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

Background:
It is estimated that 5.7 million Americans currently live with heart failure.[1] The epidemic of heart failure in the United States is influenced by a number of variables such as an aging population, the twin epidemics of obesity and diabetes, and also the prevalence of smoking and uncontrolled hypertension. Heart disease is the most common cause of death among American Indians and Alaska Natives, who are collectively 20% more likely to die from heart disease compared to all U.S. races.[2] Over one-third of American Indian and Alaska Native people who die from heart disease are under the age of 65 years.

Discussion:
Heart failure is not a disease but rather a syndrome consisting of signs and symptoms which are collectively a consequence of relative impairment in heart pump function and resulting from diverse etiologies and mechanisms. Cardiac remodeling is the process by which a combination of mechanical, neuro-hormonal, and genetic factors alters cardiac physiology resulting in hypertrophy, myocyte loss, and fibrosis. A variety of pharmacologic interventions have been identified for the effective management of heart failure and are advocated by clinical practice guidelines to reduce heart failure-related morbidity and mortality.[3-7]

For patients at high-risk for heart failure or who have structural heart disease without heart failure symptoms, in addition to a heart healthy lifestyle, an appropriate preventive strategy may include use of ACE-inhibitors, ARBs, and statins when indicated.[3] Beta-blockers are recommended for the management of most patients with structural heart disease, with or without heart failure symptoms, regardless of the presence or absence of reduced ejection fraction.[3]

For patients with left ventricular systolic dysfunction, a beta-blocker and ACE-inhibitor should be routinely offered as first line therapy, with substitution of an ARB for ACE-inhibitor intolerant patients.[4] A mineralocorticoid receptor antagonist is indicated to reduce morbidity and mortality among patients with NYHA class II-IV heart failure and ejection fraction (EF) less than 35% as well as for EF less than 40% following an acute myocardial infarction with symptomatic heart failure or with a history of diabetes mellitus.[3]

For persistently symptomatic patients of African-American descent with reduced ejection fraction and NYHA Class III-IV heart failure, the addition of a combination of hydralazine and a nitrate is

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indicated.[3] Diuretics, such as furosemide, are indicated to reduce symptoms and improve exercise capacity in patients with signs and/or symptoms of volume overload.[7]

While of less certain benefit, digoxin may be considered for patients in sinus rhythm who remain symptomatic despite treatment with an ACE-inhibitor (or ARB), a beta-blocker, and a mineralocorticoid receptor antagonist.[7]

Last year, two new agents were added to heart failure guidelines from the American Heart Association and the European Society of Cardiology. Based on results from the PARADIGM-HF randomized control trial, which showed a 20% reduction in both heart failure hospitalization and cardiovascular death in patients with chronic symptomatic heart failure with reduced ejection fraction (NYHA Class II or III) who tolerate an ACE-inhibitor or ARB, replacement by an angiotensin receptor-neprilysin inhibitor (ANRI) is now recommended to further reduce morbidity and mortality.[6] [6] Also included in updated guidelines is a new recommendation for use of the sinoatrial node blocking agent, ivabradine, to reduce heart failure-related hospitalization among patients with reduced EF on standard therapy including a beta-blocker at the maximum tolerated dose but whose resting heart rate remains above target.

Conclusion(s):
Among chronic health conditions, heart failure is particularly amenable to guideline-based management because the foundation of peer-reviewed clinical research offers clear and convincing evidence for effective strategies to reduce both morbidity and mortality. The appropriate use of various medication classes, including beta-blockers, ACE-inhibitors, ARBs, mineralocorticoid receptor antagonists, and ANRIs has been shown to reduce heart failure-related morbidity and mortality.

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
ACEi and ARB in Heart Failure
NPTC Formulary Brief
May Meeting 2017

Background:
In May 2017, the IHS National Pharmacy and Therapeutics Committee (NPTC) convened to discuss pharmacotherapy in heart failure (HF). Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have important roles in the management of heart failure and are considered a cornerstone in the treatment of heart failure with reduced ejection fraction (HFrEF)[1,2]. The NPTC last reviewed the ACEi and ARB classes (for hypertension) in August 2014 and, at that time, made no changes to the National Core Formulary (NCF). At that time, lisinopril and losartan were listed on the NCF as sole representatives in their respective medication classes. Based on the findings of this new review, no changes were made to the NCF.

