SGLT2 Inhibitors in Heart Failure
Early Initiation to Achieve Rapid Clinical Benefits

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KEY POINTS

- SGLT2i are high-value medications that demonstrate morbidity and mortality benefits within 30 days of initiation.
- SGLT2i should be initiated simultaneously or in rapid sequence with the other core pillars of GDMT before device therapy consideration.
- In-hospital initiation of SGLT2i is well tolerated and safe and reduces the risk of rehospitalization and death.
- SGLT2i reduce heart failure (HF) hospitalization in HF patients with EF greater than 40% and are a valuable potential therapy in a population with few therapeutic options.

INTRODUCTION

More than 60 million people are living with heart failure (HF) worldwide and as many as one-third may die within the next year.[1,2] Immense progress has been made in the discovery of life-saving medications for patients with HF. However, these therapies are persistently underused.[3] The recent addition of sodium-glucose cotransporter-2 inhibitors (SGLT2i), in addition to standard therapies for HF with reduced ejection fraction (HFrEF), has made them the newest class (Fig. 1) of guideline-directed medical therapies (GDMTs).[4] SGLT2i also demonstrate clinical benefits in HF with moderately reduced ejection fraction/ heart failure with preserved ejection fraction (HFmrEF/HFpEF),[5] diabetes,[6] and chronic kidney disease (CKD).[7]

In a meta-analysis of the SGLT2i randomized controlled trials (RCTs) for HFrEF, treatment with dapagliflozin and empagliflozin, resulted in a 13% reduction in all-cause mortality and a 25% reduction in cardiovascular hospitalization versus placebo.[8] These benefits were seen as soon as 12 days after initiation.[9,10] Although no formal guidelines have been published regarding the optimal timing of initiation of SGLT2i in HFrEF, the clinical benefits of SGLT2i warrant simultaneous or rapid initiation alongside the other pillars of GDMT at the time of diagnosis (Fig. 2). We will provide an overview of the benefits of SGLT2i, concomitant initiation alongside other GDMT medications, hospital initiation, cost and value considerations, and benefits in patients with HFmrEF and HFpEF.

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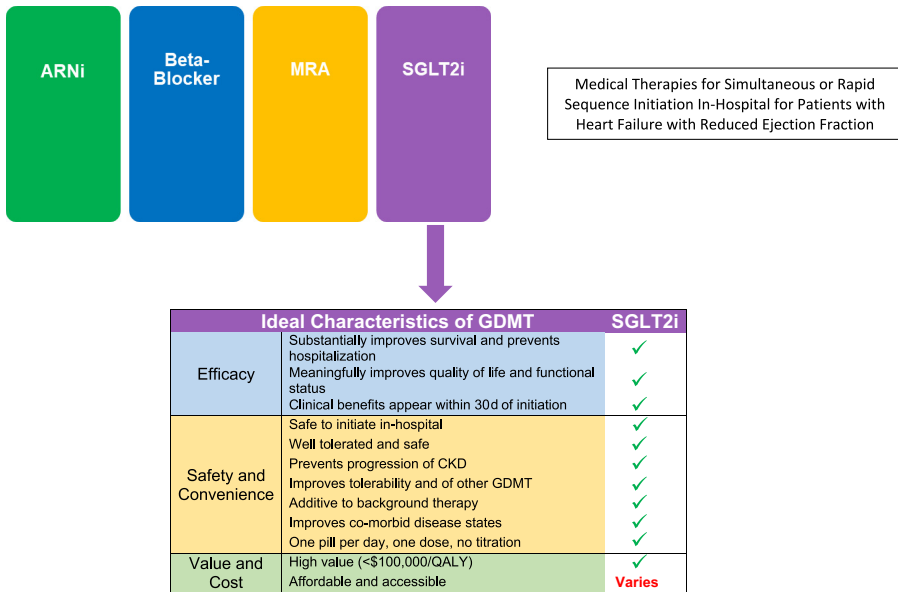Twitter: @NealDixit (N.M.D.); @boback (B.Z.); @gcfmd (G.C.F.)

