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Narrative Review

Cardiovascular Disease Management With Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes: A Cardiology Primer

Allan Zhang, BA[1]; Ramsey Kalil, MD[2]; Alexander Marzec, MD[1]; Stephanie A. Coulter, MD[2]; Salim Virani, MD[2,3]; Kershaw V. Patel, MD, MSCS[4]; Matthew W. Segar, MD, MS[2]

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas
[2]Department of Cardiology, The Texas Heart Institute, Houston, Texas
[3]Aga Khan University, Karachi, Pakistan
[4]Department of Cardiology, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas

Abstract

Patients with type 2 diabetes face an elevated risk of cardiovascular disease. This review centers on sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of drugs that, according to a growing body of evidence, may have major potential for managing cardiovascular disease in patients with type 2 diabetes. This review presents findings from multiple clinical trials suggesting that SGLT2 inhibitors can not only serve as preventive therapeutic agents but also play a role in the active management of heart failure. The discussion includes the mechanism of action of SGLT2 inhibitors, emphasizing that they enhance urinary glucose excretion, which could lead to improved glycemic control and contribute to metabolic shifts beneficial to cardiac function. Alongside these cardiometabolic effects, safety concerns and practical considerations for prescribing these agents are addressed, taking into account potential adverse effects such as genitourinary infections and diabetic ketoacidosis as well as the financial implications for patients. Despite these drawbacks, therapeutic indications for SGLT2 inhibitors continue to expand, including for kidney protection, although further research is necessary to fully understand the mechanisms driving the cardioprotective and kidney-protective effects of SGLT2 inhibitors. By synthesizing current knowledge, this review intends to inform and guide clinical decision-making, thereby enhancing cardiovascular disease outcomes in patients with type 2 diabetes.

Keywords: Diabetes mellitus; cardiovascular diseases; hypoglycemic agents; sodium-glucose transporter 2 inhibitors; glycemic control; heart failure; atherosclerosis

Introduction

Patients with type 2 diabetes are at an elevated risk for cardiovascular disease (CVD), contributing to substantial morbidity and mortality rates worldwide.[1,2] Traditionally, the management of type 2 diabetes has predominantly focused on attaining glycemic control; however, evidence has shown that this strategy does not effectively diminish the associated risk of CVD.[3-5] Some specific glucose-lowering agents have paradoxically been found to increase the risk of particular CVD events, highlighting the need for a more comprehensive and nuanced approach to type 2 diabetes treatment and an emphasis on CVD risk reduction.[6]

In response, the US Food and Drug Administration in 2008 issued guidance to industry, mandating cardiovascular outcome trials for new antidiabetic therapies.[7] The implementation of this guidance yielded critical data on

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Corresponding author: Matthew W. Segar, MD, MS, 6770 Bertner Ave, Houston, TX 77030 (msegar@texasheart.org)

3 medication classes: Dipeptidyl peptidase 4 inhibitors had neutral cardiovascular effects, select glucagon-like peptide 1 receptor agonists had cardiovascular benefits, and sodium-glucose cotransporter-2 (SGLT2) inhibitors reduced the risk of CVD.[8,9] This review aims to elucidate the utility and potential of SGLT2 inhibitors in the comprehensive management of type 2 diabetes and CVD.

Background, Trial Outcomes, and Recent Findings

Sodium-glucose cotransporters generally reabsorb glucose. They have 2 isoforms: SGLT1 and SGLT2. Though SGLT1 is found in the small intestine, SGLT2 is found primarily in the proximal renal tubule and is responsible for nearly 90% of glucose reabsorption in the kidneys. Ten SGLT2 inhibitors were formulated to curb hyperglycemia in patients with type 2 diabetes, primarily by inhibiting glucose reabsorption in the proximal renal tubule, leading to an increase in glucose excretion through the urine. This process ultimately promotes better glycemic control.[10]

