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REVIEW ARTICLE

Contemporary Pharmacologic Management of Heart Failure with Reduced Ejection Fraction: A Review

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Abstract: Heart failure with reduced ejection fraction (HFrEF) is defined as the presence of typical symptoms of heart failure (HF) and a left ventricular ejection fraction ≤ 40%. HFrEF patients constitute approximately 50% of all patients with clinical HF. Despite breakthrough discoveries and advances in the pharmacologic management of HF, HFrEF patients continue to pose a significant economic burden due to a progressive disease characterized by recurrent hospitalizations and need for advanced therapy. Although there are effective, guideline-directed medical therapies for patients with HFrEF, a significant proportion of these patients are either not on appropriate medications' combination or on optimal tolerable medications' doses. Since the morbidity and mortality benefits of some of the pharmacologic therapies are dose-dependent, optimal medical therapy is required to impact the burden of disease, quality of life, prognosis, and to curb health care expenditure. In this review, we summarize landmark trials that have impacted the management of HF and we review contemporary pharmacologic management of patients with HFrEF. We also provide insight on general considerations in the management of HFrEF in specific populations. We searched PubMed, Scopus, Medline and Cochrane library for relevant articles published until April 2019 using the following key words "heart failure", "management", "treatment", "device therapy", "reduced ejection fraction", "guidelines", "guideline directed medical therapy", "trials" either by itself or in combination. We also utilized the cardiology trials portal to identify trials related to heart failure. We reviewed guidelines, full articles, review articles and clinical trials and focused on the pharmacologic management of HFrEF.

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1. INTRODUCTION

Chronic heart failure (CHF) is a progressive medical condition characterized by recurrent hospitalizations and high mortality. The prevalence of heart failure (HF) continues to rise, owing largely to an aging population, an epidemic of hypertension, obesity, and coronary artery disease and improved survival of patients with HF [1]. It is a systemic syndrome that has a complex heterogeneous clinical course [2] characterized by periods of clinical stability and periods of decompensation. The management of HF, including device implantation [3, 4], is guided by assessment of left ventricular ejection fraction (LVEF), which has been shown to be predictive of outcomes even in the absence of symptoms [5]. Patients with HF have been traditionally categorized into 2 main clinical phenotypes based on their LVEF as HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) defines HFrEF as the presence of clinical HF with an LVEF ≤ 40% and HFpEF as the presence of clinical HF with an LVEF ≥ 50%. Patients with clinical HF and an LVEF in the range of 41% to 49% are categorized as borderline HFpEF. The present review focuses on the pharmacologic management of HFrEF and the evidence from randomized controlled trials (RCTs) that serve as the basis for use of both established and novel pharmacologic therapies. We also propose therapeutic strategies to individualize and optimize HF therapy for undertreated patients.

2. PHARMACOLOGIC MANAGEMENT OF HEART FAILURE

Guideline-directed medical therapy (GDMT) has led to a reduction in HF hospitalizations and improvement in survival among HFrEF patients. GDMT for management of

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HFrEF encompasses the clinical evaluation, diagnostic testing, and pharmacological and interventional treatments that provide tailored, optimal care for patients with HFrEF [6]. The cornerstone of pharmacologic therapy for HFrEF include agents that target the sympathetic nervous system (SNS) and the renin-angiotensin aldosterone system (RAAS), which have been recognized as the central neurohormonal pathways in the pathogenesis of HFrEF [7].

3. SYMPATHETIC NERVOUS SYSTEM (SNS) AND RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS)

HF is characterized by impairment of ventricular filling and/or ejection of blood. Low effective arterial volume leads to over-activation of the SNS and RAAS, and overproduction of anti-diuretic hormone (ADH). RAAS activation can result directly from renal hypoperfusion or SNS activation. These adaptive processes serve as compensatory mechanisms early in the course of disease, and are intended to restore an effective circulating volume and cardiac output to maintain adequate tissue perfusion. However, chronic stimulation of the SNS leads to down-regulation of the beta-adrenergic receptors, depletion of catecholamine stores and poor myocardial response to released catecholamines. Chronic adrenergic activation is also directly linked to cardiac myocyte necrosis, fibrosis and hypertrophy in animal models [8, 9]. Activation of the RAAS system leads to increased production of angiotensin II, aldosterone and ADH. The activation of these pathways leads to vasoconstriction and fluid retention, ultimately contributing to the maladaptive myocardial remodeling and hypertrophy observed in HF. Pharmacotherapy targeted at inhibiting these systems have therefore become the focus of intensive research efforts that led to revolutionizing the management of HFrEF, and the widespread use of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta adrenergic antagonists (beta-blockers) and mineralocorticoid receptor antagonists.

4. ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin Converting Enzyme Inhibitors prevent the conversion of angiotensin I to angiotensin II. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial (1987), demonstrated an astonishing 18% absolute reduction in mortality in New York heart association (NYHA)-IV HFrEF patients at 6 months in patients treated with enalapril as compared to those treated with placebo [10]. The subsequent Studies of Left Ventricular Dysfunction (SOLVD) trial (1991), demonstrated similar findings in NYHA II & III HFrEF patients, with an observed absolute reduction in all-cause mortality of 5% in the enalapril intervention arm as compared to placebo during the four year study period [11]. On the basis of an observed trend towards increased survival with the combination of isosorbide dintrate and hydralazine in patients with HFrEF in the Vasodilator Heart Failure Trial (V-HeFT) 1986, the V-HeFT II trial (1992), randomized patients with primarily NYHA II-III HFrEF on diuretics and digoxin at baseline to enalapril or isosorbide dintrate/hydralazine. This landmark trial demonstrated a 7% absolute reduction in mortality in this patient population with enalapril as compared to the combination of isosorbide dintrate/hydralazine at two years follow-up. The Survival and Ventricular Enlargement (SAVE) trial (1992), demonstrated a 19% reduction in all-cause mortality when captopril was compared with placebo among patients with left ventricular systolic dysfunction complicating acute myocardial infarction [12]. Unless contraindicated, the use of ACEI in all patients with HFrEF is a class 1 recommendation; level of evidence-A by the ACCF/AHA [6]. Therapy should be initiated at low doses and should be used cautiously in patients with renal dysfunction and/or elevated serum potassium. Some of the adverse reactions of ACEI include cough, hypotension, worsening renal function and hyperkalemia. These agents are generally well-tolerated by HFrEF patients, but patients with the advanced or end-stage disease often require down-titration or discontinuation of the medications owing to hypotension, worsening renal function, or hyperkalemia. The intolerance of ACEI in this population is a known poor prognostic indicator that suggests that advanced therapies, including transplant, may be imminent.

5. ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

Angiotensin-receptor blockers inhibit the effect of angiotensin II on type 1 angiotensin (AT-1) receptors thus inhibiting the downstream effects of angiotensin II on blood vessels and aldosterone biosynthesis. Morbidity but not mortality benefits of this therapy were observed in the Valsartan HF trial (Val-HeFT) 2001, where the addition of valsartan to standard HFrEF therapy (ACE inhibitor and/or beta blocker) was compared to placebo. In the trial, valsartan did not confer a survival benefit [13]. An important finding of this trial was that the combination of ACEI and ARBs led to worsening of renal function. The mortality benefit of ARB therapy was first demonstrated in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial (2003), which demonstrated a reduction in the composite outcome of cardiovascular mortality or heart failure hospitalizations in NYHA II-IV HFrEF patients treated with candesartan versus placebo [14]. Of particular note, patients enrolled in the CHARM-Alternative had to be intolerant to ACEI. The CHARM-Added trial demonstrated a reduction in the composite outcome of cardiovascular mortality and HF hospitalizations when candesartan was added to an ACEI as compared to placebo, but did not demonstrate a difference in all-cause mortality. As had previously been demonstrated in the Val-Heft trial, the addition of an ARB to ACEI in CHARM-Added led to increased rates of renal dysfunction and hyperkalemia [15]. The lack of marked benefit with the addition of an ARB to ACEI therapy in combination with the observed worsening of renal function led to the subsequent recommendation against the routine addition of ARBs to ACEI in patients with HF, though the addition of an ARB to ACEI therapy can be considered in patients with persistently symptomatic HF who are already on a beta blocker and in whom an aldosterone antagonist is not indicated (class IIb, LOE A). ARBs are a class 1A recommendation for use in HFrEF patients with current or prior symptoms who are ACE inhibitors intolerant [7]. ARBs should be initiated at a low dose and titrated to the maximally tolerated dose. Renal function and

serum potassium should be closely monitored within 2 weeks of the initiation of therapy. The adverse effect profile of ARB therapy is similar to that of ACE inhibitors, though there is a notably lower incidence of cough and much lower occurrence of angioedema [6], and it is, therefore, a reasonable alternative for patients who are intolerant to ACE inhibitors.

