Summary of the Clinical Problem
Since the 2017 publication of the ACC/AHA/HFSA focused update of HF guidelines, multiple clinical trials have demonstrated the significant benefits of novel medical therapies for patients with HF across the spectrum of EF.1-4 The emergence of these therapies adds nuance and complexity to the care of patients with HF.
The guideline recommends that SGLT2 inhibitors be initiated in patients with symptomatic, chronic HF with reduced EF. This recommendation (class 1, LOE A) is based on 2 large RCTs that compared dapagliflozin or empagliflozin with placebo in patients with chronic HF with reduced EF (4744 patients in the dapagliflozin trial and 3730 in the empagliflozin trial) and showed improvement in HF hospitalization and cardiovascular death.\(^1\)\(^2\) Dapagliflozin resulted in a 3.7% ARR in HF hospitalization and a 1.9% ARR in cardiovascular death, both of which were statistically significant improvements.\(^6\) Empagliflozin resulted in a significant 5.1% ARR in HF hospitalization but no significant reduction in cardiovascular death.\(^1\)

Notably, the guideline now includes a recommendation (class 1, LOE B-R) to continue guideline-directed medical therapy instituted for HF with reduced EF even after improvement in EF (ie, HF with improved EF). This is based on the TRED-HF RCT in which 51 patients with dilated cardiomyopathy with improved EF who were randomized to withdrawal of medication had a 44% relapse of HF, compared with 0% relapse in the medication continuation group.\(^7\)

The EMPEROR-Preserved trial, an RCT comparing empagliflozin with placebo in 5988 patients with left ventricular EF greater than 40% and chronic HF symptoms, demonstrated a 3.2% reduction in HF hospitalization and cardiovascular mortality.\(^1\) SGLT2 inhibitors are thus recommended (class 2a, LOE A) for patients with chronic HF with mildly reduced EF and HF with preserved EF. Mineralocorticoid antagonists and ARBs or ARNIs are also recommended for patients with HF with preserved EF (class 2b, LOE B-R) to reduce HF hospitalization.\(^5\)

Benefits and Harms
The substitution of ARNs for ACEIs and ARBs and the addition of SGLT2 inhibitor therapy to evidence-based β-blockers and mineralocorticoid antagonists are expected to reduce all-cause mortality. This guideline emphasizes the additive benefit of SGLT2 inhibitors and ARNIs. In an effort to avoid harm and add nuance to the guidelines, “value statements” were included for HF therapeutics for which cost-effectiveness studies were available. Despite the class 1 recommendation regarding in-hospital initiation of foundational HF therapeutics, for which there is strong evidence of mortality benefit, there are limited details regarding initiation and titration strategies, which may constrain robust clinical uptake.\(^8\)\(^9\)

Discussion
The new guidelines provide updated recommendations of medical therapy for patients with HF across the spectrum of EF. Importantly, the guidelines emphasize differences in treatment regimens, and their associated levels of evidence, within the context of the new universal definition of HF. These recommendations are based predominantly on strong RCT data and serve as a needed update due to the large amount of robust evidence published in HF therapeutics since the 2017 update to the 2013 HF guidelines.\(^10\)

Areas in Need of Future Study or Ongoing Research
While the addition of ARNs and SGLT2 inhibitors to established medications is now known to be effective for HF, there is a need for implementation science research to determine how best to initiate, escalate, and switch between various agents now endorsed as guideline-directed medical therapy (GDMT). This is particularly important for HF with reduced EF due to the numerous and growing evidence-based therapies. More robust data on the efficacy of ARNs in heart failure of various etiologies, as well as additional studies regarding magnetic resonance angiography use in HF with mildly reduced EF and HF with preserved EF, will almost certainly affect how these drugs are used in the future. Furthermore, research into the role of SGLT2 inhibitors for primary prevention of HF and in the management of HF with improved EF would be beneficial. More data regarding novel therapies such as vericiguat (a soluble guanylyl cyclase stimulator) and omecamtiv mecarbil (a cardiac-specific myosin activator) are needed. These drugs have been shown to benefit patients with HF with reduced EF, but the trials were conducted without optimal incorporation of updated GDMT (ie, ARNIs or SGLT2 inhibitors).

**Related Guidelines**

**2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**

**REFERENCES**