Fig. 1. Ideal characteristics of medical therapy for HF. ARNi, angiotensin receptor-neprilysin inhibitors; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid-receptor antagonists; QALY, quality-adjusted life year; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

THE NEAR-IMMEDIATE BENEFIT OF SGLT2i

Before the emergence of SGLT2i, consensus GDMT for HFrEF included beta-blockers (BBs), renin–angiotensin–aldosterone system inhibitors (RAASi)/angiotensin receptor-neprilysin inhibitors (ARNis), and mineralocorticoid-receptor antagonists (MRAs), all of which reduce mortality, morbidity, and have onset of clinical benefit within 30 days of initiation.[11] SGLT2i have likewise demonstrated this near-immediate benefit in RCTs, demonstrating improvement in cardiovascular outcomes within 30 days with dapagliflozin and empagliflozin (**Table 1**).

In analysis of the dapagliflozin in patients with HF and reduced ejection fraction (DAPA-HF) trial, the primary outcome of worsening HF event or cardiovascular death reached statistical significance in favor of the dapagliflozin arm at just 28 days and remained significant for the remainder of the trial.[12] Similarly, in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial, empagliflozin achieved statistical significance for the primary outcome of worsening HF event or death by day 12.[9] Several possible mechanisms of cardiovascular benefit derived

Fig. 2. Suggested method of simultaneous or rapid-sequence initiation of quadruple medical therapy for HFrEF with associated clinical benefits. ARNi, angiotensin receptor-neprilysin inhibitors; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid-receptor antagonists; RRR, relative risk reduction; SGLT2i, sodium-glucose cotransporter-2 inhibitors. [a] Computed versus putative placebo in analysis of PARADIGM-HF Trial.

Table 1
Summary of clinical benefits of SGLT2i in clinical trials

Trial	Sample Size (n)	Intervention	Inclusion Criteria	Setting	Primary Outcome	Overall Treatment Effect (95% CI)	Time to Significant Benefit (days)	AE Leading to Discontinuation (Drug vs Placebo)
DAPA-HF	4744	Dapagliflozin 10 mg O.D. vs placebo	LVEF $\leq$40%; NYHA II–IV; eGFR $\geq$30 mL/min/1.73 m^2	Outpatient	Worsening HF or CV death	HR = 0.74 (0.65–0.85)	28	4.7% vs 4.9%
EMPEROR-Reduced	3730	Empagliflozin 10 mg O.D. vs placebo	LVEF $\leq$40%; NYHA II–IV; eGFR $\geq$20 mL/min/1.73 m^2	Outpatient	HF hospitalization or CV death	HR = 0.75 (0.65–0.86)	12[a]	8.5% vs 8.9%
EMPA-RESPONSE-AHF	79	Empagliflozin 10 mg O.D. vs placebo	Hospitalized for acute HF; eGFR $\geq$ 30 mL/min/1.73 m^2	Inpatient	Change in dyspnea, diuretic response, length of initial hospital stay, and change in NT-proBNP	NS	–	17.5% vs 12.8%
SOLOIST-WHF	1222	Sotagliflozin 200 mg O.D. vs placebo	Type-2 diabetes; recent worsening HF; eGFR $\geq$30 mL/min/1.73 m^2	48.8% initiated inpatient and 51.2% early after discharge	Total number of CV deaths and hospitalizations and urgent HF visits	HR = 0.67 (0.52–0.85)	28	7.8% vs 6.6%
EMPEROR-Preserved	5988	Empagliflozin 10 mg O.D. vs placebo	LVEF >40%; NYHA II–IV; eGFR $\geq$20 mL/min/1.73 m^2	Outpatient	HF hospitalization or CV death	HR = 0.79 (0.69–0.90)	18	19.1% vs 18.4%

Table 1
(continued)

Trial	Sample Size (n)	Intervention	Inclusion Criteria	Setting	Primary Outcome	Overall Treatment Effect (95% CI)	Time to Significant Benefit (days)	AE Leading to Discontinuation (Drug vs Placebo)
EMPULSE	530	Empagliflozin 10 mg O.D. vs placebo	Hospitalized for acute HF; eGFR ≥ 30 mL/min/1.73 m^2	Inpatient	Win ratio (composite of death, HF events, and change in KCCQ-TSS)	Win ratio = 1.36 (1.09–1.68)	90[b]	NR

Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; DAPA-HF, dapagliflozin and prevention of adverse outcome in heart failure; eGFR, estimated glomerular filtration rate; EMPA-RESPONSE-AHF, randomized, Double-Blind, Placebo-Controlled, Multicenter Pilot Study On The Effects Of Empagliflozin On Clinical Outcomes In Patients With Acute Decompensated Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial In Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPULSE, A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaires total summary score; LVEF, left ventricular ejection fraction; NR, not reported; NS, non-significant; NT-proBNP, N-terminal (NT)-prohormone BNP; NYHA, New York Heart Association; O.D., once a day; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure

[a] Statistical significance was first reached at 12 d but was sustained from day 34.

