Practice Guideline

Optimizing sodium-glucose co-transporter 2 inhibitor use in patients with heart failure with reduced ejection fraction: A collaborative clinical practice statement

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\textbf{A B S T R A C T}

Heart failure with reduced ejection fraction (HFrEF) is a debilitating disease that is associated with substantial morbidity, mortality, and societal costs. The past three decades have brought about significant advancements in the pharmacologic management of HFrEF, and a corresponding reduction in morbidity and mortality. However, the progress to improve clinical outcomes in real-world settings has stalled in recent years, largely due to underutilization of guideline directed medical therapies (GDMT). The discovery of significant cardio-renal protection from sodium-glucose co-transporter 2 inhibitors (SGLT2i) has ushered in a new treatment paradigm for HFrEF management with SGLT2i therapy becoming an essential component of GDMT. Our Preventive Cardiology and Heart Failure services have established an innovative, multi-disciplinary, collaborative protocol to optimize management of cardiovascular risk factors and facilitate SGLT2i use in patients with HFrEF. The goal of this collaboration is to enhance utilization and safety of SGLT2i for HFrEF management by circumventing medication access issues, the major obstacle to therapy initiation. Within this protocol, our heart failure providers identify patients for the addition of SGLT2i to a background of heart failure GDMT. The patient is then referred to preventive cardiology where the team performs a comprehensive cardiovascular risk assessment, optimizes cardiovascular risk factors, and initiates SGLT2i with an emphasis on medication access, cost minimization, and mitigation of potential side effects. The heart failure team assumes responsibility for modification of heart failure-based therapies, and the preventive team manages diabetes, lipid, and metabolic-based therapies. The patient is followed by both cardiology services in a structured fashion, comparing outcome measures at regular intervals and utilizing our patient registry and bio-repository. This clinical practice statement provides a detailed evidentiary review on the cardiovascular and renal benefits of SGLT2i, outlines the rational for creation of a collaborative protocol, details a structured program that may serve as a template for enhanced heart failure management in other health systems, and addresses challenges encountered and recommendations for use.

1. Introduction

Heart failure is a prevalent and devastating cardiovascular condition that results in significant morbidity and mortality and high societal cost.\textsuperscript{[1]} The prevalence of this complex condition continues to rise, with 6.2 million Americans diagnosed in 2016 and an estimated >8 million by 2030.\textsuperscript{[1]} The lifetime risk of developing heart failure has been estimated to be as high as 20–45% and is driven substantially by rising heart failure risk factors and a rapidly aging American population.\textsuperscript{[1,2]} Common risk factors for heart failure include ischemic heart disease, diabetes, obesity, hypertension, and smoking, conditions affecting nearly 1 of every 3 US adults.\textsuperscript{[1]} Living with heart failure imposes a significant burden on affected patients, accounting for \~1 million hospitalizations annually, a 30-day heart failure readmission rate of \~25%, and significant decreases in quality of life.\textsuperscript{[1,2]} Heart failure is deadly, with mortality rates of nearly 50% within five years from diagnosis, and associated with escalating costs totaling \$30.7 billion in the US in 2012.\textsuperscript{[1]}

Though heart failure may present with a diverse set of phenotypes, the focus of this clinical practice statement will be on heart failure...
with reduced ejection fraction (HFrEF) as this subtype has clearly delineated, evidence-based, therapeutic modalities. Management of HFrEF, accounting for approximately 50% of all heart failure cases, has led to significant advancements in both pharmacological and device therapies during recent years, resulting in a corresponding reduction in morbidity and mortality. [3] Unfortunately, these improvements in clinical outcomes appear to be leveling off over time. [3] Plausible contributors to this trend may include the rising prevalence of cardiovascular risk factors and underutilization of guideline-directed medical therapies (GDMT) – omitting indicated pharmacotherapy, failure to achieve target doses, and difficulty sustaining patient adherence. [4, 5]

The discovery of sodium-glucose co-transporter 2 inhibitors (SGLT2i) is a welcome addition to the HFrEF armamentarium, but poses important questions regarding appropriate use and medication accessibility among patients with HFrEF. [6] Optimization of pharmacotherapy, particularly with novel branded agents, is frequently impeded by limited medication access, largely driven by elevated and rising medication cost. [7] These challenges were highlighted by the American Heart Association as missed opportunities that are prevalent throughout cardiovascular service lines, which has spurred an urgent call to action to address these issues and facilitate transformation of cardiovascular care.

The purpose of this clinical practice statement is to describe an innovative, multi-disciplinary, collaborative protocol established between Preventive Cardiology and Heart Failure services at our institution that was designed to optimize management of cardiovascular risk factors and facilitate clinical use of new evidence-based pharmacotherapy. The protocol advocates for enhanced utilization of pivotal heart failure pharmacotherapy, specifically optimizing use of sodium-glucose co-transporter 2 inhibitor (SGLT2i) in patients with HFrEF. Our program is focused on improving medication access, cost minimization, medication tolerability, and durable patient adherence to SGLT2i therapy. Herein, we describe the structure and function of a successful new program that potentially can be implemented elsewhere.