Beyond their glycemic effects, SGLT2 inhibitors have demonstrated cardioprotective effects in several clinical trials (Table I).[11-18] Sodium-glucose cotransporter 2 inhibitors appeared to reduce the risk of major adverse cardiovascular events (MACE), especially the risk of heart failure (HF) in patients with type 2 diabetes. One such trial was (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), a large cardiovascular outcome trial that was originally designed to test the cardiovascular safety of empagliflozin; the trial showed that this drug reduced MACE rates by 11% while reducing the risk of HF by 35%.[11] The CANagliflozin cardioVascular Assessment Study (CANVAS) trial similarly showed that canagliflozin reduced MACE risk by 14% but that the drug's greater benefit was reducing patients' risk of HF (by 33%).[12] The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial, performed in patients with both type 2 diabetes and established atherosclerotic disease, showed that ertugliflozin reduced the risk of MACE only slightly (by 3%) but reduced the risk of HF substantially (by 30%).[13] Unlike the previous trials, the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) trial chiefly enrolled patients at high risk of CVD (59.4%) in addition to patients with established CVD (40.6%); nonetheless, this trial also showed a small reduction in MACE risk (7%) and a larger reduction in HF risk (27%).[14] Given that these trials primarily enrolled patients with type 2 diabetes and without prevalent HF (EMPA-REG OUTCOME, 90.0%; CANVAS, 85.6%; VERTIS CV, 76.3%; and DECLARE-TIMI58, 90.0%),[11-14] their results demonstrate the potential therapeutic benefits of SGLT2 inhibitors for patients with type 2 diabetes who are at risk of HF.

Extending beyond cardioprotective effects, SGLT2 inhibitors have also shown kidney-protective effects in patients with type 2 diabetes (Table II).[19-21] The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial, a large clinical trial conducted in patients with type 2 diabetes and chronic kidney disease (CKD), showed that canagliflozin reduced patients' risk of the primary outcome—a composite of end-stage kidney disease, doubling of serum creatinine level, and kidney-related or cardiovascular-related death—by 30% and reduced their HF risk by 39%.[19]

Key Points

- Patients with type 2 diabetes are at an elevated risk of CVD. Traditional strategies focusing on glycemic control may not adequately mitigate this risk, underscoring the potential use of SGLT2 inhibitors in CVD management.
- The cardiometabolic effects of SGLT2 inhibitors are robust, with several trials demonstrating not only the potential of SGLT2 inhibitors for preventing HF but also their promising potential role in managing active HF.
- The promising therapeutic benefits of SGLT2 inhibitors must be balanced against potential harms such as adverse effects and the financial burden of out-of-pocket costs for patients.

Abbreviations and Acronyms

CKD	chronic kidney disease
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
RRR	relative risk reduction
SGLT2	sodium-glucose cotransporter-2

TABLE I. Findings From Clinical Trials of SGLT2 Inhibitors[a]

