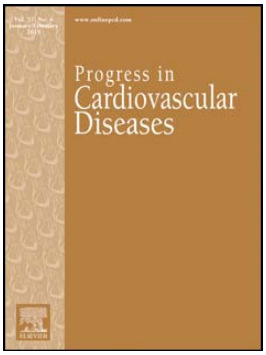


# Pharmacologic Therapy for Heart Failure with Reduced Ejection Fraction: Closing the Gap Between Clinical Guidelines and Practice

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***Manuscript Title:*** **Pharmacologic Therapy for Heart Failure with Reduced Ejection Fraction: Closing the Gap Between Clinical Guidelines and Practice**

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**Abstract**

Despite the great progress made in the management of heart failure (HF) with reduced ejection fraction (HFrEF), its prevalence continues to rise owing to an aging population and an epidemic of hypertension, obesity and coronary artery disease. For decades, angiotensin converting enzyme inhibitors and beta blockers have been the mainstay of HFrEF therapy. The recent addition of sacubitril/valsartan and ivabradine to the HF armamentarium has the potential to transform our therapeutic approach to HFrEF, while simultaneously raising some questions and uncertainties on their applicability. In this paper, we review the pathophysiology of HFrEF, discuss already established and novel evidenced-based pharmacologic therapies available for these patients. We also share some therapeutic strategies aimed to optimize HF therapy in specific undertreated patient populations including the elderly and patients with chronic kidney disease , while offering insight on how to tailor therapy in the "real-world."

**Key words:** heart failure with reduced ejection fraction, guideline directed medical therapy, management, outcomes

**Abbreviations**

ACEI: angiotensin converting enzyme inhibitors
ACCF: American College of Cardiology Foundation
AHA: American Heart Association
A-HeFT: African-American Heart Failure Trial
ANP: atrial natriuretic peptide
ARB: angiotensin receptor blocker
ARNI: angiotensin-receptor neprilysin inhibitors
BB: beta blockers
BMP: beats per minute
BNP: brain natriuretic peptide
BP: blood pressure
CHARM: Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CIBIS: Cardiac Insufficiency Bisoprolol Study
CIBIS-ELD: Cardiac Insufficiency Bisoprolol Study in Elderly
CKD: chronic kidney disease
CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study
CNP: C-natriuretic peptide
COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival Study Group
COR: class of recommendation
CV: cardiovascular
DOSE: Diuretic Optimization Strategies Evaluation
EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
FDA: Food and Drug Administration
GDMT: guideline-directed medical therapy
HF: Heart Failure
HFN-LIFE: Entresto TM In Advanced Heart Failure
HFrEF: heart failure with reduced ejection fraction
HFSA: Heart Failure Society of America
LCZ696: sacubitril-valsartan
LV: Left ventricle or left ventricular
LVEF: Left ventricular ejection fraction
LOE: level of evidence
MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
NP: Natriuretic peptides
NSR: normal sinus rhythm
NYHA: New York Heart Association
PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIONEER: ComParIson Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode
QoL : Quality of Life
RAAS: renin-angiotensin-aldosterone system
RADIANCE: Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme

RALES: Randomized Aldactone Evaluation Study
RCT: randomized controlled trial
SENIORS: Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors
SHIFT: Systolic Heart Failure Treatment with the If inhibitor Ivabradine tria
SNS: sympathetic nervous system
SOLVD: Studies of Left Ventricular Dysfunction
US: United States
Val-HeFT: Valsartan Heart Failure Trial
V-HeFT: Vasodilator in Heart Failure Trial

## Introduction

In the United States (US), 200,000 new cases of heart failure (HF) are diagnosed each year, with a total population exceeding 6 million.[1] This population is only expected to grow in view of our aging population and improving therapies.[1,2] While data regarding the successful treatment of HF with preserved ejection fraction (HFpEF) are lacking, great progress has been made in the pharmacologic therapy of HF with reduced ejection fraction (HFrEF). Guideline-directed medical therapy (GDMT) has led to significant improvement in both survival and reduction of hospitalization of HFrEF patients.[3,4] For decades, angiotensin converting enzyme inhibitors (ACEI) and beta blockers (BB) have been the mainstay of HFrEF therapy. These agents target both the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), two major neurohormonal pathways that play a crucial role in the pathogenesis of HF.[4,5] In the focused update of the HF guidelines published collaboratively by the American College of Cardiology (ACC), the American Heart Association (AHA) and Heart Failure Society of America (HFSA), two new drug classes were added after their approval by the Food and Drug Administration (FDA)—ivabradine and sacubitril/valsartan.[6-8] The addition of these new agents has the potential to transform the way we approach medical therapy in HFrEF, while

simultaneously raising questions and uncertainties on their applicability. This article aims to review the pathophysiology of HFrEF, the major HFrEF randomized controlled trials (RCT), in addition to discussing established and novel evidenced-based pharmacologic therapies available for these patients. We also discuss some therapeutic strategies aimed to optimize HF therapy in specific undertreated patient populations including the elderly and patients with chronic kidney disease (CKD), while also offering insight on how to tailor therapy in the "real-world."

## SNS and RAAS systems: Two Key HF Therapeutic Targets

The SNS, RAAS, vasopressin pathway, and the natriuretic peptides (NP) system have been identified as the key pathophysiological mechanisms leading to the onset and progression of HFrEF.[9] Naturally, these pathways have been the quintessential targets of current HF therapy.

