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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND L-S CHANG, SECTION EDITORS)

What Makes Sodium-Glucose Co-Transporter-2 Inhibitors Stand out in Heart Failure?

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Abstract

Purpose of Review We highlight the unique properties of the sodium-glucose cotransporter-2 (SGLT-2 inhibitors) which may lend favorably to their efficient integration in the background of other heart failure (HF) therapies. We also discuss the unique aspects of SGLT-2 inhibitor dosing, lack of titration needs, effects on kidney function and electrolytes, diuretic activity, and safety in the high-risk peri-hospitalization window.

Recent Findings Dapagliflozin was recently approved for the treatment of heart failure with reduced ejection fraction (HFrEF), irrespective of the presence or absence of type 2 diabetes mellitus (T2DM) based on the findings of the pivotal DAPA-HF trial. All SGLT-2 inhibitors are once daily medications with minimal drug-drug interactions and do not require titration (for HF treatment) unlike other HF medications. SGLT-2 inhibitors offer modest weight loss and blood pressure reduction without major adverse effects of hyperkalemia, making it ideal for near-simultaneous initiation with other HF medications, and use in high-risk populations (including older adults). Moreover, SGLT-2 inhibitors appear to afford long-term kidney protection in diverse populations.

Summary SGLT-2 inhibitors are the latest class of therapies to demonstrate important clinical benefits among patients with HFrEF, and their pharmacological properties favor ease of use and integration in multi-drug disease-modifying regimens.

Keywords Antihyperglycemic therapies · Diabetes mellitus · Heart failure · SGLT-2 inhibitors

Introduction

There are approximately 500 million patients with type 2 diabetes mellitus (T2DM) and 64 million patients with heart failure (HF) globally [1, 2]. T2DM and HF often co-exist with one causing a worse prognosis in the other [3, 4]. Antihyperglycemic therapies such as thiazolidinediones and saxagliptin may increase HF events and thus are discouraged among patients with established HF [5, 6]. Other therapies such as the glucagon-like peptide-1 receptor agonists (GLP-1 RA) appear to primarily target atherosclerotic disease pathways while minimally altering pathways that affect HF events.

The sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to reduce risk of HF events among various at-risk populations with T2DM (Table 1) [7–9, 10••]. SGLT-2 inhibitors block reabsorption of filtered glucose in the proximal renal tubule causing increased excretion of glucose in the urine, but they appear to have broader multi-system metabolic benefits. Four SGLT-2 inhibitors have been approved by the US Food and Drug Administration (FDA) for use in glycemic control for T2DM. In the landmark DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), dapagliflozin reduced the composite endpoint of worsening HF events or cardiovascular death by 26% compared with placebo among patients with chronic HF with reduced ejection fraction (HFrEF), irrespective of T2DM status [10••]. Based on these data, dapagliflozin has now been approved by the FDA for use in the treatment of HFrEF with or without comorbid T2DM [11]. Consistent benefits were

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Table 1 HF endpoints in select cardiovascular and kidney outcomes trials of SGLT-2 inhibitors

Trial name	Year	Population	N	Baseline HF(%)	Follow-up (years)	HF hospitalization	Primary outcome[#]
EMPA-REG Outcome[7]	2015	T2DM with CVD	7020	10	3.1	HR = 0.65 (0.50–85)	HR = 0.86 (0.74–0.99)
CANVAS[8]	2017	T2DM with CVD or CVD risk factors	10,142	14	3.6	HR = 0.67 (0.52–0.87)	HR = 0.86 (0.75–0.97)
DECLARE TIMI-58[9]	2019	T2DM with CVD or CVD risk factors	17,160	10	4.2	HR = 0.73 (0.61–0.88)	HR = 0.93 (0.84–1.03)
CREDENCE[35]	2019	T2DM with albuminuric CKD	4401	15	2.6	HR = 0.61 (0.47–0.80)	HR = 0.70 (0.59–0.82)
DAPA-HF[10]	2019	Symptomatic HFrEF with or without T2DM	4744	100	1.5	HR = 0.70 (0.59–0.83)[$]	HR = 0.74(0.65–0.85)