2. Pharmacotherapy

2.1. Historical heart failure with reduced ejection fraction pharmacotherapies

The bulk of the pivotal cardiovascular outcome trial data that formed the basis for class I recommendations for HFrEF pharmacotherapy were generated two to three decades ago. These trials established angiotensin-converting enzyme inhibitors (ACEI) [8–11], angiotensin II receptor blockers (ARB) [12–14], β-blockers [15–17], mineralocorticoid receptor antagonists (MRA) [18, 19], and vasodilators [20] as therapies proven to improve hospitalization and mortality rates among patients with HFrEF. Despite Class Ia recommendations for the use of these medications, the CHAMP-HF registry, a contemporary US-based outpatient registry showcasing real-world HFrEF treatment, identified significant gaps in use of GDMT. [4] Among eligible patients, use of ACEI/ARB, β-blockers, and MRA was 60%, 67%, and 33%, respectively, with most patients not receiving target doses. Only 1% of patients were initiated on and achieved target doses of all three major classes of pharmacotherapy. The authors concluded that: “strategies to improve guideline-directed use of HFrEF medications remain urgently needed.”

2.2. Newer heart failure with reduced ejection fraction pharmacotherapies

2.2.1. Angiotensin receptor–neprilysin inhibitor

The last six years have brought about a renaissance in HFrEF treatment with the development of two new pharmacotherapy classes with the potential to prevent and treat heart failure and its associated complications. The first of the two new classes of pharmacotherapy, angiotensin receptor–neprilysin inhibitor (ARNI), was introduced in 2014 after publication of results from the seminal PARADIGM trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial). [21] This study demonstrated that ARNI treatment reduced hospitalizations for worsening heart failure and mortality outcomes (comparable with other GDMT and on top of a background of such therapies) [21], improved quality of life measures [21], attenuated decline of estimated glomerular filtration rate (eGFR) [22], and led to incorporation of class I recommendations for ARNI treatment in major guidelines. [23, 24] Unfortunately, ARNI therapy is the most underutilized of the main classes of pharmacotherapy for HFrEF treatment, with only ~13–20% of eligible patients initiated on therapy, and only 1% of non-use attributable to the presence of contraindications. [4, 25] This indicates that the vast majority of eligible patients with HFrEF are not prescribed ARNI therapy despite strong clinical trial data and guideline-based recommendations. [4, 25]

2.2.2. Sodium-glucose co-transporter 2 inhibitors

SGLT2i are not new therapies per se but their use for improving cardiovascular outcomes is novel. SGLT2i entered the market in 2013 and were originally developed and approved for treatment of hyperglycemia in type 2 diabetes mellitus. [26] Cardiovascular benefits (including salient heart failure protection) were serendipitously discovered in response to guidance from the Food and Drug Administration (FDA) in 2008 requiring all new glucose-lowering therapies to prove cardiovascular safety before market approval. [27]

2.2.2.1. Sodium-Glucose Co-transporter 2 inhibitors in type 2 diabetes mellitus

Results from the seminal EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose) demonstrated reductions in a composite cardiovascular outcomes (myocardial infarction, stroke, and cardiovascular death), cardiovascular death, all-cause death, renal outcomes, and heart failure hospitalizations in patients with type 2 diabetes mellitus and known atherosclerotic cardiovascular disease (ASCVD). [28] Additional SGLT2i clinical trials confirmed the cardiovascular benefits in patients with diabetes. [29, 30] A meta-analysis of these large cardiovascular outcome trials evaluated the effects of empagliflozin, canagliflozin, and dapagliflozin in over 34,000 patients with type 2 diabetes and demonstrated a 23% reduction in the composite outcome of cardiovascular death or hospitalization for heart failure (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.71–0.84; p < 0.0001), and a 31% reduction in hospitalization for heart failure (HR 0.69; 95% CI 0.61–0.79; p < 0.0001). [31] These robust benefits were seen regardless of the presence or absence of cardiovascular disease or history of heart failure, but with baseline renal function conferring the strongest predictor of cardiovascular benefit. [31, 32] The cardiovascular effects of the fourth SGLT2i, ertugliflozin, appear to be less impressive compared to the rest of the class. [33] The results of subgroup analyses suggest possibly enhanced reductions in hospitalization for heart failure with or without cardiovascular death among patients with more advanced renal disease. [34, 35]

2.2.2.2. Sodium-Glucose co-transporter 2 inhibitors in heart failure

The magnitude and consistency of heart failure benefit seen in patients with type 2 diabetes mellitus led to investigations of SGLT2i therapy in patients with HFrEF, regardless of the presence or absence of diabetes. The first heart failure trial, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), was a phase III placebo-controlled trial conducted in 4744 patients with New York Heart Association (NYHA) class II, III, or IV HFrEF and elevated pro-B-type natriuretic peptide (NT-proBNP) who were randomized to dapagliflozin 10 mg daily or placebo added to background GDMT. [36] The second heart failure trial, EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction), studied a similar population of 3370 patients who were randomized to empagliflozin 10 mg daily or placebo. [37] Though there were
modest differences between patient characteristics in the DAPA-HF and EMPEROR-Reduced trials – left ventricular ejection fraction (27% vs 31%), NT-proBNP (1428 pg/mL vs 1887 pg/mL), and ARNI use (11% vs 20%), both trials demonstrated significantly reduced heart failure hospitalizations and improved quality of life measures, with an acceptable safety profile. In addition, the DAPA-HF trial demonstrated reductions in cardiovascular death and the EMPEROR-Reduced trial showed improved renal outcomes. A meta-analysis of data from the DAPA-HF and EMPEROR-Reduced trials demonstrated consistently favorable outcomes and safety across a broad spectrum of HFpEF severity. [38] Pooled results from these two trials demonstrated significant reductions in cardiovascular death or first hospitalization for heart failure: 26% relative risk reduction (RRR), (HR 0.74; 95% CI 0.68–0.82; p < 0.0001), cardiovascular death: 14% RRR, (HR 0.86; 95% CI 0.76–0.98; p = 0.027), first hospitalization for heart failure: 31% RRR, (HR 0.69; 95% CI 0.62–0.78), all-cause mortality: 13% RRR, (HR 0.87; 95%CI 0.77–0.98; p = 0.018), and a composite renal outcome (chronic dialysis, renal transplantation, or a ≥ 50% sustained reduction of eGFR): 38% RRR, (HR 0.62; 95% CI 0.43–0.90). [38] Additionally, SGLT2i use produced significant increases in quality of life measures. [36,37] It is important to note that these cardio-renal benefits occurred despite high utilization rates of standard GDMT (~92% treated with ACEI/ARB/ARNI, ~95% with a β-blocker, and ~71% with a MRA), and were maintained regardless of background HFpEF GDMT (including ARNI use) or achieved GDMT target doses (~50% or <50%). [38–42] Finally, reductions in adverse clinical outcomes were discernible within weeks of SGLT2i initiation, which is very relevant for clinical care as patients with HFpEF have a high risk for 30-day readmissions and short survival once diagnosed.

