Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of all agents recommended in patients with heart failure with reduced ejection fraction (HFrEF) by the 2022 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines published in April 2022.¹ These agents include beta-blockers (bisoprolol, metoprolol succinate, and carvedilol only), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin-neprilysin receptor inhibitors (ARNis), mineralocorticoid receptor agonists (MRAs), sodium-glucose transport protein 2 inhibitors (SGLT2i), soluble guanylate cyclase inhibitors (digoxin, vericiguat), and ivabradine. Loop diuretics are discussed in the heart failure with preserved ejection fraction formulary brief. Following clinical review and analysis, the NPTC added sacubitril-valsartan and named both formulations of metoprolol (tartrate AND succinate) to the National Core Formulary.

Discussion:
Heart failure is a common disease with increasing prevalence in the United States (US) over the last decade.² American Indian and Alaska Native (AI/AN) people die from cardiovascular (CV) disease more than any other racial group in the US.² Disproportionately high rates of comorbidities in AI/AN populations such as type II diabetes mellitus (DM) and hypertension increase the risk of heart failure. While data on rates of HFrEF in AI/AN population is limited, it is likely to be underdiagnosed and under-treated in these populations.² The Strong Heart Study identified that in AI/AN population non-insulin dependent DM is an independent risk factor for increased risk of adverse cardiac effects outside of obesity and increased arterial pressure supporting the need for early diagnosis and readily available evidence-based therapies.³

HFrEF is currently classified by the AHA/ACC as an ejection fraction (EF) ≤ 40%.

Beta-blockers have demonstrated high clinical efficacy for reduction of morbidity and mortality in HFrEF and are recommended by the AHA/ACC guidelines with a classification of recommendation of 1 (highly recommended, benefits greatly outweighing risks) and level of evidence of A (high quality evidence with more than 1 randomized controlled trial (RCT))¹. The AHA/ACC considers BB to be of high economic value. The COMET trial in 2003 demonstrated superiority of survival in HFrEF of carvedilol over metoprolol tartrate.¹¹ In 2018, a retrospective study of VA patients demonstrated a mortality benefit for carvedilol over metoprolol succinate.¹² Unfortunately no head to head trial of metoprolol tartrate versus succinate exists, however the AHA/ACC guidelines specifically recommend metoprolol succinate for the treatment of HFrEF.

Mineralocorticoid receptor agonists (MRAs), spironolactone and eplerenone, are the second pillar of GDMT for HFrEF. Again, little new data has emerged to support these agents in treatment, however the structure of the AHA/ACC recommendations now highlights these as a standard part of GDMT without a preference of either agent. MRA therapy is recommended as a 1A, and is considered to have high economic value by the AHA/ACC.

The 2022 AHA/ACC guidelines brought significant change to ACEi/ARB’s role in HFrEF therapy: they are now second line to a new class of medications called ARNis. ARNis are a relatively new class of medication, of which only one formulation is available in the United States, sacubitril-valsartan (Entresto®). The 2014 PARADIGM-HF trial demonstrated decreased deaths from CV causes and hospitalizations from HFrEF with ARNi (21.8% vs. 26.5%, with a hazard ratio (HR) of 0.80).⁵ A more recent meta-analysis comparing any ACEi/ARB to sacubitril-valsartan demonstrated 23 fewer deaths per 1000 people treated with ARNi. In 2017, the AHA recommended ACEi/ARB for treatment of HFrEF and if these were tolerated, then consideration of an ARNi to reduce morbidity and mortality, however in the 2022 updated guidelines, an ARNi is recommended as first line to reduce morbidity and mortality in HFrEF patients: “In patients with chronic symptomatic
HFRIEF, treatment with an ARNi instead of an ACEi provides high economic value”. In a meta-analysis exploring cost efficacy of an ARNi vs. ARB, it was estimated that in the US that 52,856 fewer heart failure admissions would occur per year if all qualifying inpatients were prescribed sacubitril-valsartan prior to discharge compared with enalapril. Compellingly, the US Department of Veterans Affairs placed sacubitril-valsartan on their national formulary in February 2022 preceding the new AHA/ACC guidelines due to the exceptional clinical benefits and high economic value.

The SGLT2i agent, empagliflozin, was added to the IHS National Core Formulary in 2019 following a review of DM, however data now supports the use of both empagliflozin and dapagliflozin in GDMT to reduce morbidity and mortality in HFRIEF. In the EMPEROR-Reduced trial, the reported NNT was 19 for empagliflozin to prevent one death vs. placebo. In the DAPA-HF trial, the NNT=21 for dapagliflozin vs. placebo. No head to head comparator trials exist for HFRIEF patients. The addition of SGLT2i to the AHA/ACC guidelines as a part of GDMT occurred in 2022 and is considered a 1A recommendation and provides intermediate economic value.

Several other agents including vericiguat, digoxin, and ivabradine were reviewed. These medications may play an important role in special populations with HFRIEF, but are not currently included in the GDMT recommendations by the AHA/ACC. New data exists supporting the use of vericiguat with a trend toward improvement CV death and HF hospitalizations, but with increased side effects, and thus is not currently part of GMDT for treatment of HFRIEF.

An extremely compelling meta-analysis done in 2022 demonstrated that use of GDMT (defined as use of an ARNi, MRA, beta blocker and SGLT2i) in HFRIEF patients, can extend life expectancy by 7.9 years in a 50-year old and by 5.0 years in a 70-year old. Further demonstrating the profound and direct clinical impact that the availability of these medications will have on the IHS patient population.

Findings:
In 2022, the AHA/ACC restructured their guidelines to include a four-pillar approach to the treatment of HFRIEF, termed GDMT, which includes four core therapeutic agents: BB, ARNi, MRA, and SGLT2i. After review of current data, the NPTC found compelling evidence that all four of these agents represent standard of care, substantially improved morbidity and mortality, addressed a specific and important health disparity for AI/AN patients, and enhanced critical access to the pharmacy benefits of the IHS. Thus, the NPTC added sacubitril-valsartan and named both formulations of metoprolol (tartrate AND succinate) to the National Core Formulary.

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: