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Pharmacological "Game Changers" for HFrEF Patients

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Abstract

Present guidelines strongly recommend treating HFrEF patients with medications proven to relieve symptoms, decrease hospitalizations and improve survival.By reviewing the history of treatments for HFrEF patients, the pharmacological "game changers" are evidence-based beta-blockers, aldosterone receptor blockers, isosorbide dinitrate/hydralazine and sacubitril/valsartan. To achieve beneficial results as found in clinical trials, HFrEF patients must be beta-blocked, afterload must be advanced, and renal function, potassium and magnesium must be monitored.

Keywords: *HFrEF, digitalis, loop diuretics, ACE inhibitors, angiotensin receptor blockers, carvedilol, spironolactone, isosorbide dinitrate/hydralazine, sacubitril/valsartan, mortality, ejection fraction*

Introduction

The phrase "game changers" has become a popular expression since the 1980s.It is now used not only in writing about sports figures or decisionmakers in industry, but it is also commonly used when referring to new approaches to improve medical treatments."Game changers" is now thought of as an idiom, meaning the words together reflect more meaning than they alone would, and is now in the Merriam-Webster Dictionary and the Oxford Dictionary. The focus of this brief review is to cover the history of pharmacological treatments that have evolved in treating patients with congestive Heart Failure due to reduced Ejection Fraction (HFrEF) and emphasize which therapies are recommended at this time and how to utilize these therapies for the benefit of patients.

While this article will focus on pharmacological strategies, other therapies are important in the overall management of HFrEF patients.Nonpharmacological therapies which improve symptoms and even survival in properly chosen patients include biventricular ICDs.There is increasing literature that keeping patients in sinus rhythm has major benefits, and as the technology for atrial fibrillation ablation evolves, its incorporation in the treatment of these patients appears important.Additionally, ambulatory hemodynamic sensors have been shown to decrease hospitalizations and improve mortality and are being incorporated into the long-term management of these patients.

Nonpharmacological therapies that should be mentioned that have not achieved indications but have potential in selected HFrEF patients in the future include renal denervation and chronic baroreceptor stimulation.Additionally, ongoing work on the use of cellular replacement therapies will eventually evolve to the point that patients will also benefit from stem cell infusions.

By historically reviewing the discoveries of pharmacological therapies for patients with HFrEF, our understanding of current recommendations becomes clearly focused and more comprehensive.Cardiac glycosides found in plants and in the venom of certain toads were discovered thousands of years ago [1]. The Egyptians, the Romans and the Chinese all discovered uses of cardiac glycosides. Roman writings referred to digitalis as "improving heart tones."Digitalis, which is found in the leaves of foxglove, was mentioned in 1250 A.D. in the writings of Welsh physicians. William Withering's book published in 1785 entitled "An Account of the Foxglove and Some of Its Medical Uses:With Practical Remarks on Dropsy, and Other Diseases" confirmed digitalis as a beneficial treatment for patients with HFrEF because there were no other therapies available. Digitalis works by producing a positive inotropic effect in patients with HFrEF. Digitalis also sensitizes baroreceptors, thus, inhibiting central sympathetic activity outflow resulting in afterload.Accordingly, digitalis improves patient's symptoms. Digitalis has never been shown to decrease patient mortality [2]. Maintenance dose of digitalis is based on body weight and renal function, and a narrow therapeutic window results in toxic side effects.Accordingly, the indications for digitalis at this time are New York Heart Association (NYHA) Class II-IV heart failure patients on Angiotensin-Converting Enzyme (ACE) inhibitors, evidence-based beta-blockers and diuretics who are still symptomatic.Digitalis also has an indication of rate control in congestive heart failure patients with atrial fibrillation after beta-blocker therapy [3].