[b] Analysis at a time point before 90 d not currently available.

from SGLT2i have been identified.[13] A few mechanisms that have been shown to occur early and may be the basis for the observed clinical benefits are outlined.

Reverse Ventricular Remodeling

Pathologic cardiac remodeling associated with HFrEF increases the risk for hospitalization and death by increasing the likelihood of volume overload, pump failure, or ventricular arrhythmia.[14] Reverse ventricular remodeling is observed with BB, RAASi/ARNi, and MRA usage.[15] The impact of SGLT2i on reverse ventricular remodeling was studied in the Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction (EMPA-TROPISM) trial.[16] In the 6-month trial period, the empagliflozin arm (compared with placebo) had large improvements in left ventricle (LV) end-diastolic volume (-25.1 vs -1.5 mL, $P < .001$), LV end-systolic volume (-26.6 vs -0.5 mL, $P < .001$), LV mass (-17.8 vs 4.1 g, $P < .001$), and LV sphericity. Left ventricular ejection fraction (LVEF) was also improved (6.0 vs -0.1, $P < .001$).

Although the change in LV architecture was assessed at 6 months, the magnitude of the effect combined with known early clinical benefits of SGLT2i implies that these changes are likely occurring soon after initiation. The mechanism for the rapid reverse remodeling was speculated by the same group to be due to, in part, to SGLT2i induced switching of myocardial energy consumption from glucose to fatty acids, ketone bodies, and branched-chain amino acids.[17] However, further research to elucidate the complete mechanism of SGLT2i-induced reverse ventricular remodeling is needed.

Decongestion Without Neurohormonal Compensation

Initiation of SGLT2i has been shown to cause diuresis and natriuresis without the compensatory neurohormonal activation that results from diuresis with traditional diuretics.[18] In the Randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF) trial, hospitalized patients with HFrEF were initiated on empagliflozin or placebo.[19] Although the trial showed no significant differences in the primary endpoints (change in dyspnea, diuretic response, length of stay, and N-terminal probrain natriuretic peptide level), the data reported in the exploratory outcomes suggests increased net urine output ($\sim$850 mL/d) in the empagliflozin group compared with the placebo group during the first 4 days of hospitalization.

Similarly, a single-center crossover placebo-controlled trial of stable HFrEF patients with diabetes showed that empagliflozin significantly increased fractional excretion of sodium with a resultant 138 mL ($P = .04$) reduction in plasma volume at 14 days compared with placebo.[20] Interestingly, plasma norepinephrine levels measured at 14 days increased only 0.09 nmol/L in the empagliflozin group compared with 0.7 nmol/L in the placebo group ($P = .023$). There was no difference in levels of other neurohormones (renin, aldosterone, copeptin).

These two studies suggest that SGLT2i induce a greater reduction in plasma volume by way of increased diuresis and natriuresis without the increase in compensatory neurohormonal activation that precedes ventricular remodeling.[21]

Increase in Erythropoietin

In a substudy of the Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes (EMPA-HEART) trial, investigators measured erythropoietin levels at 0, 1, and 6 months after initiation of empagliflozin.[22] At just 1 month, erythropoietin levels were significantly increased in the empagliflozin arm (compared with placebo). Additionally, hematocrit level was found to be significantly increased by 6 months in the empagliflozin arm. Hematocrit was similarly increased in the Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved) trial at just 1 month. Erythropoietin has previously been shown to have systemic cardioprotective effects[23] in addition to reducing the likelihood of anemia, a known risk factor of HF morbidity and mortality.[22,24] In patients with HFrEF, improvements in erythropoietin and hematocrit levels may be an additional early protective mechanism of SGLT2i.

