-up > 3 months	16	1

Table 4 Evaluation of symptoms after starting ivabradine

	Improvement	Unchanged	Deterioration
22 patients	15 (68%)	6 (27%)	1 (4.5%)

ivabradine was discontinued for no change in symptoms (after 30 days).

Sixteen patients were followed up for more than 3 months: in one ivabradine was discontinued for no improvement in symptoms (after 14.5 months) (Table 3).

In 15 patients (68%), the symptoms improved according to the treating clinician: reduced syncopal episodes and resolution of symptoms (Table 4).

3.2 Side Effects

One patient (4.5%) experienced mild phosphenes (flashing lights). The ivabradine dosage was slightly reduced, from 10 to 7.5 mg/day, with improvement of the symptoms. No patient experienced symptomatic bradycardia.

3.3 Electrocardiograms

EKGs were retrospectively available for analysis in 19 of the 22 patients (86%) after starting ivabradine. Changes to heart rate and QTc are shown in Table 5.

Table 5 Changes to heart rate and QTc on starting ivabradine

	Baseline, mean (SD)	Follow-up, mean (SD)	*p*
Heart rate (bpm)	82.5 (13.6)	71.3 (16.5)	< 0.05
QTc (ms)	397.6 (20.2)	398.7 (29.1)	0.44

SD standard deviation

None of the patients had an abnormal QTc interval when on ivabradine. There was a reduction in heart rate on resting EKG, from a mean (SD) of 82.5 (13.6) bpm to a mean of 71.3 (16.5) bpm ($p = 0.007$). None of the patients developed symptomatic bradycardia.

4 Discussion

This is the first observational study to describe the use of ivabradine in patients under 18 years of age with POTS. The study was retrospective and purely descriptive, with no attempt made to influence the patients' management. The data should therefore be regarded as preliminary, but as it is the first documentation of a group of pediatric patients with POTS receiving ivabradine, it is important to report initial outcome and side effects. In this group, just over two-thirds reported improvement of symptoms. The dosage was 0.1 mg/kg twice a day. Side effects were rare, with less than 5% developing temporary and mild phosphenes that did not warrant suspension of the drug; the symptom resolved on reducing the dose. There were no concerning side effects.

Ivabradine is a promising and relatively new drug. It is a selective inhibitor of the I(f) current that contributes to sinus node automaticity. The mechanism of action has been studied in detail in isolated rabbit sinoatrial node cells [7]. Ivabradine was approved by the European Medicines Agency in 2005, and it is the first clinically approved drug that targets the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. The therapeutic indications in the adult population are the symptomatic treatment of chronic stable angina in patients intolerant to, or inadequately controlled by, beta-blockers and whose heart rate exceeds 60 bpm in sinus rhythm and heart failure [1, 8–13]. The European Society of Cardiology guidelines on heart failure suggest considering ivabradine to reduce the risk of hospitalization due to heart failure in patients in sinus rhythm with an ejection fraction of $\leq 35\%$, heart rate remaining at ≥ 70 bpm, and persisting symptoms [New York Heart Association (NYHA) class II–IV] despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), angiotensin

converting enzyme inhibitor or angiotensin receptor blocker, and a mineralocorticoid receptor agonist [2, 14, 15].

Off-label indications are POTS, inappropriate sinus tachycardia and heart rate reduction before computed tomography (CT) coronary angiography [16].

There is emerging evidence of the use of ivabradine in POTS. All the studies published are retrospective or case reports. Sutton et al. [4] reported marked benefit or complete resolution of symptoms in 72% of patients, and ivabradine was well tolerated. McDonald et al. [3] concluded that 60% of patients reported a symptomatic improvement; the drug was well tolerated. The most common reason for discontinuing ivabradine was lack of efficacy. Five of 22 patients reported side effects, leading to discontinuation in two patients. Khan et al. [17] reported a case of a 44-year-old woman with POTS and dual chamber pacemaker implanted because of intermittent complete heart block. Ivabradine was successfully used to lower heart rate. There was no evidence of POTS on repeat investigation; the pacemaker check showed a maximum heart rate of 120 bpm, and the 24-h tape showed appropriate heart rate response. There was symptomatic benefit [17].

Until recently, very little was known about ivabradine in the pediatric population. Case reports have reported ivabradine being used to treat junctional ectopic tachycardia [18] and cardiomyopathy induced by inappropriate sinus tachycardia [19]. Recently, Bonnet et al. [5] published a randomized, double-blind, placebo-controlled study. They evaluated 116 children with dilated cardiomyopathy. During a 1-year follow-up, there was a reduction in heart rate and an increase in left ventricular ejection fraction and clinical status [5].

In our retrospective observational series, we report that ivabradine is well-tolerated and safe in patients younger than 18 years with POTS. One developed mild and dose-dependent phosphenes. This visual disturbance (flashing lights) is due to ivabradine interaction with the HCN1 isoform expressed in the retinal photoreceptor. The transient change in visual sensation was observed in about 15% of adult patients following initial treatment with ivabradine [20]. It has been shown that it typically resolves during treatment [21].

As with the previous studies published in the adult population in POTS, we observed 68% improvement of the symptoms.

4.1 Limitations

This is a preliminary and observational retrospective study of a small number of children prescribed ivabradine on a compassionate basis for POTS. It was purely descriptive and not randomized or blinded. Widespread implications must therefore be guarded until such time as a randomized controlled trial is published for this indication. With these caveats, at the dose used, it does appear to be safe and have some efficacy in children with POTS. As this was an observational study, there was no attempt to influence patient management. The tilt test and Holter 24-h recordings were not repeated on ivabradine to confirm reduction in heart rate.

5 Conclusions

From our limited preliminary experience, ivabradine appears to be a safe treatment for patients under 18 years of age with POTS. There is an improvement of symptoms in over two-thirds of our patients, a low incidence of phosphenes, and no other obvious side effects. Further studies are needed to assess the efficacy and the safety of this drug in a randomized controlled setting for this indication.

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Compliance with Ethical Standards

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Conflict of interest Grazia Delle Donne, Ferran Rosés Noguer, Jan Till, Tushar Salukhe, Sanjay K. Prasad and Piers E. F. Daubeney declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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SYSTEMATIC REVIEW

Ivabradine for the Treatment of Postural Orthostatic Tachycardia Syndrome: A Systematic Review

Megan E. Gee[1] · Alicia K. Watkins[1] · Jamie N. Brown[2] · Emily J. A. Young[3]

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Abstract
Introduction Postural orthostatic tachycardia syndrome (POTS) impacts millions of patients, but there is currently no gold standard treatment for this condition. Ivabradine is a novel heart rate (HR) lowering agent that acts on the sinoatrial node cells by selectively inhibiting the If-current.
Objective The objective of this systematic review is to evaluate the evidence for the efficacy and safety of ivabradine for the treatment of POTS.
Methods MEDLINE (from 1956 to August 2017) and EMBASE (from 1957 to August 2017) were queried with the following search term: "postural orthostatic tachycardia syndrome" OR "postural tachycardia syndrome" OR "chronic orthostatic intolerance" AND "ivabradine." Articles in English with clinical outcomes of human patient(s) treated with ivabradine for POTS were included.
Results The initial search identified 73 articles. After screening, 13 articles were included. Two prospective open-label trials, three retrospective cohort studies, and eight case reports evaluated the safety and efficacy of ivabradine in a total of 132 patients with postural tachycardia. Overall, ivabradine lowered HR and provided symptomatic relief of POTS without blood pressure lowering. Dizziness, nausea, headache, and fatigue were the most common side effects and often did not lead to discontinuation of treatment.
Conclusion Based on this small sample, ivabradine appears to be a reasonable option for patients with POTS who have failed or are unable to tolerate other treatment options, however, but a randomized controlled trial in this population is needed.

Key Points
Postural orthostatic tachycardia syndrome remains difficult to treat given limited effective treatment options.
Published data supports the use of ivabradine for POTS, but at this time, only open-label studies and case reports are available.
For patients who have symptomatic tachycardia and have failed other pharmacologic therapies, a trial of ivabradine is a reasonable option.

1 Introduction

Postural orthostatic tachycardia syndrome (POTS) is a form of dysautonomia that is estimated to impact millions of patients in the USA. It is identified by the presence of frequent symptoms of orthostatic intolerance for at least 6 months accompanied by an increase in heart rate (HR) of at least 30 beats per minute (bpm) within 10 min of assuming an upright posture, but without orthostatic

✉ Megan E. Gee
megangee@buffalo.edu

[1] Geriatric Research, Education, and Clinical Center, Durham VA Health Care System, 508 Fulton Street (119), Durham, NC 27705, USA

[2] Pharmacy Service, Durham VA Health Care System, 508 Fulton Street (119), Durham, NC 27705, USA

[3] Pharmacy Service, VA Tennessee Valley Healthcare System, 1310 24th Avenue South (119), Nashville, TN 37212, USA

hypotension [1]. This is substantially higher than the normal increase of 10–20 bpm and minimal change in blood pressure (BP) that is seen in individuals without POTS. Typically, the compensation for a change to an upright position occurs with approximately 500 mL of blood descending from the thorax to the abdominal cavity and limbs. However, this regulatory mechanism fails in patients with POTS [2].

Patients with POTS often present with lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, sleep disturbances, migraine headaches, or fatigue [3, 4]. To appropriately diagnose POTS, alternative causes for postural tachycardia, such as prolonged bed rest, medication use, and chronic debilitating disorders must be excluded [5]. A tilt-table test or 10-min stand test is usually implemented for a formal diagnosis [1]. POTS is often misdiagnosed as anxiety, panic attacks, chronic fatigue syndrome, or inappropriate sinus tachycardia because of the similarity between symptoms and clinical presentation of these conditions [2].

