Focus on Managing Patients with Chronic Heart Failure

EXPERT perspectives

OVERVIEW

James Tauras, MD, provides his perspectives on issues related to the rapidly evolving pharmacologic management of chronic heart failure. Dr. Tauras emphasizes guideline-directed medical therapy as recommended in the *2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure*, including the real-world use of ivabradine and sacubitril/valsartan. He discusses other issues intended to help improve the health outcomes, including reducing the 30-day readmission rate, of patients with heart failure.

CONTENT AREAS

- Benefits of switching from ACE inhibitor or ARB to sacubitril/valsartan
- Role of aldosterone receptor agonist in heart failure with preserved ejection fraction
- Benefits of treating hypertension in heart failure
- Role of B-type natriuretic peptide as a biomarker
- Precautions when prescribing ivabradine, sacubitril/valsartan
- Strategies for reducing hospital readmission

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Focus on Managing Patients with Chronic Heart Failure

Target Audience
This activity was developed for cardiologists, primary care physicians, nurse practitioners, nurses and other health care professionals who have an interest in heart failure.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Construct appropriate pharmacological regimens based upon an understanding of the pathophysiologic mechanisms of heart failure
- Individualize treatment to reduce the burden of secondary heart failure hospitalizations
- Integrate new heart failure medications into patient management
- Implement strategies to improve patient self-management
- Implement strategies to address institutional gaps in inpatient, transitional and outpatient practice/care

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Focus on Managing Patients with Chronic Heart Failure

1. If a patient with HFrEF is doing well with guideline-directed therapy that includes an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, why should consideration be given to switching to sacubitril/valsartan?

The mortality benefit by inhibiting the renin-angiotensin-aldosterone system was demonstrated nearly 3 decades ago by the CONSENSUS and SOLVD trials.[1,2] In the SOLVD trial, treatment with enalapril over a mean of 41.4 months was shown to reduce the risk of death by 16% among patients with mild-to-moderate symptoms.[2] Based upon these findings, an angiotensin converting enzyme inhibitor (ACE-I) has been a primary component of treatment for heart failure with reduced ejection fraction (HF*r*EF). Evidence suggests that treatment with an angiotensin receptor blocker (ARB) also confers a mortality benefit, but the evidence is less robust.[3, 4]

Against this gold standard of ACE inhibition with enalapril in HF*r*EF, the PARADIGM-HF trial compared the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan.[5] In PARADIGM-HF, patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less (N=8442) were randomized to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily, both in addition to guideline-directed medical therapy.

After a median follow-up of 27 months, the trial was stopped early since the primary outcome (composite of cardiovascular death or hospitalization for heart failure) had occurred in 21.8% of patients treated with sacubitril/valsartan and 26.5% of patients treated with enalapril (hazard ratio 0.80; 95% confidence interval 0.73-0.87). Moreover, cardiovascular death (hazard ratio 0.80; 95% CI 0.71-0.89) and hospitalization for heart failure (hazard ratio 0.79; 95% CI 0.71-0.89) were significantly less common with sacubitril/valsartan than enalapril. Sacubitril/valsartan also significantly reduced the symptoms and physical limitations of heart failure. Patients treated with sacubitril/valsartan were more likely to experience symptomatic hypotension than patients treated with enalapril, but rarely required treatment discontinuation. Patients treated with enalapril were more likely to experience cough, serum creatinine ≥2.5 mg/dL, and serum potassium >6.0 mEq/L. Angioedema rates were very low in both arms of the trial, however, patients with prior angioedema were excluded from the trial.

Based on the results of PARADIGM-HF, the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines recommend: "In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality."[6]

2. Are there patients with heart failure with preserved ejection fraction (HFpEF) who might benefit from treatment with an aldosterone receptor antagonist?