Discussion:
Angiotensin Converting Enzyme Inhibitors:
The review focused heavily on HFrEF as ACEi and ARBs are most strongly recommended and show the greatest benefit in these patients. It is well established that ACEi reduce morbidity and mortality in HFrEF based on primary literature of trial data[3,4] but most trials have used enalapril. All ACEi are similar with regard to safety, dosing adjustments, monitoring and precautions[5]. A landmark meta-analysis published in 1995 concluded that there was an ACEi class effect in HF[6]. The study showed a significant reduction in mortality (OR=0.77; 95% CI: 0.67 to 0.88, $p<0.001$), a reduction in the combined endpoint of mortality or hospitalization in HF (OR=0.65; 95% CI: 0.57 to 0.74, $p<.001$) and an equivalent effect across the ACEi class (no statistical heterogeneity was detected among the various agents).

Subsequent studies have suggested that differences among the ACEi class may exist. A meta-analysis published in 2016 reported enalapril to have the greatest hemodynamic effect but also the most adverse events. The meta-analysis noted that ramipril had the lowest incidence all-cause mortality and lisinopril had the highest all-cause mortality, comparatively[7]. Despite these findings, authors concluded that there was no statistical difference in any ACEi and that no conclusive recommendations could be made[7]. Another study published in 2016 also suggested heterogeneity among the ACEi class[8]. This study reported that ramipril had the highest probability of reducing death among ACEi. However, due to short-term durations and limited number of ramipril trials included in the analysis, the study did not demonstrate statistically significant results (i.e., benefit) for any ACEi.

Angiotensin Receptor Blockers:
Only candesartan and valsartan are FDA indicated in the treatment of HF. Losartan is the current NCF agent for the ARB class. Losartan does not have an FDA indication for HF but is routinely used off label for this indication. All ARBs are similar regarding safety, dosing adjustments, monitoring and precautions[9]. The outcomes data to support candesartan and valsartan are derived from well-known studies (CHARM and Val-HeFT, respectively).

In an effort to determine whether losartan had benefit over an ACEi in HF, the ELITE study was undertaken in 1997[10]. Losartan was compared against captopril and, as a secondary measure, demonstrated a non-statistically significant 32% reduction in death and/or hospitalization for HF. This trend was largely driven by a 46% decrease in all-cause mortality ($p=0.035$). Because these results were secondary endpoints and thus not hypothesized a priori, the investigators attempted to replicate these results in the ELITE II study[11]. The ELITE II study concluded with no mortality benefit seen with losartan versus captopril. Interestingly, both ELITE studies used the 50mg doses of losartan; researchers suggested the dosing may have been suboptimal in this trial. Subsequently, the HEAAL trial was conducted to evaluate the dose-dependent effect of losartan (50mg vs. 150mg) in HF[12]. Losartan 150mg was found to be superior in the composite endpoint of all-cause mortality and HF admission (HR=0.90; 95% CI, 0.82 to 0.99; $p=0.027$). Hypotension, hyperkalemia and renal impairment were all more common in the 150mg arm but did not lead to differences in discontinuation rates between study groups.

A subsequent study published in 2009 compared 4 ARBs (candesartan, irbesartan, losartan, valsartan) using VA data from 1996 to 2002 and concluded there are no statistical differences in mortality between the ARBs studied[13].

Neither American nor European consensus guidelines recommend a specific ACEi or ARB over other agents within their respective drug classes[1,2]. Additionally, these guidelines recommend using ARBs only when ACEi are not tolerated.

Findings:
The benefits of ACEi can generally be considered a class effect in HFrEF and no specific ACEi is favored among the ACEi indicated for HF (i.e., captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril). The strength and volume of evidence supporting the role of ARBs in HFrEF, when clinically indicated, is less clear (vs. ACEi) and only three ARBs are generally accepted for use in HF management (candesartan, losartan, valsartan). While candesartan and valsartan have FDA indications for HF treatment, losartan remains commonly prescribed based on clinical trial data supporting its use in HFrEF[12]. When losartan is used, clinicians should target a 150mg daily dose in HFrEF patients[12].

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