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Indian Health Service National Pharmacy and Therapeutics Committee Beta Blockers in Heart Failure NPTC Formulary Brief May Meeting 2017

Background:
Heart failure is a complex syndrome affecting 5.7 million adults in the United States (US) and costs the US more than $30.7 billion annually[1]. The management of patients with structural heart disease and symptoms of heart failure is based on left ventricular ejection fraction (LVEF). Heart failure is categorized as heart failure with reduced ejection fraction (HFrEF) when the LVEF is ≤40% or heart failure with preserved ejection fraction (HFpEF) for LVEF ≥50%. Beta-blockers are considered first line therapy for patients with HFrEF as these medications antagonize neurohormonal remodeling by blocking the action of norepinephrine and epinephrine on beta-adrenergic receptors on the heart and blood vessels. The 2013 American College of Cardiology Foundation / American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure recommends the use of a "life-saving" beta-blocker for patients with HFrEF (i.e., those beta-blockers shown to reduce morbidity and mortality in patients with heart failure): bisoprolol, carvedilol, and metoprolol succinate. Bisoprolol and metoprolol succinate are beta-1 selective beta-blockers, but carvedilol antagonizes alpha and beta-1 and -2 receptors. The current National Core Formulary (NCF) for Indian Health Service includes carvedilol (*immediate release formulation*) and metoprolol (formulation not specified) as well as atenolol and propranolol. In May 2017, the National Pharmacy and Therapeutics Committee (NPTC) reviewed heart failure management to determine if changes to the NCF were necessary to optimize heart failure treatment with regard to currently available beta-blockers. Based on the findings on the NPTC review, no modifications were made to the NCF.

Discussion:
Beta-blockers are a first-line therapy in HFrEF, but recommendations vary slightly between guidelines. The recommendations are summarized as follows:

2013 ACCF/AHA Guideline for the Management of Heart Failure:

Use of 1 of the 3 beta-blockers proven to reduce mortality (bisoprolol, carvedilol, metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality[2].

2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure:

A beta-blocker (bisoprolol, carvedilol, metoprolol succinate, nebivolol) is recommended, in addition an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of hospitalization and death[3].

In this Issue…

2016 VA Beta-Blockers in HFrEF: Recommendations for Use:

A beta-blocker that has proven to reduce mortality (bisoprolol, carvedilol, metoprolol succinate) is recommended for patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality[4].

The COMET trial, the landmark trial that led to the exclusion of metoprolol tartrate from the current practice guidelines, was reviewed[5]. This study compared metoprolol tartrate 50 mg twice daily to carvedilol 25 mg twice daily in patients with NYHA class II-IV HFrEF with a previous admission for cardiovascular reasons. This study found that metoprolol tartrate was inferior to carvedilol (HR=0.83; 95% CI: 0.74-0.93; p=0.0017) in reducing all-cause mortality. It should be noted that the dose of metoprolol tartrate was below the target dose for metoprolol, which may have impacted study findings.

The NPTC also reviewed literature published after the 2013 ACCF/AHA guidelines to assess appropriateness of current guideline-directed beta-blocker selection. The published literature included one comparative effectiveness analysis, two network meta-analyses, and three meta-analyses.