INITIATION OF SGLT2i WITH OR WITHOUT BACKGROUND THERAPY

The most effective method to maximize relative risk reduction of HF hospitalization and all-cause mortality is simultaneous or rapid sequence initiation of all four pillars of GDMT.[25] Traditional sequencing methods, aiming to maximize BB and RAASi dosage before MRA or SGLT2i initiation, result in unnecessary delays in the initiation of crucial GDMT agents. In fact, the effectiveness of SGLT2i is not dependent on the presence or absence of background HFrEF therapy, and they are well tolerated (and even act synergistically) with other GDMT agents.

In Docherty and colleagues's analysis of the DAPA-HF trial, there was a consistent benefit of dapagliflozin over placebo regardless of whether patients were optimized on guideline-recommended doses, only partially optimized, or were not on GDMT at all.[26] Additionally, in the Empagliflozin in Patients Hospitalized for Acute Heart Failure (EMPULSE) trial, 33% of patients presented with *de novo* HF and were not yet on GDMT, but SGLT2i still demonstrated a magnitude of the effect similar to DAPA-HF and EMPEROR-Reduced.[27]

Importantly, SGLT2i may increase tolerance for other GDMT agents. In both the DAPA-HF and EMPEROR-Reduced trials, patients on MRA that were randomized to treatment with SGLT2i were less likely to experience hyperkalemia.[28,29] In turn, this may be a contributing reason for why patients on SGLT2i have less discontinuation of MRA for which hyperkalemia is a common side effect and reason for discontinuation.[29] The mechanism of MRA tolerance is not known.

Moreover, SGLT2i are consistently associated with reduced adverse kidney outcomes and slow the progression of CKD.[30,31] Therefore, the reno-protective benefits of SGLT2i will likely result in fewer patients discontinuing RAASi/ARNi therapy due to reductions in glomerular filtration rate (GFR).[31]

Although benefits to BB tolerance have not been shown, SGLT2i have minimal blood pressure effect in patients with low blood pressure and are unlikely to result in intolerance to BB due to hypotension. In hypertensive patients, SGLT2i can act as effective antihypertensives, exhibiting a reduction in systolic blood pressure (SBP) of ~3 to 9 mm Hg versus placebo in several trials.[32] However, in a subgroup analysis of patients with an SBP less than 110 mm Hg in the EMPEROR-Reduced trial, no blood pressure difference was seen during the duration of the trial in the empagliflozin group versus placebo group.[33] Similar findings in the SBP less than 110 mm Hg group were seen in the analysis of the DAPA-HF trial.[34] In both trials, the effect size of SGLT2i on the primary outcomes was consistent across all SBP levels.[33,34]

To date, no pillar of GDMT has demonstrated any diminishment of effect by the presence of any combination of background therapy.[35] SGLT2i continue this trend, demonstrating additive the benefit that may actually enable tolerance for additional therapy. Additionally, due to the minimal adverse effects, the initiation of SGLT2i is unlikely to limit efforts to initiate and titrate the other pillars of GDMT.

SGLT2i BEFORE DEVICE THERAPY

Implantable cardiac defibrillators (ICDs), cardiac resynchronization therapy (CRT), and transcatheter edge-edge mitral valve repair (TEER) are three therapies with a demonstrated mortality benefit in eligible populations with HFrEF.[4] To ensure the maximal benefit and demonstrate medical necessity, guidelines recommend, with all three therapies, that patients be initiated on GDMT (and typically up-titrated during a period ≥3 months) before consideration for intervention.[4,36] Although SGLT2i were not a pillar of core GDMT at the time of the landmark trials for these interventions, it is logical as the standard of GDMT evolves to ensure the initiation of SGLT2i before these invasive procedures. Especially, as the benefits of SGLT2i can be achieved rapidly, at a single dosage, and may induce reverse cardiac remodeling of the heart to such a degree that the device therapy is no longer required. For example, in the EMPA-TROPISM trial, LVEF increased by 6% points over the 6-month trial period.[16] This change would push many patients above the 35% LVEF threshold for ICD or CRT consideration. Additionally, although no trial has specifically evaluated improvement in secondary mitral regurgitation (MR) with SGLT2i, we can assume that SGLT2i are likely to have a beneficial effect on secondary MR due to the significant reverse cardiac remodeling effect seen in EMPA-TROPISM.[17] Thus, many patients with secondary MR after initiation of SGLT2i may no longer qualify for TEER, which requires, at least moderate-severe MR on optimal GDMT before intervention.[36]

SHOULD SGLT2i BE INITIATED DURING HOSPITALIZATION?