Chronic stimulation of the SNS leads to desensitization and down-regulation of the beta-1 receptors in both the myocardium and baroreceptors. Over time, this results in a decreased ability of the myocardium to respond to elevated catecholamine levels. Heart rate variability and baroreceptor dysfunction have consistently been observed in chronic HF patients.[9] Studies have demonstrated that excessive sympathetic activation is associated with cardiac myocyte apoptosis, hypertrophy, and myocardial necrosis.[10]

One downstream effect of ongoing sympathetic stimulation is the ensuing chronic over-activation of the RAAS cascade. RAAS stimulation leads to increased concentrations of renin, angiotensin II, aldosterone and vasopressin. The circulation of additional renin triggers the production of angiotensin II. Angiotensin II, one of the most vasoactive peptides, contributes to LV remodeling and may lead to the endothelial dysfunction observed in HF.[9]

NP have become a new target for future HF therapies. Vasoactive peptides such as NP, bradykinin, and adrenomedullin are degraded by the enzyme neprilysin.[8] The neurohormonal

overactivation that occurs in HF can be offset by the inhibition of neprilysin, as increased levels of these vasoactive peptides help to prevent the long-term deleterious effects of sodium retention, vasoconstriction, and maladaptive remodeling.[8] The most recently approved drug and the angiotensin-receptor neprilysin inhibitor (ARNI) focuses on the aforementioned pathway. Figure 1 summarizes the targets in the RAAS and SNS pathways with their respective therapeutic interventions.

## The Good: HF therapy That Improves Survival

Evidence-based medicine obtained through RCTs has remained the catalyst in driving the development and progress made in HF therapy. From the early vasodilator trials[11-14] to the most recent ARNI study,[8] each trial has been a stepping stone for the next. The major pharmacologic HFrEF trials are outlined in Table 1.

### *ACEI therapy*

ACEI have been a mainstay of treatment for many years given their mortality and morbidity reducing abilities in the HFrEF population. With an ACC/AHA class of recommendation (COR) I and level of evidence (LOE) A recommendation, they are sure to remain a pillar in HFrEF therapy.[4-6] Multiple large and multicenter RCT have shown these therapies to improve functional capacity and symptoms, decrease hospitalizations, and most importantly reduce mortality in both ischemic and non-ischemic cardiomyopathy.[13,14] The first ACEI trial with favorable results was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which studied the effects of enalapril vs. placebo in patients with New York Heart Association (NYHA) class IV HF.[13] The enalapril arm exhibited a 40% relative risk reduction in mortality, improvement in NYHA classification, reduction in heart size, and

decreased medication requirements when compared to the placebo arm.[13] Following the results of the CONSENSUS trial yielded the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial,[14] which aimed to further explore the role of ACE-inhibition in NYHA class II and III patients. SOLVD-treatment reinforced the survival benefit and reduction in hospitalizations in these patients with less severe HF.[14] Starting and target doses for ACEI is further described in Table 2.

***ARB therapy***

Following the success of the CONSENSUS[13] and SOLVD[14] trials prompted the hypothesis that additional inhibition of the RAAS pathway at a different level could be beneficial in chronic HF. The Valsartan HF Trial (Val-HeFT)[15] tested the addition of valsartan versus placebo in NYHA class II-IV patients who were already receiving background medical therapy which included ACEI in most patients and in approximately one-third, BBs.[15] Although no survival benefit was found in the valsartan arm, improvement in NYHA class, quality of life (QoL) and ejection fraction (EF) was seen when compared to the placebo arm, as well as a reduction in hospitalizations. In the post hoc observation of adverse events, the group receiving combination therapy of valsartan, an ACEI and a BB carried a statistically significant negative effect on mortality. In contrast, patients receiving only valsartan had a reduction in mortality risk It should be noted that the patients who were not on a background ACEI were not deemed "intolerant" but the therapy was chosen by the referring physician.[15]

The Candesartan in HF Assessment of Reduction in Mortality and Morbidity Trial (CHARM)[16] compared the use of candesartan versus placebo in addition to standard therapy with ACEI, BB, and aldosterone antagonists. In comparison to the findings of Val-HeFT, CHARM found a significant reduction of all-cause mortality, cardiovascular (CV) death and HF

hospitalizations in the candesartan arm. Interestingly and unlike Val-HeFT, concomitant ACEI use did not negate the beneficial effects of candesartan.[16] ARBs are a reasonable alternative for those patients intolerant of ACE as they antagonize the angiotensin II receptor, thus avoiding kinase inhibition. In turn, this results in a lower incidence of cough and angioedema.[4]

***BB Therapy***

SNS activation is one of the many pathophysiologic abnormalities that leads to chronic HF.[9] Sympathetic antagonists have been studied and proven to reduce morbidity and mortality in HF.[17,18] In this regard, several trials have elucidated the beneficial effects of BB, the first being the Cardiac Insufficiency Bisoprolol Study (CIBIS II).[17] CIBIS II aimed to show that bisoprolol, when compared to placebo, reduced morbidity and mortality in HF. With a significant mortality and morbidity benefit when compared to placebo, the trial was stopped early. Interestingly, while mortality benefit was seen in non-ischemic patients, the greatest effect in CIBIS-II was seen in ischemic cardiomyopathy patients with NYHA class III symptoms.[17]

The U.S. HF Study Group[18] compared carvedilol to placebo in patients with chronic HF, primarily NYHA II and III, and was ultimately stopped early given the significant morbidity and survival benefits seen in the treatment group, although not powered to test mortality directly. Several years later, the Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS) trial[19] reaffirmed these benefits in moderate-severe HF.