In 2015, the Heart Rhythm Society (HRS) released an expert consensus statement recommending the utilization of non-pharmacologic interventions as the first-line treatment for POTS [3]. These non-pharmacologic interventions may include discontinuing medications that might worsen POTS, increasing fluid intake to 2–3 L daily and increasing salt intake to 10–12 g daily. Patients should also wear compression stockings to reduce venous pooling and participate in regular exercise for aerobic reconditioning and resistance training. Presently, there is no pharmacologic treatment with a US Food and Drug Administration (FDA)-approved indication for POTS. The pharmacologic interventions included in the expert consensus statement are fludrocortisone, pyridostigmine, midodrine, and low-dose propranolol. Each of these agents has a class IIb recommendation, which is reflective of benefits equivalent to, or possibly exceeding, the risks of therapy. Clonidine and alpha-methyldopa received the same class IIb recommendation, specifically for patients with prominent hyperadrenergic features. Notably, all of these agents affect BP in addition to their HR-lowering effects, and as a result, orthostatic symptoms may be worsened by these pharmacologic treatments [3]. Additionally, many of these agents have central nervous system (CNS) depressant effects, which further limits tolerability. A well-tolerated therapy that treats the physiologic problem of elevated HR without affecting BP is needed to improve quality of life in patients with POTS.

Ivabradine is a HR-lowering agent that was approved by the FDA in 2015 with the labeled indication for reducing the risk of hospitalization for worsening heart failure in a highly selected group of patients with stable, symptomatic chronic heart failure with reduced ejection fraction [6]. However, this agent has been available for use in Europe since 2005 [7]. It acts on the sinoatrial node cells by selectively inhibiting the I_f current in a dose-dependent manner [8]. As a result, the diastolic depolarization of sinoatrial node cells is slowed and HR is reduced. It does not affect myocardial contractility, and therefore, ivabradine has no significant effect on BP [9, 10]. In clinical trials, ivabradine was well tolerated with minimal side effects. The most common adverse effects of ivabradine, compared to placebo, included bradycardia (10% vs 2%), hypertension (8.9% vs 7.8%), atrial fibrillation (8.2% vs 6.6%) and phosphenes or visual brightness (2.8% vs 0.5%). Phosphenes are a luminous phenomenon characterized by transient enhanced brightness such as a halo, image decomposition, or colored bright lights in a limited area of the visual field and are generally triggered by sudden variations in light intensity [6]. Ivabradine is not a recommended agent in the 2015 HRS expert consensus statement. However, it is mentioned with positive results from one single-center, open-label study [3, 11]. Notably, it was approved by the FDA only 1 month prior to publication of the HRS statement, and was not yet available for use in the USA at that time [3].

The management of POTS can be challenging, and there is currently a paucity of tolerable, effective treatment options. A subset of patients may be unresponsive or unable to tolerate traditional therapies. Considering the mechanism of action for ivabradine, it may be a viable alternative for patients who develop hypotension or fatigue from alternate therapies. The objective of this article is to review available literature evaluating the efficacy and safety of ivabradine for the treatment of POTS.

2 Methods

2.1 Literature Search

MEDLINE (1956 to August 2017) and EMBASE (1957 to August 2017) were queried with the following search terms: “postural orthostatic tachycardia syndrome” OR “postural tachycardia syndrome” OR “chronic orthostatic intolerance” AND “ivabradine”. References for each included article were also evaluated for possible inclusion in the systematic review. The literature search was performed and described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

2.2 Study Selection

Clinical studies and case reports were included if clinical outcomes of human patient(s) treated with oral ivabradine

for POTS were evaluated. Animal studies and articles written in languages other than English were excluded. The titles and abstracts of the search results were first screened for possible inclusion. The full texts of these reports were then reviewed to determine final eligibility for inclusion in the systematic review. Authors (MEG and AKW) independently performed the literature review and study selection. Any disagreements were resolved by a third author (JNB).

2.3 Data Extraction

Authors, publication date, study design, study location, patient demographics, ivabradine treatment dose and duration, prior medication use for treatment of POTS, concomitant medication treatment regimens, clinical outcomes including subjective (improvement of symptoms) and objective (change in HR) measures, and ivabradine-related adverse drug events were extracted from each included study using a standardized data extraction process.

3 Results

3.1 Study Selection

Figure 1 describes the literature search. Initially, 73 articles were identified. After screening titles and abstracts and removing duplicates, the full texts of 46 articles were reviewed to determine final eligibility. Final inclusion consisted of two prospective open-label trials, three retrospective cohort studies, and eight case reports of ivabradine use for POTS in a total of 132 patients [11, 13–24]. A summary of included prospective open-label trials, cohort studies, and case reports can be found in Tables 1 and 2.

3.2 Literature Review

Barzilai and Jacob conducted a prospective, open-label, single-dose, pre- and post-trial that included POTS patients with orthostatic intolerance for at least 6 months [13]. Orthostatic intolerance was defined as increased HR of at least 30 bpm without concomitant decrease of BP of more than 20/10 mmHg within 10 min of standing or during a head-up tilt on at least three different occurrences. Patients were excluded for active smoking, pregnancy, uncontrolled thyroid or adrenal disorders, or any history of systemic illness that could influence autonomic function. Eight patients met inclusion criteria and were recruited within a year period. The average age was 31 ± 3 years, six patients were female, and the average duration of POTS symptoms was 2.6 ± 1 years. Three participants were taking fludrocortisone and six were taking propranolol at the beginning of the trial. All participants were required to stop these treatments at least

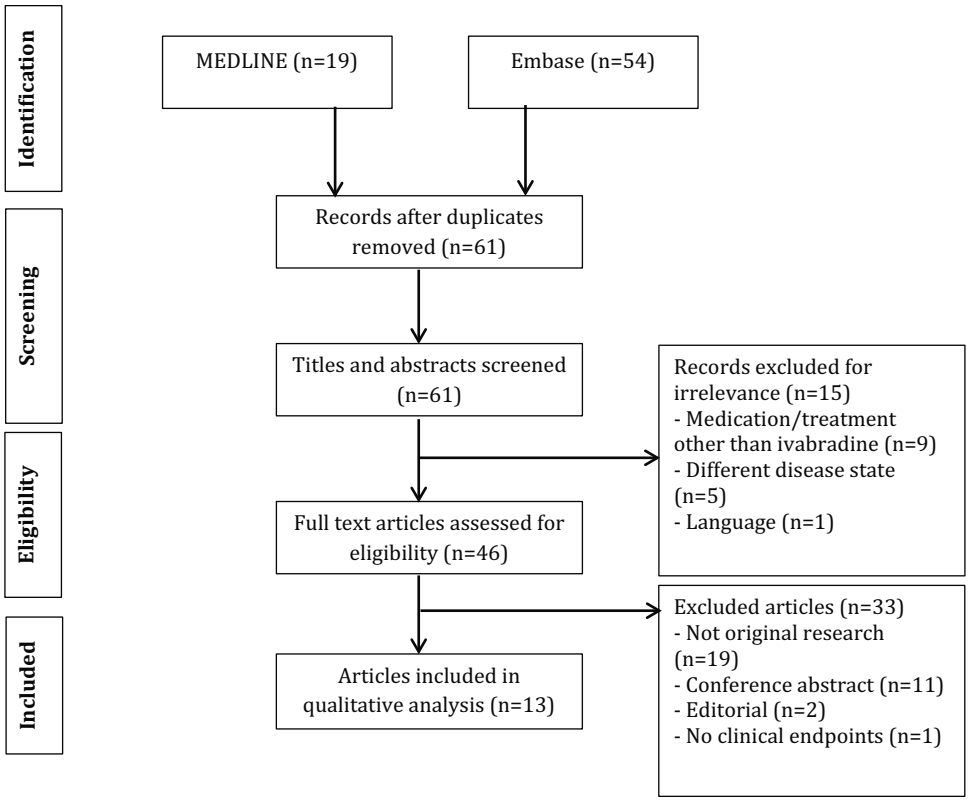

Fig. 1 Flow diagram for reference search and selection of articles for analysis

Table Summary of open-label trials and cohort studies evaluating outcomes of ivabradine in postural orthostatic tachycardia syndrome

Author	Study design	No. of patients	Ivabradine dose	Treatment duration	Outcome	Results	Adverse reactions
Barzilai et al. [13]	Prospective open-label	8	7.5 mg	One time dose	Proportion of patients with Improvement in tilt test induced symptoms HR post head tilt test	100% ↓17 bpm ($P < 0.01$)	NR
Sutton et al. [14]	Prospective open-label	23	Initial: 5 mg/day in 1–2 doses Range: 5–20 mg/day Mean: 10.7 mg/day	Mean of 15 months (Range: 2–40 months)	Likert scale of symptom improvement	Complete resolution: 34.8% ($n = 8$) Great improvement: 43.5% ($n = 10$) No benefit: 21.7% ($n = 5$) Deterioration: 0%	Visual side effects 9% ($n = 2$); study discontinuation due to unspecified side effect 4% ($n = 1$)
McDonald et al. [11]	Retrospective cohort study	20	Initial: 2.5 mg once daily Range: 2.5–15 mg/day Mean: 5 mg/day	Mean of 25 weeks (range: 7–113 weeks)	Self-assessment tool for symptoms	Improved palpitations: 55% ($n = 11$) Improved tachycardia: 55% ($n = 11$) Improved fatigue: 40% ($n = 8$)	Visual abnormalities: 10% ($n = 2$) dizziness: 5% ($n = 1$) fatigue 5% ($n = 1$)
Delle Donne et al. [15]	Retrospective cohort study	22	Initial: 2.5 mg twice daily Range: 5–15 mg/day Mean: 9.5 mg/day	Mean of 4.6 months (range: 0.9–17 months)	Symptom response HR	Improvement: 68.2% ($n = 15$) Unchanged: 27.3% ($n = 6$) Deterioration: 4.5% ($n = 1$) ↓11.2 bpm ($P < 0.05$)	Mild phosphenes: 4.5% ($n = 1$)
Ruzieh et al. [16]	Retrospective cohort study	49	Initial: 2.5 mg twice daily Range: 2.5–10 mg twice daily Mean: 10.9 mg/day	Range: 3–12 months	Symptom response Sitting HR Standing HR	Overall Improvement: 77.6% ($n = 38$) Improved palpitations: 88.4% Improved lightheadedness: 76.1% ↓5.6 bpm ($P = 0.01$) ↓12.3 bpm ($P < 0.001$)	Phosphenes: 18% ($n = 9$) Nausea: 8.2% ($n = 4$)

bpm beats per minute, *HR* heart rate, *NR* not reported

24 h prior to the start of study testing. The protocol consisted of a six-phase tilt test, with monitoring for orthostatic symptoms, BP, and HR occurring during each phase. The testing protocol was repeated 60–80 min following a single 7.5 mg dose of ivabradine. All patients self-reported improvement of symptoms of orthostasis, including dizziness, blurred vision, and palpitations, after ivabradine administration. Post-tilt HR significantly decreased from 118 ± 4 bpm without treatment to 101 ± 5 bpm following ivabradine administration ($P < 0.01$). Resting HR decreased by 4 ± 1 bpm, but this was not a statistically significant reduction. Ivabradine did