Yes, although the data are limited. Initial evidence came from the Aldo-HF trial, which intended to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in patients with HF*p*EF.[7] Subsequent to Aldo-HF, the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial examined the effects of spironolactone over a longer period (mean follow-up of 3.3 years) and in more patients (N=3445).[8] Patients with symptomatic HF*p*EF (left ventricular ejection fraction ≥45%) were randomized to spironolactone 15 to 45 mg/day or placebo. The primary outcome (composite of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization) occurred in 18.6% and 20.4% of spironolactone and placebo patients, respectively (hazard ratio (HR) 0.89; 95% CI 0.77 to 1.04). Of the components of the primary outcome, only the incidence of heart failure hospitalization was significantly lower in the spironolactone group (12.0% vs 14.2%, respectively; HR 0.83; 95% CI 0.69 to 0.99). Spironolactone increased the serum creatinine level (10.2% vs 7.0%), doubled the rate of hyperkalemia (18.7% vs 9.1%), and reduced the rate of hypokalemia 16.2% vs 22.9%), respectively.

Regional variation in the primary outcome was noted in which subjects from Russia/Georgia had a 4-fold lower rate of the primary endpoint compared with subjects from North America and South America. There was significant regional variation in entry demographic and primary endpoint between Russia/Georgia and the Americas. Additionally, a subset of the

Russia/Georgia population, despite having been in the treatment arm, had nondetectable levels of the metabolite of spironolactone. A post hoc analysis showed that there was a significant treatment effect with spironolactone with regards to the primary outcome, a composite of cardiovascular death and hospitalization for heart failure. Based on the original trial findings and the post hoc analysis, the ACC/AHA/HFSA HF Guidelines gave a IIB B-R recommendation for spironolactone in HF*p*EF.

These investigations suggest that in patients with symptomatic HF*p*EF with left ventricular ejection fraction ≥45%, elevated brain natriuretic peptide (BNP) level, or heart failure admission within the past year, with estimated glomerular filtration rate >30 mL/min/1.73 m^2, serum creatinine <2.5 mg/dL, and serum potassium <5.0 mEq/L, spironolactone might be considered, especially in those with an elevated BNP level.[6] Close monitoring of renal function and serum potassium is recommended.

3. The importance of treating hypertension has been emphasized in the 2017 ACC/AHA/HFSA heart failure guidelines. What are the specific recommendations and what is the evidence?

Three new recommendations related to hypertension have been added to the heart failure guidelines. The first, which relates to reducing the incidence of heart failure, states: "In patients at increased risk, stage A heart failure, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg."[6] The recommendation is based on the results of several trials, including the Systolic Blood Pressure Intervention Trial (SPRINT).[9-13] In SPRINT, 9361 patients with systolic blood pressure (SBP) ≥130 mm Hg and increased risk of cardiovascular disease, but without diabetes, were randomized to a SBP target <120 mm Hg (intensive treatment) or <140 mm Hg (standard treatment). Treatment according to an algorithm that included all major classes of antihypertensive agents was encouraged but not required.

Throughout the 3.26 years of follow-up in SPRINT, the mean SBP was 121.5 and 134.6 mm Hg in the intensive and standard treatment groups, respectively. The trial was stopped early due to a significantly lower rate of the primary composite endpoint (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or cardiovascular death) in the intensive treatment vs standard treatment group (1.65% vs 2.19% per year; HR 0.75; 95% CI 0.64 to 0.89). For heart failure, the rates were 0.41% vs 0.67% per year, respectively (HR 0.62; 95% CI 0.45 to 0.84), demonstrating significant benefit in reducing the risk of heart failure with blood pressure lowering in patients at increased risk of cardiovascular disease. Although SPRINT utilized a target SBP <120 mm Hg, the target SBP <130 mm Hg recommended for clinical practice is to allow for the 5 to 10 mm Hg higher blood pressure when taken in the office setting.

The other 2 recommendations in the 2017 heart failure guidelines relate to patients with existing heart failure. In the first of these: "Patients with HF*r*EF and hypertension should be prescribed guideline-directed medical therapy titrated to attain systolic blood pressure <130 mm Hg."[6] While investigations to evaluate the benefits of blood pressure reduction in the setting of HF*r*EF have not been conducted, evidence from the SPRINT trial indicates that blood pressure lowering is associated with fewer adverse cardiovascular events in patients at higher risk.