Finally, the Metoprolol CR/XL Randomized Intervention Trial in congestive HF (MERIT-HF)[20] was a RCT which studied NYHA class II-IV patients assigned either to placebo or metoprolol CR/XL, with a primary endpoint of all-cause mortality. MERIT-HF reduced all-

cause mortality and hospitalizations for worsening HF, while simultaneously improving NYHA class and QoL.[20]

As evidenced in the previously mentioned RCTs, metoprolol succinate controlled release/extended release (CR/XL), carvedilol, and bisoprolol are the only approved BB to use in HFrEF. The use of one of these three agents carries a COR I LOE A recommendation and should be initiated in all patients with chronic HFrEF.[4-6] Patients who are not taking these specific BBs, but qualify for HFrEF diagnosis should be changed to one of the three discussed above.

***Aldosterone antagonist therapy***

Aldosterone plays a considerable role in the pathophysiology of HF and RAAS pathway.[9] The use of an aldosterone inhibitor was first highlighted in the Randomized Aldactone Evaluation Study (RALES).[21] Patients with NYHA III-IV symptoms were randomized to receive spironolactone, an aldosterone antagonist, or placebo in addition to an ACEI and loop diuretic.[21] The trial was discontinued early due to a 30% reduction in the risk of death in the spironolactone group. In addition to mortality benefits, it showed morbidity benefits through symptom improvement and NYHA class regression.[21] Of note, 10% of male patients who were treated with spironolactone reported gynecomastia or breast pain, a side effect attributed to the nonselective properties of spironolactone that allow the drug to bind to progesterone and androgren receptors. [21]

Following RALES the Eplerenone in Mild Patients Hospitalization and Survival Study in HF (EMPHASIS-HF)[22], enrolled NYHA class II HFrEF patients with an EF of 35% or less and were randomized to receive eplerenone vs. placebo. Eplerenone was found to reduce all-cause morbidity and reduce hospitalizations when added to standard HF therapy.[22] Given that eplerenone is more selective to the aldosterone receptor than spironolactone, gynecomastia was

quite rare and observed in less than 1% of trial participants. Hyperkalemia was the most common adverse event noted in the treatment arm of the trial.[22]

Candidates for aldosterone receptor antagonist therapy include those with NYHA class II-IV HF with an LVEF of less than 35% who are already receiving background therapy with a BB and ACEI.[4-6] This ACC/AHA COR I LOE A recommendation specifies that in order to deem a NYHA class II HF patient a candidate for aldosterone antagonists they should have been either hospitalized for a CV condition or have elevated plasma NP levels. Additionally, patients with an LVEF of 40% or less following an acute myocardial infarction, who develop HF symptoms or have diabetes mellitus should be initiated on an aldosterone antagonist.[4-6]

***Hydralazine and isosorbide dinitrate therapy***

The potential therapeutic benefit in HFrEF patients with combination hydralazine and isosorbide dinitrate was first explored in the Vasodilator-HF Trial (V-HeFT I).[11] In this trial patients with chronic HF already taking digoxin and diuretics were randomized to either placebo, prazosin, or hydralazine plus isosorbide dinitrate therapy. This trial aimed to evaluate if a mortality benefit existed with use of these vasodilator therapies. The group treated with both hydralazine and isosorbide dinitrate showed a statistically significant mortality reduction at two years, in addition to an improvement in LV function.[11]

The approval of ACEI use in HFrEF coincided closely in time to V-HeFT I prompting V-HeFT II.[12] This trial compared enalapril to hydralazine plus isosorbide dinitrate, and found that the ACEI had a more favorable effect on mortality than the vasodilator combination.[12] Upon retrospective analysis of the V-HEFT I and II trials, it was noted that African-Americans were more likely to respond to the combination of hydralazine and isosorbide dinitrate, whereas enalapril only provided a mortality reduction in their Caucasian counterparts. This interesting

observation was theorized to be related to a lower bioavailability of nitric oxide and a more active RAAS within the black subgroup.[11,12]

These striking discoveries prompted further investigation by means of the African-American HF Trial (A-HeFT)[23] which targeted blacks with NYHA III and IV symptoms and dilated LVs. This landmark study published in 2004 confirmed the previous findings that the addition of a fixed-dose combination of isosorbide dinitrate and hydralazine to standard HF therapy in this population was associated with a significant reduction in all-cause mortality and hospitalizations while also improving QoL.[23]

Two major recommendations were generated through the gains of these trials. The first endorses the use of combination hydralazine and isosorbide dinitrate to reduce morbidity and mortality in NYHA III and IV African American patients with HF who are already receiving ACEI and BB therapy. The second advises that the same therapy may be useful in reducing mortality and morbidity in this same cohort who are unable to tolerate an ACEI or ARB.[4-6]

**The Bad: HF Therapy for Symptom Relief**

***Diuretic therapy***

Diuretic therapy has maintained a seat at the table in the management of HF therapy through its symptom relief properties. Bearing in mind that it holds no mortality benefit, diuretics are mainly used for symptom relief in patients who present with acute decompensated HF and fluid retention.[24] These agents should be used in conjunction with GDMT.