To improve symptomatic patients with HFrEF, diuretics were discovered. Loop diuretics are used for relief of symptoms. Diuretics, while improving symptoms, have never been shown to decrease mortality [4]. When managing a patient with HFrEF, treatment becomes more challenging when the patient has chronic kidney disease [5]. Long-term strategies to maintain renal function make management easier and decrease morbidity and mortality in these patients [6].With the use of diuretic therapy, it is important to

keep the potassium between 4 and 5 mEq/L and magnesium above 2 mg/dL to decrease ventricular arrhythmias [7]. Chronic diuretic therapy in patients who have poor nutrition can result in thiamine depletion and produces a beriberi-like disease, but this is unusual with efforts to maintain nutrition in patients.Thiamine replacement at 100 mg a day orally is the therapy.If patients are on chronic diuretic therapy for a long period of time, they sometimes can develop zinc deficiency which causes them to have a metallic taste, and this is easily replaced with zinc sulfate 324 mg a day orally.

With the discovery of ACE inhibitors, the concept of afterload reduction as part of treatment for patients with HFrEF evolved. Use of ACE inhibitors to prevent and/or treat HFrEF was the first therapy shown to decrease mortality [8,9]. ACE inhibitor indications include post-MI patients regardless of ejection fraction, patients with diabetes and one of the following:hypertension, elevated total cholesterol, low HDL cholesterol, cigarette smoking, microalbuminuria, NYHA Class II, III and IV heart failure and asymptomatic left ventricular systolic dysfunction, if they have an ejection fraction ≤ 40% [3].Many ACE inhibitor trials have been done, and ACE inhibitors approved for use in patients with HFrEF include captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril and trandolapril.

Angiotensin Receptor Blockers (ARB) that have been approved for treatment of congestive heart failure in patients with HFrEF include valsartan and candesartan cilexetil [10,11].

Sympathetic nervous system hyperactivity actually occurs earlier than activation of the renin-angiotensin-aldosterone system in patients with HFrEF [12]. The increased sympathetic activity affects all vascular beds with greater activity noted in the heart and kidney. In contrast, evidence for chronic sympathetic nervous system hyperactivity in patients with heart failure with preserved left ventricular ejection fraction is limited. With the understanding that sympathetic nervous system hyperactivity occurs in patients with HFrEF, many beta-blocker trials were carried out.Some beta-blockers showed neutral effect.Some beta-blockers, if they had intrinsic sympathomimetic activity, showed deleterious effects. For example, bucindolol, which is similar to carvedilol, is a nonselective beta-blocking agent with weak alpha1-blocking properties, but unlike carvedilol, it has inverse agonist and intrinsic sympathomimetic activity and was not found to be beneficial in patients with HFrEF [13]. Three beta-blockers have been shown to decrease mortality in patients with HFrEF, and they include carvedilol, bisoprolol and metoprolol succinate [14-16].

Carvedilol is a third-generation beta-blocker that has $beta_1$-, $beta_2$- and $alpha_1$-blocking properties and also has strong antioxidant effects.Carvedilol has been approved for NYHA Class I, II, III and IV and post-MI patients, if the patient's ejection fraction is <40%. Metoprolol succinate has beta1-blocking properties and has been approved for NYHA Class II and III [3]. Bisoprolol has beta1-blocking properties but is not approved by the FDA for treatment of heart failure.

Evidence-based beta-blocker therapy in patients with HFrEF should be initiated early once the patient is euvolemic. Dosage needs to be started low because with initiation of therapy there is a transient decrease in cardiac output.Dosage should be increased slowly, but it should be increased to the point that the patient is "beta-blocked," meaning a resting heart rate in the 60s. When patients are beta-blocked, the ejection fraction usually improves over 3 to 6 months.Carvedilol has on average been shown to improve ejection fraction by 7-8% [17,18]. Metoprolol succinate and bisoprolol have been shown to improve ejection fraction on average by 4%.Both nonselective and selective traditional beta-blockers have been shown to increase insulin resistance, facilitate weight gain of approximately 1 kilogram per 6 months and worsen hypertriglyceridemia by approximately 13%.In contrast, carvedilol in hypertensive, diabetic patients has been found to have a neutral effect on insulin resistance, weight and triglycerides. This favorable metabolic profile also suggests that carvedilol is a better choice compared to traditional beta-blockers in these high-risk patients [19].If immediate release carvedilol is used, dosing should be every 12 hours so the beta receptors are blocked over each 24-hour period. Initiation of evidence-based beta-blocker therapy is important in patients with HFrEF because until beta-blocker therapy has been initiated, the risk of sudden death is high.