6. BETA-ADRENOCEPTOR ANTAGONISTS (BETA-BLOCKERS)

Beta-blocker therapy has become a cornerstone in the pharmacologic management of HFrEF in recent decades. Beta blockers target the adrenergic receptor and inhibit the systemic effects of chronic sympathetic activation. While landmark trials have demonstrated mortality and morbidity benefits with the use of beta-blockers in HFrEF, the benefit does not appear to be a class effect, as the benefits have only been demonstrated with specific beta blockers. In the Cardiac Insufficiency Bisoprolol Study (CIBIS), bisoprolol was compared to placebo in HFrEF patients. Bisoprolol reduced hospitalizations and improved the NYHA functional status by at least one as compared to placebo [16]. The subsequent CIBIS-II 1999 trial demonstrated a 5% absolute reduction in all-cause mortality in stable NYHA III-IV HFrEF patients with the use of bisoprolol as compared to placebo [17]. The Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF) 1999, demonstrated a 34% relative risk reduction in all-cause mortality per patient-year in HFrEF patients treated with metoprolol succinate as compared to placebo. A composite outcome of all-cause mortality and all-cause hospitalizations was also reduced with the use of Metoprolol XL [18]. The study was stopped earlier than intended due to a dramatic mortality benefit that was noted during an interim analysis of the study. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study (2002), explored the benefits of carvedilol in HFrEF. In the study, carvedilol reduced annual mortality rates, hospitalizations and cardiogenic shock when compared to placebo [19]. A large, well-designed head-to-head trial comparing metoprolol to carvedilol was accomplished in the Carvedilol Or Metoprolol European Trial (COMET). While the findings of the trial suggested that carvedilol reduced all-cause mortality when compared to metoprolol in HFrEF patients with NYHA II-IV symptoms [20], the patients randomized to metoprolol were given metoprolol tartrate, a formulation of metoprolol that had not been demonstrated in RCTs to provide a mortality benefit in HFrEF. Moreover, the target doses of the beta blockers in the two arms of the trial were not equivalent. MERIT-HF, CIBIS-II, and COPERNICUS have served as the basis of evidence for the ACCF/AHA class 1A recommendation for the use of metoprolol succinate, bisoprolol or carvedilol in all HFrEF patients unless contraindicated. Beta blockade should be initiated at a low dose and titrated to the maximally tolerated dose. Caution should be exercised in patients with bradycardia and those with symptomatic reactive airway disease. In patients with HF exacerbation who have been compliant with beta blocker therapy, it is safe to continue therapy in the absence of cardiogenic shock. On the other hand, beta blockers should not be initiated in HFrEF patients with fluid overload until euvolemic state is achieved. Initiation of a beta blocker prior to discharge is recommended provided intravenous inotropic therapy for the management of HF was not required [7]. We have previously reported that beta blocker therapy is safe for use in patients with positive urine toxicology testing for cocaine except for those with concomitant signs and symptoms of acute cocaine intoxication [21]. The dose of the chosen beta-blocker should be titrated to the maximally tolerated target dose that was used in the relevant clinic trial except when limited by adverse effects.

7. MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)

Mineralocorticoid receptor antagonists inhibit the effect of aldosterone on the mineralocorticoid receptors, thereby preventing the downstream effects of aldosterone on sodium and water retention. The evidence for their use was first demonstrated in the Randomized Aldactone Evaluation Study (RALES) 1999 trial. In RALES, the addition of spironolactone to standard HF therapy resulted in an 11% absolute reduction in all-cause mortality as compared to placebo. The trial also demonstrated a 35% relative reduction in HF hospitalizations and an improved NYHA functional class in NYHA III-IV patients with an LVEF <35% [22]. Over 90% of the patients enrolled in RALES were on an ACEI at baseline and two-thirds were on digoxin, though only about 10% of the patients were on a beta blocker. Eplerenone, a relatively more selective MRA, was first studied in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) 2003 where it conferred a 15% relative reduction in mortality in patients with left ventricular dysfunction and HF complicating acute myocardial infarction. Eplerenone was also associated with reductions in sudden cardiac death and HF hospitalizations [23]. These findings led to further investigation on the impact of use of eplerenone in patients with NYHA II HFrEF. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) 2011 trial demonstrated a reduction in death and hospitalizations in patients with LVEF =<35% and NYHA class II symptoms by eplerenone as compared to placebo [24]. Unlike the RALES trial, most (86.6%) of the patients enrolled in the EMPHASIS-HF trial were on a beta blocker at baseline. These trials provided evidence for adding MRA therapy, which should be done carefully. MRA therapy is a class 1, LOE-A recommendation for NYHA II-IV patients with an LVEF <35% who are already receiving beta blocker and ACEI therapy. NYHA II HFrEF patients who are considered for MRA therapy should have a history of cardiovascular hospitalization for HF or laboratory evidence of elevated plasma natriuretic peptide levels. MRA therapy is also a class 1, LOE-B recommendation for patients with an LVEF of <40% following acute myocardial infarction, who develop HF symptoms or have diabetes mellitus [7]. In this group of patients, therapy with a beta blocker and ACEI should be initiated prior to MRA therapy. Since MRAs are potassium sparing diuretic, the major side effect associated with their use is hyperkalemia, especially when used concomitantly with an ACEI or ARB. Therefore, they should not be initiated in patients with serum creatinine greater than 2.5 mg/dl in men or 2.0 mg/dl in women (or an estimated glomerular

filtration rate <30 ml/min/1.73 m^2), and/or a potassium level greater than 5.0 mEq/L [7]. Careful risk assessment and close monitoring is necessary during the initiation and maintenance of MRA therapy. Renal function and potassium levels should be checked within the first 2 weeks of the initiation of therapy and subsequently depending on the stability of the patient's renal function. Gynecomastia may occur with spironolactone.