Furosemide, bumetanide, and torsemide are three loop diuretics that are commonly used in clinical practice (Table 3).[25] Furosemide is the most widely used due to low cost, longevity, and provider familiarity. Nonetheless, both bumetanide and torsemide have better bioavailability and as a result are more efficacious in some situations.[26] In cases of refractory volume retention,

thiazide diuretics may be used in conjunction to loop diuretics.[25-28] A noteworthy study to consider when managing diuretic therapy is the Diuretic Optimization Strategies Evaluation (DOSE) trial[29] which showed no difference in outcomes between continuous infusion versus bolus dosing of furosemide in patients hospitalized for HF. In addition, there was no observed difference in the safety and efficacy of bolus injections in comparison to continuous infusions of loop diuretics. However, the higher dose resulted in better diuresis. [29]

***Digoxin***

Heralded as the oldest known CV drug, digoxin acts by increasing contractility through inhibition of the Na+/K+ATPase in the myocardium.[30] Though not effective at reducing mortality, this medication has been shown to decrease hospitalizations and improve functional class.[31,32] Current guidelines recommend to consider digoxin for HF patients who remain symptomatic despite the use of mortality reducing GDMT.[5,6] Another utility of digoxin in the HFrEF population is in patients with atrial fibrillation in whom a rate control strategy is preferred, and may be considered for those patients unable to tolerate a BB or who remain inadequately rate controlled on maximum doses of BB.[5,6]

Owing to a narrow therapeutic range, careful consideration should be given to the side effects and potential toxicity of digoxin prior to initiation. In light of this, digoxin use has significantly decreased, particularly in the era of safer and more proven HFrEF therapies such as BB, ACE and ARNIs. Findings from the Randomized Assessment of Digoxin on Inhibitors of the ANgiotensin Converting Enzyme (RADIANCE)[33] and Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)[34] trials suggest that withdrawal of digoxin in patients with HFrEF can result in worsening clinical symptoms, thus we recommend caution when discontinuing therapy.

## The Ugly: Inotropic Therapy

Despite their often controversial presence on the HF scene, continuous inotrope therapy maintains an important role in a few circumstances.[35] The two most commonly used inotropes in HFrEF are dobutamine, a beta-agonist, and milrinone, a phosphodiesterase-3 inhibitor.[35] The net effect of both of these inotropes on the myocardium is amplified calcium influx resulting in increased LV contraction. Both agents have the potential to cause peripheral vasodilation and hypotension, but is often more pronounced with milrinone. In addition, providers should be aware of their arrhythmogenic nature.[35]

Data has shown that routine use of these agents for acute decompensated HF without low-output or shock or for long-term treatment of HFrEF increases mortality.[36] Accordingly, current ACC/AHA guidelines urge against this practice.[5] Clinical scenarios that inotropes may be appropriate is in the setting of cardiogenic shock where inotropes can serve as a bridge-to-decision or as a palliative therapy. When employed as a bridge, the goal should be clearly defined, whether that includes initiation and uptitration of GDMT, addition of cardiac-resynchronization therapy, or advanced HF therapies such as mechanical circulatory support and cardiac transplantation. As a final resort, and in the absence of candidacy for advanced HF therapies, palliative inotropes may be used for symptomatic relief during end of life care.[5]

## The New Kids on the HF Block

### *Ivabradine therapy*

Ivabradine was approved for use in the US in 2015 and is a selective inhibitor of the $I_f$ current in the sinoatrial node. The primary therapeutic effect is heart rate reduction and is exclusive of any other effects on the heart or vascular system. The major publication driving

drug approval in the US was the Systolic HF treatment with the *I*f inhibitor ivabradine Trial (SHIFT) trial. [7] This European-based study aimed to assess the benefit of heart rate reduction with ivabradine in moderate to severe HF patients, with the vast majority of the enrollees falling into NYHA class II and III. The composite primary endpoint of CV death or hospital admission for worsening HF showed a relative risk reduction of 18%, but was driven by the reduction in HF hospitalizations.[7]

Ivabradine carries a class IIa LOE B-R recommendation in the most recent ACCF/AHA/HFSA guidelines,[6] and is indicated to reduce hospitalizations in NYHA II and III patients with symptomatic HFrEF who are receiving GDMT, but most importantly a BB at a maximum tolerated dose.[6] These patients should have a heart rate greater than 70 beats per minute (bpm) at rest and be in normal sinus rhythm (NSR). The adoption of this drug has been slow in the US and more data is needed to evaluate its full benefit in our HFrEF patient population.