Out of historical order, but appropriate to the discussion of pharmacologic management of HFrEF patients, is the development of ivabradine [20]. Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with a left ventricular ejection fraction of <35%, who are in sinus rhythm with a resting heart rate of >70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Evidence-based beta-blocker therapy benefits may be mediated, in part, by heart rate lowering.Heart rate reduction is a potential therapeutic target in patients with HFrEF since an elevated heart rate is associated with worse cardiovascular outcomes [21]. While the relative contribution of increased heart rate versus the underlying neurohormonal abnormalities is difficult to determine, the beneficial effects of ivabradine, an agent that acts solely by decreasing heart rate, suggest that an elevated heart rate per se contributes to an adverse outcome in patients with HFrEF. Possible detrimental effects of elevated heart rate include heart rate-related increase in myocardial oxygen consumption and decrease in myocardial perfusion.

With activation of the renin-angiotensin-aldosterone system and resultant congestion in the liver, patients with HFrEF have secondary aldosteronism. Aldosterone receptor blockers in treating HFrEF patients have become strongly recommended [22,23]. Agents available include spironolactone and eplerenone. Indications are for NYHA Class III and IV and post-MI if ejection fraction is <40% [3]. Contraindications are baseline potassium >5 mEq/L and serum creatinine >2.5 mg/dL. The half-life of spironolactone is 18 hours while the half-life of eplerenone is 6 hours, and so while both require long-term monitoring for hyperkalemia, the risk is higher with spironolactone.

Another therapy for afterload reduction is the combination of isosorbide dinitrate and hydralazine.This was initially tested in an African American heart failure trial [24]. African Americans tend to make less nitric oxide by the endothelium. Isosorbide dinitrate is a nitrogen donor and hydralazine is a free radical scavenger, and this combination was studied in African Americans with NYHA Class III or IV heart failure, already on ACE inhibitor or ARB, beta-blocker, loop diuretic, spironolactone or digoxin for, at least, 3 months.Dose achieved was isosorbide dinitrate 40 mg

and hydralazine 75 mg orally every 8 hours.The results improved survival by 43%, reduced heart failure hospitalization by 39% and improved quality of life with side effects being headache and dizziness.This therapy now is adjunctive to standard therapy not only in African Americans but in any patient, particularly if they have renal dysfunction and cannot be on ACE inhibitor or angiotensin receptor blocker [3].

The latest addition to pharmacologic treatment of patients with HFrEF is the combination of sacubitril/valsartan [25]. This compound was compared to enalapril in patients with NYHA Class II-IV heart failure, ejection fractions <40%, elevated BNP and guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists.The patient's systolic blood pressures had to be >95 mmHg, estimated GFR >30 mL/min/1.73 m2and serum potassium <5.4 mEq/L at randomization.Patients were randomized if it was proven that they could be on, at least, 10 mg of enalapril daily for, at least, 4 weeks.After randomization, sacubitril/valsartan was more effective than enalapril, reducing the risk of cardiovascular death by an incremental 20%, reducing risk of hospitalization by incremental of 21%, reducing all-cause mortality by 16% and improving symptoms and quality of life.