The final recommendation relates to patients with stage C HF*p*EF and states: "Patients with HF*p*EF and persistent hypertension after management of volume overload should be prescribed guideline-directed medical therapy titrated to attain SBP <130 mm Hg."[6] As with HF*r*EF, data are limited, although the use of increasing doses of nitrates in HF*p*EF have been shown to be associated with a lower level of physical activity, suggesting possible harm.[14] Available data do not otherwise provide clear guidance as to the choice of antihypertensive therapy in HF*p*EF, although renin-angiotensin-aldosterone system inhibition, especially with a mineralocorticoid antagonist, or with an ACE-I, ARB, or ARNI, may be the preferred approach.[6]

4. Is the use of B-type natriuretic peptide as a biomarker ready for prime time? If so, under what circumstances?

B-type natriuretic peptide (BNP), as well as N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), has been used to assist in the diagnosis or exclusion of heart failure as a cause of symptoms such as dyspnea or weight gain in the chronic and acute care settings.[15-17] The role of BNP or NT-proBNP for the purpose of reducing hospitalizations or deaths remains unclear.[6] Note that BNP, but not NT-proBNP, is a substrate for neprilysin, thus sacubitril/valsartan increases only BNP levels. Consequently, NT-proBNP can still be used as a diagnostic marker when a patient is being treated with an ARNI, but BNP is not reliable since it is increased by neprilysin inhibition.

The 2017 heart failure guidelines recommend the use of BNP or NT-proBNP as a biomarker for heart failure in several settings, 2 of which are new.[6] The first of the new roles is as a screening tool for the prevention of heart failure. The St. Vincent's Screening to Prevent Heart Failure (STOP-HF) trial showed that screening with BNP followed by further investigation and treatment, as appropriate, reduced the occurrence of left ventricular dysfunction.[18] The second new role is to establish a postdischarge prognosis following heart failure hospitalization. Predischarge natriuretic peptide levels and their relative change during hospital treatment have been shown to be strong predictors of the risk of death or hospital readmission for heart failure.[19-21] Patients with higher predischarge natriuretic peptide levels, and those whose natriuretic peptide level do not decrease with inpatient treatment, have worse outcomes.[20]

Additional recommendations related to the use of BNP and/or NT-proBNP are included in the 2017 guidelines. One remains unchanged from the 2013 guidelines, while 2 have been modified. Below is a summary:.

Status	Recommendation	Comment/Rationale
Unchanged	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic heart failure	—
Modified	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of heart failure	In the ambulatory setting, BNP, NT-proBNP provide incremental diagnostic value, especially with unclear etiology of dyspnea.[15] In the emergency setting, BNP/NT-proBNP have higher sensitivity than specificity and may be more useful for ruling out rather than ruling in heart failure.[22]
Modified	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated heart failure	Higher levels of BNP/NT-proBNP on admission are usually associated with greater risk for clinical outcomes, including all-cause and cardiovascular mortality, morbidity, and composite outcomes in patients with decompensated heart failure.[17,19]

5. Are there any precautions that need to be taken with ivabradine? Sacubitril-valsartan?

In the SHIFT trial (N=6538), ivabradine was associated with several cardiac effects **(Table 1)**.[23] Symptomatic bradycardia occurred in 5% and 1% of patients treated with ivabradine vs placebo, respectively, and atrial fibrillation in 9% vs 8%, respectively. Consequently, patients treated with ivabradine should be monitored for atrial fibrillation, as well as heart rate reduction and symptoms of bradycardia. The onset of phosphenes is generally within the first 2 months of treatment, after which they may occur repeatedly. Phosphenes are generally mild to moderate in intensity.[24]

Ivabradine is extensively metabolized in the liver and intestines by cytochrome P450 3A4 (CYP3A4) enzymes. Consequently, concomitant use of ivabradine and medications or other substances that induce (eg, St. John's wort, rifampicin, barbiturates, phenytoin) or inhibit (eg, ketoconazole,

macrolides, diltiazem, verapamil, HIV protease inhibitors, grapefruit juice) CYP3A4 enzymes is to be avoided.[24]