***Angiotensin receptor-neprilyin inhibitor therapy***

The newest agent on the market has the potential to bring new enthusiasm to the treatment of HFrEF. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF)[8] sought to test the hypothesis that the addition of neurohormonal inhibition to RAAS inhibition via the ARB mechanism may be superior to ACEI alone. This double-blind trial compared a twice daily combination form of the ARB valsartan and the neprilysin-inhibitor sacubitril, otherwise known as LCZ696, to twice daily enalapril (10 mg twice daily) in NYHA class II-IV HF patients. The impressive 20% reduction in the endpoint of CV deaths or hospitalizations for HF in those treated with LCZ696 lead to early trial termination.[8]

The reduction in mortality and HF hospitalizations observed in this trial prompted the focused update of the ACC/AHA HF guidelines.[6] The COR I LOE B-R recommendation calls for replacement with ARNI in NYHA class II and III patients who are tolerating therapy with an ACEI or ARB to further reduce mortality.[6]

In regard-to the side effect profile, the results were very similar between the two drugs with the exception of a slightly higher rate of non-life threatening angioedema and hypotension in the LCZ696 group. It is important to note that an ACEI should not be co-administered with an ARNI and that, if already taking an ACEI, patients are recommended to discontinue the ACE-inhibitor at least 36 hours prior to starting sacubitril/valsartan.[6,8] More clinical trial data is warranted for additional recommendations including its use in hospitalized patients..

## Misconceptions, Uncertainties and Opportunities to Optimize GDMT

### *Drug selection, initiation and titration*

Step-wise initiation and titration of GDMT to efficacious doses as seen in RCTs is imperative to obtain any and all morbidity and mortality benefits in HF patients. Regardless of symptom severity, ACEI therapy remains first-line therapy followed by BB therapy.[4-6] We recommend starting at low doses with uptitration and frequent clinical assessment during that period. Following ACEI initiation, serum creatinine and potassium levels should be assessed within 1 to 2 weeks.

As previously mentioned, and unlike ACEIs, the benefits obtained with BB therapy are not a class effect, therefore only metoprolol succinate, carvedilol or bisoprolol should be used in HFrEF.[4-6] Early initiation of BB therapy is imperative and prescribers need not wait until target doses of ACEI are achieved prior to adding it.[37,38] This strategy has led to greater improvement in symptoms and reduction in the risk of death when compared to delayed use of BBs until

maximal dose ACE is reached.[37,38] It is acceptable to discontinue BB therapy in the setting of marked hypoperfusion. Moreover, among patients admitted for new onset HF, initiation of BB before discharge has been shown to increase adherence and likelihood to achieve target doses and is recommended in the Guidelines.[39]

When changing from one BB to another, current data suggest starting the new agent at an equivalent dose with close monitoring of clinical status and adverse events. During the up-titration period, the risk of hypotension can be avoided by administering the BB and the ACEI at different times of day. In addition, BB should be titrated to maximally tolerated dose regardless of target heart rate as recent data suggested that titration of BB doses may provide a greater benefit than reduction of heart rate in well treated HFrEF patients.[4,40]

***Patients with CKD***

The use of ACEI and aldosterone antagonists in patients with CKD continues to be a conundrum in clinical practice. Data regarding the use of these agents within this population remain scarce, as most HF trials exclude patients with significant renal dysfunction. Hence the conventional wisdom has been to avoid the use of these therapies entirely in patients with impaired renal function. Guidelines recommend the use of these agents with caution in patients with advanced renal impairment and with clear directions in regard to creatinine and potassium levels that would preclude the use of these agents.[5,6] Despite the aforementioned, we believe these agents and underused, are potentially safe, and should be used (with caution) as they have the ability to benefit this population.

The element of renal dysfunction that exists in a large majority of HF patients is quite indicative of the struggle clinicians face in the complexities of the cardio-renal relationship. The increased prevalence of CKD in the HFrEF population highlights that ACEI and aldosterone

antagonist use may be beneficial in improving renal perfusion and decreasing congestion through their systemic vasodilatory properties as well as providing renal protection. It is important to note that patients with CKD stages 1-3 have been included in landmark HF clinical trials and data suggest survival benefit when used in this patient population.[41] In addition a recent study[42] suggested a strong association between ACEI use and survival in HFrEF patients with severe renal impairment, which may be indicative that ACEI use may be associated with an even higher absolute mortality reduction in this population.[42]

***The elderly***

Elderly patients now represent the largest group of HFrEF patients and paradoxically, limited data exists on the efficacy of GDMT in this population due to their under-representation and frequent exclusion from large clinical trials.[1] Without question, age related physiological changes and drug metabolism in the elderly put them at higher risk for adverse events.[43] Moreover, comorbid conditions such as renal and liver impairment further complicate the elderly's response to drugs and increase their risk for adverse events such as hypotension and bradycardia. Despite the scarcity of data in the elderly, there are two noteworthy trials. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)[44] included over 2000 patients over the age of 70 who were randomized to receive either nebivolol or placebo. Treatment with this agent was found to be statistically significant in decreased all-cause mortality and CV hospitalization. Strengths of the trial include the exclusive focus on the older cohort of HF patients and an extensive follow-up of 21 months.[44] Limitations in this trial primarily include the use of nebivolol, a BB that does not carry a HFrEF indication, and the presence of HFpEF patients due to laxity in the inclusion criteria. Nevertheless, the study offered some valuable lessons with regard to tolerability and

response to therapy in the elderly.[44] The CIBIS in Elderly (CIBIS-ELD)[45] was another large study that focused on drug specific side effects. This multicenter, double-blind superiority trial of bisoprolol versus carvedilol included 883 elderly HF patients with both HFpEF and HFrEF. Although tolerability was low, no differences between the 2 groups were seen in the primary end point as defined by reaching and maintaining guideline-recommended target doses after 12 weeks of therapy.[45] Intriguingly, adverse events varied among the two drugs in the trial. While bradycardia was more common in the bisoprolol group, pulmonary adverse events were more likely to occur with carvedilol. Despite the above-mentioned studies, many important questions remain unanswered on the efficacy and safety of HF GDMT in the elderly.[45] Large clinical trials and data from national registries are essential to close this knowledge gap.