Currently, the combination sacubitril/valsartan has been approved by the American College of Cardiology, American Heart Association, Heart Failure Society of America and European Society of Cardiology guidelines for the treatment of patients with HFrEF who remain symptomatic after adequate treatment with evidence-based beta-blocker, aldosterone receptor blocker and ACE inhibitor or ARB [3]. ACE inhibitor therapy should be discontinued for, at least, 36 hours before initiating sacubitril/valsartan to decrease the risk of angioedema.In spite of the benefits of combination sacubitril/valsartan in the PARADIGM-HF trial and subsequent post hoc analysis, there are some questions that should be answered in clinical practice. For example, in the PARADIGM-HF trial, patients who received the combination sacubitril/valsartan were more likely to have lower blood pressure values than in the enalapril group. Lower blood pressure has been proposed as a factor that could explain the benefits of sacubitril/valsartan over enalapril on cardiovascular mortality and heart failure hospitalizations.Taking into account that in PARADIGM-HF the doses of enalapril were not those recommended for the treatment of heart failure in practice guidelines, the question should be answered whether sacubitril/valsartan benefits are similar with the higher recommended doses of enalapril.However, a recent post hoc analysis of the PARADIGM-HF trial showed efficacy of sacubitril/valsartan over enalapril when both were at lower doses than the target doses [26].Another analysis showed that factors, such as lower systolic blood pressure, lower estimated glomerular filtration rate, higher N-terminal pro-B-type natriuretic peptide and ischemic cause of heart failure, were associated with higher risk for run-in noncompletion of PARADIGM-HF [27]. So, these factors should be identified and taken into account when deciding to use this novel drug combination in real world patients. Finally, there are many questions about the cost-effectiveness of sacubitril/valsartan in clinical practice.Currently, there are some studies in progress to answer this issue, but a recent analysis reveals that sacubitril/valsartan provides a net small but substantial benefit in the current care of patients with HFrEF.

	HFrEF Medications	
	Improves EF	**Decreases Mortality**
Digitalis	-	-
Loop Diuretics	-	-
ACE inhibitor and/or ARB	-	Yes
Carvedilol /bisoprolol/ metoprolol succinate	Yes	Yes
Aldosterone blockade	-	Yes
Isosorbide dinitrate / hydralazine	-	Yes
Sacubitril/valsartan	-	Yes

Table 1. *Comparison of pharmacologic agents in the treatment of HFrEF patients*

Protective Therapies	
	Number needed to Treat for 1 Year to Save 1 Life (total mortality)
Hope (ramipril)	221
4S (simvastatin)	159
SAVE (captopril)	86
PARADIGM-HF (sacubitril/ valsartan)	32
MERIT-HF (metoprolol succinate)	26
A-HeFT (isosorbide dinitrate/ hydralazine)	17
COPERNICUS (carvedilol)	14
RALES (spironolactone)	9

Table 2. *Effectiveness of cardiovascular protective therapies.*

In comparing the pharmacologic agents presently available for HFrEF patients, as shown in table 1, it is noted that digitalis and loop diuretics have no effect on the ejection fraction and do not decrease mortality.Evidence-based beta-blockers, carvedilol, bisoprolol and metoprolol succinate are unique in that they over time improve the ejection fraction as well as decrease mortality. ACE inhibitor, ARB, aldosterone blockade, isosorbide dinitrate and hydralazine and sacubitril/valsartan all decrease mortality. Thus, the more recent pharmacologic agents are the recommended agents to use in HFrEF patients and are "game changers."

While it is difficult to compare trials because of different patient selection, it is useful to put cardiovascular therapies in perspective by using the calculation of number of patients needed to treat for one year to save one life.As shown in table2, the HOPE trial in which patients had borderline hypertension and were treated with ACE inhibitor as primary prevention took a much larger number to treat to save a life, as would be expected [28].A statin trial with simvastatin was a secondary prevention trial, and the number

needed to treat is listed [29].The heart failure trials showed that ACE inhibitor alone with digitalis and diuretics require 86 patients to treat.Of note, carvedilol and spironolactone are very effective in that regard, and sacubitril/valsartan, in addition to these molecules, is effective.

In summary, the long-term challenge is to prevent patients from developing symptomatic HFrEF by treating hypertension, reversing left ventricular hypertrophy, avoiding post-MI remodeling and modifying coronary risk factors. Present guidelines strongly recommend treating patients with HFrEF with multiple medications proven to improve clinical outcomes as well as survival [30]. The guidelines are not just recommendations; they are proven recommendations due to carefully performed multicenter trials [31]. Use of these medications require proper dosing to achieve results, as found in the trials. Patients must be beta-blocked with evidence-based beta-blockers, afterload must be advanced as tolerated and renal function, potassium and magnesium monitored.

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