Clinical trial (publication year)	Medication	No.	Criteria for enrollment	Participants with type 2 diabetes, %[a]	Median follow-up, y	Primary end point			Secondary end point		
						Description	Hazard ratio (95% CI)	RRR, %	Description	HF hazard ratio (95% CI)	RRR, %
EMPA-REG OUTCOME (2015)[11]	Empagliflozin	7,020	Established CVD	100	3.1	Cardiovascular death, myocardial infarction, or stroke	0.86 (0.74-0.99)	11	Primary end point + hospitalization for unstable angina	0.65 (0.50-0.85)	35
CANVAS (2017)[12]	Canagliflozin	10,142	Established CVD (66%) or at high risk of CVD (34%)	100	3.6	Cardiovascular death, myocardial infarction, or stroke	0.86 (0.75-0.97)	14	Hospitalization for HF	0.67 (0.52-0.87)	33
DECLARE-TIMI58 (2019)[14]	Dapagliflozin	17,160	Established CVD (41%) or at high risk of CVD (59%)	100	4.2	Cardiovascular death, myocardial infarction, or ischemic stroke	0.93 (0.84-1.03)	7	Hospitalization for HF	0.73 (0.61-0.88)	27
DAPA-HF (2019)[15]	Dapagliflozin	4,744	LVEF ≤40%	45	1.5	Cardiovascular death or worsening HF	0.74 (0.65-0.85)	26	Hospitalization for HF or cardiovascular death	0.70 (0.59-0.83)	25
VERTIS CV (2020)[13]	Ertugliflozin	8,246	Established atherosclerotic disease	100	3.0	Cardiovascular death, myocardial infarction, or stroke	0.97 (0.85-1.11)	3	Hospitalization for HF	0.70 (0.54-0.90)	30
EMPEROR-Reduced (2020)[16]	Empagliflozin	3,730	Class II-IV HF, LVEF ≤40%	50	1.3	Cardiovascular death or hospitalization for HF	0.76 (0.67-0.87)	35	Hospitalization for HF	0.70 (0.58-0.85)	30
EMPEROR-Preserved (2021)[17]	Empagliflozin	5,988	Class II-IV HF, LVEF >40%	49	2.2	Cardiovascular death or hospitalization for HF	0.79 (0.69-0.90)	21	Hospitalization for HF	0.71 (0.60-0.83)	27
DELIVER (2022)[18]	Dapagliflozin	6,263	HF, LVEF >40%	45	2.3	Cardiovascular death or worsening HF	0.82 (0.73-0.92)	18	Worsening HF	0.79 (0.69-0.91)	23

CVD, cardiovascular disease; HF, heart failure; LVEF, left ventricular ejection fraction; RRR, relative risk reduction; SGLT2, sodium-glucose cotransporter-2.

[a] All trials for which the percentage of patients with type 2 diabetes is 100% had type 2 diabetes as an entry criterion in addition to the other criteria listed.

TABLE II. SGLT2 Inhibitor Clinical Trials and Associated Composite Kidney Results[a]

Medication	Clinical trial (publication year)	No.	Participants with type 2 diabetes, %	Median follow-up, y	Primary kidney outcome hazard ratio (95% CI)	HF hazard ratio (95% CI)
Canagliflozin	CREDENCE (2019)[19]	4,401	100	2.62	0.70 (0.59-0.82)	0.61 (0.47-0.80)
Dapagliflozin	Dapa-CKD (2020)[21]	4,094	67	2.4	0.61 (0.51-0.72)	0.71 (0.55-0.92)
Empagliflozin	EMPA-KIDNEY (2023)[20]	6,609	46	2.0	0.72 (0.64-0.82)	0.84 (0.67-1.07)

HF, heart failure; SGLT2, sodium-glucose cotransporter-2.

[a] All trials for which the percentage of patients with type 2 diabetes is 100% had type 2 diabetes as an entry criterion in addition to the other criteria listed.

Not only were such kidney-protective effects witnessed in patients with type 2 diabetes, but subsequent trials found similar benefits in patients without type 2 diabetes. In A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD), 67% of patients had type 2 diabetes, and 33% of patients did not.[21] A total of 89.5% of participants also had established CKD according to estimated glomerular filtration rate criteria. The Dapa-CKD trial found an overall significant relative risk reduction (RRR) of 39% for its primary outcome, a composite of sustained decline in estimated glomerular filtration rate of at least 50%, end-stage kidney disease, and death from kidney-related or cardiovascular causes.[21] Subgroup analysis, however, showed that the RRR of the primary outcome was greater for patients without type 2 diabetes (50%) than for patients with type 2 diabetes (36%). With regard to secondary end points, Dapa-CKD found a significant RRR of 29% for the composite of HF and death from cardiovascular causes. The EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trial, in which 46% of patients had type 2 diabetes as well as CKD, similarly showed that empagliflozin reduced patients' risk of the primary outcome—progression of kidney disease or death from cardiovascular causes—by 28% and their risk of the composite of HF and death from cardiovascular causes by 16%.[20]