**CVD* cardiovascular disease; *CKD* chronic kidney disease; *HF* heart failure; *HFrEF* heart failure with reduced ejection fraction; *HR* hazard ratio; *T2DM* type 2 diabetes mellitus

#For EMPA-REG OUTCOME and CANVAS, the primary outcome was a 3-point composite of major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infraction, or non-fatal stroke). For DECLARE-TIMI 58, the co-primary outcome was 3-point MACE and a composite of cardiovascular death or hospitalization for HF. For CREDENCE, the primary outcome was a renal composite of end stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular cause. For DAPA-HF, the primary outcome was a composite of worsening HF or CV death

observed with a second SGLT-2 inhibitor, empagliflozin, in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial among patients with chronic HFrEF with or without T2DM. Among over 2000 patients in the contemporary CHAMP-HF (Change the Management of Patients with Heart Failure) registry with HFrEF and comorbid T2DM, the use of SGLT2 inhibitors (2.4%) was low, suggesting a large potential for therapeutic optimization [12].

Core therapies, including β-blockers, mineralocorticoid receptor antagonists, renin-angiotensin-aldosterone system (RAAS) inhibitors, and angiotensin-receptor neprilysin inhibitors, have been shown to reduce mortality in HFrEF patients [13]. In addition, certain therapies appear to safely lower risk of hospitalization for HF, including vericiguat, a soluble guanylate cyclase stimulator [14]. Furthermore, several other therapies are being actively investigated to continue to expand the therapeutic armamentarium available for treatment of HFrEF, including omecamtiv mecarbil, a novel selective cardiac myosin activator [15]. Despite the growing list of evidence-based therapies available to improve outcomes in HFrEF, combination use in clinical practice has remained low. For instance, in a contemporary outpatient registry, < 1% of patients were simultaneously being treated with target doses of a β-blocker, mineralocorticoid receptor antagonist, and renin-angiotensin system inhibitor [16, 17]. The reasons underlying these therapeutic gaps are likely multifactorial, but they highlight inefficiencies with traditional approaches of stepwise medication changes in clinical practice. It is critical that simultaneous or near-simultaneous initiation of evidence-based therapies is considered to improve the rates of guideline-directed medical therapy and in turn afford patients with the life-prolonging benefits of combination medical therapies [18••].

SGLT-2 inhibitors stand out as a drug class which uniquely fits into the current HF therapeutic regimen. In this review, we highlight their unique properties which may lend favorably to their efficient integration in the background of other HF therapies. We also discuss the unique aspects of SGLT-2 inhibitor dosing, lack of titration needs, effects on kidney function and electrolytes, diuretic activity, and safety in the high-risk peri-hospitalization window.

Use of SGLT-2 Inhibitors After Worsening HF Events

The period immediately after a worsening HF event has often been described as the "vulnerable phase" as it is characterized by high rates of readmission and mortality. A post-hoc analysis of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial showed that the proportion of patients with a second HF readmission within 45, 60, and 90 days was almost 2 times higher in individuals treated with placebo compared with empagliflozin [19••]. Moreover, the proportions of patients with HF re-hospitalization or cardiovascular death and HF re-hospitalization or all-cause death were significantly higher in the placebo group versus empagliflozin at all time points. Similarly, in DAPA-HF, patients enrolled shortly after hospitalization for HF derived greater absolute benefits in reduction in HF events compared with patients randomized remote from a HF event or who had never been hospitalized [10••]. These results indicate that SGLT-2 inhibitors may have

a role in improving outcomes in patients with acute HF, a hypothesis that is actively being tested in several modest-sized randomized clinical trials. Initial data from the EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients with Acute Decompensated Heart Failure) trial showed that empagliflozin reduces a combined endpoint of worsening HF, re-hospitalization for HF, or death at 60 days in patients with acute HF [20••]. However, no significant change in visual analog scale dyspnea score, diuretic response, or length of hospital stay was observed. Unfortunately, the large SOLOIST WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure, NCT03521934), which was evaluating the novel combination SGLT-1/2 inhibitor sotagliflozin, was terminated early by the sponsor due to complexities with coronavirus disease 2019 (COVID-19).