Table 2 Summary of case reports evaluating outcomes of ivabradine in postural orthostatic tachycardia syndrome

Author	Patient age	Sex	Ivabradine dosage	Treatment duration	Outcome	Adverse reactions	Case details/notes
Meyer et al. [17]	19 years old	Female	NR	3 months	Alleviation of symptoms: tachycardia, postural palpitations, light-headedness	NR	Developed POTS following stressful event; also given psychosocial support
Nakatani et al. [18]	42 years old	Female	2.5 mg once daily	NR	Improved orthostatic symptoms, alleviation of syncope	Allergic reaction (details NR)	Previously unable to tolerate alpha-agonists, beta-blockers, calcium channel blockers, or digoxin
Aliyev et al. [19]	30 years old	Male	5 mg twice daily	5 days and 6 months	Alleviation of syncopal episodes (in upright position and during carotid sinus massage), paroxysmal atrial fibrillation	NR	Patient had fluctuating HR associated with drop in BP prior to POTS diagnosis
Khan et al. [20]	44 years old	Female	5 mg twice daily	6 weeks	No residual inappropriate sinus tachycardia	Mild transient visual disturbances	Pacemaker in place: HR from 107–140 down to 80–90. All < 120 at 6-week checkup. Continued therapy despite ADR
Oztunc et al. [21]	17 years old	Female	NR	6 months	No complaint of dizziness or tachycardia at follow-up	NR	First treated with metoprolol 1 mg/kg/day for 2 months, midodrine 10 mg three times daily for 45 days without benefit. Information provided about increase in HR and BP prior to, but not during, treatment
Hersi [22]	25 years old	Female	5 mg twice daily	2 days and 4 months	Alleviation of fatigue, weakness, palpitations, tingling and coldness in feet	NR	HR had increased from 80 bpm to 139 bpm upon standing; average of 80 bpm after ivabradine was started. The patient also ran out of medicine, symptoms returned, then resolved again upon restarting
Jamil-Copley et al. [23]	25 years old	Female	5 mg twice daily	3 weeks	Alleviation of sharp pain in head, palpitations, lightheadedness, syncopal collapsing episodes	NR	HR 100–146 before ivabradine, 90 bpm while on ivabradine
Ewan et al. [24]	21 years old	Female	2.5 mg twice daily then 5 mg twice daily	NR	Improved Fatigue Impact Score from 102 to 52 (range 0–160) Improved orthostatic grading scale score from 19 to 9 (range 0–20) Improved HR from 120–160 to 90–95	NR	Unable to tolerate beta-blockers or verapamil in the past

ADR adverse drug reaction, *BP* blood pressure, *bpm* beats per minute, *HR* heart rate, *NR* not reported

not affect BP or cardiovascular vagal tone. No adverse drug reactions were reported [13].

Sutton et al. conducted a prospective open-label trial that included 25 patients who experienced an HR increase greater than 35 bpm during a tilt test if aged 19 or older, or an HR increase greater than 40 bpm if aged 18 years or younger [14]. All included patients were compliant with the fluid intake recommendation of 3 L/day, salt intake of 6 g/day, and physical counter measures for symptom management. Twenty-one patients (84%) were female and 23 patients (92%) experienced palpitations at baseline. The average age was 33 years (range 17–70 years), and the average duration of POTS symptoms was 9 years. Thirteen patients (52%) were taking midodrine at the time of inclusion. During the tilt test, all 25 patients experienced pre-syncope and palpitations and 16 patients (64%) had a profound fluctuation of BP of greater than 30 mmHg. Ivabradine was started at 5 mg/day and titrated up to

20 mg/day as needed for symptomatic relief. The mean ivabradine dosage was 10.7 mg/day, and treatment duration ranged from 2 to 40 months (mean duration 15 months). Repeat tilt test during or following ivabradine treatment was not completed. Response to ivabradine treatment was categorized as deterioration, no change, improvement of symptoms without abolition, or abolition of symptoms. Two patients (8%) discontinued ivabradine treatment prior to assessment: one due to pregnancy and one due to unspecified side effects. Of the remaining 23 patients, at follow-up, eight patients (34.8%) reported abolition of symptoms, ten (43.5%) had improvement in symptoms without abolition, and five (21.7%) reported no change. Overall, 18 patients (78.3%) experienced relief of POTS symptoms following ivabradine use, and three (13%) were able to discontinue midodrine after starting ivabradine. Two patients (8.7%) reported visual side effects, but both patients continued therapy and the side effects later resolved [14].

McDonald et al. [11] completed a retrospective cohort study that identified patients with POTS who were started on ivabradine therapy 2.5 mg once daily, with dose titration at follow-up according to symptoms. A self-reporting assessment tool was developed to assess efficacy, change in symptoms, and side effects. Twenty-two patients were identified, but two patients were considered lost to follow-up due to a lack of documentation. Of the remaining 20 patients, each had tried at least one other medication prior to taking ivabradine, most commonly a beta-blocker. Fourteen patients (70%) returned the self-reporting assessment tool; medical record documentation was reviewed for the remaining six patients (30%). The mean ivabradine daily dose was 5 mg in one or two divided doses (range 2.5–15 mg/day), and the mean duration of treatment was 25 weeks (range 7–113 weeks). During follow-up, three patients (15%) took ivabradine in combination with fludrocortisone and one (5%) used ivabradine in combination with midodrine. Eleven patients (55%) had continued ivabradine at the time data were collected. Based on the self-reporting assessment tool, all patients that continued ivabradine reported decreased palpitations and tachycardia and eight patients (57%) reported improvement in fatigue. Nine patients (45%) reported having discontinued ivabradine because of a lack of effect ($n = 6$), side effect ($n = 2$), or change to alternate agent ($n = 1$). The side effects that led to discontinuation were mild, including dizziness ($n = 1$) and increased fatigue ($n = 1$). Two patients reported visual abnormalities of phosphenes, but did not discontinue therapy as a result of the disturbance [11].

Delle Donne et al. [15] recently completed a retrospective cohort study that identified pediatric patients (less than 18 years of age) treated with ivabradine for POTS from February 2008 to June 2014. Twenty-two patients were identified, 15 of whom were female. All patients had adopted non-pharmacologic therapies for POTS, and a tilt test was performed to confirm POTS diagnosis. Fourteen patients (63.6%) were on at least one other medication for POTS prior to starting ivabradine, most commonly fludrocortisone. Ivabradine therapy was initiated at 2.5 mg twice daily and titrated up to 7.5 mg twice daily based on symptomatic response. Median follow-up was 4.6 months. Mean HR was reduced significantly from 82.5 bpm to 71.3 bpm ($P < 0.05$). Five patients (22.7%) discontinued ivabradine, one due to worsening of symptoms, two for lack of improvement, and two for complete resolution of symptoms. Fifteen patients (68.2%) reported improvement of POTS symptoms. One patient experienced phosphenes, which resolved with dosage reduction from 10 mg/day to 7.5 mg/day [15].

Ruzieh et al. led a retrospective cohort study that included 49 patients with POTS who were treated with ivabradine at a syncope and autonomic dysfunction clinic between January 2010 and October 2016 [16]. Patients were started on ivabradine 2.5 mg twice daily and titrated based on symptoms. Three patients (6.1%) continued on 2.5 mg twice daily, 35 patients (71.4%) were titrated to 5 mg twice daily, ten patients (20.4%) took 7.5 mg twice daily, and one (2%) required 10 mg twice daily dosing. Thirty-eight patients (77.6%) reported overall improvement of POTS symptoms while taking ivabradine. On average, patients had tried 3.0 ± 1.5 medications prior to starting ivabradine, most commonly beta-blocker or calcium channel blocker (67.3%), or selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (57.1%). At least one medication for POTS was discontinued in 17 patients (34.7%). Ivabradine significantly lowered sitting and standing HR (78.1 ± 10.7 vs 72.5 ± 7.6, $P = 0.01$ and 107.4 ± 14.1 vs 95.1 ± 13.7, $P < 0.001$, respectively). The most improved symptoms were palpitations (88.4%) and lightheadedness (76.1%). Sixteen patients (32.7%) stopped taking ivabradine (11 due to lack of response, two for cost-related reasons, and three after complete resolution of symptoms), but no patients discontinued due to side effects. Nine patients (18.4%) experienced phosphenes and four patients (8.2%) reported nausea [16].

Eight case reports were identified describing the safety and efficacy of ivabradine for POTS [17–24]. The patients ranged from 17 to 44 years of age, with an average age of 28 years, and seven patients were female. Four patients were treated with ivabradine 5 mg twice daily. One patient was started at 2.5 mg twice daily and titrated up to 5 mg twice daily, one patient received 2.5 mg once daily, and the exact dosing strategy was not discussed in the remaining two cases. Treatment duration ranged from 3 weeks to

6 months and benefit was reported as early as 2–5 days after initiation of therapy [19, 22]. Three patients had failed alternate therapies for management of POTS, which included beta-blockers, calcium channel blockers, alpha-blockers, midodrine, and digoxin [18, 21, 24]. All eight patients reported improvement in dizziness, tachycardia, lightheadedness, and alleviation of syncopal episodes, although measurements of HR after the initiation of ivabradine were not consistently reported [17–24]. Two case reports documented adverse reactions to ivabradine treatment: one mild transient visual disturbances and one allergic reaction [18, 20]. Despite the mild visual disturbances, ivabradine was continued because the patient experienced significant improvement in POTS symptoms [20]. No details of the allergic reaction were included in the publication [18].

