

Does Sacubitril/Valsartan Pose a Treatment Conundrum for Management of Heart Failure?

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Characteristics and Classifications of Heart Failure

Progression of heart failure (HF) results in unfavorable symptoms, such as dyspnea, fatigue or peripheral edema due to abnormal cardiac structure or function.¹ Etiology of HF is primarily ischemic but can also be non-ischemic, such as from long-standing hypertension.¹ About 50% of the population with HF have reduced ejection fraction (HFrEF), which is associated with an important prognosis: lower ejection fraction (EF) is associated with higher mortality.¹ In clinical trials, HFrEF is often defined as an EF of 40% or less, and it is only in these patients that drug therapy is consistently effective.² However, HF with preserved EF (HFpEF) is also associated with significant mortality and has become increasingly prevalent. HFpEF rates now approach 50% of all cases of HF and is difficult to manage with drug therapy.² If HFpEF is suspected, presence for structural heart disease should be investigated.¹

Investigators routinely use the New York Heart Association (NYHA) functional classification, which is based on patient symptoms, to select subjects for clinical HF drug trials. For example, patients with NYHA class I have no symptoms, whereas patients with NYHA class IV may have symptoms at rest.² Independent of EF, there is a strong correlation between symptom severity and risk for hospitalization or death.^{1,2}

Drug Management of Heart Failure with Reduced Ejection Fraction

In patients with HFrEF, pathological 'remodeling' of the ventricle occurs with increasing ventricle enlargement and decline in EF.¹ This maladaptive progression is thought to be largely due to neurohormonal activation by the renin-angiotensin system (RAAS) and the sympathetic nervous system – systems, when activated long-term, detrimentally remodel heart tissue.¹ The basis of standard HFrEF treatment is to stop this remodeling process.

The goals of treatment in patients with HF are to relieve symptoms, prevent hospitalization admission and decrease mortality.¹ No drug therapy has shown to effectively improve health-related quality of life.² For years, 3 classes of disease-modifying therapies – ACE-inhibitors (or angiotensin receptor blockers [ARB]), beta-blockers, and aldosterone antagonists – have been fundamentally important in modifying the course of HFrEF and should be strongly considered in each patient with HFrEF. Recently, the neprilysin inhibitor sacubitril, combined with a maximally dosed ARB, was added to this medley of drug classes.³ All 4 types of drugs are neurohormonal antagonists and are complementary in the management of HFrEF.

Pivotal Heart Failure Drug Trials

ACE-inhibitors should be prescribed to all patients with HFrEF.² Landmark clinical trials of ACE-inhibitors demonstrated early and significant *absolute* risk reduction in all-cause mortality versus placebo of 4.5%⁴ and 15%⁵ in patients with mild and severe symptomatic HFrEF, respectively. Target doses of ACE-inhibitors are convincingly correlated with greater mortality reduction.⁶ Further trials of ACE-inhibitors have consistently proven significant mortality benefit.⁷ The landmark beta-blocker trials were conducted in patients with mild to severe symptomatic HFrEF already on an ACE-inhibitor.⁸⁻¹⁰ These trials showed an additional *absolute* reduction in all-cause mortality by another 5-7% within 1 year when a beta-blocker was added to an ACE-inhibitor relative to an ACE-inhibitor alone.⁸⁻¹⁰ Strong and consistent evidence demonstrates that an ACE-inhibitor and beta-blocker should be initiated in all patients with HFrEF without contraindications.⁸⁻¹¹

Aldosterone antagonists also have a major role in the management of HFrEF. Both spironolactone and eplerenone have demonstrated significant mortality benefit when added to an ACE-inhibitor.^{12,13} Evidence for use of spironolactone came before beta-blockers were widely used and was studied in patients with more severely symptomatic HFrEF.¹² Spironolactone resulted in an *absolute*

risk reduction in all-cause mortality of 11% within 2 years.¹² Eplerenone also provides additional reduction in cardiovascular (CV) mortality and hospital admissions for HF when it is added to an ACE-inhibitor (or ARB) and beta-blocker in patients with mildly symptomatic HFrEF.¹³ The addition of an aldosterone antagonist to an ACE-inhibitor and beta-blocker in symptomatic HFrEF is recommended and guidelines provide clear recommendations for mitigating risk for hyperkalemia with these agents.^{1,2}

There is also some evidence for use of an ARB in HFrEF. However, the evidence of benefit is more clear when an ARB is substituted for an ACE-inhibitor in patients intolerant to an ACE-inhibitor.¹⁴⁻¹⁶ Similar to target doses of ACE-inhibitors, target doses of ARBs are more effective than lower doses at reducing HF-associated mortality and morbidity outcomes.¹⁷ ARBs are strongly recommended in patients with HFrEF who are intolerant to an ACE-inhibitor, though guidelines also detail circumstances in which the addition of an ARB to an ACE-inhibitor and beta-blocker (but not aldosterone antagonist) may be reasonable.^{1,2} Table 1 lists the drugs and target doses that have demonstrated reduction in mortality and morbidity outcomes.

Table 1. Doses of Drugs with Mortality Benefit in Patients with HFrEF.¹

ACE-inhibitor	Target Dose
Captopril	50 mg t.i.d.
Enalapril	10-20 mg b.i.d.
Lisinopril	20-35 mg once daily
Ramipril	5 mg b.i.d.
Trandolapril	4 mg once daily
Aldosterone Antagonist	Target Dose
Eplerenone	50 mg once daily
Spironolactone	25-50 mg b.i.d.
Angiotensin Receptor Blocker (ARB)	Target Dose
Candesartan	32 mg once daily
Valsartan	160 mg b.i.d.
Beta-blocker	Target Dose
Bisoprolol	10 mg once daily
Carvedilol	25-50 mg b.i.d.
Metoprolol Succinate (ER/XL)	200 mg once daily
Neprilysin Inhibitor/ARB	Target Dose
Sacubitril/Valsartan	200 mg b.i.d.

Abbreviations: b.i.d. = twice daily; ER/XL = extended-release; t.i.d. three times daily

With the exception of diuretics, the therapeutic value of other drugs periodically used for HFrEF is less well defined. Digoxin may be useful to reduce risk of hospitalizations for HFrEF but has consistently demonstrated no effect on mortality.^{18,19} The therapeutic niche for ivabradine is still uncertain after only one trial found it reduced hospitalizations, but not mortality, in HFrEF patients in normal sinus rhythm with a resting heart rate of 70 beats-per-minute or more.²⁰ Evidence for use of hydralazine combined with isosorbide dinitrate is well documented in Black patients already on standard HFrEF therapy²¹ and is a reasonable fourth-line option in any HFrEF patient without contraindications.^{1,2}

A New Neurohormonal Antagonist: Sacubitril/Valsartan

Sacubitril/valsartan is the first HF drug approved in years that demonstrates mortality benefit in HFrEF. However, evidence for its use is limited to only one trial that compared sacubitril/valsartan 200 mg twice daily (n=4,187) with enalapril 10 mg twice daily (n=4,212).²² A careful, step-wise approach was used to maximize safety in the study. First, a single-blind run-in period was

used to determine which eligible patients could tolerate enalapril 10 mg twice daily; then a second single-blind run-in period was utilized to determine which of those patients could tolerate sacubitril/valsartan 200 mg twice daily.²² Over 20% of eligible patients were not eligible for randomization into the clinical trial, mostly because of intolerance to the target doses.²²

Randomized patients had stable, mildly symptomatic HFrEF (NYHA II or III) and were on a concomitant beta-blocker and diuretic.²² The mean EF was 29%.²² Most patients were white males. Females, Blacks, and U.S. citizens were largely under-represented in the study.²²

There was a 4.7% absolute risk reduction in the primary endpoint, which was a composite of death from CV causes or first hospitalization for HF, with use of sacubitril/valsartan (enalapril 26.5% vs. sacubitril/valsartan 21.8%; hazard ratio [HR] 0.80; 95% CI, 0.73 to 0.87; $p < 0.001$).²² Thus, 22 patients need to be treated (NNT) for 27 months with sacubitril/valsartan instead of enalapril to prevent one hospitalization for HF or one death from a CV cause.²² All-cause mortality was also significantly reduced with sacubitril/valsartan compared to enalapril (17.0% vs. 19.8%, respectively; HR 0.84; 95% CI, 0.76 to 0.93; $p < 0.001$; NNT 36).²² During the trial, 19.8% of patients stopped sacubitril/valsartan prematurely and 17.8% of patients stopped enalapril prematurely.²² There was a higher incidence of symptomatic hypotension (14.0% vs. 9.2%; $p < 0.001$) and angioedema (0.45% vs. 0.24%) with sacubitril/valsartan than with enalapril.²²

Conclusion

The results from this new trial are certainly promising. Time will tell how safe and tolerable sacubitril/valsartan is in real-world settings. But before prescribers start replacing ACE-inhibitors with sacubitril/valsartan, some limitations should be considered. First, the specific order of the single-blind run-in phases likely introduced bias early in the trial. Second, about 20% of patients in each arm discontinued the study prematurely, which is concerning after accounting for the additional 20% of eligible patients who were not randomized due to intolerability of either drug in the initial run-in phases. It is unclear how many patients in real world settings will be able to tolerate the dose studied in the trial; lower doses may be better tolerated but may not be any more effective than far less costly ACE-inhibitor or ARB. Third, it is unclear if the efficacy seen with sacubitril/valsartan can be attributed to the addition of sacubitril to bioequivalent 320 mg daily dose of valsartan used in the trial,³ or if it can be attributed to the high valsartan dose alone. Both valsartan and enalapril doses studied were optimal,^{4,14,23} but a 40 mg daily dose of enalapril may have been a more reasonable comparator.²⁴⁻²⁷ A comparison of sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain its place in therapy in HFrEF. In time, these limitations may be adequately addressed. However, with the plethora of time-tested evidence for use of ACE-inhibitors, a selective and cautious approach is reasonable before ACE-inhibitors are indiscriminately substituted for a new and more costly drug.

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