8. HYDRALAZINE-ISOSORBIDE DINITRATE THERAPY

The combination of hydralazine with isosorbide dintrate (ISDN) provides vasodilator properties which help reduce both preload and afterload. The Vasodilator Heart Failure Trial (V-HeFT) 1986, demonstrated a trend towards improved survival when ISDN was combined with hydralazine as compared to prazosin or placebo in patients with HFrEF [25]. The African-American Heart Failure Trial (A-HeFT) demonstrated improved survival and a reduction in hospitalizations among black HFrEF patients with the addition of hydralazine/ISDN to standard therapy of an ACEI, beta-blocker, and diuretics [26]. The trial was terminated prematurely based on an interim analysis that demonstrated a 4% absolute reduction in all-cause mortality and 33% relative reduction in first hospitalizations due to HF. The findings of this study formed the basis for recommending this medication combination by the ACCF/AHA for self-described African Americans with NYHA class III-IV HFrEF who are already receiving optimal therapy with an ACEI and beta blocker. This combination is also recommended in a similar cohort of HF patients intolerant to ACEI or ARB therapy [7].

Corin, a transmembrane protease that is expressed in cardiomyocytes is present in most Blacks. The corin allele has been linked with prognosis in Black HFrEF patients receiving ISDN. The protease cleaves pro-atrial natriuretic peptide (ANP) and pro-brain natriuretic peptide (BNP) into their biologically active forms. A mutation in the corin gene product significantly reduces natriuretic peptide processing capacity and imparts degradation to its biologically active forms. As such, the corin I555(P568) allele has been associated with increased risk of death and HF hospitalization in HFrEF patients receiving standard neurohormonal blockade. However, the addition of fixed-dose combination of hydralazine/ISDN reduces this risk in Blacks [27].

9. NEWER THERAPIES

9.1. Angiotensin Receptor-Neprilysin Inhibitor (ARNI) Therapy

Neprilysin is a neutral endopeptidase and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatory, and anti-proliferative effects. The mortality and morbidity benefits of ARNI therapy in HFrEF were first evaluated by the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), 2002. The primary endpoint was a combined risk of death or HF hospitalization. The study demonstrated that Omapatrilat was not inferior but not superior to ACEI alone in reducing the risk of a primary clinical event. The trial was stopped prematurely due to a markedly increased risk of angioedema [28]. Omapatrilat is a medication combining a neprilysin inhibitor and ACEI. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) 2014, was the first mortality trial to evaluate the use of ARNIs in heart failure patients. The trial was terminated early after interim analysis of the study found a 20% relative reduction in the composite outcome of cardiovascular mortality or HF hospitalization with ARNI therapy as compared to enalapril in NYHA class II-IV HFrEF patients. In the study, ARNI therapy led to a relative risk reduction in all-cause mortality of 16% [29]. The ARNI was generally well tolerated except for a higher rate of non-fatal angioedema and symptomatic hypotension. The ARNI group had lower rates of renal impairment, hyperkalemia and cough when compared to the enalapril group. Caution should be taken in patients who are already on an ACEI before switching to ARNI. Concomitant administration or use of either agent within 36 hours of discontinuation of one or the other is contraindicated and should be avoided, largely owing to the increased risk of angioedema that had been found with the combination of these agents in the OVERTURE trial. Although the target enalapril dose (10 mg twice daily) used in PARADIGM-HF differs from that used in clinical practice, it is similar to the target dose that demonstrated benefit in the CONSENSUS and SOLVD trials. As such, in patients with NYHA class II-III HFrEF who are tolerant to ACEI or ARB therapy, replacement by an ARNI is a class 1B recommendation to further reduce morbidity and mortality [6]. The comParIson Of sacubitril/valsartan versus Enalapril on Effect on ntpRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial (2018), demonstrated the safety, tolerability and efficacy of this therapy compared to enalapril when initiated during hospitalization for acute decompensated HF. Unlike the PARADIGM-HF trial, the PIONEER-HF trial exclusively enrolled patients hospitalized for a primary diagnosis of acute on chronic HF [30].