- The comparative effectiveness analysis found no significant difference in mortality between metoprolol succinate and carvedilol in patients with either ischemic HFrEF or non-ischemic HFrEF[6].
- One network analysis compared beta-blockers to investigate whether the morbidity and mortality benefits of beta-blockers were a class effect[7]. The analysis found a significant survival benefit when a beta-blocker was used (OR=0.71; 95% CI: 0.64 to 0.80; p<0.001) but comparison between beta-blockers found no significant benefit of one agent over others. The researchers did note that data directly comparing beta-blockers to each other was lacking.
- A second network meta-analysis compared all medications used for the treatment of HFrEF and found that beta-blockers were better than placebo in reducing all-cause mortality (HR=0.57; 95% CI: 0.33 to 0.94; p(better)=0.99), and the combination of sacubitril/valsartan, a beta-blocker and a mineralocorticoid receptor antagonist resulted in the greatest mortality reduction (HR=0.37; 95% CI: 0.19 to 0.65; p(better)=1.0)[8].
- Two meta-analyses compared carvedilol to beta-1 selective beta-blockers. One study found carvedilol reduced all-cause mortality compared with beta-1 selective beta-blockers (atenolol, bisoprolol, metoprolol, or nebivolol) in patients with HFrEF (RR 0.85; 95% CI: 0.78 to 0.93; p<0.001)[9]. Of note, this meta-analysis included beta-1 selective beta-blockers that have been shown to be inferior to carvedilol such as metoprolol tartrate. A second meta-analysis compared carvedilol to metoprolol in patients with HFrEF (either tartrate or succinate) and found carvedilol and metoprolol succinate have similar effects in reducing all-cause mortality (HR=1.12; 95% CI 0.91 to 1.39; p=0.29), but carvedilol was superior to metoprolol tartrate (OR=0.79; 95% CI: 0.68 to 0.91; p=0.001)[10], a result which was largely influenced by the COMET trial.
- A third meta-analysis compared beta-blockers (any) to placebo and found beta-blockers reduced mortality (RR=0.37; 95% CI: 0.12 to 0.47; p=0.03) compared to placebo[11].

Findings:

Beta-blockers have been shown to reduce morbidity and mortality in patients with HFrEF. Beta-blockers should be titrated slowly to the target dose as tolerated to maximize benefit. Current clinical practice guidelines support the use of one of the "life-saving" beta-blockers for the management of HFrEF (bisoprolol, carvedilol, metoprolol succinate). The current NCF includes carvedilol (immediate release) and metoprolol. Recently published literature strengthens current clinical practice guidelines and, as such, no changes were made to the NCF. Literature suggesting morbidity and mortality reduction is a class effect is limited to meta-analyses without direct comparison. At this time, evidence is insufficient to support the use of any of these three agents over the others. Therefore, the current agents available on the NCF provide adequate prescribing options for patients with HFrEF.

For questions about this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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Indian Health Service
National Pharmacy and Therapeutics Committee
Mineralocorticoid Receptor Antagonists in Heart Failure
NPTC Formulary Brief
May Meeting 2017

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed heart failure (HF) at the May 2017 meeting. One of the drug classes reviewed in the treatment of HF was the mineralocorticoid receptor antagonists (MRAs). The MRAs are also referred to as aldosterone receptor antagonists (ARA) or aldosterone antagonists (AA). The two agents in this class, spironolactone and eplerenone, were reviewed. Spironolactone has been in use since the 1960s, originally for hypertension and as a potassium sparing diuretic for volume overload in HF.[1] As knowledge of mineralocorticoid receptors (MRs) increased, the use of spironolactone in HF became more common. Eplerenone was developed through chemical modification of spironolactone to enhance binding MRs while reducing binding to progesterone and androgen receptors to decrease side effects of gynecomastia, impotence, and menstrual irregularities.[2] It was FDA-approved in 2002 for use in HF.

Current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) heart failure guidelines recommend the use of MRAs in patients already receiving an ACEI (or ARB) and beta blocker for NYHA class II-IV with LVEF <35% unless contraindicated to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF). MRAs are also recommended to reduce morbidity and mortality following acute myocardial infarction (MI) in patients with LVEF <40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated. Inappropriate use of MRAs is potentially harmful in patients with potassium levels of >5.0 mEq/L (life-threatening hyperkalemia) or serum creatinine levels <2.5 mg/dl in men or <2.0 mg/dl in women (renal insufficiency).[3]