Ivabradine is contraindicated in acute decompensated heart failure; blood pressure <90/50 mm Hg; sick sinus syndrome, sinoatrial block, 3rd degree atrioventricular block (unless a functioning pacemaker is present); resting heart rate <60 beats per minute prior to treatment; severe hepatic impairment; pacemaker dependence; concomitant use with strong CYP3A4 inhibitors

Sacubitril-valsartan

In the PARADIGM-HF trial (N=8399), sacubitril-valsartan was associated with several adverse events **(Table 2)**.[5] Consequently, patients treated with sacubitril-valsartan should be monitored for signs and symptoms of angioedema and hypotension, while renal function and serum potassium should be monitored in susceptible patients.[25]

Concomitant use of ARNI and ACE-I with sacubitril-valsartan is contraindicated due to heightened risk of angioedema. Concomitant use of ARNI and ARB is to be avoided as the ARNI already has an ARB component. As lithium levels have been found to be elevated in patients using ARBs, lithium levels should be carefully monitored when coadministered with an ARNI.[25]

Sacubitril-valsartan is contraindicated in patients with a history of angioedema with previous ACE-I or ARB therapy. To reduce risk of angioedema, a 36-hour washout period should be used between the last dose of ACE-I and first dose of sacubitril-valsartan.

Table 1. Selected adverse events with ivabradine from the SHIFT trial.

	Ivabradine	Placebo
All	75%	74%
Heart failure	25%	29%
Bradycardia		
Symptomatic	5%	1%
Asymptomatic	6%	1%
Atrial fibrillation	9%	8%
Phosphenes, visual brightness	3%	1%

Table 2. Common adverse events with sacubitril-valsartan.

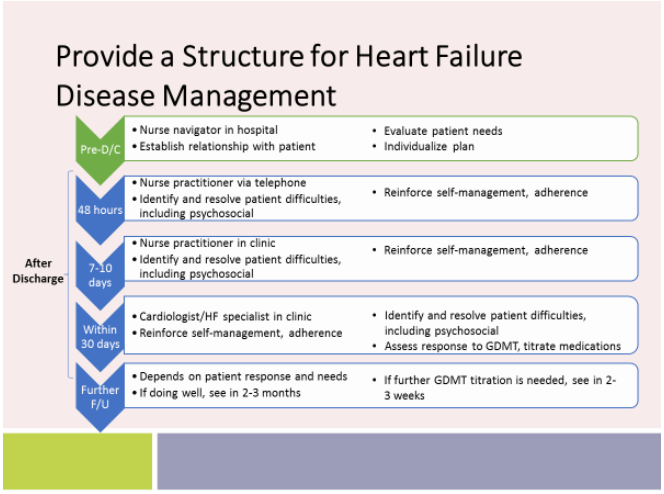
	Sacubitril-Valsartan	Enalapril
Symptomatic hypotension	14.0%	9.2%
Serum potassium >6 mEq/L	4.3%	5.6%
Serum creatinine >2.5 mg/dL	3.3%	4.5%
Cough	11.3%	14.3%

6. KS is a 58-year-old male admitted for worsening heart failure symptoms (ejection fraction 30%). This is his third, admission in the past 5 months. He admits to frequently forgetting to take his medications as prescribed. During each admission, he feels much improved within a few days. What advice do you have?

Frequent hospitalization for heart failure is common, with a quarter of Medicare fee-for-service patients readmitted within 30 days after hospitalization.[26] As shown in the SHIFT trial, patients with poor medication adherence are more likely to suffer cardiovascular death or be hospitalized for heart failure.[27] Thus, promoting patient adherence and overall self-management are critical to improve long-term outcomes of patients with heart failure.

Keys to promoting self-management include working collaboratively with the patient to identify and solve barriers to patient self-management, including psychosocial, family, and logistical barriers such as affordability and transportation to appointments.[28] The collaborative process is best done in a system of care that involves other members of the heart failure team, including family members. Patient education is best

initiated prior to hospital discharge, with discharge instructions provided in writing.[29] Recent evidence indicates that use of a predischarge heart failure checklist reduces heart failure hospitalization, improves patient outcomes including reduced mortality, and increases patient adherence to guideline-directed medical therapy.[30] Key components include lifestyle management, medication use, self-monitoring plan, rescue plan, and follow-up appointments.[29] Frequent follow-up by a member of the heart failure team after patient discharge is strongly recommended, with some follow-up done via telephone, email, or other mutually agreed upon medium **(Figure)**. At least 1 clinic visit with a heart failure specialist is recommended within 30 days of discharge.