9.2. Ivabradine Therapy

Ivabradine selectively inhibits the pacemaker current (I_f) in the sinoatrial node to slow the heart rate. In the Systolic Heart failure treatment with the I_f inhibitor ivabradine (SHIFT) trial (2010) enrollment was limited to NYHA II-IV HFrEF patients with a resting heart rate of ≥70 bpm and at least one HF-related hospitalization in the prior year. The trial demonstrated that the addition of ivabradine to contemporary medical therapy (ACE inhibitor/ARB, beta blockers, and a MRA) resulted in an 18% relative reduction in the composite outcome of HF mortality or hospitalization. The benefit of ivabradine was mostly driven by a 26% relative reduction in HF hospitalization [31]. Of particular note, there was no demonstrable all-cause mortality benefit. Although patients enrolled in this trial were on guideline directed medical therapy that has demonstrated mortality benefit in different trials, only 25% of patients studied were on optimal doses of beta-blocker therapy. Therefore, it is important to initiate and titrate these agents to their maximally tolerated doses prior to consideration of ivabradine therapy. Of utmost importance is to ensure that the optimal tolerable dose of beta blocker has been achieved. The addition of ivabradine is

a class IIa, LOE-B recommendation to reduce HF hospitalization for symptomatic NYHA II-III HFrEF patients receiving maximal tolerated doses of GDMT and in sinus rhythm with a heart rate of 70 bpm or greater at rest [6].

9.3. Diuretics

Diuretics remain the cornerstone for decongesting and optimizing volume status in acutely decompensated HFrEF patients. This includes medications that block the Na+/K+/Cl- transporter in the loop of Henle and the Na+/Cl- co-transporter in the distal convoluted tubule of the kidney resulting in salt and water loss to restore euvolemia. Furosemide, a loop diuretic, is the most widely used in HF patients. Other loop diuretics like bumetanide and torsemide are less commonly used, though they have significantly better oral bioavailability, in particular in patients with decompensated heart failure. Thiazide diuretics in addition to a loop diuretic may be used in patients with diuretic resistance. Chronic kidney disease, medication non-adherence as well as compensatory tubular hypertrophy in response to salt loss are common causes of diuretic resistance. Optimal dosing of diuretics and assessment of volume status is vital in achieving euvolemia while minimizing the risk of significant renal impairment. Diuretics should be administered intravenously to optimize bioavailability in patients with acute decompensated HF. The Diuretic Optimization Strategy Evaluation (DOSE) trial (2011) did not demonstrate a benefit with the use of continuous IV diuretic therapy as compared to a bolus strategy [32, 33], and demonstrated that a high dose bolus strategy resulted in more rapid symptomatic improvement at 72 hours as compared to a low dose bolus strategy at the cost of an increased rate of transient renal dysfunction when used in hospitalized patients with acute decompensated HF [32].

9.4. Digoxin

Digoxin inhibits the Na+/K+ ATPase, thereby increases intracellular Na+ concentration. Increased intracellular Na+ reduces the Na+ concentration gradient required for efflux of Ca2+ via the Ca2+/Na+ exchanger, resulting in the increased intracellular Ca2+ that accounts for the mild positive inotropic effects of digoxin. It had been the mainstay of therapy for patients with HF until fairly late in the 20th century. The Digitalis Investigation Group (DIG) 1997 trial demonstrated that digoxin led to a relative reduction in HFrEF hospitalizations by 28% but did not impact mortality in these patients as compared to placebo [34]. The ACCF/AHA recommend consideration of digoxin for adjunctive use in HFrEF patients with persistent symptoms despite the use of guideline directed medical therapy [7]. Patient selection for use of this therapy is extremely important especially given its serious side effects. A retrospective analysis of the patients included in the DIG trial showed that serum digoxin concentrations (0.5-0.7 ng/ml) were associated with reduced death from worsening heart failure and a neutral effect on cardiovascular death not due to worsening HF. In this study, serum digoxin concentrations (1.6-2.0 ng/ml) were associated with increased mortality [35]. Doses of digoxin that achieve a plasma concentration in the range of 0.5-0.9 ng/ml are suggested by the ACCF/AHA. Although toxicity may occur at any supra-therapeutic dose of digoxin, overt toxicity is commonly associated with levels > 2 ng/ml [7]. Digoxin toxicity may present as cardiac arrhythmias, nausea, vomiting, visual disturbances, disorientation and confusion.