The combined results from pivotal cardiovascular outcome trials demonstrate a progressive decline in all-cause mortality with the addition of each successive evidence-based pharmacotherapy. The estimated 2 year mortality is reduced from a baseline of 35% to 10% with 4-class GDMT consisting of ANRI, β-blocker, MRA, and SGLT2i (Fig. 1). [43] It is plausible that the addition of SGLT2i to GDMT will reduce disease progression and extend longevity across a broader spectrum of patients with HFpEF in real-world applications. A decision analytic model estimated that of the 3.1 million patients with HFpEF living in the United States, 69% (2.1 million) would be eligible for SGLT2i therapy that may prevent over 34,000 deaths annually, if optimally implemented. [43] Estimates of the lifetime effect of conventional “dual” drug therapy (β-blocker and ACEI or ARB) as compared to comprehensive “quintuple” drug therapy (β-blocker, ARNI [ARB and neprilysin inhibitor], MRA, and SGLT2i) suggest a 62% additional reduction in cardiovascular death or hospitalization for heart failure (HR 0.38; 95% CI 0.30–0.47) and 47% reduction in all-cause mortality (HR 0.53; 95% CI 0.40–0.70) with the latter. [44] This translates into an additional 2.7–8.3 and 1.4–6.3 extra years (depending on age of therapy start) free from cardiovascular death or hospitalization for heart failure and survival, respectively. [44] Thus, a rapidly growing body of evidence strongly supports the addition of SGLT2i to the armamentarium of GDMT, establishing SGLT2i as the 5th pillar of proven HFpEF pharmacotherapies and a key component of the recent suggestion that comprehensive therapy with a combination of β-blocker, ACEI / ARB, neprilysin inhibitor, MRA, and SGLT2i is the new standard of care for patients with HFpEF (Fig. 2 - Central Illustration). [6]

2.2.2.3. Sodium-Glucose co-transporter 2 inhibitors in kidney disease. Another important clinical finding from clinical trials of SGLT2i therapy, and one that may impart heart failure benefit, is renal protection. This is significant due to the complex interplay between the triad of heart...
failure, chronic kidney disease (CKD), and type 2 diabetes mellitus. Up to 50% of heart failure patients have type 2 diabetes mellitus and/or CKD, with each condition independently increasing the risk for hospitalization and/or death and predisposing to medication toxicities as the conditions approach end-stage disease. [45,46] A meta-analysis of data from the large cardiovascular outcome trials evaluating empagliflozin, canagliflozin, and dapagliflozin demonstrated a significant 45% reduction in progression of a composite of renal disease outcomes (worsening renal function, end-stage renal disease [ESRD], or renal death), (HR 0.55; 95% CI 0.48–0.64; p < 0.0001). [31] The renal protective effects were further demonstrated in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, which showed a 30% RRR (p = 0.00001) in the composite outcome of ESRD, doubling of serum creatinine, or death from renal or cardiovascular causes in high risk patients with type 2 diabetes mellitus and advanced CKD. [47] Taking the renal benefit a step further, the results of the DAPA-CVD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial established dapagliflozin as an efficacious agent in patients with CKD regardless of the presence or absence of diabetes, down to an eGFR of 25 ml/min at enrollment. Dapagliflozin reduced the composite outcome of a sustained decline in eGFR ≥50%, ESRD, or death from renal or cardiovascular causes by 39% (HR 0.61; 95% CI 0.51–0.72; p < 0.001). [48] Both the CREDENCE and DAPA-CVD trials were prematurely stopped for overwhelming benefit, as recommended by the data and safety monitoring committee. Also, in both trials, SGLT2i use was associated with ~30% RRR in the composite endpoint of cardiovascular death or hospitalization for heart failure, despite a low prevalence (<15%) of heart failure at baseline. This indicated that heart failure benefit occurs even among very high risk patients with advanced CKD, a comorbidity commonly associated with HFpEF.