4 Discussion

Based on the evidence presented in this review, ivabradine appears to be an effective treatment for lowering HR and providing symptomatic relief without affecting other cardiac functions in patients with POTS. The benefit of ivabradine was demonstrated in two prospective open-label trials, three retrospective cohort studies, and eight case reports which evaluated the use of ivabradine for POTS [11, 13–24]. In the pre- and post-study, a single 7.5 mg dose of ivabradine alleviated symptoms of dizziness, blurred vision, and palpitations and lowered average post-tilt test HR from 118 bpm to 101 bpm, with the test performed 60–80 min after ivabradine administration ($P < 0.01$) [13]. With consistent twice daily dosing retrospectively reviewed, symptomatic response was improved in 55–78% of the included pediatric and adult patients and HR was significantly lowered without any significant change in BP or major side effects [11, 13, 15–24]. In the only prospective chronic dosing study, 72% of patients had complete resolution or great improvement in symptoms and eight patients (32%) reported complete resolution of syncope [14].

Ivabradine effectively improved symptoms of POTS in patients who had failed alternate therapies in the past. Specifically, the majority of patients had failed at least one treatment in the retrospective cohort studies, as well as in three case reports [11, 15, 16, 18, 21, 24]. Ruzieh et al. documented that on average, three medications were trialed prior to starting ivabradine [16]. Similarly, prior to starting the open-label trial conducted by Barzilai and Jacob, three patients were taking fludrocortisone and six were taking propranolol for management of POTS. All of these patients were required to discontinue treatment 24 h prior to the tilt table testing without and with ivabradine [13]. Considering that many of these patients reported improvement of POTS symptoms from ivabradine use, it is feasible that ivabradine could be utilized in POTS patients who have failed alternate treatments. However, it is not clear if any patients were treatment-naïve prior to the use of ivabradine for the treatment of POTS. Therefore, there is insufficient evidence to support preference of ivabradine over the agents recommended by the 2015 HRS expert consensus statement in those naïve to pharmacologic treatment.

Alternately, ivabradine was used as add on therapy for some patients with persistent symptoms of POTS while on alternate agents. Specifically, three patients responded to ivabradine in combination with fludrocortisone and 11 in combination with midodrine [11, 14]. In other studies, concomitant medications were allowed; however, patients utilizing combination treatment for POTS were not differentiated in the results of these studies. Previous reports for POTS patients have suggested that using lower doses of multiple agents rather than maximizing a single agent may achieve optimal response [25]. Both fludrocortisone and midodrine have peripheral effects; therefore, combination therapy with ivabradine may provide further benefit for control of HR.

Dosing in the case reports, cohort studies, and open-label studies, excluding the 7.5 mg single-dose study, ranged from 2.5 to 20 mg/day for up to 113 weeks. When reported, initial dosages ranged from 2.5 mg once daily to 5 mg twice daily, with the most commonly studied starting dosage being 5 mg/day in one or two doses. The mean maintenance dosage studied was approximately 9.4 mg/day. These starting and maintenance dosages are lower than those recommended by the European Medicines Agency (EMA) and the FDA for the treatment of symptomatic chronic heart failure: initiate ivabradine at 5 mg twice daily and increase to a maximum dosage of 7.5 mg twice daily [6, 7]. Notably, both organizations do recommend decreasing to 2.5 mg twice daily if a patient experiences symptoms of bradycardia at a higher dosage [6, 7]. Therefore, based on the literature currently available evaluating ivabradine for the treatment of POTS, it is reasonable to initiate at low dosages of 2.5 mg once or twice daily and to adjust on the basis of the patient's response and tolerability [13, 19, 22]. A summary of recommendations for the treatment of POTS can be found in Fig. 2.

The benefits of ivabradine in these studies are likely a result of the selective inhibition of the pacemaker I_f current without adverse hemodynamic effects. Unlike traditional HR-lowering agents such as calcium channel blockers and beta-blockers, ivabradine has no effect on myocardial contractility, ventricular repolarization, or intracardiac conduction [26]. Orthostasis, which is a limiting factor for many other POTS treatment options, was not reported with

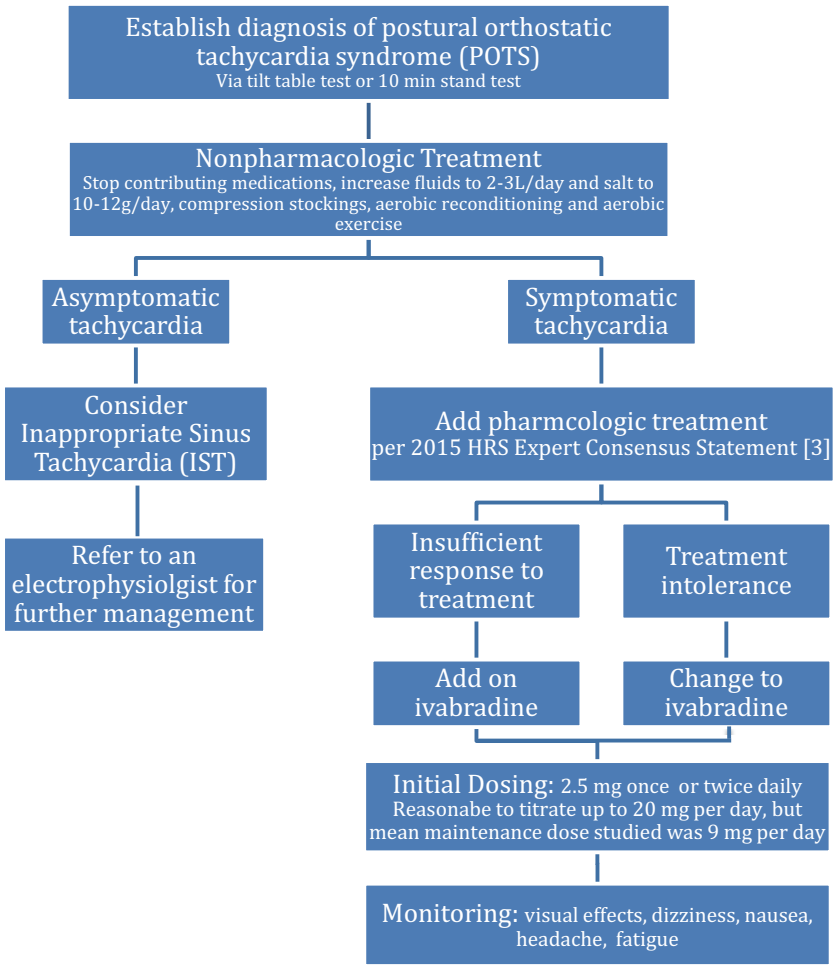

Fig. 2 Recommendations for the treatment of postural orthostatic tachycardia syndrome. *HRS* Heart Rhythm Society

ivabradine use in large, randomized controlled trials of ivabradine for heart failure with reduced ejection fraction and stable coronary artery disease with angina [27, 28]. In the studies reviewed, ivabradine was well tolerated and the most common reported side effects were mild in nature, including dizziness, nausea, headache, fatigue, and phosphenes. Of the 124 patients with POTS treated with multiple doses of ivabradine, only five patients (4%) discontinued ivabradine because of an adverse outcome: three due to side effects (one dizziness, one increased fatigue, one unknown), one due to allergic reaction, and one due to clinical worsening (pediatric patient) [11, 14, 15, 18]. However, an additional 13 patients (10.5%) did discontinue therapy due to lack of response to treatment [11, 14, 15]. Also, one patient (0.8%) stopped after finding an alternative treatment, one patient (0.8%) stopped due to pregnancy, and two patients (1.6%) stopped because of insurance coverage [11, 14, 16]. Notably, 16 patients (12.9%) discontinued therapy in the setting of clinical improvement [11, 14–16, 18]. Fifteen patients (12%) reported visual changes including phosphenes, but none discontinued ivabradine based on this [11, 14–16, 20]. Considering its unique mechanism of action, if patients are unable to tolerate alternate therapies for POTS because of adverse reactions such as dizziness or fatigue secondary to hypotension or CNS depression, ivabradine appears to be a viable therapy to consider.

This analysis has several limitations to consider, including the review of studies and cases with small sample sizes or that present data only from an individual practice site. Additionally, when examining case reports, there is an inherent selection bias, in which unsuccessful trials with ivabradine may not have been brought forth for publication. In addition, the included case reports were generally heterogeneous and imprecise in the clinical detail provided and the quality of evidence available for critical review. In regards to the open-label trials, one of the two included 16 patients who experienced fluctuation in BP, which is not consistent with the diagnostic criteria for POTS [14]. Furthermore, the utilization of patients' self-assessment of symptomatic improvement without consistent measurement of objective outcomes limits interpretation and

application of some of the data. Lastly, for patients with an established diagnosis of POTS, information about duration of symptoms and prior treatment regimens was often not available.

One additional limitation, not related to these studies, but related to off-label use of this recently FDA-approved agent, is cost. This is evidenced by two patients who discontinued ivabradine therapy after insurance approval ended after 1 year in the Ruzieh et al. study [16]. With an average wholesale price for a one-year supply of medication ranging from approximately US $3000 up to US $12,000 depending on dosage required, the traditional therapies recommended in the 2015 HRS expert consensus statement with generic options are likely to be more accessible options for patients and prescribers in this era of prior authorization requirements [29].

No universal regimen has been identified that effectively treats all patients with POTS, and some patients are unable to tolerate the treatment options recommended by the 2015 HRS expert consensus statement because of increased fatigue, hypotension, and other adverse reactions [3]. Despite limited evidence, ivabradine is a promising therapy being considered for the treatment of POTS, especially owing to the lack of apparent effect on cardiovascular functions other than HR lowering [5]. Unfortunately, the data currently available is severely limited; only 132 patients in total were evaluated in the published reports included in this review. Therefore, a placebo-controlled, randomized clinical trial, or preferably a trial with an active comparator such as propranolol, is needed to further determine the role of ivabradine in the treatment of POTS.