Other trials have demonstrated that SGLT2 inhibitors also have cardioprotective effects in patients without type 2 diabetes (Table I).[15-18] In the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF), in which all patients had prevalent HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] ≤40%) and 45% of patients also had type 2 diabetes, the effects of dapagliflozin were similar across patients with and without type 2 diabetes, reducing their risk of the primary outcome (a composite of worsening HF and death from cardiovascular causes) by 26% and their risk of the composite of HF and death from cardiovascular causes by 25%.[15] The EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial of empagliflozin in patients with HFrEF, of whom 50% also had type 2 diabetes, similarly found a 35% RRR for the composite of HF and death from cardiovascular causes.[16] The effect of empagliflozin was similar for patients with type 2 diabetes (RRR, 28%) and for patients without type 2 diabetes (RRR, 22%). The EMPEROR-Reduced trial also showed that empagliflozin reduced the relative risk of HF by 30%.

Sodium-glucose cotransporter-2 inhibitors have also been shown to have cardioprotective effects in patients with HF with preserved or only mildly reduced LVEF, regardless of whether they have type 2 diabetes. In the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial of empagliflozin, 33% of patients had HF with a mildly reduced LVEF (LVEF >40% to <50%), and 67% of patients had HF with preserved LVEF (LVEF ≥50%).[17] Forty-nine percent of patients also presented with type 2 diabetes. EMPEROR-Preserved found a significant RRR of 21% for the primary outcome—a composite of HF and death from cardiovascular causes—and this benefit was similar for patients with type 2 diabetes (21%) and patients without type 2 diabetes (22%). Empagliflozin appeared less effective, however, in patients with higher LVEF. Patients with an LVEF between 40% and 50% had a significant risk reduction of 29%, and patients with an LVEF of at least 50% but less than 60% had a

significant risk reduction of 20%, whereas patients with an LVEF of at least 60% had a (noninferior) risk reduction of only 13%. The EMPEROR-Preserved trial also found a significant risk reduction of 27% for patients with HF. In the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial, 34% of patients had HF with a mildly reduced LVEF, and 66% of patients had HF with a preserved LVEF; 45% of patients presented with type 2 diabetes. The DELIVER trial found that dapagliflozin significantly reduced the risk of the primary outcome (RRR, 18%), a composite of worsening HF and cardiovascular death.[18] The effect was similar in patients with type 2 diabetes (RRR, 17%) and in patients without type 2 diabetes (RRR, 19%), but unlike EMPEROR-Preserved, the DELIVER trial showed that the beneficial effect of SGLT2 inhibitors may vary according to LVEF, although this association was not statistically significant. With regard to secondary end points, dapagliflozin significantly reduced patients' risk of HF (RRR, 23%).

These trials highlight not only the potential of SGLT2 inhibitors for preventive cardiovascular and kidney interventions but also their potential value in the active management of HF, CVD, and end-stage kidney disease.

Mechanism of Action

Multiple mechanisms of action have been proposed to explain how SGLT2 inhibitors confer cardiovascular protection. First, SGLT2 inhibitors are believed to improve ventricular loading conditions through their inherent natriuretic and diuretic effects.[22] Under normal physiologic conditions, SGLT2 reabsorbs most of the filtered glucose and sodium in the kidneys the proximal tubule. When SGLT2 inhibitors prevent this process, however, urinary excretion of both glucose and sodium increases. These phenomena are known as *glucosuria* and *natriuresis,* respectively. The net result of this action is augmented diuresis because water tends to follow the excreted sodium, leading to increased urine production and volume. The reduction in plasma volume improves preload and lessens ventricular wall stress.[23] A mediation analysis of the VERTIS CV trial notably observed that approximately 50% of the reduction in HF-related hospitalizations could be attributed to an ertugliflozin-mediated decrease in plasma volume.[24]