***Incorporating Sacubitril/Valsartan into Clinical Practice***

With a 20% reduction in CV mortality,[8] there is no doubt that sacubitril/valsartan is by far the most efficacious HFrEF therapy developed in the last decade supplanting both ACEI and ARB therapies. Despite this, there has been a very slow adoption of this novel drug in the HF community. Cost may be a factor in the slow implementation of this ANRI into clinical practice, though other concerns exist and have been raised from experts in the field as well as community providers. One of those concerns includes a middle dose of enalapril compared to a higher equivalent dose of valsartan. Often times translating clinical trial results and implementing them to daily practice can be challenging. The reality is patients tend to be older as compared to clinical trials, and frequently possess comorbidities that would be otherwise exclude them from clinical trials. An important limiting factor in prescribing this therapy is low BP. In the PARADIGM-HF study,[8] roughly 1/5 of patients were excluded in the run-in phase due to hypotension in either the sacubitril/valsartan or enalapril group.[8] For this reason,

we recommend caution when using this agent in the elderly, in patients with borderline-low BP, or in the advanced HF population. We urge clinicians to use the "start low and titrate slow" approach as it is likely the safest method to avoid such events. Identifying the patient population that will benefit most from this drug can also be arduous. The majority of patients enrolled in PARADIGM-HF were stable patients with NYHA class II patients, which leaves uncertainty in the efficacy and safety of this drug in sicker patients. In a recent study,[46] 84 % of HFrEF patients in the US were projected to be good candidates for ARNI therapy highlighting the clear opportunity to expand the use of this drug in patients who would benefit the most.[46] Two additional clinical trials are underway: ComParIson Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode (PIONEER-HF) study and the EntrestoTM In Advanced Heart Failure HFN-LIFE trial. The PIONEER study will be exploring the safety and efficacy of in-hospital initiation of ARNI therapy and its potential role among patients hospitalized for acute decompensated HF. The LIFE trial will focus on the utility of ARNI therapy in patients with advanced HF.

## Conclusion and Future Directions

The journey to efficacious pharmacologic therapy in HFrEF has been far from fleeting. Beginning with the V-HeFT trial[11] in 1986 which set the stage by introducing vasodilator therapy in the HF arena, and ending most recently with the PARADIGM-HF trial,[8] major milestones have been met along the way. For decades, ACEI, BB, aldosterone antagonists and combined therapy with hydralazine- isosorbide dinitrate have been the mainstay therapies for HFrEF. With the most recent focused updates to the ACC/AHA Guidelines for the management of HF,[6] several new pharmacologic interventions are now available and may provide superior survival benefits in comparison to established agents. One fundamental take-away message is that

provider familiarity with proper patient selection, initiation, maintenance, and adverse events related to the different drug classes is of the utmost importance. Continued collection of data through clinical trials and registries related to this chronic illness is key in ensuring progressive treatment options with a special focus on previously understudied populations in the literature. It is only through this undertaking that we can begin to remedy the HF epidemic.

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**Tables and Figures Legends:**

Figure 1. RAAS and SNS targets for therapeutic interventions.

Table 1. Major pharmacologic HFrEF trials.

Table 2. Currently Available Pharmacotherapy for HFrEF. Adapted from Yancy et al.[6]

Table 3. Commonly Used Diuretics in HFrEF.