5 Conclusions

POTS remains challenging to treat because of the limited effective treatment options. The published data support the use of ivabradine for POTS, but at this time, only retrospective and prospective open-label studies and case reports are available. For patients who have symptomatic tachycardia and have failed other pharmacologic therapies, a trial of ivabradine is a reasonable option. Additional research is warranted to fully elucidate the role of ivabradine for the treatment of POTS and to identify the patients most likely to gain benefit from treatment.

Compliance with Ethical Standards

Conflict of interests Megan E. Gee, Alicia K. Watkins, Jamie N. Brown and Emily J. A. Young declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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Expanded algorithm for managing patients with acute decompensated heart failure

Joyce N. Njoroge[1] · Baljash Cheema[1] · Andrew P. Ambrosy[2] · Stephen J. Greene[2] · Sean P. Collins[3] · Muthiah Vaduganathan[4] · Alexandre Mebazaa[5,6] · Ovidiu Chioncel[7,8] · Javed Butler[9] · Mihai Gheorghiade[1]

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Abstract
Heart failure is a complex disease process, the manifestation of various cardiac and noncardiac abnormalities. General treatment approaches for heart failure have remained the same over the past decades despite the advent of novel therapies and monitoring modalities. In the same vein, the readmission rates for heart failure patients remain high and portend a poor prognosis for morbidity and mortality. In this context, development and implementation of improved algorithms for assessing and treating HF patients during hospitalization remains an unmet need. We propose an expanded algorithm for both monitoring and treating patients admitted for acute decompensated heart failure with the goal to improve post-discharge outcomes and decrease rates of rehospitalizations.

Keywords Heart failure · Acute decompensated heart failure, rehospitalizations · HFrEF

Introduction

Heart failure is not a single disease, but a heterogeneous clinical syndrome that is the manifestation of various cardiac and noncardiac abnormalities. It is commonly seen in individuals 65 years and older and is associated with high rates of morbidity and mortality [1]. Patients hospitalized for heart failure with reduced ejection fraction (HFrEF) have a mortality and readmission rate as high as 15 and 30%, respectively, at 60–90 days post-discharge which has remained unchanged in the past decade despite the advent of novel therapies and monitoring modalities [2]. Hospitalization and rehospitalizations are strong predictors of negative outcomes such as mortality in heart failure (HF) patients [3]. In this context, development and implementation of improved algorithms for assessing and treating HF patients during hospitalization remains an unmet need.

In this article, we propose and provide rationale for the use of the following systematic approach during the three phases of hospitalization (initial assessment, inpatient, and post-discharge): (1) adopt a regimented framework for assessing and treating acute decompensated HF, (2) treat beyond clinical congestion, (3) augment use of underused therapies known to improve outcomes, (4) identify and treat noncardiac comorbidities, and (5) emphasize importance of post-discharge follow-up visits. The aim is to utilize tools and strategies for purposes of improving post-discharge clinical outcomes and decreasing rates of rehospitalization.

Adopt a regimented approach to assessing and treating acute decompensated heart failure

The approach to managing acute decompensated HF (ADHF) patients admitted to the hospital has not changed significantly

✉ Joyce N. Njoroge
joyce.njoroge@northwestern.edu

[1] Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[2] Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Durham, NC, USA

[3] Vanderbilt University Medical Center, Nashville, TN, USA

[4] Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA

[5] Department of Anesthesia and Critical Care, Inserm U942, Hôpitaux Universitaires Saint-Louis-Lariboisière, Paris, France

[6] University Paris Diderot, Paris, France

[7] Institute of Emergency for Cardiovascular Diseases "Prof C.C.Iliescu", Bucharest, Romania

[8] University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

[9] Department of Medicine, University of Mississippi, Oxford, MS, USA

in the past few decades [4–6]. The current treatment algorithm for ADHF focuses on targeting signs and symptoms of congestion with diuretics and vasodilators. However, there are many more factors to consider during the three different phases of admission.

During the initial phase in the emergency department, it is reasonable to use a more focused six-axis assessment model previously described by Gheorghiade et al. by determining de novo vs. chronic HF, clinical severity, precipitants, heart rate and rhythm, blood pressure, and comorbidities [7]. This can guide the triage and initiation of necessary immediate therapies that can be performed in the emergency department before admission.

Once patients are admitted, we propose a transition to a more thorough evaluation using a newly proposed eight-axis model depicted in Fig. 1. This transition is demonstrated in Fig. 2. In the inpatient setting, in addition to treating congestion, there are eight important cardiac and noncardiac entities that have been shown to contribute to the development and exacerbation of HFrEF specifically. These include coronary artery disease, hypertension, myocardial disease, pericardial disease, electrical abnormalities, valvular disease, medical noncompliance, and comorbidities including renal disease, iron deficiency, lung disease, and diabetes. These conditions become equally important in the management of heart failure with preserved ejection fraction (HFpEF) exacerbations as the cardiac pathophysiology is still poorly understood. Focus on comorbidity management in addition to decongestion is suggested in this cohort as a temporizing measure. As indicated in Fig. 1, determination of ejection fraction is crucial early during the second phase of hospitalization in order to guide assessment and therapies, with the three widely accepted categories being (1) HFrEF if ≤40%, (2) mid-range EF if between 41 and 49%, and (3) HFpEF if ≥50% [8].

A comprehensive cardiovascular assessment can be achieved by further imaging modalities that are more readily available in the second phase of hospitalization. These include echocardiography to determine systolic and diastolic function as well as valvular disease, cardiac MRI to evaluate for pericardial disease (for those without an implantable cardioverter defibrillator or permanent pacemaker), nuclear single-photon

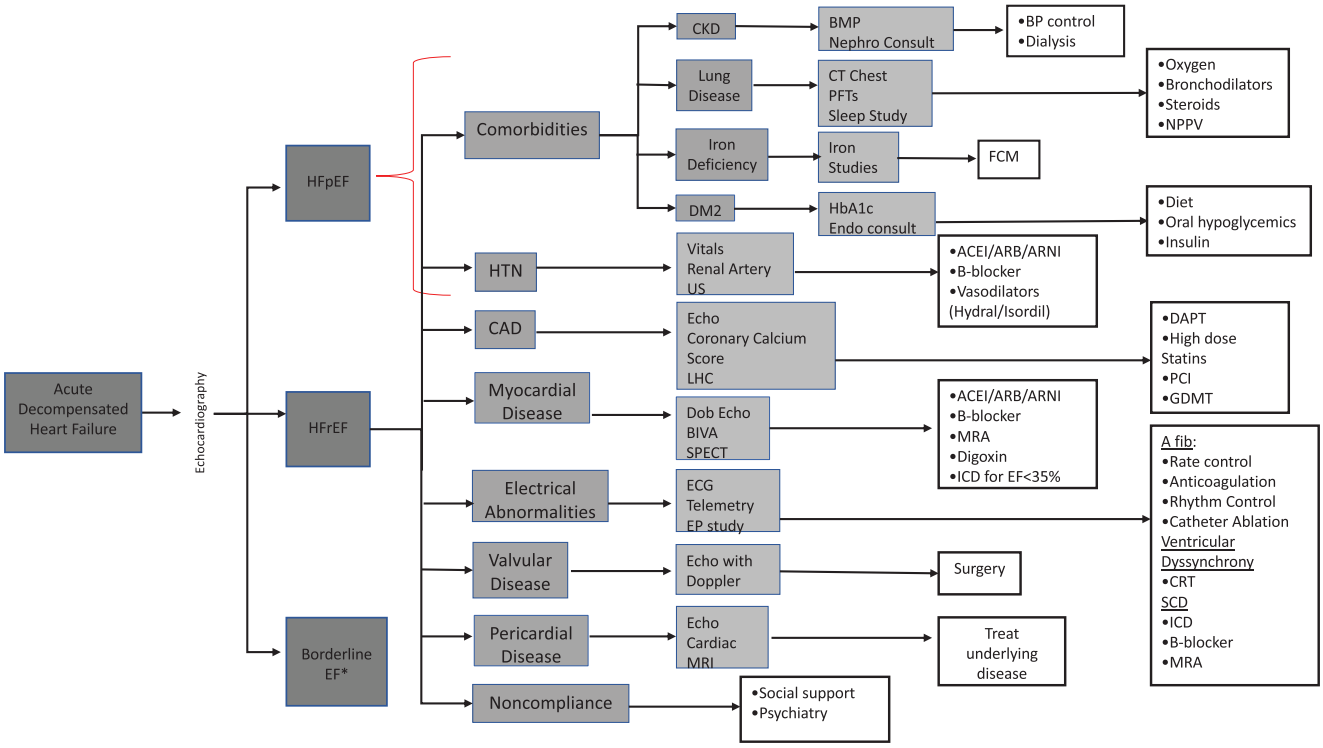

Fig. 1 Eight-axis algorithm for managing ADHF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; EF, ejection fraction; HTN, hypertension; CAD, coronary artery disease; CKD, chronic kidney disease; DM2, diabetes mellitus type 2; US, ultrasound; echo, echocardiogram; LHC, left heart catheterization; Dob Echo, dobutamine echocardiography; BIVA, bioelectrical impedance vector analysis; SPECT, single-protein emission computed tomography; ECG, electrocardiogram; EP, electrophysiology; BMP, basic metabolic panel; PFT, pulmonary function test; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter defibrillator; FCM, ferrous carboxymaltose; BP, blood pressure; NPPV, noninvasive positive pressure ventilation; DAPT, dual anti-platelet therapy; PCI, percutaneous intervention; GDMT, guideline-directed medical therapy; Afib, atrial fibrillation; CRT, cardiac resynchronization therapy. Borderline EF (asterisk) is also known as HFmrEF, heart failure with moderately reduced ejection fraction.