Sodium-glucose cotransporter-2 inhibitors may improve cardiac function by altering metabolic pathways.[10,25] It has been suggested that in patients taking SGLT2 inhibitors, augmented glucose elimination increases reliance on lipids and ketones for energy.[26] This "fuel shift" hypothesis proposes that by reducing glucose as a metabolic substrate, SGLT2 inhibitors may induce an adaptive response, leading to increased lipid and ketone oxidation. This could potentially enhance cardiac efficiency and function by providing a more efficient energy substrate for the heart because the myocardium can generate more adenosine triphosphate per oxygen molecule from fatty acids and ketones than from glucose.[27] This metabolic reprogramming could also potentially alleviate glucotoxicity, lipotoxicity, and insulin resistance, which are substantial contributing factors to the pathophysiology of both type 2 diabetes and HF. This dual mechanism of action might provide a plausible explanation for the cardiovascular benefits observed with SGLT2 inhibitors beyond their glucose-lowering effects.[27]

Finally, SGLT2 inhibitors may improve cardiovascular function by reducing adipose tissue in the epicardium, thus also reducing the amount of proinflammatory mediators that such tissues may release.[28] In patients with type 2 diabetes, studies have demonstrated a connection between epicardial adipose tissue and coronary heart disease through the release of proinflammatory mediators such as interleukin-6 and tumor necrosis factor α.[28] It should be noted, however, that although SGLT2 is not found in the heart, epicardial adipose tissue does express such transporters.[29] Studies have shown that dapagliflozin increases the uptake of glucose, reduces the secretion of inflammatory mediators, and enhances the differentiation of epicardial adipose tissue cells, thus providing another avenue through which SGLT2 inhibitors could exert cardioprotective effects.[29]

Cardiometabolic Effects

Even beyond their role in glycemic control, SGLT2 inhibitors confer benefits across a wide range of physiologic parameters, including blood pressure, body weight, lipid profiles, kidney effects, and arterial stiffness, and they have notable beneficial effects on cardiovascular outcomes (Fig. 1). By exerting these cardioprotective effects and improving glycemic control, SGLT2 inhibitors substantially lower weight in patients with type 2 diabetes.[30] Prior studies showed that patients treated with dapagliflozin lost an average of 3 kg, two-thirds of which was attributable to a reduction in body fat, over a 6-month period.[31] The mechanism by which such weight loss occurs can partly be attributed

