Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Beta Blockers in Heart Failure***
-May 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].

- **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.

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

References:

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