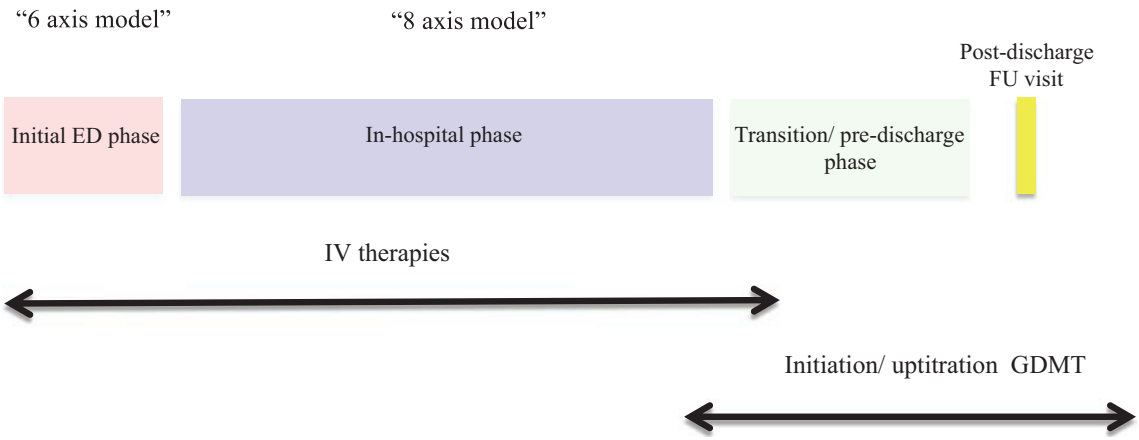

Fig. 2 Transition to expanded eight-axis assessment model. ED, emergency department; FU, follow-up; IV, intravenous; GDMT, guideline-directed medical therapy

emission computed tomography (SPECT) to assess for viable myocardium, and dobutamine stress echocardiography to determine contractile reserve. This information can provide important information for therapies to initiate before discharge. In patients with HFrEF and dysfunctional but viable myocardium, a robust body of evidence supports the potential to improve systolic function with the optimization for guideline-directed medical therapy. For example, the CHRISTMAS (Carvedilol Hibernation Reversible Ischaemia Trial, Marker of Success) study demonstrated that patients with HFrEF and viable myocardium determined by SPECT had an increase in EF when treated with carvedilol [9]. There is also a relationship between the level of myocardial viability and the percent of improvement in EF with carvedilol [10, 11]. Lastly, the inpatient setting allows for easier communication between consulting services to optimize comorbidities.

Each HF patient has varying degrees of the aforementioned conditions contributing to their specific disease process. Occam's Razor—the idea that a singular entity as causal is preferred over multiple contributors—is generally not the appropriate approach in HF patients. Evaluation of all possible components is necessary to develop individualistic treatment plans with multiple therapeutic targets which may confer potential for reversibility of cardiac dysfunction.

Treat beyond clinical congestion

Clinical congestion in HF encompasses the long-recognized signs and symptoms of HF, namely, dyspnea, orthopnea, rales, and peripheral edema. However, much less appreciated is the situation of hemodynamic congestion, defined as elevated left ventricular diastolic pressure despite minimal to absent clinical evidence of HF. The development of clinical and hemodynamic congestion falls on a spectrum of disease severity; as hemodynamic congestion continues to progress, symptoms of clinical congestion start to present themselves up to weeks later [12, 13] (Fig. 3). A number of patients lay somewhere on this continuum complaining of dyspnea but not presenting with systemic signs. In one study of 50 patients, the aforementioned signs were absent in 42% of congested patients with proven elevated pulmonary capillary wedge pressure (PCWP) [14]. Many patients may be discharged with improved symptoms but with persistently high left ventricular filling pressures as demonstrated with elevated N-terminal pro-brain-type natriuretic peptide (NT-proBNP), provoked orthopnea, and poor exercise capacity [15]. Outlined below are additional tools and techniques to increase the sensitivity of evaluation for persistent congestion.

Dyspnea and orthopnea measurement scales Dyspnea and orthopnea are common presenting symptoms that act as subjective marker for congestion in a patient with ADHF. The current standard assessment of dyspnea is a poor surrogate outcome. In hospital, physician-assessed and patient-reported dyspnea was not independently associated with post-discharge quality of life, survival, or readmissions [16]. Although dyspnea relief remains a goal of therapy for hospitalized patients with heart failure with reduced ejection fraction, this measure may not be a reliable surrogate for long-term patient-centered clinical outcomes with the current assessment approach.

The Likert scale and the visual analogue score (VAS) are tools that minimize subjectivity while assessing the level of orthopnea or dyspnea. Using both scales in conjunction results in an increased strength in sensitivity of evaluation by measuring multiple specific aspects of dyspnea [17]. For example, the provocative dyspnea severity score combines both dyspnea and orthopnea assessments into a single scale [18].

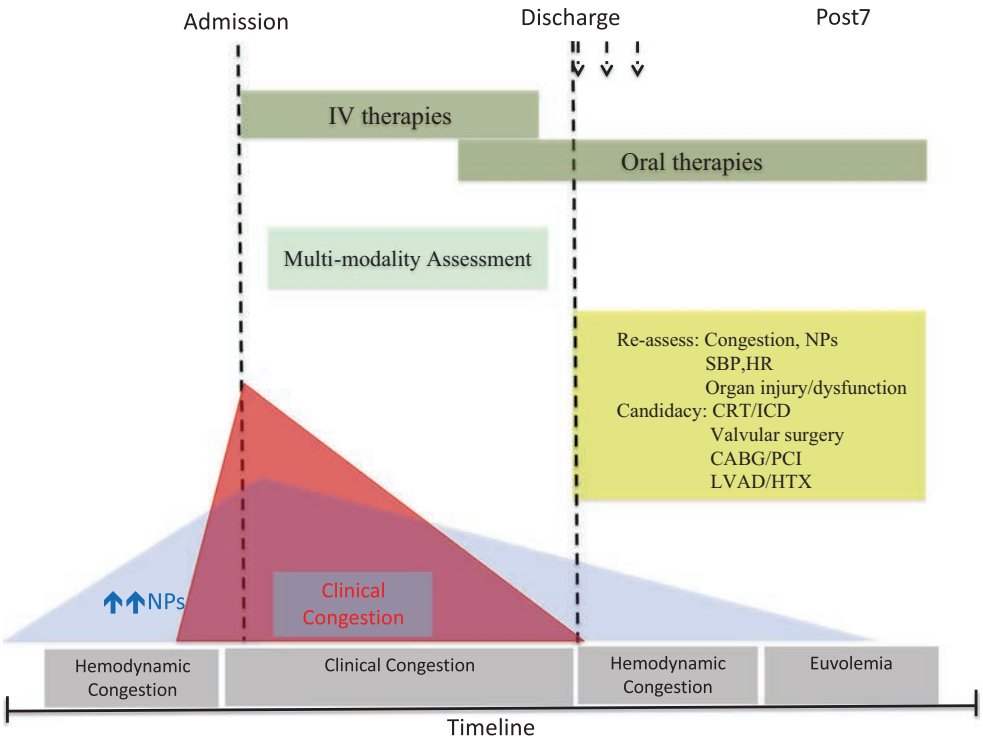

Fig. 3 Congestion timeline with associated therapeutic recommendations. The spectrum of hemodynamic and clinical congestion requires a thoughtful therapeutic timeline. Hemodynamic congestion typically is initiated in the outpatient setting and progresses to clinical congestion possibly requiring admission for management. IV therapies and a thorough multi-modality assessment should be performed as outlined above. Realize that hemodynamic congestion with persistent elevation of LVEDP may be present despite improvement of symptoms. Using the highlighted techniques and tools can further improve hemodynamic congestion before discharge. Post-discharge reassessment is crucial to achieve true euvolemia and prevent re-congestion. Initiation of advanced therapies must be considered on a case by case basis. IV, intravenous; NPs, natriuretic peptides; SBP, systolic blood pressure; HR, heart rte; CRT, cardiac resynchronization therapy; ICD, invasive cardiac defibrillator; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; LVAD, left ventricular assist device; HTX, heart transplant

These objective tools represent a patient-centered metric to compare congestion from admission to discharge to ensure symptomatic improvement.

Orthostatic vital signs In individuals with normal cardiac function and intravascular volume levels, the typical reflex response to positional changes from sitting to standing includes mild reduction in blood pressure and increase in heart rate [19]. However, in decompensated patients with intravascular congestion, these positional changes can have paradoxical effects. Based on the Frank–Starling curve, sarcomeres in congested HF patients are initially overstretched but shrink within ideal range with decreased venous return and resultant decreased preload, causing an improved contractility [20]. Therefore, orthostasis may result in increased cardiac output and improved blood pressures which could indicate intravascular congestion requiring further diuresis. This tool has limitations in utility among patients with hypertrophic cardiomyopathy, aortic stenosis, or atrial fibrillation.

The Valsalva maneuver In an individual with normal intravascular volume levels, there is a multi-phase response to sustained Valsalva maneuver. Immediately after initiating Valsalva, the increased intrathoracic pressure causes a brief spike in blood pressure followed by decreased venous return and increased systemic vascular resistance causing a drop in blood pressure below baseline. After the strain is released, the reduced intrathoracic pressure causes a further drop in blood pressure followed by increased venous return and decreased vascular resistance (and, therefore, decreased afterload) which allows for a rebound blood pressure elevation [21]. Conversely, in patients with congestion, the release of strain results in a persistently elevated blood pressure due to increased LV diastolic pressure and persistently elevated central pressures [22]. This maneuver has proven to have high correlation with invasively measured ventricular filling pressures demonstrating its utility in monitoring intravascular volume status [23].

The 6-min walk test (6MWT) is a simple tool to elicit symptoms of congestion that may not be present at rest. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial found that the 6MWT was one of the most reliable predictors of mortality after hospitalization for worsened HF, alongside PCWP measurements [24]. The 6MWT can be used both in

the inpatient setting prior to discharge and for continued monitoring during the third phase of outpatient follow up.

Natriuretic peptide measurement Comparing the serum level of NT-proBNP on admission and prior to discharge can ensure the correct therapeutic trajectory [25]. NT-proBNP is cleaved from BNP, has more stability in vivo, and has been shown to have higher sensitivity and specificity compared to circulating BNP levels [26]. Patients with persistently elevated NT-proBNP prior to discharge have been found to have significantly higher risk for rehospitalization or death [27]. The utility of monitoring serial NT-proBNP levels in the inpatient setting is challenged by a delay in serum level changes compared to intravascular congestion progression. However, it has been shown that a reduction in NT-proBNP levels by at least 30% from admission is associated with an improvement in post-discharge outcomes [28].