**Figure 1**

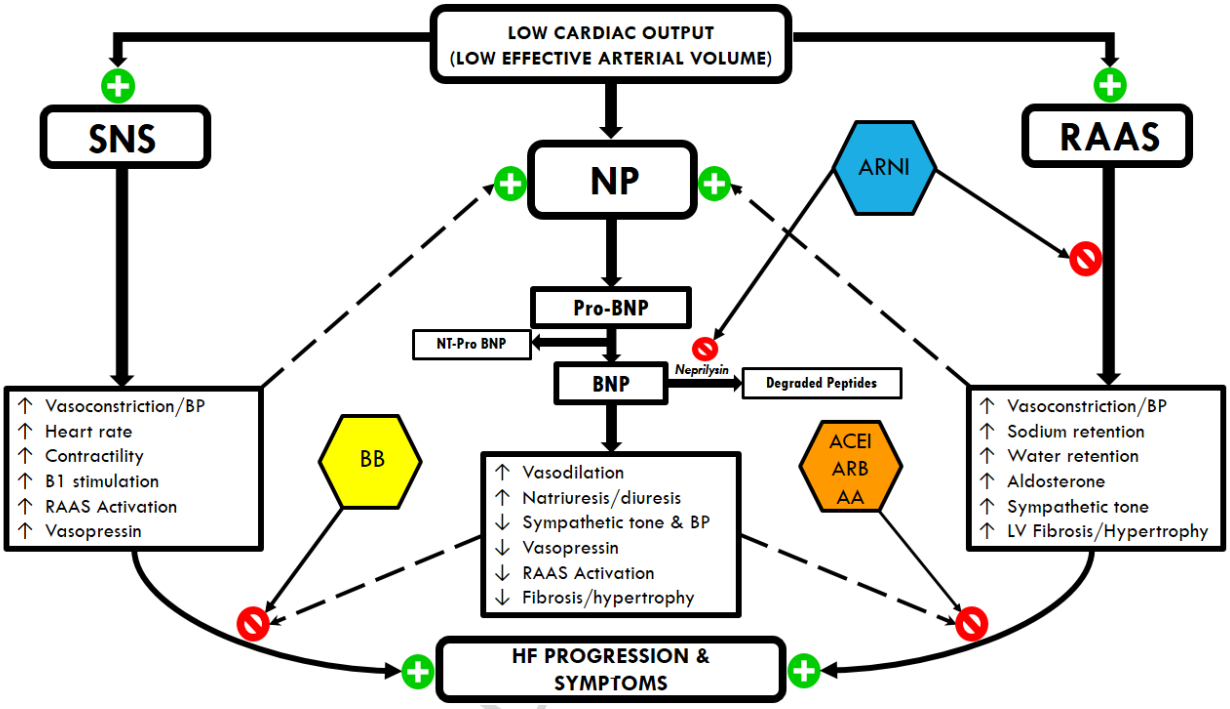

**Table 1. Major pharmacologic HFrEF trials.**

| Clinical Trial Acronym | Year | Trial Population Characteristics | HF Background Therapy (>50%) | Intervention | Comparator | Mortality/Morbidity Findings | Mortality Reduction |
|---|---|---|---|---|---|---|---|
| **V-HeFT I**[11] | 1986 | Mild to moderate HF<br>LVEF <45% | Digoxin, diuretics | Hydralazine<br>Isosorbide dinitrate OR Prazosin | Placebo | ↓ in mortality<br>↑improvement in LV function in hydralazine/isosorbide dinitrate group | 38% |
| **CONSENSUS**[13] | 1987 | NYHA IV HF<br>Increased heart size | Diuretics, spironolactone, digitalis | Enalapril | Placebo | ↓ in mortality<br>↓ NYHA class, heart size and medication requirements | 27% |
| **SOLVD-Treatment**[14] | 1991 | NYHA II, III<br>LVEF ≤35% | Digoxin, diuretics | Enalapril | Placebo | ↓ in mortality<br>↓ in hospitalizations | 16% |
| **V-HeFT II**[12] | 1991 | NYHA II,IV | Digoxin, diuretics | Hydralazine Isosorbide dinitrate | Enalapril | ↓ in mortality<br>enalapril group at 2 years<br>↔hospitalizations between groups | N/A |
| **US Carvedilol HF Study**[18] | 1996 | NYHA II, III, IV<br>LVEF ≤35% | ACEI, digoxin, diuretics | Carvedilol | Placebo | ↓ in mortality hospitalizations | 65% |
| **CIBIS II**[17] | 1999 | NYHA III, IV<br>LVEF <35% | ACEI, digoxin, diuretics | Bisoprolol | Placebo | ↓ in mortality and hospitalizations in bisoprolol group | 34% |
| **MERIT-HF**[20] | 1999 | NYHA II, III, IV<br>LVEF <40% | ACEI, diuretics | Metoprolol XL | Placebo | ↓ in mortality and hospitalizations<br>↑ functional class and QOL in metoprolol group | 39% |
| **RALES**[21] | 1999 | NYHA III-IV<br>LVEF ≤35% | ACEI, digoxin, diuretics | Spironolactone | Placebo | ↓ in mortality<br>↑ NYHA class and QOL | 30% |
| **COPERNICUS**[19] | 2001 | NYHA IV<br>LVEF <25% | ACEI/ARB, digoxin,diuretics | Carvedilol | Placebo | ↓ in mortality and hospitalizations | 35% |
| **Val-HeFT**[15] | 2001 | NYHA II, III, IV<br>LVEF<40%<br>Increased heart size | ACEI, digoxin, diuretics | Valsartan | Placebo | ↔ all-cause mortality<br>↓ hospitalizations<br>↑ NYHA class, QOL | N/A |
| **CHARM**[16] | 2004 | NYHA II, III, I V<br>LVEF≤40% | ACEI, BB, digoxin, digoxin | Candesartan | Placebo | ↓ in mortality<br>Reduction in mortality and hospitalizations | 33% |
| **A-HeFT**[23] | 2004 | NYHA III, IV<br>AA patients<br>Increased heart size | ACEI, BB, dgoxin, diuretics | Hydralazine/ isosorbide dinitrate | Placebo | ↓ in mortality and hospitalizations | 43% |
| **SHIFT**[7] | 2010 | NYHA II, III, IV<br>LVEF ≤35%<br>Resting HR ≥70 bpm in NSR | ACEI, aldosterone antagonist, BB, diuretics | Ivabradine | Placebo | ↓ hospitalizations | N/A |
| **EMPHASIS-HF**[22] | 2011 | NYHA II<br>LVEF ≤35% | ACEI, BB, diuretics | Eplerenone | Placebo | ↓ in mortality and hospitalizations | 37% |
| **PARADIGM-HF**[8] | 2014 | NYHA II, III, IV<br>LVEF ≤35% | Aldosterone antagonist, BB, diuretics | LCZ696 (sacuibitril/valsartan) | Enalapril | ↓ in mortality and hospitalizations<br>↑ QOL in LCZ696 group | 16% |

