REVIEW ARTICLE

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Gliflozins in the Management of Cardiovascular Disease

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Although phlorizin was first isolated from the bark of the apple tree by Petersen in 1835,[1] it was not until a half century later that it was discovered by von Mering to have glucosuric properties.[2] In the 1980s, it was learned that the glucosuria resulted from phlorizin's inhibition of glucose reabsorption by the renal tubules, which reduced blood glucose concentrations in rats with diabetes.[3] Phlorizin consists of glucose and two joined aromatic rings, is poorly absorbed, and requires parenteral administration to elicit a robust glucosuric response.

The reabsorption of glucose from the glomerular filtrate is an active process, which is linked to sodium and requires a carrier protein, referred to as a sodium–glucose cotransporter (SGLT). Two isoforms of SGLT have been described: SGLT1, which is located primarily in the small intestine, with little effect on the renal tubule; and SGLT2, which is the subject of this review. SGLT2 has low-affinity and high-capacity properties[4] and is found almost exclusively in the epithelial cells of the proximal renal tubule, where it is responsible for more than 90% of glucose reabsorption and 65% of sodium reabsorption. The SGLTs are coupled to accessory protein MAP17, which is required for glucose transport, and are encoded by genes in the *SLC5A* family.[5]

In the 1990s, Tsujihara et al., working at Tanabe Seiyaku, a Japanese pharmaceutical company, studied a variety of phlorizin derivatives.[6] The company developed an orally absorbed SGLT2 inhibitor, the first synthetic SGLT2 inhibitor that reduced hyperglycemia in rats with diabetes.[7] In 1999, Oku et al. suggested that this inhibitor could represent a new approach to the treatment of type 2 diabetes.[8] Several other pharmaceutical companies then began to develop SGLT2 inhibitors.[9] Clinical trials showed that this class of drugs, also referred to as gliflozins, was safe, reduced glycated hemoglobin levels by approximately 0.5 to 1.1%,[10] and — because the drugs are not insulin-dependent — did not cause hypoglycemia unless administered with other glucose-lowering agents. Between 2012 and 2017, the Food and Drug Administration (FDA) and the European Medicines Agency approved canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin for reducing hyperglycemia in patients with type 2 diabetes.

In 2008, before the approval of the SGLT2 inhibitors, concern about the cardiovascular safety of rosiglitazone, a popular antidiabetic agent,[11] led the FDA to issue a Guidance for Industry recommending that sponsors of new or recently approved antidiabetic agents "demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."[12] To satisfy this requirement, a number of large clinical outcome trials were conducted to evaluate such agents, including SGLT2 inhibitors, which had important actions on the heart and kidneys. This article reviews the actions of SGLT2 inhibitors and their implications.

CARDIOVASCULAR OUTCOME TRIALS

PATIENTS WITH DIABETES AND ARTERIOSCLEROTIC CARDIOVASCULAR DISEASE

The relationship between type 2 diabetes and both coronary artery disease and renal disease is well established.[13] The first completed large clinical outcome

trial of an SGLT2 inhibitor in patients with type 2 diabetes, the EMPA-REG OUTCOME trial, compared empagliflozin with placebo in 7020 patients with cardiovascular disease.[14] The primary end point was major adverse cardiac events (i.e., death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). Not only was empagliflozin shown to be safe, but it also appeared to be cardioprotective. The hazard ratio in the empagliflozin group, as compared with the placebo group, was reduced (hazard ratio, 0.86, 95% confidence interval [CI], 0.74 to 0.99) (Table 1). The risks of prespecified secondary end points were all reduced significantly as well, including cardiovascular death (by 38%); also reduced significantly were the risk of hospitalization for heart failure (by 35%) and all-cause death (by 32%). These reductions were observed across a broad spectrum of heart-failure risks, with significant beneficial effects observed as early as 2 to 3 weeks after the start of therapy. These favorable results were quite surprising to both the endocrine and cardiology communities, but the prevention of hospitalization for heart failure was soon and repeatedly confirmed.