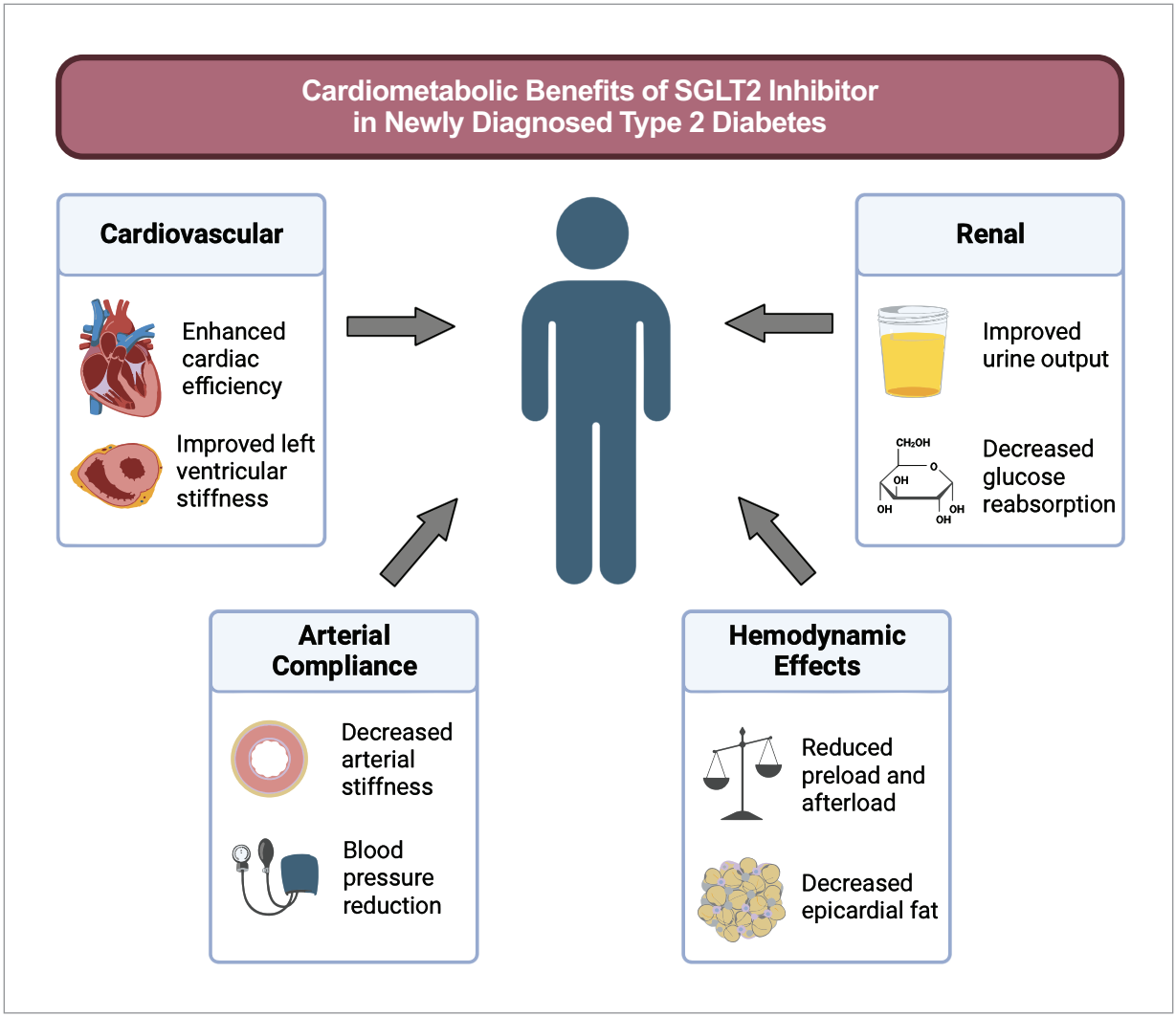

Fig. 1 Cardiometabolic benefits of SGLT2 inhibitors in the management of type 2 diabetes.

SGLT2, sodium-glucose cotransporter-2.

to calorie deficits as a result of glucosuria. When SGLT2 inhibitors block the reuptake of glucose into the bloodstream, caloric loss results, thus enhancing weight reduction. These effects therefore provide another possible mechanism for SGLT2 inhibitors' cardioprotective effects, with weight reduction potentially helping reduce the risk of CVD in patients with type 2 diabetes.[24]

Sodium-glucose cotransporter-2 inhibitors also reduce blood pressure in patients with type 2 diabetes. One meta-analysis showed that over 3 months, SGLT2 inhibitors reduced patients' average systolic blood pressure by 3.8 mm Hg.[32] Such reductions in blood pressure can be explained by 2 mechanisms. First, SGLT2 inhibitors have been observed to decrease both kidney and systemic arterial stiffness, physiologic factors associated with hypertension.[33] Second, SGLT2 inhibitors increase diuresis, thus decreasing intravascular volume and blood pressure. Coupled with an improved lipid profile characterized by a modest increase in high-density lipoprotein cholesterol and a decrease in triglycerides, these antihypertensive effects may augment the cardiovascular benefits of these drugs.[34]

Safety Concerns

Sodium-glucose cotransporter-2 inhibitors block the reabsorption of sodium and glucose, leading to glucosuria, which can be a nidus for infection.[35] Clinical trial data

suggest that patients who take SGLT2 inhibitors have more genital mycotic infections than patients on placebo. For example, both the EMPA-REG OUTCOME and EMPEROR-Preserved trials showed higher rates of genital mycotic infections in the empagliflozin group, and the EMPEROR-Preserved trial observed an elevated risk of urinary tract infections.[11,17]