9.5. Inotropic Therapy

Intoropes improve cardiac contractility in addition to their drug-specific pharmacologic effects. The most frequently used inotropes in HFrEF patients are dobutamine and milrinone. Dobutamine stimulates B1, B2 and A1 receptors leading to the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP) by adenyl cyclase. This results in increased intracellular calcium leading to improved force of contraction. Milrinone inhibits phosphodiesterase-3 preventing the conversion of cAMP to its inactive form. Increased cAMP leads to increased intracellular calcium with resultant positive inotropic effect. Although they have not demonstrated improved outcomes, these therapies have found their use in improving the hemodynamics in cardiogenic shock or markedly low cardiac output states. To minimize side effects from this therapy, it is preferable to use low doses and for the shortest period of time necessary to improve hemodynamics and end organ perfusion [7]. Arrhythmias and infections have been reported as the common causes of rehospitalizations in patients on long term inotropic therapy [36]. Increased mortality rates have been reported with long term outpatient use for treatment of advanced HF [1]. However, survival on inotropes for patients who are not candidates for transplant or left ventricular assist device appears to be slightly better than previously reported [37]. The arrhythmogenic and hypotensive effects are more pronounced in patients with renal impairment. Better survival has been suggested with milrinone as compared to dobutamine [37, 38]. Risk assessment and careful patient selection for this therapy is therefore important. The ACCF/AHA recommend inotropes only for a specific category of HFrEF patients and in specific clinical contexts including temporary use for inotropic support in cardiogenic shock patients pending definitive therapy, and continuous inotropic support as a palliative therapy or bridge to transplant in stage D HFrEF patients refractory to guideline directed medical therapy. Use is discouraged in hospitalized patients without documented severe systolic dysfunction and cardiogenic shock [7].

9.6. General Considerations

Legitimate concerns arise with initiation and/or uptitration of some pharmacologic therapies for optimization of GDMT in certain clinical scenarios. It is imperative to continue to optimize patients to achieve medication doses that were proven to have morbidity and mortality benefit in the aforementioned clinical trials. However, due to specific patient comorbidity or advancing disease the optimal tolerable medication doses may be far less than the guideline-recommended target doses achieved in clinical trials. In fact, certain guideline directed medical therapy may be completely withdrawn as the disease progresses. Different strategies for medication up titration are employed by clinicians. A safe strategy may require adhering to the "Start slow, Go slow" approach. Prior to medication initiation, we recommend a careful individualized review of contraindications for

specific therapy. Beta adrenergic antagonists should not be initiated and should be discontinued in patients with symptomatic sinus bradycardia or advanced atrio-ventricular nodal block. However, when clinically indicated for mortality benefit, permanent cardiac pacing may be employed to allow its use [39]. In patients with new onset HF, predischarge initiation of therapy has been shown to increase adherence and chances of achieving target efficacious doses with no increase in hospital length of stay [40, 41]. However, in HFrEF patients who require inotropic therapy for management of decompensated heart failure, extreme caution is advised when initiating beta adrenergic antagonists during the same hospitalization [7]. For use as part of guideline directed therapy, beta adrenergic antagonists should be discontinued in patients on continuous intravenous dobutamine for management of advanced HF. Initiation of beta adrenergic antagonist therapy without waiting until target doses of ACEI are achieved has been shown to have morbidity and mortality benefits compared to delaying initiation of therapy till target doses of ACEI has been achieved [7, 42].

In patients with renal dysfunction, caution should be employed with initiation and use of aldosterone antagonist and ACEI. However, therapy should not be unduly discontinued in patients with only mild dysfunction especially as seen during short-term diuresis in patients with acute decompensated heart failure. Since use of both therapies have mortality benefit in specific HFrEF population, the ACC/AHA/HFSA have provided specific renal function threshold for safe initiation and discontinuation of therapy as aforementioned [7]. In patients with low lean body mass, impaired renal function, and the elderly (>70 years of age) digoxin should be started at low doses (0.125 mg daily or every other day) [7].

In patients with sinus node dysfunction, use of ivabradine is discouraged [43]. The use of ARNI is associated with increased risk of hypotension [6] therefore caution is required with the use of this therapy in elderly patients and those with borderline low blood pressure. In patients with chronic HF specific triggers have been identified to prompt referral for advanced therapies. Some of these triggers include recurrent hospitalizations, escalating diuretic requirements, intolerance to standard therapies, frequent ICD shocks, weight loss without other causes (cardiac cachexia), symptomatic low systolic blood pressure (<90 mmH), hyponatremia, rising blood urea nitrogen / creatinine, and extremely limited functional capacity (peak VO2< 12 to 14ml/kg/min, 6-MWT <300m, extremely poor exercise tolerance) [7].

Atrial fibrillation may worsen heart failure symptoms and conversely, worsened HF can promote the initiation of atrial fibrillation as well as a rapid ventricular response [7]. Although a rhythm-control strategy has not been shown to be superior to a rate-control strategy in patients with HF [7], prioritizing the rhythm-control strategy in HFrEF patients with new onset atrial fibrillation may be beneficial in preventing subsequent atrial remodeling and structural atrial abnormality. Beta adrenergic antagonists are the preferred agents for rate-control unless otherwise contraindicated. Digoxin may be used as an effective adjunct [7].

In hospitalized patients with hyponatremia and volume overload especially as seen in advanced heart failure, vasopressin V2 receptor antagonists may be used to improve serum sodium concentration. However, long-term therapy with V2 receptor antagonists has not been shown to impact outcomes in patients with heart failure [7, 44].