Noninvasive hemodynamic monitoring can be used throughout the three phases of hospitalization for HF. In the emergency department, utilization of ultrasound technology is becoming more convenient with the advent of hand-held devices. Evaluation of inferior vena cava (IVC) compressibility or distension can easily be performed to distinguish between systemic congestion and fluid redistribution [29]. Goonewardena et al. determined that bedside ultrasound of IVC, even with a hand-held device, identified patients with ADHF who would go on to be readmitted for HF exacerbations based on plethoric IVCs with lower collapsibility indexes [30].

Newer imaging modalities, such as bioelectrical impedance vector analysis (BIVA), are being tested as options for intravascular assessment. The use of transthoracic bioelectrical impedance analysis as a marker of fluid accumulation is still gaining traction in the clinical world but it has demonstrated reliability in measuring cardiac output and index when compared to invasive methods [31].

Augment use of underused therapies known to decrease rehospitalizations

Current guideline-directed medical therapy (GDMT) has been well outlined by institutions including the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) [32]. Despite the well-established body of evidence supporting these guidelines for HFrEF, there remain significant gaps in provision of recommended therapies to patients who qualify for them. This "risk-treatment paradox" and "clinical inertia" may stem from focus on the potential short-term destabilization of clinical status, rather than consideration of the potential long-term benefits of therapy. For example, robust evidence suggests that worsening renal function in the setting of augmented decongestive therapy or initiation of renin–angiotensin–aldosterone system (RAAS) blockade does not negatively impact prognosis, but rather represents a net benefit to the patient [33–36]. Nonetheless, these patients frequently have their ACE inhibitors and angiotensin receptor blockers (ARBs) stopped without reinitiation prior to discharge. Similarly, in African American patients with stable hemodynamics, less than 25% are discharged on hydralazine and isosorbide dinitrate despite data proving morbidity and mortality benefits in this cohort [37]. Below (and summarized in Table 1) are examples of therapies in HFrEF patients that need to be highlighted for initiation either prior to discharge or during outpatient follow-up in order to further minimize the risk-treatment paradox and promote cardiac dysfunction reversibility.

Digoxin has proven hemodynamic benefits and has been associated with decreased readmission rates. As such, it is endorsed by guidelines to use in appropriate patients with persistent symptoms and rehospitalizations for HFrEF. However, in the last decade, there has been a decrease in prescription rate to only 20–40% from 80% at the peak of its clinical utility [38]. Data suggesting increased mortality with digoxin are uniformly observational and subject to confounding. The DIG trial demonstrated that digoxin, when added to diuretics and ACEi in patients with chronic HFrEF in sinus rhythm, decreased hospitalizations without affecting mortality [39]. This neutral effect on mortality in a large randomized trial is notable amid persistent concerns over the safety of digoxin in routine clinical practice. Moreover, the neutral mortality effect of digoxin in the DIG trial was seen despite the trial protocol calling for aggressive dosing of the agent to achieve serum digoxin concentrations above current guidelines [32]. Evidence suggests that dosing in line with ACC/AHA guidelines further improves the risk-benefit ratio of digoxin therapy.

Mineralocorticoid receptor antagonists Less than 33% of eligible patients admitted for HF are started on mineralocorticoid receptor antagonists (MRAs) before discharge [40] despite data showing that MRAs significantly reduce early hospitalization rate [41]. In addition to blocking aldosterone's effect on the RAAS, MRAs have been able to prevent aldosterone's promotion of cardiomyocyte fibrosis, oxidative injury, and cardiac remodeling [42]. At higher doses, MRAs can also provide natriuretic benefits and has been used in cirrhotic patients for this effect for years [43]. Importantly, spironolactone is one of the only medications to have a possible role in minimizing the readmission risk in HFpEF patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial [44].

Torsemide The three most commonly used loop diuretic formularies are furosemide, bumetanide, and torsemide. Furosemide historically has been the most frequently used diuretic initially due to cost and early marketing (furosemide

Table 1 Summary of underutilized heart failure therapies

Therapy	Recommendation	Supporting trials
Digoxin	Use in refractory HFrEF in addition to GDMT to decrease rate of rehospitalization	DIG Trial (1997)
MRAs	HFrEF patients with NYHA III–IV symptoms	RALES (1999)
	HFpEF patients with normal renal function	TOPCAT (2014)
Torsemide	Consideration of torsemide over furosemide as oral loop diuretic therapy in patients with difficult to treat congestion or diuretic resistance	TRANSFORM-HF (current)
Thiazides	Use in combination with loop diuretics in diuretic resistant patients	CLOROTIC (current)
Ivabradine	HFrEF patients on maximal GDMT with standing HR > 70 BPM	SHIFT (2010)
ARNIs	HFrEF patients in place of ACEI	PARADIGM-HF (2014)
		PIONEER-HF (current)
Ultrafiltration	In ADHF with congestion refractory to medical therapy (level of evidence: C)	RAPID-CHF (2005)
		CARRESS-HF (2012)

HFrEF heart failure with reduced ejection fraction, *GDMT* guideline-directed medical therapy, *NYHA* New York Heart Association, *HFpEF* heart failure with preserved ejection fraction, *HF* heart failure, *HR* heart rate, *BPM* beats per minute, *ARNI* angiotensin receptor–neprilysin inhibitors, *ACEI* ACE inhibitor, *ADHF* acute decompensated heart failure

being available in the 1960s and torsemide in 1990s) [45]. Although definitive clinical outcome data are lacking, compelling data support torsemide as having distinct advantages over other available loop diuretics [46, 47]. Torsemide has a significantly better bioavailability independent of the presence of gut edema or renal dysfunction [48, 49]. Compared to furosemide's variable bioavailability from 10 to 90% depending on disease state, torsemide's bioavailability is reliably > 80% independent of medical status [50]. An added benefit of torsemide is its longer duration of action (12–18 h) compared to furosemide and bumetanide (6 to 8 h) and its decreased tendency for hypokalemia. The TRANSFORM-HF (Torsemide Comparison with Furosemide for Management of HF) trial is a large-scale randomized controlled trial currently enrolling approximately 6000 patients hospitalized for HF and will compare the effects of torsemide and furosemide on long-term clinical outcomes (NCT03296813).

Thiazide diuretics Patients who require chronic diuretic use can frequently develop loop diuretic tolerance due to distal nephron segment hypertrophy and enhanced sodium reabsorption proximal to the diuretic's site of action [51]. Thiazide diuretics can play an important part in potentiating the sodium excretion effects of loop diuretics in these patients [32]. By targeting the distal tubules, thiazides provide a synergistic effect when combined with standard loop diuretics and prevent reabsorption of sodium and water in the ascending loop of Henle and distal convoluted tubules [52]. A current ongoing CLOROTIC (Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure) trial aims to determine utility of combined loop and thiazide diuretic compared to loop diuretic use alone (NCT01647932).

Ivabradine is a chronotropic agent that decreased heart rate and, therefore, cardiac work. It has shown to be beneficial in a specific cohort of chronic HF patients with EF < 35% and heart rate > 70 BPM where it decreased the rate of HF hospitalizations and death from HF[32]. Initiation in the post-discharge phase should be considered among HFrEF patients already receiving optimal doses of standard GDMT [53]. However, in the stable HF patient admitted for acute decompensation, consideration should be made to initiate prior to discharge. The PRIME-HF (Predischarge Initiation of Ivabradine in the Management of Heart Failure) trial is a randomized prospective study that aims to monitor the rate of continued treatment of ivabradine if started in the predischarge period rather than in clinic (NCT02827500). This information can help guide recommendations for timeline of initiation of therapy.

Angiotensin receptor and neprilysin inhibitors (ARNI) have been shown to improve vasodilation and natriuresis by inhibiting endothelin, vasopressin, sympathetic activity, and the RAAS [54]. The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated better outcomes in HFrEF with treatment with ARNI compared to ACEI [55, 56]. Post hoc analysis of the PARADIGM-HF suggests that these benefits extend to improving clinical outcomes following hospitalization for HF and initiation should be considered during outpatient clinic visits [57]. The ongoing PIONEER-HF (comparison of sacubitril/valsartan versus enalapril on effect on NT-proBNP in patients stabilized from an acute heart failure episode) trial is a large, randomized, double-blind prospective study that aims to assess the effect on congestion by monitoring NT-proBNP levels in the post-discharge setting (NCT02554890).

Ultrafiltration The interdependence of cardiac and renal function is well recognized, with dysfunction of one organ commonly affecting the other. Balancing cardiac decongestion and renal function is a common struggle that physicians face when treating acute decompensated HF patients [58]. Ultrafiltration offers an option to further decongest HF patients with renal dysfunction. However, the current data on risk-benefit analysis is inconclusive. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial tested the effects of ultrafiltration for continued fluid removal in the presence of worsening renal failure but demonstrated an increased association with more adverse events, worsening renal function, and no significant difference in clinical outcomes [59]. Alternatively, the AVOID-HF (Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure) trial did not see a difference in adverse events between ultrafiltration and loop diuretic treatment groups [60]. Importantly, there was a longer duration between initial and subsequent HF events within 90 days in the ultrafiltration group compared to diuretic therapy. This study was terminated early for funding reasons but provides incentive to further evaluate its validity as part of an empiric strategy for congestion refractory to aggressive pharmacologic therapy [61–63].

Identify and treat noncardiac comorbidities

Heart failure exacerbations commonly result from the interplay between the underlying cardiac substrate and amplifying mechanisms such as diabetes mellitus, renal failure, and COPD. In patients with HF, a significant number experience rehospitalizations or death secondary to comorbidities rather than heart disease itself. The prognostic significance of noncardiac comorbidities is equally important in HF patients with preserved, mid-range, and reduced ejection fraction [64]. In HFpEF, with potential exception of spironolactone, randomized controlled trials of various therapies have thus far failed to demonstrate improved outcomes. Therefore, there is an increased interest in targeting and optimizing comorbidities as a temporizing measure pending further research for proven therapies. The prevalence and prognostic implications of comorbidities in HFrEF and HFpEF have been previously discussed, but a few specific comorbidities deserve notable mention.