Diabetic ketoacidosis (DKA) is a serious, potentially life-threatening complication primarily characterized by hyperglycemia. Key symptoms include increased urination, thirst, weight loss, and weakness.[14,36,37] Patients often experience gastrointestinal symptoms, as well, such as vomiting, abdominal pain, and nausea. Notably, euglycemic DKA is a variant in which patients, often treated with SGLT2 inhibitors, have normal glucose levels (<11.1 to 13.9 mmol/L [<200 to 250 mg/dL]), despite having DKA.[38] This condition arises from a combination of relative insulin deficiency and elevated counterregulatory hormones such as glucagon. It is commonly triggered by conditions such as fasting, infection, substance intoxication, liver disease, and SGLT2 inhibitor use, which involve reduced glucose availability and increased urinary glucose excretion.[36] Effective management of DKA involves replenishing fluids and electrolytes and administering insulin therapy because patients typically present with both dehydration and electrolyte imbalances.[37]

Several additional safety concerns require further attention and careful management. First, patients already receiving diuretic therapies may have volume depletion and hypotension, so any concomitant diuretic medications may require adjustment to prevent excessive volume depletion.[39] Second, in patients taking insulin or insulin secretagogues, SGLT2 inhibitors can cause hypoglycemia.[40] As a result, blood glucose levels should be carefully monitored after SGLT2 inhibitor use begins.[40]

Practical Considerations

Patients treated with SGLT2 inhibitors should be monitored for changes in kidney function, blood pressure, and glycemia.[41] In particular, although a modest decrease in estimated glomerular filtration rate is expected after initial SGLT2 inhibitor treatment, a trial discontinuation of SGLT2 inhibitors is suggested if serum creatinine rises more than 30% above baseline levels.[42] Patients treated concurrently with insulin and SGLT2 inhibitors are also at greater risk of hypoglycemia; additional caution is warranted, and glucose levels should be measured regularly.[41]

Multiple clinical trials have provided further evidence that SGLT2 inhibitors reduce HF risk for patients with type 2 diabetes. The DAPA-HF, EMPEROR-Preserved, DELIVER, and EMPEROR-Reduced trials have all shown that SGLT2 inhibitors are not merely preventive but cardioprotective, even in patients with established HF.[15-18] The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guideline for managing HF therefore gave SGLT2 inhibitors a class 1 recommendation for patients with symptomatic chronic HFrEF (Fig. 2), based primarily on the reductions in HF-related hospitalizations and cardiovascular mortality seen with these drugs.[43] For patients at high risk of HF (stage A HF) or pre-HF (stage B HF), the guideline similarly assigned SGLT2 inhibitors a class 1 recommendation. For patients with mildly reduced or preserved ejection fraction, the guideline assigned SGLT2 inhibitors a class 2a recommendation.

Patient-related financial burdens should also be considered when selecting an antihyperglycemic medication. At $500 to $600 per month, SGTL2 inhibitors may be prohibitively costly for some patients.[44] Studies have shown that with a cost per quality-adjusted life-year of $65,000 to $85,000, SGLT2 inhibitors have intermediate value, indicating moderate cost-effectiveness in patients with HFrEF and with or without type 2 diabetes.[43,45,46] It should be noted, however, that these studies suggest that in patients with HFrEF, cost-effectiveness decreases as HF severity increases.[45,47] Future studies should evaluate whether clinical risk scores and biomarkers can be used to identify which patients with type 2 diabetes may experience the greatest benefit from SGLT2 inhibitors.[48-50]

Conclusions

Evidence from an extensive body of clinical trials indicates that SGLT2 inhibitors have noteworthy cardiovascular and metabolic benefits, thereby establishing their value as a therapeutic option for patients with or at risk for CVD. Though the cardioprotective potential of SGLT2 inhibitors is promising, further research is necessary to fully