2.2.2.4. Mechanisms of cardiorenal benefit from sodium-glucose co-transporter 2 inhibitors

Significant work has previously been published that investigated the mechanisms by which SGLT2i exert heart failure benefit. Though more work is needed to fully elucidate these mechanisms, several salient hypotheses have been proposed that include improvement in conventional cardiovascular risk factors (hyperglycemia, dyslipidemia, hypertension, and elevated body mass index [BMI]), improvement in hemodynamics, natriuretic effects, reduced cardiac and renal remodeling, inhibition of hormone dysregulation, use of more efficient metabolic substrates, ion channel inhibition, anti-inflammatory effects, and anti-oxidant effects. [26]

2.2.2.5. Sodium-Glucose co-transporter 2 inhibitors side effect profile & monitoring parameters

The SGLT2is are generally a well-tolerated class of medications but a brief discussion of relevant side effects and monitoring parameters is warranted. In the DAPA-HF trial, there were no discernable differences in side effects between the dapagliflozin and placebo groups. [36] In the EMPEROR-Reduced trial, the only reported difference in side effects was a higher rate of genitral tract infection in the empagliflozin group compared to placebo. [37] Infection risk has been the most common side effect reported in large cardiovascular outcome trials, predominantly genital mycotic infections (candida vaginitis in females [< 5–10%] and balanitis in males [< 2–4%]). [49] These are generally mild in nature, resolve quickly, and uncommonly recur. If treatment is required, usually topical antifungals are sufficient, though oral fluconazole may be needed in more severe cases. Proper counseling is paramount and should focus on daily hygienic measures such as rinsing or wiping after voiding and before bed to ensure no urinary glucose is left in contact with the skin or undergarments. For patients with a history of severe or recurrent mycotic infections, SGLT2i may not be the most appropriate treatment option, since these individuals have a higher incidence of mycotic infections during SGLT2i therapy (> 20% in females and > 10% in males). [50] Urinary tract infections have been reported, but have not been shown to occur at a higher rate as compared to placebo within the large cardiovascular outcome trials. [49] Patients who are prone to have frequent UTIs can have severe ascending urinary tract infections. Case reports of a rare, rapidly progressive life-threatening form of necrotizing fasciitis in the perineal area, called Fournier gangrene, lead to an FDA label update for SGLT2i in 2018. The causal association with SGLT2i use is contentious, but given the serious nature of this infection, patients should promptly notify a healthcare professional about any symptoms of tenderness, redness, or swelling in the genital and/or perineal area. [51]

Pertinent to patients with HFREF are the hemodynamic effects of SGLT2i, which include both blood pressure lowering and volume depletion. These agents can lower systolic and diastolic blood pressure by an average of ~4–6 and ~1–2 mmHg, respectively. [51] There is also a mild diuretic effect associated with SGLT2i use, resulting in 24-hour urine volumes increasing by ~300 ml/day and an initial reduction in eGFR of ~3–5 ml/min, occurring over the first few weeks, but then followed by stabilization and ultimately improvement over time compared to placebo. [29,47] Initially, concern for acute kidney injury (AKI) with SGLT2i use was raised, prompting an FDA warning, but the results of a meta-analysis have reassuringly shown a consistent 25% lower risk of AKI (p < 0.0001) among SGLT2i users compared to placebo. [52] In addition, SGLT2i use has been shown to be safe and efficacious in individuals with baseline eGFR as low as 25 ml/min. [48]

The hemodynamic effects of SGLT2i may be more pronounced in patients who are elderly, have more severe hyperglycemia, are taking higher doses of SGLT2i, are treated with loop diuretics, or have more severe renal impairment. [51] Among HFpEF patients on GDMT consisting of multiple antihypertensives and diuretics, particularly in the setting of low blood pressure with fluctuating renal function, vigilant monitoring for signs and symptoms of hypotension and volume depletion is required. In some cases, to pre-emptively avoid adverse effects related to hypotension and volume depletion, initiating SGLT2i at a lower dose (i.e. dapagliflozin 5 mg daily instead of 10 mg daily) or instituting dose reductions of loop diuretics and other antihypertensive medications may be advisable. Counseling patients to record daily weights and blood pressures, maintain appropriate hydration, and undergo periodic assessment of renal function is also advised.

Although SGLT2i do not directly induce hypoglycemia, due to their insulin-independent mechanism of action with reduced glucosuria with lower blood glucose levels (ceasing somewhere ~40–80 mg/dl), the risk of hypoglycemia is increased primarily in combination with insulin or insulin secretagogues. [26] However, dose adjustments for insulin or insulin secretagogues are not routinely recommended when initiating SGLT2i owing to the increased risk for diabetic ketoacidosis (DKA). Among patients with well controlled Hgba1c levels at baseline, or known history of frequent hypoglycemic events, a dose reduction or discontinuation of insulin or insulin secretagogues is prudent. [53] DKA in patients taking SGLT2i typically occurs at normal or modest blood glucose elevation and is exceedingly rare, [53] possibly restricted to patients with occult type 1 diabetes or maturity onset diabetes of the young (MODY). The risk of DKA is heightened in patients with type 1 diabetes mellitus, substantially reduced endogenous insulin secretion, a history of DKA, excessive alcohol use, illicit drug use, or in those hospitalized, acutely ill, or with reduced food/water intake. [54] Patients should be counseled to monitor for early symptoms and signs of ketoacidosis and to discontinue SGLT2i use and seek immediate medical attention should these occur. [51,54] Prevention of DKA entails avoiding the risk factors noted above, as well as discontinuing SGLT2i at least 3 days before intentional fasting or a planned surgery. [53]

Lower limb amputations are rare side effects that were seen only with canagliflozin use in the CANVAS trial, prompting an FDA black box warning in 2017 that was later rescinded in August 2020. [55] Though the causality of the association between SGLT2i and amputation remains ambiguous, caution is suggested in those who may be at increased risk due to a history of prior amputation, peripheral vascular disease, severe peripheral neuropathy, and those with diabetic foot ulcers or infections. [53] In addition, preventive foot care with patient
daily self-examinations and provider assessment (visual and monofilament) should be routinely practiced.