Abbreviations: HFrEF, heart failure with reduced ejection fraction; HF, heart failure; V-HeFT: Vasodilator in Heart Failure Trial; LV, Left ventricle or left ventricular; LVEF, left ventricular ejection fraction; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; NYHA, New York Heart Association; SOLVD, Studies of Left Ventricular Dysfunction; US, United States; ACEI, angiotensin-converting-enzyme inhibitors; CIBIS, Cardiac Insufficiency Bisoprolol Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; QOL, quality of life; RALES, Randomized Aldactone Evaluation Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study Group; ARB, angiotensin receptor blockers; Val-HeFT, Valsartan Heart Failure Trial; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; BB, beta blockers; A-HeFT, African-American Heart Failure Trial; SHIFT, Systolic Heart Failure Treatment with the If inhibitor Ivabradine trial; HR, heart rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

**Table 2. Currently Available Pharmacotherapy for HFrEF.**

| Drug | Starting dose | Maximum daily dose | Mean dose achieved in clinical trials | COR | LOE |
|---|---|---|---|---|---|
| **$I_f$ channel inhibitor** | | | | | |
| Ivabradine | 5 mg QD | 7.5 mg BID | 6.4 mg BID (at 28 days)<br>6.5 mg BID (at 1 year) | II | B-R |
| **ARNI** | | | | I | B-R |
| **Sacubitril/Valsartan** | 49/51 mg BID (therapy may be initiated at 24/26 mg BID) | 97/103 mg BID | 375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID | | |
| ***ACE*** | | | | I | A |
| **Captopril** | 6.25 mg TID | 50 mg TID | 122.7 mg QD | | |
| **Enalapril** | 2.5 mg BID | 10-20 mg BID | 16.6 mg QD | | |
| **Fosinopril** | 5-10 mg QD | 40 mg QD | N/A | | |
| **Lisinopril** | 2.5-5 mg QD | 20-40 mg QD | 32.5-35 mg QD | | |
| **Ramipril** | 1.25-2.5 mg QD | 10 mg QD | N/A | | |
| **Trandolapril** | 1 mg QD | 4 mg QD | N/A | | |
| **Perindopril** | 2 mg QD | 8-16 mg QD | N/A | | |
| **Quinapril** | 5 mg BID | 20 mg BID | N/A | | |
| ***ARB*** | | | | | |
| **Candesartan** | 4-8 mg QD | 32 mg QD | 24 mg QD | | |
| **Losartan** | 25-50 mg QD | 50-150 QD | 129 mg QD | | |
| **Valsartan** | 20-40 mg BID | 160 mg BID | 254 mg QD | | |
| ***BB*** | | | | | |
| **Bisoprolol** | 1.25 QD | 10 mg QD | 8.6 mg QD | | |
| **Carvedilol** | 3.125 mg BID | 50 mg BID | 37 mg QD | | |
| **Carvedilol CR** | 10 mg QD | 80 mg QD | N/A | | |
| **Metoprolol Succinate** | 12.5-25 mg QD | 200 mg QD | 159 mg QD | | |
| **Aldosterone anatgonists** | | | | I | A |
| **Spironolactone** | 12.5-25 mg QD | 25 mg QD or BID | 26 mg QD | | |
| **Eplerenone** | 25 mg QD | 50 mg QD | 42.6 mg QD | | |
| ***Hydralazine and isosorbide Dinitrate*** | | | | I | A |
| **Fixed dose combination** | 37.5 mg hydralazine/ 20 mg isosorbide dinitrate TID | 5 mg hydralazine/ 40 mg isosorbide dinitrate TID | ~175 mg hydralazine/90 mg isosorbide dinitrate QD | | |
| **Hydralazine and isosorbide** | Hydralazine: 25 to 50 mg, TID or QID and isosorbide dinitrate: 20 to 30 mg TID or QID | Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses | N/A | | |

Abbreviations: GDMT, guideline directed medical therapy; HFrEF, heart failure with reduced ejection fraction; mg, milligram; ARNI, angiotensin receptor-neprilysin inhibitor; QD, every day; BID, twice daily; ACE, angiotensin-converting-enzyme inhibitor; TID, three times daily; ARB, angiotensin receptor blocker; BB, beta blocker; CR, controlled release; QID, four times daily

**Table 3. Properties of Commonly Used diuretics in HFrEF**

| Agent | Potency | Oral:IV | Duration of Effect | Bioavailabilty | Half life |
|---|---|---|---|---|---|
| **Furosemide** | 1x | 2:1 | 6-8 hrs | 10-100 % | 2 |
| **Bumetanide** | 40x | 1:1 | 4-6 hrs | 80-100 % | 1-1.5 |
| **Torsemide (not available IV)** | 2x | 1:1 | 6-16 hrs | 80-100 % | 3.5 |

Abbreviations: x, times; IV, intravenous; hrs, hours.

Conflict of interest: None.