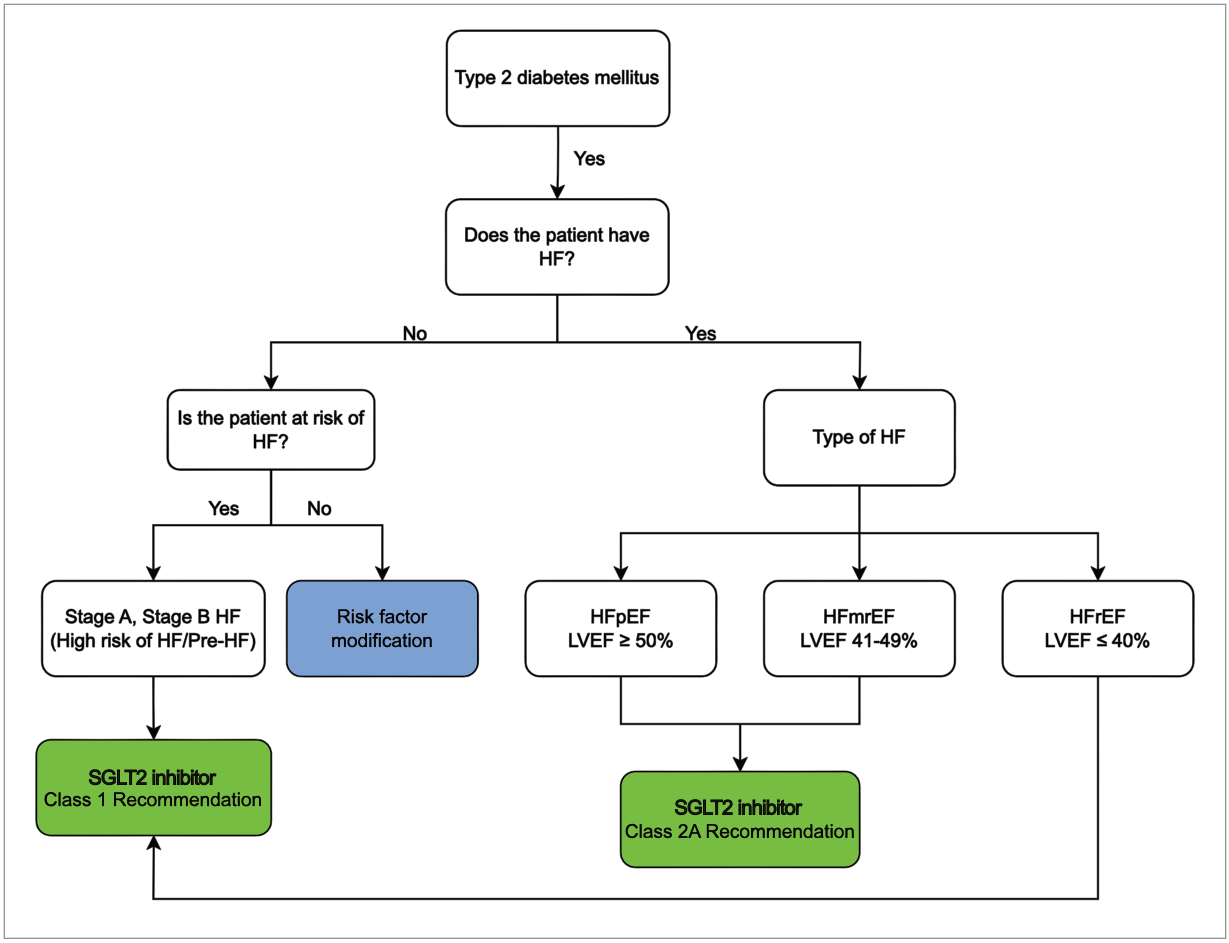

Fig. 2 Chart summarizes treatment recommendations for patients with type 2 diabetes who have established HF or are at risk of HF.

HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT-2, sodium-glucose cotransporter-2.

understand the underlying mechanisms driving these effects. The barriers to prescribing these agents must also be considered, including potential adverse effects and the financial burden associated with out-of-pocket costs for patients with type 2 diabetes. Indications for the use of SGLT2 inhibitors are nevertheless continuing to expand. As clinicians' understanding of this therapy evolves, it is anticipated that SGLT2 inhibitors will continue to play a central role in the management of type 2 diabetes and its attendant risk of CVD.

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