Although additional investigation is required to fully elucidate the mechanisms mediating SGLT2i benefits and adverse effects, early evidence indicates several off-target effects, including inhibition of the sodium-hydrogen exchanger (NHE), as plausible explanations for the wide-range of effects exhibited among this drug class. [56]

2.2.2.6. Sodium-Glucose co-transporter 2 inhibitors regulatory & guideline updates. Three of the four SGLT2i medications currently on the market (empagliflozin, canagliflozin, and dapagliflozin) have FDA-labeled indications to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with HFREF. [59] However, it is expected that empagliflozin will also receive an FDA indication for HFREF following the results from the recently published EMPEROR-Reduced trial. In addition, guidelines from several major professional societies recommend the use of SGLT2i to reduce the risk for heart failure complications in patients with type 2 diabetes, [46,53,60-67] as well as in nondiabetic patients with HFREF. [66-68]

2.2.2.7. Place in therapy for sodium-glucose co-transporter 2 inhibitors. Based on the totality of the evidence, SGLT2i are highly recommended therapies in patients who are at high risk of or with established cardiovascular disease. Within the diabetes treatment paradigm, metformin is still the preferred initial therapy, with SGLT2i or glucagon-like peptide-1 receptor agonists (GLP-1 RA) recommended as next add-on therapies in patients with ASCVD, high risk of ASCVD, heart failure, or established kidney disease, independent of HbgA1C level. [53,63] Specifically for patients with heart failure or risk of heart failure, SGLT2i represent one of the most efficacious treatments for prevention of disease development. Among patients with concurrent HFREF and diabetes, SGLT2i are the only agents documented to reduce heart failure-related outcomes. As a result, SGLT2i use should be preferentially utilized to reduce the burden of heart failure and its associated complications.

Among patient with HFREF, SGLT2i therapy is recommended in symptomatic patients established on maximally tolerated doses of, or with documented intolerances to, GDMT consisting of ACEI or ARB, or ARNI and β-blocker, and MRA. Though SGLT2i therapy is a welcome addition to GDMT, several lingering clinical questions exist.

Do patients need to be on target doses of guideline-directed medical therapy prior to initiating sodium-glucose co-transporter 2 inhibitors?

To garner the full benefit of HFREF based-therapies, every effort should be made to achieve target doses, but in the real-world setting this is not always feasible due to dose-related side effects. Thus, achievement of maximally tolerated doses of background GDMT is not a prerequisite prior to the addition of SGLT2i given data to suggest cardiovascular benefit regardless of achievement of GDMT target doses. [39]

Should mineralocorticoid receptor antagonists be added prior to use of sodium-glucose co-transporter 2 inhibitors?

Baseline use of MRA in the DAPA-HF and EMPEROR-Reduced trials was >70% due to inclusion criteria requiring or encouraging use of MRA. A recent subanalysis of the EMPEROR-Reduced trials demonstrated use of MRA did not influence heart failure or renal outcomes. [42] However, the trial did suggest that the addition of SGLT2i promoted improved MRA adherence, an important finding in the high risk heart failure population and another proposed benefit of SGLT2i initiation. Since MRA are associated with significant reductions in clinical endpoints (comparable to or greater than results from SGLT2i), as well as high clinician familiarity, good patient tolerability, and low cost, it seems prudent to recommend use of MRA in patients with heart failure prior to use of SGLT2i, when clinically feasible. However, if intolerances preclude MRA use, SGLT2i are an acceptable alternative. Scenarios most likely to favor SGLT2i use in lieu of MRA include adverse events such as hyperkalemia or gynecomastia. Additionally, MRA lack the renal bene-

fit displayed by SGLT2i, thus if the clinician identifies a patient at high risk for renal complications, SGLT2i may be a more appropriate agent.

Should angiotensin receptor–neprilysin inhibitor be added prior to use of sodium-glucose co-transporter 2 inhibitors?

Baseline use of ARNI in the DAPA-HF and EMPEROR-Reduced trials were <20% with inclusion criteria requiring some form of inhibitor of the renin-angiotensin system (ACEI, ARB, or ARNI) but not ARNI specifically. As ARNI and SGLT2i are associated with similar improvements in heart failure, mortality and quality of life outcomes, and are both expensive branded medications, clinician choice and patient preference (side effect profile, once daily versus twice daily dosing) may play a larger role in therapy delineation between these two agents. Another factor to consider is renal function. Though both agents display an attenuation in renal deterioration, SGLT2i appear to display a more pronounced effect and significantly reduce hard renal endpoints such as progression to ESRD and renal death. If the decision is made to circumvent MRA and/or ARNI for SGLT2i therapy, it is reassuring that the cardio-renal benefits from SGLT2i were achieved regardless of background HFREF GDMT. [39-42] Additionally, both therapies have been shown to be cost-effective in patients with HFREF and display comparable value to one another. [69,70]

3. Medication access

3.1. Underutilized pharmacotherapy

The clinical landscape of heart failure pharmacotherapy encompasses several classes of disease-modifying and life-prolonging medications, but optimal utilization of these agents has proved challenging. [4,25,71] A similar scenario is occurring for SGLT2i use, with several studies documenting a dearth of SGLT2i prescribing. Rates of SGLT2i use in real-world analyses of patients with diabetes and cardiovascular disease are reported to range from only 1.4 to 9% of eligible patients meeting criteria for use. [72-76] Just as concerning are the low rates of prescribing by cardiologists, accounting for only 5 to 6% of SGLT2i prescriptions. [72,76] Potential contributors to the lack of widespread adoption of evidenced-based and guideline-directed SGLT2i therapy are multifactorial and include medication intolerance, clinical inertia, low comfort with prescribing a new medication, problems with medication access, and medication cost – the latter two widely implicated as major reasons perpetuating this treatment gap. [71]