Despite advances in GDMT and targeted health policy, readmission and mortality rates within 30 days of HF hospitalization have not substantially declined.[37,38] A major contributing factor is exceedingly frequent deferral of initiation and titration of GDMT for HFrEF in both inpatient and outpatient settings.[3] Patients discharged from the hospital without a core pillar of GDMT have a >75% of not being started on that medication in the following year.[35] Thus, given the strong clinical inertia in the outpatient setting and the rapid benefits of all four pillars of GDMT (see **Table 1**), in-hospital initiation of core GDMT has massive potential to reduce HF hospitalization and mortality.

Although SGLT2i were initiated in the outpatient setting in the landmark DAPA-HF and EMPEROR-Reduced trials,[10,39] there is no

evidence to suggest that in-hospital initiation is unsafe. On the contrary, ample evidence exists that support the notion for in-hospital initiation of SGLT2i. In the EMPA-RESPONSE-AHF trial, empagliflozin was initiated in stable hospitalized HFrEF patients and continued for 30 days.[19] As previously mentioned, the study did not meet its primary outcomes, but all safety outcomes were met, with no difference in adverse events or drug discontinuation with the empagliflozin group compared with placebo. In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial, the dual SGLT1/SGLT2 inhibitor, sotagliflozin, reduced the primary endpoint of cardiovascular mortality or HF hospitalization/urgent care visit by 33% versus placebo in patients with HF and diabetes.[40] In the trial, sotagliflozin was initiated before or shortly after hospital discharge, and there was no heterogeneity in efficacy between the subgroups started in-hospital or shortly after hospital discharge. Benefits were seen in the first 28 days from initiation. Serious adverse events led to a discontinuation rate in the sotagliflozin group of only 3.0% (vs 2.8% in the placebo group). Most recently, the EMPULSE trial demonstrated the safety rapid clinical benefits in hemodynamically stable HF patients initiated on SGLT2i early during hospitalizations for acute HF.[27] Patients initiated on empagliflozin were 36% more likely to receive clinical benefit than those initiated on placebo during the 3-month study period. Significant improvement in symptoms was noted at just 15 days. No safety concerns were identified, and there was more drug discontinuation in the placebo arm.

Although there are clear and compelling benefits with in-hospital initiation of SGLT2i, there is no consensus at which point during a hospitalization to initiate SGLT2i relative to other GDMT. Although some would point to the augmented diuresis with SGLT2i seen in the EMPA-RESPONSE-AHF trial as a reason to initiate as early as possible (before ARNi, BB, and MRA), this did not result in a shorter length of stay.[19] In EMPULSE, the median time of initiation was 3 days into admission with patients having to demonstrate clinical stability as evidenced by an SBP greater than 100 mm Hg, no symptomatic hypotension, no increase in intravenous (IV) diuretics or use of IV vasodilators within 6 h, and no IV ionotropic support within 24 h. Factors such as upcoming procedures, renal function, and adjustment of diabetes medications may also influence the timing of initiation.[41] Fortunately, as complete benefits of SGLT2i are obtained at the initial dosage, the main priority should simply be the initiation of the medication beforedischarge.

Initiation of GDMT in-hospital is crucially important with one in four patients dying or rehospitalized within 30 days of discharge of an HF hospitilizaiton.[42] In-hospital initiation of SGLT2i is safe and results in rapid clinical benefits that reduce hospitalization and death in the high-risk post-discharge period.

COST AND VALUE CONSIDERATIONS

SGLT2i are relatively new drugs on the market and as such will likely be under patent in the United States until at least 2025. Consequentially, out-of-pocket drug costs for SGLT2i, which can be upwards of $300 per month, are unaffordable for many patients without extra efforts to increase the accessiblity.[41] Because of additional time and resources needed to obtain SGLT2i for patients, clinicians may feel reluctant to use SGLT2i alongside other pillars of GDMT. Due to costs, hospitals and payers may avoid adding SGLT2i to covered formularies. However, these barriers are worth overcoming to realize the impressive morbidity and mortality benefit of the medication class. A cost-effectiveness analysis by Isaza and colleagues showed that in the United States, dapagliflozin costs $68,300 per quality-adjusted life year (QALY) gained.[43] This figure is far below the $150,000 per QALY threshold that the ACC/AHA set for low-value interventions and on par with ARNi, which also remain under patent.[44,45] Moreover, more frequent in-hospital initiation may further increase value due to a larger absolute risk reduction in the high-risk postdischarge period.[46] In the treatment of HF, where few medications have demonstrated mortality benefit and the four pillars of therapy have additive clinical benefit, it is the best interests of patients and the health care system to ensure access to SGLT2i.