Use of SGLT-2 Inhibitors in Older Patients with HF

Almost half of patients with T2DM are above 65 years of age [21]. As these individuals are at high risk of hypoglycemia, guidelines recommend less stringent glycemic control compared with younger patients [22]. SGLT-2 inhibitors pose a low risk of hypoglycemia (< 1%) in older adults, which is considerably lower than sulfonylureas and incretin-based therapies [23]. Moreover, older individuals typically have arterial stiffness leading to isolated systolic hypertension. SGLT-2 inhibitors have been shown to reduce oxidative stress and improve endothelial function leading to improvement in arterial stiffness [24, 25]. It is possible that SGLT-2 inhibitors may also have a favorable effect on blood pressure in patients with hypertension, leading to decreased polypharmacy. In the context of HF treatment, in DAPA-HF, dapagliflozin decreased the risk of mortality and worsening HF across a broad spectrum of age [26••]. Moreover, there was no significant difference in tolerability or adverse events between dapagliflozin and placebo in older individuals [26••].

SGLT-2 Inhibitor Dosing and Lack of Need for Titration

All SGLT-2 inhibitors are once daily medications and have minimal drug interactions. The main exception is canagliflozin, which is a P-glycoprotein substrate (modest inhibition); specifically, co-administration with digoxin may increase plasma levels of digoxin [27]. It is important to that note that while higher SGLT-2 inhibitor doses may offer greater glycemic control, large cardiovascular outcomes trials have shown little evidence exists for dose heterogeneity with respect to cardiovascular benefits in T2DM. In addition, completed and ongoing HF trials have tested fixed doses of SGLT-2 inhibitors without need for titration.

Evidence to date from trials of T2DM suggest general class effects. Although the SGLT-2:SGLT-1 relative receptor affinity varies among the different agents, all CVOTs with SGLT-2 inhibitors have shown consistent benefit in preventing HF events among patients with at-risk populations with T2DM. Of note, the cardiovascular outcomes trial testing ertugliflozin has completed [28].

SGLT-2 Inhibitors and Diuretic Activity

SGLT-2 inhibitors are associated with osmotic diuresis and natriuresis, which may be synergistic when used in combination with a loop diuretic [29••]. However, distinct from the widely used loop diuretics, SGLT-2 inhibitors may preferentially result in reduction in interstitial volume compared with intravascular volume, thus resulting in less compensatory RAAS activation [29••, 30]. In DAPA-HF, dosing of concomitant loop diuretics was only modestly lowered during the trial. It is suggested that clinicians actively monitor volume status after SGLT-2 initiation and consider decreasing loop diuretic dosing, especially if dizziness or orthostatic hypotension is encountered [31].

SGLT-2 Inhibitors and Kidney Function

Chronic kidney disease (CKD) is a key risk factor for the development and progression of HF [32]. The recent CARMELINA trial (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) showed that a substantially higher risk of HF hospitalization was observed in patients with estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 compared with those with eGFR > 60 mL/min per 1.73 m^2 [33]. Multiple SGLT-2 inhibitors have shown kidney outcome benefits (Table 2) [34••]. In the CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), canagliflozin reduced the risk of doubling of serum creatinine, end stage kidney disease, or mortality due to cardiovascular or renal cause by 30% [35••]. The DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial was recently prematurely halted for overwhelming efficacy and is the first trial to evaluate patients with CKD with and without T2DM [36]. In a meta-analysis of trials evaluating SGLT2 inhibitors for treatment of T2DM, these therapies were shown to reduce the risk of dialysis, transplantation, or mortality due to renal disease by 33%, and in fact were shown to decrease the risk of future episodes of acute kidney injury by 25% [37]. Furthermore, this observed benefit was present across all eGFR subgroups including eGFR < 45 mL/min per 1.73 m^2. Indeed, the reduction

Table 2 Effects of SGLT2 inhibitors on kidney outcomes

Study	Population	AKI (RR; 95%CI)	ESKD (RR; 95%CI)	Composite of renal worsening, ESKD or death due to renal cause (RR; 95%CI)	eGFR cutoff for inclusion (mL/min per 1.73 min^2)
CREDENCE[35]	Albuminuric CKD	0.85 (0.64–1.13)	0.68 (0.54–0.86)	0.66 (0.53–0.81)	≥ 30
EMPA-REG Outcome[7]	T2DM with CVD	0.76 (0.62–0.93)	0.60 (0.18–1.98)	0.54 (0.40–0.75)	≥ 30
CANVAS[8]	T2DM with CVD or CVD risk factors	0.66 (0.39–1.11)	0.77 (0.30–1.97)	0.53 (0.33–0.84)	≥ 30
DECLARE TIMI 58[9]	T2DM with CVD or CVD risk factors	0.69 (0.55–0.87)	0.31 (0.13–0.79)	0.53 (0.43–0.66)	≥ 60^

AKI acute kidney injury; *ESKD* end-stage kidney disease; *RR* relative risk; *CI* confidence interval; *eGFR* estimated glomerular filtration rate; *CVD* cardiovascular disease; *CKD* chronic kidney disease. ^=Creatinine clearance based on Cockcroft-Gault equation

in HF hospitalization was higher in patients with worse baseline kidney function; a 40% reduction in HF hospitalization was observed among patients with eGFR < 60 mL/min per 1.73 m^2 compared with 31% and 12% reductions in patients with eGFR ≥ 60 to < 90 mL/min per 1.73 m^2 and eGFR ≥ 90 mL/min per 1.73 m^2, respectively [37].

Pre-initiation kidney function is encouraged to be > 30 mL/min per 1.73 m^2 for dapagliflozin when used for HF treatment as tested in the DAPA-HF trial. While glycemic effects appear to be limited at low eGFR, the HF benefits associated with dapagliflozin are anticipated across a broad eGFR range. Although SGLT-2 inhibitors affect a small expected initial dose-dependent reduction in eGFR within the first couple of weeks, eGFR subsequently stabilizes and is linked with kidney protective effects with long-term use [38]. As such, this modest decline in eGFR early after treatment initiation likely represents a pharmacodynamic effect rather than resulting in true kidney injury. Similar to considerations around initiation of RAAS inhibitors, the initiation of SGLT-2 inhibitors among patients with HF may be safest during periods with relative stability of eGFR [39].

SGLT-2 Inhibitors and Other HF Therapies

There are currently many therapies approved for glycemic control and HFrEF therapy. This can lead to considerable polypharmacy (with attendant non-compliance). While the optimal sequence of HFrEF therapies is uncertain, near-simultaneous or clustered initiation of drugs may be feasible for many patients. One of the common reasons why guideline-directed medical therapy is not started in clustered fashion by specialists is because of fears of hyperkalemia (due to RAAS inhibition) and low blood pressure. While patients with elevated blood pressures, including those with resistant hypertension [40], may derive clinically important blood pressure reduction with SGLT-2 inhibitors, for most patients, SGLT-2 inhibitors cause minimal blood pressure lowering, with a mean reduction in systolic and diastolic blood pressure < 4 mmHg across various cardiovascular and kidney outcomes trials [39, 41, 42]. Moreover, SGLT-2 inhibitors are not associated with increased risk of hyperkalemia. Therapies which do not offer cardiovascular risk reduction or mortality benefit in HF, such as calcium channel blockers, should be deprescribed if low blood pressure with SGLT-2 initiation is a concern. As SGLT-2 inhibitors exert a diuretic effect, a dose adjustment in concomitant loop diuretics may be necessary based on clinical signs and symptoms during follow-up. Congestive signs and symptoms and orthostatic hypotension should be closely monitored.

In the DAPA-HF trial, 11% of the patients were on background angiotensin receptor neprilysin inhibition (ARNI) at enrollment. Subgroup analyses showed that the beneficial effect of dapagliflozin on HF outcomes was consistent independent of background ARNI use, suggesting additive and incremental effects [43]. Moreover, the mechanism of action of both drug types is distinct; hence, the use of both newer additions to the HFrEF regimen should be encouraged in HFrEF.