Finally, it is critically important that patient education go beyond increasing patient knowledge about heart failure by helping patients acquire the skills needed to successfully manage their disease. For example, this goes beyond patients understanding how to monitor their heart failure and being willing and able to do it successfully.

7. Case Study

A 60-year-old African American man was hospitalized 3 weeks ago for HF*r*EF. At discharge, his treatment plan was

- Cardiac rehabilitation
- Furosemide 40 mg every morning
- Candesartan 8 mg every morning
- Metoprolol XL 200 mg very morning
- Isosorbide dinitrate 20 mg three times daily

Past medical history

- Long-standing hypertension
- Smokes 1 pack of cigarettes a day
- Frequent alcohol use

Family history

- Mother is deceased; had a history of type 2 diabetes mellitus
- Father is deceased; had a history of hypertension, chronic kidney disease

At his follow-up office visit today,

- He reports that he has not been able to return to work as an office manager. He feels tired and has difficulty walking up 1 flight of stairs.
- Physical examination
  - Body mass index 32.4 kg/m^2
  - Mildly short of breath while sitting
  - Heart: blood pressure 142/92 mm Hg; pulse 76 beats/minute; 2/6 systolic ejection murmur
  - Lungs: mild wheezing
  - Skin: cool, 2+ pedal edema bilaterally
- Echocardiogram: left ventricular ejection fraction 25%
- Electrolytes: normal; potassium 4.8 mEq/L

Estimated glomerular filtration rate: 42 mL/min/1.73 m^2

What changes would you make to his treatment plan?

The primary objective for the visit is to improve the patient's symptoms and overall functioning. Review of his current treatment plan shows that it is not consistent with the recommendations in the 2017 ACC/AHA guidelines for the management of HF*r*EF.[6] These include

- Counseling regarding smoking cessation and alcohol avoidance should be initiated.
- Volume overload can be improved, as well as morbidity and mortality benefit conferred, by starting spironolactone 25 mg orally daily. Serum potassium should be closely monitored and the patient instructed to weigh himself every 1-2 days.
- Blood pressure remains above the target of 130/80 mm Hg for HF*r*EF. After management of volume overload, the dose of candesartan should be titrated upward from the current dose of 8 mg once daily (maximum 32 mg/day). Alternatively, unless the patient has a history of angioedema, consideration may be given to discontinuing candesartan and initiating sacubitril-valsartan 24/26 mg twice daily (and uptitrating to its maximal dose of 97/103 twice a day as the patient tolerates) to control blood pressure and further reduce morbidity and mortality.[5]
- His heart rate remains elevated despite maximal beta-blocker therapy, ie, metoprolol XL 200 mg once daily. Ivabradine 5 mg twice daily can be considered to improve quality of life and reduce heart failure hospitalization.[23,31,32]
- The combination of isosorbide dinitrate and hydralazine is recommended in self-identified African American patients to reduce morbidity and mortality.[33] The addition of hydralazine may be considered after the above changes have been implemented and the patient stabilized. This can be done by switching the patient to the fixed-dose combination of hydralazine/isosorbide dinitrate at an initial dose of 37.5/20 mg 3 times daily. In clinical trials, the mean daily dose of hydralazine/isosorbide dinitrate was 175/90 mg. With the combination of hydralazine/isosorbide dinitrate, close monitoring of blood pressure is advised, particularly if sacubitril-valsartan is initiated since the concomitant use of isosorbide dinitrate/hydralazine and sacubitril-valsartan is not well studied.
- Consideration may also be given to use of an implantable cardioverter-defibrillator provided that his survival is estimated to be longer than 1 year.
- Finally, steps to improve patient self-management should be initiated as discussed in question 6.

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