The CANVAS Program, comprising the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), evaluated canagliflozin in 10,142 patients, two thirds of whom had a history of cardiovascular disease.[15] The primary end point was major adverse cardiac events, which were significantly reduced (hazard ratio, 0.86; 95% CI, 0.75 to 0.97 (Table 1). This benefit was observed across a broad range of subgroups defined by baseline glycated hemoglobin level, presence or absence and severity of albuminuria, and duration and intensity of treatment for type 2 diabetes.[21] Of the various prespecified secondary end points, hospitalization for heart failure showed the greatest reduction (hazard ratio, 0.67; 95% CI, 0.52 to 0.87), a directional effect that was subsequently observed in all the clinical cardiovascular outcome trials with SGLT2 inhibitors.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial enrolled 4401 patients with type 2 diabetes and arteriosclerotic cardiovascular disease with associated albuminuric renal disease.[16] CREDENCE was primarily a renal outcome trial (see below), but the cardiovascular outcomes are included here. The prespecified cardiovascular end points were all reduced significantly: major adverse clinical events (hazard ratio, 0.80; 95% CI, 0.67 to 0.95), hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80), and the combination of hospitalization for heart failure or cardiovascular death (hazard ratio, 0.69; 95% CI, 0.57 to 0.83) (Fig. 1).

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial enrolled 17,160 patients who had or were at risk for atherosclerotic cardiovascular disease.[17] This trial had the lowest-risk study population of any of the cardiovascular outcome trials. Dapagliflozin did not reduce cardiovascular adverse events, one of the coprimary end points, but did result in a lower rate of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.83; 95% CI, 0.73 to 0.95) (Fig. 1). The rates of cardiovascular death and death from any cause were significantly reduced among patients at high risk, which included patients with heart failure and a reduced ejection fraction[22] and patients with previous myocardial infarction.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) randomly assigned 8246 patients with type 2 diabetes and established atherosclerotic cardiovascular disease to ertugliflozin or placebo.[18] No significant effect on cardiovascular death was observed. However, there was a significant reduction in first hospitalizations for heart failure (hazard ratio, 0.70; 95% CI, 0.54 to 0.90) (Table 1).

McGuire et al. conducted a meta-analysis of the five placebo-controlled, double-blind outcome trials of SGLT2 inhibitors in patients with type 2 diabetes that are summarized above.[20] A total of 46,969 patients with type 2 diabetes, of whom 31,116 had arteriosclerotic cardiovascular disease, were randomly assigned to a study group. As shown in Table 1, significant reductions were noted in major adverse cardiac events, cardiovascular death, and hospitalization for heart failure.[20,23]

In contrast to the SGLT2 inhibitors discussed above, sotagliflozin inhibits both SGLT1 and SGLT2. SGLT1 acts in part by slowing intestinal absorption of glucose, which may cause mild diarrhea. It has been studied in two placebo-controlled trials involving patients with type 2 diabetes. The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial enrolled 1222 patients who had recently been hospitalized for decompensated heart fail-

Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE–TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.[14]; CANVAS Program, Neal et al.[15]; CREDENCE, Perkovic et al.[16]; DECLARE–TIMI 58, Wiviott et al.[17]; VERTIS CV, Cannon et al.[18]; and SCORED, Bhatt et al.[19] Data are also based on a meta-analysis by McGuire et al.[20]

† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

ure (Table 2).[27] Treatment was begun very early — either in the hospital or 2 days after discharge. The primary end point, a composite of cardiovascular death, hospitalization for heart failure, or urgent visits for heart failure, was reduced in the sotagliflozin group (hazard ratio, 0.67; 95% CI, 0.52 to 0.85). The Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial enrolled 10,584 patients with type 2 diabetes and chronic kidney disease who were at risk for arteriosclerotic cardiovascular disease (Table 1).[19] The primary end point, the same as for SOLOIST-WHF, was reduced significantly (hazard ratio, 0.74; 95% CI, 0.63 to 0.88) (Fig. 1). The total numbers of myocardial infarctions and strokes were also reduced.