SGLT-2 Inhibitors and Adjustment of Other Antihyperglycemic Therapies

Among the large group of patients with HFrEF without concomitant T2DM, dapagliflozin did not appear to lower hemoglobin A1c compared with placebo [10••]. As such, there does not appear to be any concerns related to hypoglycemia among this population. For patients with concomitant T2DM, a modest glycemic effect is anticipated. The DAPA-HF trial did not have any protocolized modification of background antihyperglycemic therapies. When initiating SGLT-2 inhibitors in HFrEF and T2DM, certain antihyperglycemic therapies (such as sulfonylureas or dipeptidyl-peptidase-4 inhibitors) may be stopped or dose reduced. When polypharmacy is of high concern, combination formulations of metformin and SGLT-2 inhibitors are available and may be considered.

While metformin has represented a foundational therapy for T2DM, about half of patients enrolled in the DAPA-HF trial were not on background metformin; these patients still derived significant clinical benefits. As such, when treating HFrEF, the staged introduction of metformin prior to SGLT-2 inhibitors is likely not required for cardiovascular benefit.

Side Effects of SGLT-2 Inhibitors

SGLT-2 inhibitors are generally well tolerated, including among patients with HF [44]. Serious adverse events were infrequent in the DAPA-HF trial. One of the more common side effects of SGLT-2 inhibitors is genital yeast infections, including vulvovaginal candidiasis and balanitis. These infections typically present early during treatment course and are more commonly seen in older women and uncircumcised men. These infections can often easily be treated with topical antifungal creams or single-dose oral antifungal therapy and typically do not require discontinuation of SGLT-2 inhibitor therapy. Patients should be specifically counseled about maintenance of perineal hygiene. In 2018, the FDA released a warning related to 12 cases of Fournier's gangrene, a rare but serious and potentially disfiguring perineal infection associated with SGLT-2 inhibitors [45].

Though rare, euglycemic diabetic ketoacidosis has also been associated with SGLT-2 inhibitors among patients with T2DM. As such, among patients with HF and comorbid T2DM, special attention should be given to HF patients who have poor oral intake and are expected to undergo elective surgeries. Canagliflozin, dapagliflozin, and empagliflozin should each be discontinued at least 3 days before scheduled surgery, while ertugliflozin should be discontinued at least 4 days before scheduled surgery [46]. Patients should be counseled about the common symptoms of ketoacidosis such as altered mental status, vomiting, and abdominal pain and should be advised to curb excessive alcohol intake. It is noteworthy that among patients with HF without T2DM, diabetic ketoacidosis does not appear to be a concern, and no cases were observed in the large DAPA-HF trial in this subset.

Unanswered Questions

Currently, large clinical trials are evaluating the potential for the use of SGLT-2 inhibitors in HF with preserved ejection fraction (HFpEF). The ongoing DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) will provide further insights regarding the role of SGLT-2 inhibitors for this high-risk entity without current effective treatment options. SGLT-2 inhibitors may play a role in reversing adverse cardiac remodeling as observed in the EMPA-HEART (Effects of Empagliflozin on Cardiac Structure, Function, and Circulating Biomarkers in Patients with Type 2 Diabetes) CardioLink 6 trial in which patients treated with empagliflozin experienced early and significant reduction in left ventricular mass regression [47••]. The ongoing PRESERVED-HF (Effects of Dapagliflozin on Biomarkers, Symptoms, and Functional Status in Patients with Preserved Ejection Fraction Heart Failure) and EMBRACE-HF (Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients with Heart Failure) will give further information regarding the effect of SGLT-2 inhibitors on cardiac biomarkers, structure, and hemodynamics.

Conclusion

SGLT-2 inhibitors represent the most recent class of therapies that have been shown to modify clinical course and improve life expectancy among patients with HFrEF. Fixed-dose, once daily dosing without need for titration or frequent electrolyte/kidney function monitoring all favor its safe and feasible introduction in multi-drug regimens across a broad range of HFrEF patients. Ongoing trials will evaluate if other patients with HF, including those with HFpEF and who are hospitalized for worsening HF, may similarly benefit from this class of therapies.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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