The European Society of Cardiology (ESC) also recommends the use of MRAs in patients with HFrEF and LVEF <35% already taking ACEI (or ARB) and beta blockers to reduce mortality and HF hospitalization. These guidelines recommend using MRAs with caution in patients with impaired renal function and serum potassium >5 mmol/L (or >5 mEq/L). The ESC, unlike ACCF/AHA, addressed MRA use in heart failure with preserved ejection fraction (HFpEF) by suggesting that treating hypertension in HF is important and MRAs are an appropriate choice along with ACEI, ARB, and diuretics.[4]

Discussion:
Three landmark trials established the use of MRAs in treating HF. The Randomized Aldactone Evaluation Study (RALES) included patients with NYHA class III or IV HF, LVEF <35%, and already receiving an ACEI. The study group found that treatment with spironolactone resulted in a 30% reduction in death (RR 0.7; 95% CI: 0.60-0.82; $p<0.001$), a 35% reduction in hospitalizations (RR 0.65; 95% CI: 0.54-0.77; $p<0.001$), and significant improvement in symptoms of HF ($p<0.001$). The spironolactone group did show significant ($p<0.001$) increases in serum creatinine and potassium, but these were not clinically important. Gynecomastia or breast pain was reported by 10% of the men in the spironolactone group versus 1% in the placebo group ($p<0.001$).[5]

The Eplerenone Post-Acute MI Heart Failure Efficacy and Survival Study (EPHESUS) was an international, multi-center, randomized controlled trial that evaluated eplerenone versus placebo. Use of eplerenone resulted in decreased death from any cause (RR 0.85; 95% CI: 0.75-0.96; $p=0.008$) and death or first hospitalization from cardiovascular (CV) causes (RR 0.87; 95% CI: 0.79-0.95; $p=0.002$). Patients were on optimal pharmacotherapy (ACEI or ARB, possibly diuretics and beta blockers) and had LVEF <40%. Incidence of hyperkalemia was significantly higher in the eplerenone group ($p<0.001$).[6]

The Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) study evaluated patients with NYHA class II (mild HF) and a LVEF <35%. This randomized, double-blind, placebo controlled trial showed a significant decrease in death from CV cause or first hospitalization for heart failure in the eplerenone-treated group (HR 0.63; 95% CI: 0.54-0.74; $p<0.001$). Again, hyperkalemia was found to be significantly higher with the eplerenone group.[7]

There are no large studies of spironolactone in mild or asymptomatic HF. A small study suggested that spironolactone use (in addition to optimal therapy) may reduce risk of HF and slow progression of disease in those with less advanced symptoms. A study with larger sample size is needed to determine if the effect seen in the EMPHASIS-HF study is a class effect.[8]

The use of MRAs in HFpEF may be beneficial. The 2014 TOPCAT (Treatment Of Preserved Cardiac function with an Aldosterone anTagonist) study evaluating spironolactone did not show significant reduction in the primary outcome, a composite of death from CV causes, aborted cardiac arrest, and hospitalization for management of HF. A post-hoc analysis suggested MRAs may be a potential treatment for HFpEF, but further prospective, adequately powered, randomized, controlled studies are needed.[9]

Findings:
Spironolactone is currently listed on the IHS National Core Formulary (NCF). After reviewing the MRA class, no modifications were made to the NCF. Current guidelines do not recommend either agent over the other at this time. Both MRAs are currently approved for use in HF and have similar safety concerns in regard to renal function and hyperkalemia. Spironolactone at a dose of 12.5 to 50 mg/day is a reasonable choice to add to ACEI (or ARB) and beta blocker therapy in the treatment of HFrEF. Caution is advised in patients with reduced renal function. Close monitoring of potassium is recommended in both ESC and ACCF/AHA guidelines. The ACCF/AHA guidelines have more stringent recommendations, suggesting that potassium be monitored at 2-3 days and 7 days after initiation of therapy, then at least monthly for 3 months, then every 3 months thereafter.[3] Eplerenone may be an option for those patients experiencing gynecomastia while taking spironolactone.

For questions about this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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