PATIENTS WITH HEART FAILURE

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial[24] addressed two critically important issues: although heart failure was present in a fraction of the patients who were studied in the aforementioned trials, DAPA-HF was limited to patients who had heart failure with ejection fractions below 40%; 55% of the 4744 patients enrolled did not have type 2 diabetes. The patients randomly assigned to dapagliflozin had significant reductions in cardiovascular death or hospitalization for heart failure (the primary end point) (hazard ratio, 0.74; 95% CI, 0.65 to 0.85) and a significant (31%) reduction in hospitalization for heart failure. All-cause mortality and outpatient worsening of heart failure were also reduced.[28,29] The improvements were similar in patients with and in those without type 2 diabetes, indicating that the cardiovascular benefits of the SGLT2 inhibitor were independent of its glucose-lowering properties.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) had a design that was similar to the DAPA-HF design but enrolled patients with more severe systolic dysfunction.[30] Again, the cardiac benefit was observed both in patients with and in those without type 2 diabetes. The benefit was also seen across a spectrum of risk for heart failure, level of N-terminal pro–B-type natriuretic peptide (NT-proBNP), renal function, and glucose level at baseline.[31] A meta-analysis involving the 8474 patients in the DAPA-HF

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

* Data sources for the trials are as follows: DAPA-HF, McMurray et al.[24]; EMPEROR-Reduced, Packer et al.[25]; EMPEROR-Preserved, Anker et al.[26]; SOLOIST-WHF, Bhatt et al.[27] The abbreviation eGFR denotes estimated glomerular filtration rate, LVEF left ventricular ejection fraction, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

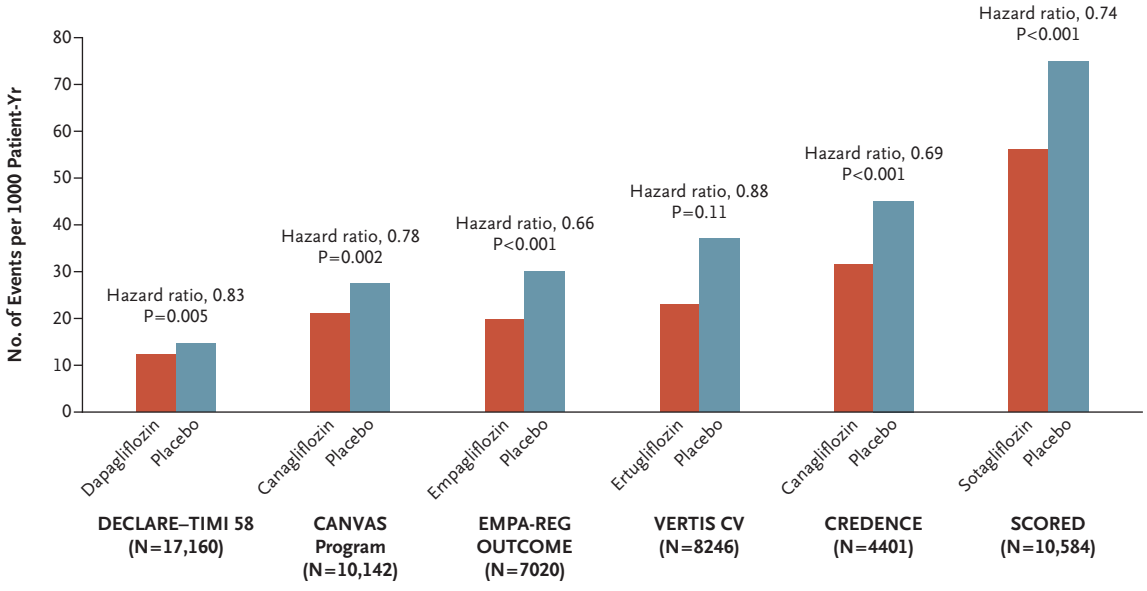

Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.