3.2. Multi-disciplinary team-based care strategy

In response to the rising burden of cardiovascular disease, the American Heart Association Presidential Advisory issued a call to action in 2019 to address urgent challenges in cardiovascular disease prevention and treatment. [5] This report described missed opportunities at each stage of the cardiovascular disease care continuum, specifically highlighting an urgent need to address failures to incite risk factor modifications, use proven first-line therapies, improve access to advanced treatments, and reduce barriers of care such as rising medication costs to patients. These goals require changes in practice dynamics and implementation of more comprehensive and multi-disciplinary delivery of healthcare, which are needed to improve medication access, reduce cost, and facilitate longitudinal management – a concept supported by major cardiovascular organizations. [61,68,77-81] Examples of successful comprehensive and multi-disciplinary care delivery systems within the cardiovascular sector have been described by the work within our Center for Preventive Cardiology, as well as other medical centers. Our care delivery model utilizes a multi-disciplinary team approach, relying on patient-centered management with coordinated contributions from physicians, advanced practice providers, a registered nurse, a clinical pharmacist, a diettian, and medical assistants, that is supported by an NIH-funded research laboratory and a bio-repository to merge clinical care with “beyond standard-of-care” translational investigations.
This standardized approach has allowed us to optimize care for our patients while generating previously published data regarding our experiences in establishing a successful proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) clinic and using pharmacotherapy with new evidence-based cardiovascular indications. [7,82-84]

Implementation of our multi-disciplinary PCSK9i clinic resulted in medication approval rates of 97% and discontinuations due to cost of only 2.3%, both significantly improved compared to usual care at that time, ~50% and up to ~35%, respectively. [83,85] Recently, we described how use of pharmacotherapy with new evidence-based cardiovascular indications, consisting of PCSK9i, eicosapentaenoic acid (EPA), SGLT2i, and GLP-1 RA, required additional provider intervention beyond issuing the prescription in 78.1% of cases. [7] The majority of these interventions (73.8%) consisted of obtaining medication access (i.e., insurance prior authorizations and appeals) and/or cost minimization strategies (i.e., copay cards and patient assistance programs). Ultimately, we successfully obtained medication access for ~75% of patients, with cost being the main reason for medication non-adherence. Additionally, our study demonstrated a robust use of cardiovascular protective diabetes medications (SGLT2i and/or GLP-1 RA) in 70% of our eligible patients, far exceeding low rates <10% seen nationally. [72-76] Heart failure specific examples of multi-disciplinary care have been shown to improve use of GDMT and attainment of target doses [86], as well as reductions in hospitalizations for heart failure and mortality rates. [87]

Another aspect to consider is that as healthcare moves from a fee-for-service to a value-based structure, reimbursements are increasingly tied to actions that add quality and value. This is particularly true for heart failure services, where health-systems are rewarded for measures that add quality care and penalized for adverse outcomes. Therefore, it is paramount to develop collaborative best practices and protocols that optimize risk factor modification, rely on evidence-based disease-modifying and life-saving pharmacotherapy, and increase quality of care for heart failure patients.

4. A proposed protocol for SGLT2i initiation

In response to the call to action to bridge clinical guideline and practice treatment gaps in the management of cardiovascular disease, our Preventive Cardiology and Heart Failure services collaborated to address access to and optimization of SGLT2i therapy in patients with heart failure. An additional goal and important aspect of our collaborative effort has been to identify and optimize cardiovascular risk factor management. This collaborative protocol is novel and timely, bringing together opposing ends of the cardiovascular spectrum, prevention and end-stage disease management, for the comprehensive care of patients with HFpEF. The protocol is approved by our institutional IRB (IRB protocol #00,022,192) and allows us to prospectively follow our patients in a structured fashion, comparing outcome measures at regular intervals and utilizing our registry and bio-repository to facilitate discovery work on unique phenotypes. The clinical team consists of: 1) Preventive Cardiology service: endocrinologists, advanced practice providers, a registered nurse, a clinical pharmacist, a dietitian, and medical assistants, and 2) Heart Failure service: cardiologists, a registered nurse, and medical assistants. The protocol is divided into three separate roles encompassing the responsibilities of heart failure providers, preventive cardiology providers and the preventive cardiology pharmacist, as described below (Fig. 3).

4.1. Roles for heart failure providers

4.1.1. Prior to sodium-glucose co-transporter 2 inhibitor initiation

The heart failure provider identifies potential SGLT2i candidates seen routinely within the Heart Failure service. General qualifying and disqualifying traits for SGLT2i initiation in our protocol are listed in

| Time Point | Heart Failure Provider | Preventive Cardiology Provider | Preventive Cardiology Pharmacist |
|------------|------------------------|-------------------------------|----------------------------------|
| Screening  | Identify SGLT2i candidates | Adjust HF Tx, order lab tests/ imaging, refer to prevention protocol | CV Risk Assessment |
| Enrollment | F/u SGLT2i order lab tests/ imaging | Add SGLT2i, order lab tests/ imaging, refer to prevention protocol | SGLT2i Follow up (access, cost, counseling) |
| Initiation | Clinic visit physical lab & imaging assessment | Clinic visit physical lab & imaging assessment | Available for consultation |
| Follow up  | Referral to cardiac rehabilitation | Referral to cardiac rehabilitation | Referral to cardiac rehabilitation |

Fig. 3. Structure of Collaborative Protocol and Work Flow Between Preventive Cardiology and Heart Failure Services for SGLT2i Optimization. CV, cardiovascular; F/u, follow up; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; Tx, treatment.