SGLT2i USE IN PATIENTS WITH HEART FAILURE AND EJECTION FRACTION GREATER THAN 40%

Patients with HFmrEF and HFpEF have traditionally been a difficult patient population to treat.[47] RAASi, ARNi, and MRA may have modest benefits. However, SGLT2i have recently been shown in multiple trials to improve morbidity and symptoms across the entire EF spectrum of HF to a much greater degree than RAASi, ARNi, and MRA.[5,27,40]

The SOLOIST-WHF trial was the first to suggest the benefit of the SGLT inhibitor mechanism in patients with HFpEF.[40] In prespecified subgroup analysis of patients with EF $\geq$ 50%, sotagliflozin reduced the primary endpoint of cardiovascular death or urgent visits/hospitalizations for HF by

52% compared with placebo. Subsequently, the EMPEROR-Preserved trial, showed a 21% decrease in the primary outcome of cardiovascular death or HF hospitalization with empagliflozin versus placebo in patients with HF and an EF ≥ 40%.[5,48] This benefit reached statistical significance only 18 days after randomization. Of note, the reduction in the primary outcome was driven almost entirely from a reduction in HF hospitalizations. Additionally, in prespecified subgroup analysis, benefit was found across all EF ranges but was greatest in the EF ≤50% group. Unfortunately, both trials failed to achieve the elusive goal of all-cause mortality benefit with drug therapy in an HF population with EF greater than 40%. Even still, SGLT2i are an effective treatment to reduce HF hospitalizations for patients with HFmrEF or HFpEF. In the EMPULSE trial, the clinical benefits achieved were similar for patients with EF ≤40% and greater than 40% further demonstrating the benefits of SGLT2i therapy apply irrespective of EF group.[27] The totality of evidence suggests that early in-hospital initiation of SGLT2i should be the standard of care for patients with HF, irrespective of EF.

SUMMARY

SGLT2i are the newest member of the core HFrEF therapies that improve morbidity and mortality and accrue benefit within 30 days of initiation in large-scale RCTs. Initiation of SGLT2i should occur as soon as possible either in simultaneous or in rapid sequence with other GDMT agents. Furthermore, consideration for device therapy such as ICD, CRT, and TEER should wait until the initiation of SGLT2i. In-hospital initiation of SGLT2i is well tolerated and crucial given the risks of death and re-hospitalization after discharge and pervasive clinical inertia in the outpatient setting. SGLT2i are high-value medications, and efforts should be made to reduce acquisition costs for patients. More recent data favor initiation of SGLT2i in patients with HFmrEF/HFpEF to reduce the risk of hospitalization due to HF and demonstrates the benefits of early in-hospital initiation, irrespective of EF in patients hospitalized with HF.

CLINICS CARE POINTS

- SGLT2i demonstrate morbidity and mortality benefits within 30 days of initiation, possibly related to rapid reverse cardiac remodeling, reduced congestion, and increases in the cardioprotective and hematocrit-stimulating hormone, erythropoietin
- To maximize total relative risk reduction in morbidity and mortality, SGLT2i should be initiated simultaneously or in rapid sequence with the other core pillars of GDMT
- Due to LVEF and cardiac structure improvements induced by SGLT2i, consideration for device therapies such as ICD, CRT, and TEER should occur after SGLT2i initiation
- In-hospital initiation of SGLT2i is well tolerated and safe and reduces the risk of rehospitalization and death
- SGLT2i are lifesaving, high-value medications, and patient affordability is a key issue
- SGLT2i have more recently shown to reduce heart failure (HF) hospitalization in HF patients with EF greater than 40% and are a valuable potential therapy in a population with few therapeutic options

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