Comorbid diabetes mellitus and heart disease have been shown to have significantly poor overall outcomes. Concurrent diabetes can be seen in up to 44% of HFrEF patients [65] and 32–45% of HFpEF patients [66]. Among patients with diabetes, the most common clinical complication is due to cardiovascular disease, especially HF [67]. However, cumulative data from prior studies suggests that hyperglycemia per se is not a therapeutic target in HF, with multiple glucose-lowering therapies conferring heightened risk for HF events despite added glucose control [68, 69]. In the recent EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) study, empagliflozin, a sodium–glucose cotransporter-2 (SGLT2) inhibitor, demonstrated a positive effect on cardiovascular risk [70]. Specifically, there was a reduction in mortality secondary to cardiovascular etiology as well as a decreased risk of hospitalization for HF compared to placebo (hazards ratio 0.65) [71]. Similar findings were seen with canagliflozin, another SGLT2 inhibitor, in the CANVAS (Canagliflozin Cardiovascular Assessment Study) trial [72]. The mechanism of improved cardiac outcomes is not thought to be due to glycemic control, but the exact pathophysiology is still unknown.

Iron deficiency is a common comorbidity in chronic HF that has been shown to be an indicator of more advanced disease [73] as well as reduced functional capacity and quality of life [74]. Iron deficiency itself has been seen in 33% of CHF patients with or without anemia and is associated with a reduced event-free survival at 36 months [75]. The deficiency of iron specifically is related to poor outcomes independent of anemia or bone marrow hypoproduction. The RED-HF (Reduction of Events with Darbepoetin Alfa in Heart Failure) trial demonstrated no benefit with treatment with darbepoetin injections in patients with iron-deficiency anemia [76]. The IRONOUT-HF (Iron Repletion Effects on Oxygen Uptake in Heart Failure) trial did not demonstrate benefit in routine oral iron supplementations in HFrEF patients with iron deficiency based on exercise tolerance (6MWT) and peak oxygen uptake [77]. However, studies have shown improved outcomes with intravenous (IV) iron supplementation. The FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) study demonstrated improvement in patient-reported quality of life and exercise capacity with intravenous ferric carboxymaltose (FCM) in iron-deficient patients with and without anemia [78]. The trial also found a significantly lower rate of death due to worsening HF in the FCM arm. Likewise, the CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure) trial demonstrated similar results with an improvement in functional capacity measured with 6MWT [79]. In the EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Heart Failure and Iron Deficiency) trial, the treatment with IV FCM also improved peak oxygen consumption, an objective marker of exercise tolerance [80].

Emphasize post-discharge follow-up visits

There is a period about 2–3 months after discharge known as the vulnerable phase when morbidity and mortality significantly increase compared to any other point in the timeline from admission [81]. This is usually due to short-term worsening of hemodynamics in the setting of suboptimal therapy, medication and diet noncompliance, and other factors. It is

becoming increasingly apparent that we must have patients followed up closely in outpatient cardiology clinics early during this period to prevent worsening congestion, renal function, and neurohormonal maladaptations [82].

In order to determine who is at highest risk of poor outcomes during this vulnerable phase, patients can be risk-stratified based on certain prognostic indicators. Hypotension (low systolic blood pressure), ventricular dyssynchrony, anemia, persistently elevated BNP, and hyponatremia have all been found to carry a negative prognosis in patients with AHF [83]. An additional risk-stratifying tool in the peri-discharge period is the Kansas City Cardiomyopathy Questionnaire (KCCQ), a self-reported quality of life report for functional status evaluation. Green et al. determined that patients with stable chronic HF or low New York Heart Association (NYHA) staging consistently had higher KCCQ scores and patients with decompensated HF or higher NYHA staging had lower scores [84]. Notably, a higher KCCQ score prior to discharge was associated with a higher 30-day HF readmission rate [85]. The symptoms evaluated by KCCQ tend to be the chief complaints upon re-presentation to the hospital among HF patients. Therefore, KCCQ, as well as the aforementioned clinical signs, has significant utility in a risk prediction model to minimize rehospitalizations when signs of congestion are not present.

Although evidence supporting the exact goals and duties of the early post-discharge visit are lacking, the ACC and AHA mention the goal for immediate post-discharge office centering on reassessment of volume status and renal function, and ensuring current medications are in line with guideline-directed medical therapy (GDMT). For prognostic purposes, repeat biomarker testing can be considered [86]. Additionally, recent research has demonstrated a prognostic rationale for monitoring troponin I levels with an elevated serum level at 1 month predicting increased clinical events at 12 months [87]. Further follow-up must focus on optimizing GDMT, assessing new targets for intervention, and managing comorbid conditions in order to prevent further precipitants and exacerbations [88]. Reflection on other factors such as optimizing macronutrient and micronutrient status must also be considered. Patient coaching is equally crucial to ensure continued follow-up and adherence to medications and diet.

Cardiac rehabilitation is a three-axis program that focuses on improving cardiovascular health, preventing deterioration, and minimizing rehospitalization by counseling patients about healthy lifestyle management, exercise training, and stress reduction. In the HF-ACTION (heart failure: a controlled trial investigating outcomes of exercise training) study, cardiac rehabilitation was found to improve health-related quality of life (self-reported using KCCQ and EQ-5D questionnaires) [89]. However, data indicates that only 10% of eligible patients receive a referral at time of hospital discharge [90]. With the advent of novel access to counseling and cardiac rehab through the internet and mobile phones [91], the barriers to incorporating these non-medical therapeutic measures in daily life are minimized.

Ambulatory invasive hemodynamic monitoring is a novel intervention for continuous assessment in the outpatient setting. The CardioMEMS is an implantable device that measures PCWP to provide early warning of congestion prior to progression requiring inpatient management. Abraham et al. studied its use in NYHA class III HF patients and observed a 30% relative risk reduction at 6 months post-implantation [92]. Although it carries inherent risks during implantation in addition to increased cost compared to standard of care, this device may prove useful for selected patients.

Lastly, patients with severe stage D or NYHA class III-IV HF must be evaluated for invasive devices such as invasive cardiac defibrillators and ventricular assist devices when clinically indicated whether in the inpatient or outpatient setting. Both the ESC and ACC/AHA guidelines elucidate when these invasive devices are indicated, and early identification of candidates is crucial for preventing continued deterioration of cardiac function [8, 32].

Conclusion

The pathophysiology behind heart failure development and exacerbation is multifaceted and, as such, should be assessed more thoroughly. We present an algorithm utilizing a multimodality assessment of precipitating and aggravating factors and a guideline for improved management of acute decompensated heart failure. This paper highlights the importance of thorough assessment, individualized treatment plans beyond clinical congestion with underutilized therapies, inclusion of noncardiac comorbidities, and continuing management following hospitalization. We aim to provide guidance to improve overall cardiac function and, therefore, minimize rehospitalization rates among heart failure patients.

Compliance with ethical standards

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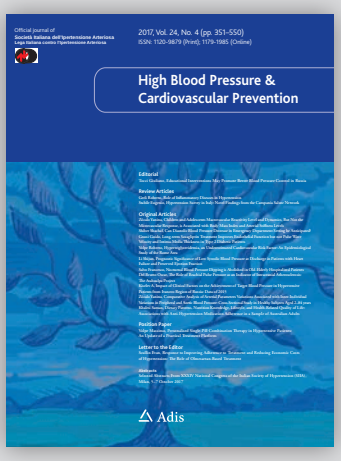

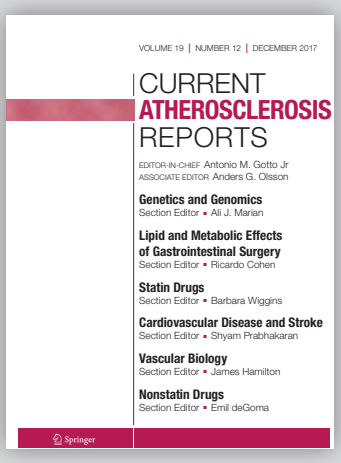

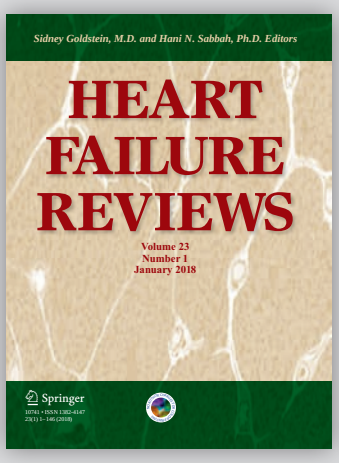

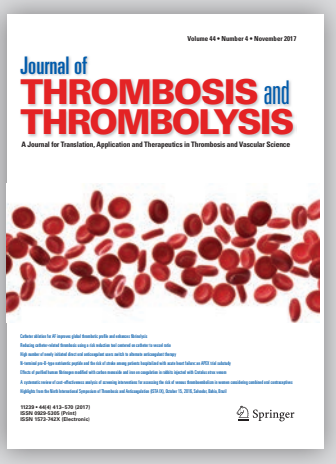

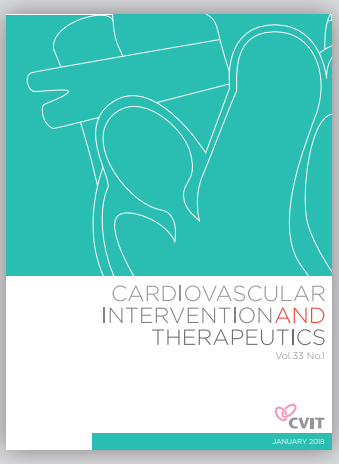

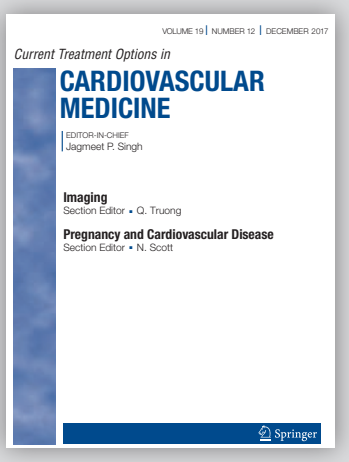

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