Anemia which may occur in patients with advanced heart failure has been independently associated with disease severity and mortality, and iron deficiency appears to be uniquely associated with reduced exercise capacity [6]. Intravenous iron supplementation may be used to improve functional capacity and quality of life in HFrEF patients with anemia and iron deficiency (ferritin <100 ng/ml or 100 to 300 ng/ml if transferrin saturation is <20%) who do not have alternative causes for their anemia. Of note, erythropoietin should not be used for management of anemia in HFrEF patients except in those with concomitant chronic kidney disease [6, 45].

Sleep disordered breathing is common in patients with HF. Thus a high degree of suspicion for sleep disorders should be maintained for these patients [7]. Kaneko *et al*. demonstrated that treatment of obstructive sleep apnea by continuous positive airway pressure reduces systolic blood pressure and improves left ventricular systolic function [46]. The ACCF/AHA recommend the use of CPAP in HFrEF patients with OSA to improve sleep quality, apnea-hypopnea index, and nocturnal oxygenation [6].

Reduced physical activity that characterizes CHF may result in maladaptive changes in skeletal muscle. The inability of the heart to meet the demands of the muscle during exercise triggers secondary compensatory mechanisms that result in overactivation of signals originating from the skeletal muscle receptors (mechano-metaboreceptors). This response promote the activation of SNS, RAA and atrial natriuretic peptide systems causing a paradoxical increase in peripheral vascular resistance, abnormal skeletal muscle perfusion and metabolism, and atrophy of oxidative muscle fibres. These peripheral changes contribute to reduced exercise capacity and increased the tendency to fatigue in CHF patients [47-49]. Deconditioned states resulting from reduced physical activity have also been thought to contribute to this unique skeletal muscle myopathy. Although the molecular adaptations of skeletal muscles in CHF patients are not completely understood, therapeutic interventions that target these maladaptive muscle responses may improve exercise capacity and fatigue, and should be explored.

10. TRIALS IN THE HORIZON AND FUTURE DIRECTIONS

Few trials exploring newer medications with alternative therapeutic targets beyond GDMT are underway.

The EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with Reduced ejection fraction (EMPEROR-Reduced) study is a phase III multicenter randomized, double-blind trial that seeks to evaluate the efficacy and safety of once daily empagliflozin versus placebo on top of GDMT in patients with symptomatic chronic HFrEF. Empagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT-2) historically used for the treatment of diabetes mellitus.

The genomic analysis of enhanced response to HF therapy in African Americans (GRAHF-2) is also underway to evaluate the clinical outcome of treatment with a fixed dose

combination of isosorbide / hydralazine (FDC I/H) in African American HFrEF patients with the GNB3 TT genotype versus those with GNB3 C genotype. The G protein beta sub unit (GNB3) T haplotype is far more prevalent in blacks than whites, associated with low renin hypertension, and has been linked to an enhanced therapeutic response to FDC I/H. This trial will evaluate the impact of GNB3 TT genotype as a marker of enhanced therapeutic response to FDC I/H in African Americans with HFrEF.

The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) is a phase III double blind placebo-controlled clinical trial that evaluates omecamtiv mecarbil, a novel activator of cardiac myosin, when added to standard of care in reducing the risk of cardiovascular death or heart failure events.

CONCLUSION

Great advances in the pharmacologic management of HFrEF have been made over the past few decades and several new therapies have emerged resulting in a paradigm shift in the selection of appropriate medication combination. Pharmacologic agents with proven morbidity and mortality reduction have been incorporated as GDMT, and are recommended for use in all HFrEF patients who can tolerate them without adverse effects or contraindications (Table **1**). Judicious practice entails both optimizing pharmacologic management and recognizing patients who require advanced therapy in whom continued pharmacologic management alone is not likely to provide clinical stability. Optimization of pharmacologic therapy does not only involve up-titration of medications but also include selecting appropriate individualized medication combination. Providers' knowledge and understanding of HF clinical trials, and familiarity with medication adverse effects are crucial for appropriate patient selection, timing of medication initiation, selecting appropriate individualized medication combination and safe titration. Although determining the optimal timing for advanced therapies is challenging, utilization of specific identified triggers is helpful. Further clinical trials that address new therapeutic options and strategies in patients with HF including previously understudied HFrEF populations are vital to the future advancement of pharmacologic therapy.

LIST OF ABBREVIATIONS

ACC/AHA/HFSA	=	American College of Cardiology/American Heart Association/ Heart Failure Society of America
ACCF/AHA	=	American College of Cardiology

Table 1. Pharmacologic agents, Putative effects and usefulness in management of heart failure with reduced ejection fraction.