Table 1. The heart failure provider discusses with the patient potential risks and benefits of initiating SGLT2i, and shared-decision making determines the most appropriate treatment plan. If SGLT2i therapy is desired, a referral is placed to the Preventive Cardiology service for consideration of SGLT2i and assessment and management of other cardiovascular risk factors. The heart failure provider retains responsibility for adjusting background heart failure medications in preparation for possible initiation of SGLT2i, with anticipation of the antihypertensive and diuretic effects from the SGLT2i. Laboratory and imaging studies listed in Table 2 are also ordered at this time.

4.1.2. Post-sodium-glucose co-transporter 2 inhibitor initiation

The Heart Failure service communicates with the patient within 1–2 weeks of SGLT2i initiation to assess heart failure status and makes additional adjustments to background heart failure medications, if needed. The patient schedules follow up visits with the Heart Failure service at an initial interval of 1–3 months depending on stability of the patient at baseline, then every 6 months thereafter. The Heart Failure service assumes the primary role of handling the day-to-day communications with the patient regarding volume status, blood pressure, heart failure signs and symptoms, and adjustments to heart failure-based pharmacotherapies.

4.2. Roles for preventive cardiology providers

4.2.1. Prior to sodium-glucose co-transporter 2 inhibitor initiation

One of our preventive cardiology providers sees the patient in consultation and conducts a comprehensive cardiovascular risk assessment and implements cardiovascular and associated risk factor standards of care management strategies, including candidacy for SGLT2i initiation. The preventive cardiology provider discusses with the patient potential risks and benefits of initiating SGLT2i and through shared-decision making determines the most appropriate treatment plan. When SGLT2i initiation is appropriate and agreed upon, the preventive cardiology provider prescribes the medication, orders additional laboratory and/or imaging studies, as needed, and consults the preventive cardiology pharmacist. The preventive cardiology provider will adjust background diabetes pharmacotherapy if clinically indicated to avoid potential adverse events, principally hypoglycemia if co-prescribed with insulin or insulin secretagogues. Additional glucose-lowering medications will be sequentially added for patients with uncontrolled hyperglycemia. Also important to note, the preventive cardiology provider will notify the referring heart failure provider and the primary care provider regarding therapy changes to help coordinate care across treatment teams.
Table 1
Qualifying and disqualifying traits for SGLT2i initiation in patients with HFrEF.

| Qualifying trait | Disqualifying trait |
|------------------|---------------------|
| 1. NYHA class II–IV symptoms + increased natriuretic peptides | 1. Type 2 diabetes mellitus, obesity, hypertension, cardiovascular disease, or other concurrent cardiovascular risk factors |
| oNT-proBNP ≥600 pg/mL | oOn treatment HgbA1C ≥6.5% |
| ≥400 pg/mL if hospitalization for heart failure within preceding 12 months | oA1C is not a definitive cut off especially if background diabetic therapy (i.e., sulfonylureas, insulin, etc.) is to be reduced or eliminated |
| ≥900 pg/mL if concurrent atrial fibrillation/flutter | oOn treatment HgbA1C ≥6.5% |
| oMaximally tolerated doses (or documented intolerances) of: | 2. Type 2 diabetes + established CVD or multiple risk factors for CVD with: |
| ACEI / ARB / ARNI | oMaximally tolerated doses (or documented intolerances) of metformin |
| oβ-blocker | oOn treatment HgbA1C ≥6.5% |
| oPossibly MRA (provider discretion) | 3. Type 1 diabetes or history of diabetic ketoacidosis |
| 2. Renal dysfunction | oSevere diabetic nephropathy |
| eGFR <30 ml/min | oSevere peripheral vascular disease |
| oRapidly declining renal function | oPeripheral neuropathy |
| oRecurrent AKI (>50% change in eGFR) | oRecurrent diabetic foot infections |
| 3. Type 1 diabetes or history of diabetic ketoacidosis | 7. History of recurrent genital candidiasis and/or UTI, or increased risk for genital candidiasis and/or UTI |
| 4. Severe aortic stenosis | ![](https://example.com/figure1.png)

The SGLT2i agent and dose selection are important decisions that are guided by randomized controlled trial data and FDA-approved indications. For patients with HFrEF, the only FDA-approved SGLT2i agent with a HFrEF specific indication is dapagliflozin and therefore it is our default agent, but depending on insurance formulary restrictions and coverage, empagliflozin is also clinically acceptable in light of a presumably impending FDA approval for HFrEF indication. For patients with type 2 diabetes mellitus, with or without concurrent cardiovascular disease, canagliflozin, dapagliflozin, and empagliflozin are acceptable agents and agent selection depends on insurance coverage and cost minimization. Ertugliflozin is currently considered to have inferior cardiovascular benefit given the available clinical trial data and FDA-approved indications. It is unclear at this time if the apparent inferiority is a consequence of differences in populations studied or intrinsic drug properties of ertugliflozin compared to other SGLT2i. It is hoped that additional investigations will clarify this subject. For dosing optimization, beneficial cardio-renal effects appear to manifest at the lowest possible dose for empagliflozin (10 mg daily) and canagliflozin (100 mg daily), so titration to the higher dosage (25 mg and 300 mg, respectively) may only be needed if additional glycemic control is warranted. For dapagliflozin, the higher dose (10 mg daily) was studied and should be the target dose used when prescribing this agent.

