INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Heart Failure with Preserved Ejection Fraction (HFpEF)***

-May 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of medications used in the management of Heart Failure with Preserved Ejection Fraction (HFpEF). The diagnosis of HFpEF requires clinical symptoms of heart failure, diastolic dysfunction, and an ejection fraction (EF) ≥50%. For clarity:

CLINICAL SYNDROME	EJECTION FRACTION (EF)
Heart Failure with Reduced Ejection Fraction (HFrEF)	< 40%
Heart Failure with Mildly-Reduced/Mid-Range Ejection Fraction (HFmrEF)	41-49%
Heart Failure with Preserved Ejection Fraction (HFpEF)	≥ 50%

Regardless of cause or EF, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening heart failure. While several classes of medications reduce morbidity and mortality in HFrEF, trials in HFpEF have almost universally failed to show benefit until recent trials of sodium-glucose co-transporter 2 (SGLT2) inhibitors. In 2019, the NPTC performed a comparative review of various anti-diabetic drug classes in which empagliflozin was added to (and remains on) the National Core Formulary. Following clinical review and analysis of HFpEF management, the NPTC voted to **ADD torsemide or bumetanide** to the National Core Formulary.

Discussion:

Major heart failure (HF) guidelines continue to recommend diuretics, specifically loop and thiazide diuretics, to improve signs and symptoms of fluid overload, but do not specify a preferred diuretic agent.[1,2] A 2019 meta-analysis of head-to-head trials of furosemide and torsemide found that torsemide decreased the risk of hospitalization for HF, although the relevance of data derived from these older trials in current HF management remains unclear. Unfortunately, no head-to-head trials of torsemide and bumetanide were identified.[3] Both oral torsemide and oral bumetanide have demonstrated greater and more consistent bioavailability than oral furosemide, which may offer an advantage to the former agents.[4] Agency procurement trends are also favorable for these agents. A range of treatments options within the diuretic class is supported for individualization of patient treatment plans.

Most drug trials have failed to demonstrate benefit for HFpEF, despite proven benefit in HFrEF or promising pathophysiologic reasoning. The following table briefly reviews HFpEF drug classes and their supporting evidence:

CLASS	EVIDENCE SUMMARY
ACEi	Moderate-low certainty: little/no effect on CV and all-cause mortality, HF hospitalization, QOL[5]
B-blockers	Low certainty: +reduction in CV mortality, not all-cause mortality. No evidence: HF hosp or QOL[5]
Digoxin	DB RCT* (DIG Ancillary): no effect on CV or all-cause mortality, HF or CV or all-cause hosp[6]
CCBs	No evidence. Non-dihydropyridine CCBs are often considered 1st line for rate control in HFpEF[2]
Ivabradine	Low certainty: no effect on mortality, QOL, other adverse events. No data on hospitalization[8]
Nitrates	DB RCT* (NEAT-HFpEF): decreased daily activity level, no improvement of QOL[9]
PDE5i	DB RCT* (RELAX): no effect on clinical status, 6 minute walk distance, or peak O2 consumption[10]

**DB RCT = Double-blind, randomized controlled trial; QOL = Quality of Life*

Only empagliflozin has demonstrated efficacy for HFpEF in the primary endpoint of a large RCT. The EMPEROR-Preserved trial was a DB RCT of 5988 class II-IV HF patients with EF of >40%, followed for a mean of 26.2 months on either empagliflozin 10mg PO daily or placebo. Empagliflozin reduced HF hospitalization (HR 0.73 [95% CI: 0.61-0.88, p<0.001] and NNT=22) but did not significantly affect mortality or QOL. In subgroup analyses, diabetes did not affect the outcome but empagliflozin may have performed better at lower EFs.[11] Reduction of HF hospitalizations may be a class effect of SGLT2 inhibitors; the DELIVER trial (dapagliflozin) is now complete and results should be published soon.[12]

The TOPCAT trial of spironolactone did not find a positive result in its primary endpoint.[13] Subsequent analysis, however, found statistically unlikely differences in outcomes between study sites in Russia/Georgia and those in the Americas, including well-established outcomes like hyperkalemia.[14] When stored blood samples were later tested for canrenone, a spironolactone metabolite, 30% of the samples from Russia were negative (indicating non-adherence) in participants

randomized to spironolactone who claimed to be taking the study drug.[15] Re-analysis of the Americas' patient data demonstrated positive outcomes for the primary endpoint, HF hospitalizations, as well as cardiovascular mortality.[14]

The CHARM-Preserved trial of candesartan did not produce positive results for any primary or secondary endpoints. Statistical adjustments, compensating for disparities between intervention and placebo groups, produced a borderline positive result for HF hospitalizations.[16] Subsequent analyses, however, found that this positive result disappeared for those with an EF >50%.[17] A recent Cochrane review published in 2021 concluded with high certainty that angiotensin II receptor blockers (ARBs) have little to no effect on HFpEF outcomes.[5]

The PARAGON-HF trial of sacubitril-valsartan, a combination ARB and neprilysin inhibitor referred to as an "ARNI", also did not produce positive results for any of the primary or secondary outcomes. The authors emphasized significant reductions in HF hospitalization however for 2 of the 12 pre-specified subgroups; women and those with EFs of 45-57%.[18]

Based on the above data,

STRENGTH	2022 AHA/ACC GUIDELINE RECOMMENDATIONS[2]
MODERATE	*SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality*
WEAK	*Mineralocorticoid antagonists (MRAs) may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum*
WEAK	*ARBs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum*
WEAK	*ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum*

Of note, the European Society of Cardiology (ESC) does not currently recommend any medications specifically to treat HFpEF. Data from the EMPEROR-Preserved study was published too late to be included in their review (ESC) process.[1]

Findings:

Loop and thiazide diuretics are recommended in HFpEF for relief of fluid overload. While no diuretic agent is specifically preferred, it is reasonable to consider torsemide or bumetanide based on data suggesting reduction in HF hospitalizations and more predictable bioavailability. For HFpEF, only empagliflozin demonstrated positive results for a primary endpoint, reducing HF hospitalizations, with a Number Needed to Treat (NNT) of 22. An MRA, ARB, or ARNI may be considered, based on weak evidence, for patients with HFpEF and EFs on the lower end of the spectrum.

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