Heart failure has been called a disease of the elderly, as its prevalence increases with age.\textsuperscript{1,2} The average age at the time of heart failure diagnosis is 80 years.\textsuperscript{2} In patients treated for heart failure, the risk of hospitalization and mortality also increases with advancing age.\textsuperscript{2,3} Despite this, elderly patients have largely been excluded from clinical trials evaluating heart failure therapies, and may be inadequately represented in heart failure treatment guidelines.\textsuperscript{2}

Sacubitril/valsartan, a novel heart failure agent marketed as Entresto™, was FDA-approved in 2015 on the basis of clinical trial data which included geriatric patients. Earlier this year, the American College of Cardiology, American Heart Association, and Heart Failure Society of America (ACC/AHA/HFSA) released a focused update to their clinical practice guidelines in order to provide treatment recommendations for the use of sacubitril/valsartan. This article will provide an overview of sacubitril/valsartan’s actions in the treatment of heart failure and describe its current place in therapy.

Indication & Mechanism of Action
Sacubitril/valsartan is FDA-approved to reduce the risk of cardiovascular death and hospitalization in patients with New York Heart Association (NYHA) class II, III, or IV heart failure and reduced ejection fraction. It is typically used in place of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in conjunction with other heart failure therapies.\textsuperscript{4}

Sacubitril is converted by esterases into its active metabolite LBQ657, a neprilysin inhibitor; valsartan is an ARB.\textsuperscript{4} Sacubitril/valsartan is the first available combination of these medication classes. Neprilysin degrades a variety of endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. By inhibiting neprilysin, LBQ657 increases levels of these peptides, which results in vasodilation, natriuresis, diuresis, and inhibition of maladaptive remodeling. Valsartan selectively blocks the angiotensin II type-1 receptor, inhibiting angiotensin II-related vasoconstriction, sodium retention, and vascular growth.\textsuperscript{5}

Clinical Trial Data
Sacubitril/valsartan was approved on the basis of the PARADIGM-HF trial, a large, multinational, randomized, double-blind, active-controlled trial enrolling over 8400 patients with heart failure and a reduced ejection fraction.\textsuperscript{6} Patients who completed two single-blind run-in phases with enalapril and sacubitril/valsartan were randomized to receive enalapril 10mg or sacubitril/valsartan 200mg twice daily. The majority of patients were also receiving beta-blockers, diuretics, and aldosterone (mineralocorticoid) antagonists, and were categorized as having NYHA class II (approximately 70%) or class III (approximately 24%) heart failure. The mean age of trial participants was 64 years.\textsuperscript{6}
Sacubitril/valsartan was found to reduce the composite risk of cardiovascular death or hospitalization for worsening heart failure by 20% compared to enalapril (21.8% vs. 26.5%; hazard ratio = 0.80, p<0.001). This equated to a Number Needed to Treat (NNT) of 22 for the primary efficacy outcome. Sacubitril/valsartan also reduced the risk of death from any cause by 16% vs. enalapril, with a NNT of 36. Symptom scores, measured by the Kansas City Cardiomyopathy Questionnaire, worsened in both groups; however, the decline was significantly less with sacubitril/valsartan than with enalapril.6

Subjects receiving sacubitril/valsartan reported a higher incidence of symptomatic hypotension than those receiving enalapril, with a Number Needed to Harm of 20. Reports of cough, elevated serum creatinine, and elevated serum potassium were more common in subjects receiving enalapril.6

Subgroup analyses showed a significant benefit with sacubitril/valsartan in patients ≥65 years of age for both the composite endpoint and for cardiovascular death alone. This benefit was not found in patients ≥75 years of age; however, the analysis was likely underpowered to detect a difference due to a low number of patients in this age range enrolled.6

The PARADIGM-HF trial was stopped early due to the positive results obtained in the sacubitril/valsartan group.6 Because the study compared a high dose ARB (valsartan 103mg BID, equivalent to valsartan 160mg BID in single-agent formulations) to a relatively low dose ACE inhibitor (enalapril 10mg BID), it is unclear if the large benefit would remain when comparing sacubitril/valsartan to higher doses of ACE inhibitors or ARBs.

Additional analyses of the PARADIGM-HF trial data have been published.7-10 One such analysis demonstrated that sacubitril/valsartan is superior to enalapril for improving cardiovascular outcomes in diabetic patients with heart failure across a wide range of glycated hemoglobin levels.7 In addition, sacubitril/valsartan was found to significantly improve cardiovascular outcomes compared to enalapril in patients across the spectrum of baseline heart failure risk.8 Sacubitril/valsartan has also been shown to be superior to enalapril for preventing the progression of heart failure in surviving patients and reducing the risk of cardiac death and death from worsening heart failure.9-10

Clinical Practice Guidelines
In 2013, the American College of Cardiology Foundation and American Heart Association jointly issued practice guidelines for the management of heart failure, with pharmacologic recommendations based on stage of heart failure.11 ACC/AHA stages of heart failure correspond to the NYHA functional classification as described in the Table on the next page.
According to ACC/AHA guidelines, Stage A patients require no specific pharmacologic therapy aside from appropriate management of hypertension and hyperlipidemia, and Stage D patients require specialized interventions such as mechanical circulatory support and/or cardiac transplantation. Therefore, the majority of ACC/AHA treatment recommendations focus on patients with Stage B and Stage C heart failure.

In the 2013 guidelines, ACE inhibitors are recommended for all patients with Stage B heart failure to prevent heart failure symptoms and reduce mortality. In patients intolerant or contraindicated to ACE inhibitors, ARBs may be used. ACC/AHA does not recommend one ACE inhibitor or ARB over another. Other agents to be considered based on patient specific factors include beta-blockers, statins, diuretics, aldosterone receptor antagonists, hydralazine, isosorbide dinitrate, and digoxin.\textsuperscript{11}

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Table. Comparison of ACC/AHA stages of heart failure and NYHA functional classification

<table>
<thead>
<tr>
<th>ACC/AHA Stage</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for heart failure without structural heart disease or symptoms of heart failure</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease without signs or symptoms of heart failure</td>
<td>I No limitation of physical activity; Ordinary physical activity does not cause heart failure symptoms</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of heart failure</td>
<td>I No limitation of physical activity; Ordinary physical activity does not cause heart failure symptoms, II Slight limitation of physical activity. Comfortable at rest, but less than ordinary activity causes heart failure symptoms, III Marked limitation of physical activity; Comfortable at rest, but less than ordinary activity causes heart failure symptoms, IV Unable to carry on any physical activity without heart failure symptoms, or heart failure symptoms at rest</td>
</tr>
<tr>
<td>D Refractory heart failure requiring specialized interventions</td>
<td>IV Unable to carry on any physical activity without heart failure symptoms, or heart failure symptoms at rest</td>
</tr>
</tbody>
</table>

\textit{Adapted from 2013 ACC/AHA Guidelines for the Management of Heart Failure}\textsuperscript{11}
The 2013 ACC/AHA guidelines included similar recommendations for patients with Stage C heart failure. However, due to the approval of sacubitril/valsartan as well as the sinoatrial node modulator ivabradine, the ACC, AHA, and Heart Failure Society of America (HFSA) published a Focused Update on New Pharmacological Therapy for Heart Failure in September 2016. This update focused on the place of therapy for these two new agents in patients with Stage C heart failure only.12

The ACC/AHA/HFSA 2016 guidelines provide a strong (Class 1) recommendation for the use of an ACE inhibitor, ARB, or sacubitril/valsartan for all patients with Stage C heart failure with reduced ejection fraction in order to reduce heart failure-related morbidity and mortality. The recommendations for ACE inhibitor or ARB use are based on high-quality evidence from more than one randomized clinical trial. The recommendation for sacubitril/valsartan is based on moderate-quality evidence from one or more randomized clinical trials. Beta blockers and/or aldosterone antagonists are also recommended along with an ACE inhibitor, ARB, or sacubitril/valsartan in certain patients. The guidelines further recommend sacubitril/valsartan as the preferred agent over an ACE inhibitor or ARB in patients with chronic symptomatic heart failure with reduced ejection fraction NYHA class II or III who can tolerate an ACE inhibitor or ARB.12

The ACC/AHA/HFSA 2016 focused update also provided safety-related recommendations specific to sacubitril/valsartan. Sacubitril/valsartan should not be used along with an ACE inhibitor or within 36 hours of the last ACE inhibitor dose. In addition, sacubitril/valsartan should not be given to patients with a history of angioedema.12

Note that the 2016 focused update refers generically to the class of angiotensin receptor-neprilysin inhibitors (also called ARNIs); however, sacubitril/valsartan is the only available agent in this pharmacologic class.

Guidance for Long-Term Care

AHA and HFSA jointly issued a scientific statement on heart failure management in skilled nursing facilities in 2015.13 The AHA/HFSA statement reflects the recommendations from the ACC/AHA guidelines, but further indicates that treatment should be individualized within the context of the patient specific goals. Adverse effects, costs, drug-drug interactions, and personal preferences should be considered, and treatment should focus on minimizing symptoms, improving quality of life, and reducing hospitalizations.13

AMDA – The Society for Post-Acute and Long-Term Care Medicine updated their clinical practice guidelines for the management of heart failure in the post-acute and long-term care settings in 2015.14 These guidelines rely heavily on the pharmacologic treatment recommendations provided by the ACC/AHA, but have not been updated to reflect the 2016 focused update. Additionally, AMDA recommends loop diuretic therapy in patients with evidence of fluid retention as well as the avoidance of non-steroidal anti-inflammatory drugs in heart failure patients.14

Due to the date of the drug’s approval, neither the AHA/HFSA nor AMDA guidelines specifically addresses the use of sacubitril/valsartan.
Summary

Sacubitril/valsartan is the first neprilysin inhibitor and ARB combination approved to reduce the risk of cardiovascular death and hospitalization in patients with NYHA class II-IV heart failure and reduced ejection fraction. In a large, multinational clinical trial, sacubitril/valsartan was shown to significantly reduce the risk of cardiovascular death and hospitalization for heart failure compared to enalapril in patients with heart failure.

Based on this data, heart failure treatment guidelines were recently updated to recommend an ACE inhibitor, ARB, or sacubitril/valsartan for all patients with stage C heart failure with reduced ejection fraction. The guidelines further recommend sacubitril/valsartan over an ACE inhibitor or ARB in patients with chronic symptomatic heart failure with reduced ejection fraction NYHA class II or III. However, uncertainty remains regarding the effectiveness of sacubitril/valsartan in patients aged greater than 75 years, as clinical trial data was underpowered to detect a significant benefit in this subgroup.

References:

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