4.2.2. Post-sodium-glucose co-transporter 2 inhibitor initiation
The preventive cardiology provider will see the patient in follow up visits within an initial interval of 1–3 months depending on stability of the patient at baseline, then every 6 months thereafter in stable patients. The Preventive Cardiology team assumes the primary role of SGLT2i side effect management, adjustments to diabetes based pharmacotherapies, as well as optimization of cardiovascular and associated risk factor control identified during the pre-SGLT2i visit.

4.3. Roles for preventive cardiology pharmacist
The preventive cardiology pharmacist is consulted when an SGLT2i is prescribed. The preventive cardiology pharmacist’s roles within the SGLT2i pathway are four-fold: (1) secure medication access, (2) implement cost minimization strategies, (3) ensure medication tolerability and adherence, and (4) assist with care coordination. To secure medication access, the pharmacist obtains prior authorization for the SGLT2i,
changing the agent or appealing insurance denials if required. After authorization is obtained, measures to reduce patient out-of-pocket cost are employed (i.e., copay cards, patient assistance programs, switching to contracted pharmacies). The pharmacist then notifies the patient and providers of SGLT2i approval and counsels the patient on SGLT2i indication, mechanism, dosing, side effects, laboratory and imaging follow up, and provider follow up. The pharmacist follows up with the patient 1–2 weeks after SGLT2i initiation to ensure tolerability of the medication and answer any outstanding questions from the patient and/or provider, as well as ongoing involvement throughout the duration of SGLT2i use.

### 4.4. Preliminary results

Among our initial cohort of 20 patients with HFpEF enrolled in this structured protocol, 15 (75%) have successfully implemented treatment with SGLT2i and have been followed for a mean of 29 weeks. In five patients, SGLT2i were never prescribed due to patients possessing disqualifying traits (renal dysfunction, hypotension, DKA risk). Of those initiated on SGLT2i therapy, 14 (93%) remain on therapy, with one discontinuation due to side effects consisting of symptomatic hypotension. The mean time from consultation to SGLT2i initiation was ~9 days, with prior authorization required in eight (53.3%) patients, and cost minimization strategies needed in ten (66.7%) patients. Mean patient out-of-pocket expense was <$20 per month. We will continue to recruit additional patients to collect longer term follow-up data in accordance with the IRB-approved protocol and assess clinical outcomes within a larger cohort of patient. Outcomes of this endeavor will be reported in the future.

### 4.5. Challenges

Though our initial experience with this collaborative protocol for SGLT2i use in patients with HFpEF has been a success, several challenges to the implementation and/or continuation of the collaborative service have been encountered and are worth describing. First, polypharmacy is a concern. As has been discussed, patients with HFpEF are already receiving multi-drug therapy as part of GDMT, therefore adding another medication to an already extensive medication list (at least 5–6 medications just for the HFpEF indication), may pose a significant challenge and patient opposition.

Second, cost implications must also be taken into consideration. Cost is routinely among the most prevalent reasons for medication non-adherence, accounting for non-adherence in 1 of 8 Americans. [88] This is particularly true when patient out-of-pocket expense is $50 or more per month. [89–91] With a boom in cardiovascular pharmacotherapies utilizing novel mechanisms of action or repurposed with new cardiovascular indications, the likelihood that patients will be on one or more of these expensive non-generic medications is increasingly common. The retail cost for each of these medications ranges from ~$400–1000 per month, with patient out-of-pocket expense varying substantially based on insurance type (i.e., commercial, Medicare, Medicaid, etc.) and access to financial assistance programs (i.e., copay cards and/or patient assistance programs).

The third challenge relates to the number of providers involved in a patient’s care. Though collaborative protocols such as ours offer many benefits, distributing patient care roles among multiple healthcare personnel and engaging the expertise of specific departments and roles, the sheer number of providers involved can be a source of confusion for the patient and care teams alike. This problem can be minimized by open and clear communication of goals and clinical care decisions. These three challenges are complex and entrenched issues that advocate for a wide-sweeping healthcare reform on several levels.

### 5. Conclusion and summary recommendations

Heart failure is a debilitating disease with substantial morbidity, mortality, and societal costs. There have been significant advances in pharmacotherapy for patients with HFpEF, most recently the arrival of SGLT2i, that reduce cardiovascular events and saves lives. Implementation of these disease-altering and life-saving therapies, particularly the newer branded medications, has been considerably low. Several reasons account for this dilemma, most prominently limited medication access and high patient cost. In addition, nearly 80% of patients require additional action by the care team after appropriate prescribing of an FDA-approved, guideline-supported, and efficacious medication, such as SGLT2i. This is beyond the bandwidth of any single provider and necessitates the use of a multi-disciplinary team approach to accomplish these services.

Herein we have described an innovative collaborative protocol between the Preventive Cardiology and Heart Failure services in our institution. Our protocol utilizes the combined expertise of Heart Failure providers, Preventive Cardiology providers, and Preventive Cardiology pharmacist to deliver comprehensive and collaborative care to patients with HFpEF by assessing cardiovascular risk, implementing the optimal cardiovascular risk-reducing strategies, improving medication access and adherence, reducing medication costs, and coordinating care across multiple care teams Table 3. Although we have focused on use of SGLT2i in this description, the same strategies can be readily applied to multi-disciplinary implementation of use of other medications. Such a team structure and collaborative protocol may serve as a template for enhanced heart failure management in other health systems to help bridge treatment gaps within this vulnerable population.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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