Pharmacologic Agents	Putative Effects	Usefulness
Angiotensin Converting Enzyme Inhibitors	Inhibits the conversion of angiotensin I to angiotensin II	Inhibits the systemic effects of chronic RAAS activation. Improves survival
Angiotensin-receptor blockers	Inhibits the effect of angiotensin II on type 1 angiotensin (AT-1) receptors	Inhibits the systemic effects of chronic RAAS activation. Improves survival
Beta-blockers	Inhibits the adrenergic receptors	Inhibits the systemic effects of chronic SNS activation. Control of heart rate. Improves survival
Mineralocorticoid receptor antagonists	Inhibits the effect of mineralocorticoids on its receptors	Inhibits the systemic effects of chronic RAAS activation. Improves survival
Hydralazine with isosorbide dintrate (ISDN)	Vasodilators. Reduces both preload and afterload	Control of systemic blood pressure. Improves survival
Angiotensin receptor-neprilysin inhibitor (ARNI)	Natriuresis, vasodilation, and anti-proliferative effects	Control of systemic blood pressure. Improves survival
Ivabradine	Inhibits the pacemaker current (I_f) in the sinoatrial node	Control of heart rate. Improves morbidity (HF hospitalization)
Diuretics	Blocks the Na+/K+/Cl- transporter in the loop of Henle and the Na+/Cl- co-transporter in the distal convoluted tubule of the kidney	Diuresis and optimizing volume status. Improves symptoms in acute decompensated HF
Digoxin	Inhibits the Na+/K+ ATPase in myocardial cells resulting in the increased intracellular Ca2+	Increases cardiac muscle contractility (mild positive inotropic effect)
Dobutamine	Stimulates B1, B2 and A1 receptors leading to conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP) by adenyl cyclase resulting in the increased intracellular Ca2+	Increases cardiac muscle contractility (Positive inotropic effect)
Milrinone	Inhibits phosphodiesterase-3 leading to increased cAMP levels and thus increased intracellular calcium	Increases cardiac muscle contractility (Positive inotropic effect)

RAAS indicates renin angiotensin aldosterone system; SNS – sympathetic nervous system; HF – heart failure.

		Foundation/American Heart Association
ACEI	=	Angiotensin Converting Enzyme Inhibitors
ADH	=	Anti-diuretic Hormone
A-HeFT	=	The African-American Heart Failure Trial
ANP	=	Atrial Natriuretic Peptide
ARB	=	Angiotensin Receptor Blockers
ARNI	=	Angiotensin Receptor-Neprilysin Inhibitor
BNP	=	Brain Natriuretic Peptide
cAMP	=	Cyclic Adenosine Monophosphate
CHARM	=	Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity
CHF	=	Chronic Heart Failure
CIBIS	=	Cardiac Insufficiency Bisoprolol Study
COMET	=	Carvedilol Or Metoprolol European Trial
CONSENSUS	=	The Cooperative North Scandinavian Enalapril Survival Study
COPERNICUS	=	The Carvedilol Prospective Randomized Cumulative Survival
DIG	=	Digitalis Investigation Group
DOSE	=	The Diuretic Optimization Strategy Evaluation
EMPEROR-Reduced	=	The EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with Reduced ejection fraction
EMPHASIS-HF	=	The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	=	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
FDC I/H	=	Fixed Dose Combination of Isosorbide / Hydralazine
GALACTIC-HF	=	The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure
GDMT	=	Guideline-Directed Medical Therapy
GNB3	=	G Protein Beta Sub Unit
GRAHF	=	The Genomic Analysis of Enhanced Response to HF Therapy in African Americans
HF	=	Heart Failure
HFpEF	=	Heart Failure with Preserved Ejection Fraction
HFrEF	=	Heart Failure with Reduced Ejection Fraction
ISDN	=	Isosorbide Dintrate
LOE	=	Level of Evidence
LVEF	=	Left Ventricular Ejection Fraction
MERIT-HF	=	The Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure
MRA	=	Mineralocorticoid Receptor Antagonists
NYHA	=	New York Heart Association
OVERTURE	=	Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
PARADIGM-HF	=	The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIONEER-HF	=	The comParIson Of sacubitril/valsartan *versus* Enalapril on Effect on ntpRo-bnp in patients stabilized from an acute Heart Failure episode
RAAS	=	Renin-Angiotensin Aldosterone System
RALES	=	Randomized Aldactone Evaluation Study
RCTs	=	Randomized Controlled Trials
SAVE	=	The Survival and Ventricular Enlargement
SGLT-2	=	Sodium-Glucose Cotransporter 2
SHIFT	=	Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial
SNS	=	Sympathetic Nervous System
SOLVD	=	The Subsequent Studies of Left Ventricular Dysfunction
Val-HeFT	=	Valsartan Heart Failure Trial
V-HeFT	=	Vasodilator Heart Failure Trial

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CONFLICT OF INTEREST

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