Outcomes are shown in ascending order of frequency from left to right. Data sources for the six trials are as follows: DECLARE–TIMI 58, Wiviott et al.[17]; CANVAS Program, Young et al.[21]; EMPA-REG OUTCOME, Zinman et al.[14]; VERTIS CV, Cannon et al.[18]; CREDENCE, Perkovic et al.[16]; and SCORED, Bhatt et al.[19]

and EMPEROR-Reduced trials showed that the primary end point, hospitalization for heart failure or cardiovascular death, was reduced significantly and almost identically among patients with and those without type 2 diabetes.[32]

In industrialized nations, approximately half of patients with heart failure have a preserved ejection fraction.[33] A number of drugs have been evaluated in such patients but have not improved cardiac function. However, two trials, one with a mineralocorticoid antagonist[34,35] and the other with sacubitril–valsartan, an angiotensin receptor–neprilysin inhibitor,[36] have provided encouraging, but not definitive, results. The SOLOIST-WHF trial[27] showed an improvement in the primary outcome (see above) in the group of 250 patients with diabetes and a preserved ejection fraction who were randomly assigned to sotagliflozin.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejec-

tion Fraction (EMPEROR-Preserved), which enrolled 5988 patients with an ejection fraction of 40% or higher, was the largest placebo-controlled trial dedicated to this condition.[25,26] The patients were treated with beta-blockers, inhibitors of the renin–angiotensin–aldosterone system, and statins. In the group of patients randomly assigned to empagliflozin, the primary end point, cardiovascular death or hospitalization for heart failure, was reduced (hazard ratio, 0.79; 95% CI, 0.69 to 0.90), as was the secondary end point of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88). The benefits of empagliflozin were almost identical in patients with and in those without type 2 diabetes.[25] A pooled analysis of the effects of empagliflozin in the EMPEROR-Reduced and EMPEROR-Preserved trials showed a benefit across the spectrum of ejection fractions from <25% to 65%.[37] The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial (ClinicalTrials.gov number, NCT03619213) is studying the effect of dapagliflozin in patients with a left ventricular ejection fraction above 40%.[38] Results are expected shortly.

PATIENTS WITH KIDNEY DYSFUNCTION

Diabetic kidney disease occurs in approximately 40% of patients with type 2 diabetes and is the leading cause of chronic kidney disease.[39] The EMPA-REG OUTCOME trial[14] was the first to show a significant reduction in the development or worsening of kidney function,[40] defined as the composite of a doubling of the serum creatinine level, an increase in albuminuria, initiation of renal replacement therapy, or death due to kidney disease. This end point was reduced (hazard ratio, 0.61; 95% CI, 0.53 to 0.70). Beneficial effects of empagliflozin on the kidneys were also observed across the spectrum of kidney function in the EMPEROR-Reduced trial.[30,31] Although the administration of empagliflozin produced an initial dip in the estimated glomerular filtration rate (eGFR), it was followed by a slowing in the decline, as compared with placebo.[41] This transient dip has been observed with other SGLT2 inhibitors as well and has not led to safety concerns.[42]

In the CANVAS Program,[15] canagliflozin was similarly associated with a reduced decline in the eGFR and a reduction in albuminuria.[43] CREDENCE was the first large clinical outcome trial in which the primary end point was kidney function.[16] Patients with type 2 diabetes, an average eGFR of 56.2 ml per minute per 1.73 m^2 of body-surface area, and an elevated albumin:creatinine ratio were enrolled in the study. The primary composite kidney outcome was reduced (hazard ratio, 0.70; 95% CI, 0.59 to 0.82), as was albuminuria. The DECLARE–TIMI 58 trial[17] evaluated patients with type 2 diabetes earlier in the course of their kidney disease. Nevertheless, the renoprotection provided by dapagliflozin was similar to that observed with empagliflozin and canagliflozin in patients with more severe renal dysfunction.[44]

A meta-analysis of these four clinical end point trials (EMPA-REG OUTCOME, CANVAS Program, CREDENCE, and DECLARE–TIMI 58),[45] involving 38,723 patients with type 2 diabetes, showed that as compared with patients receiving placebo, those who received SGLT2 inhibitors had a significant reduction in the risk of progression to dialysis, transplantation, or death due to kidney disease (relative risk, 0.67; 95% CI, 0.52 to 0.86). This benefit was observed in all four trials, irrespective of the baseline eGFR and across a wide range of urinary albumin:creatinine ratios, and it was independent of the glycemic effect. In the aforementioned trials limited to patients with heart failure and a reduced ejection fraction,[24,30] the improvement in the composite kidney outcomes was similar in patients with and in those without type 2 diabetes. This finding led to a dedicated kidney outcome trial, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD).[46] At baseline, the patients had a mean eGFR of 43 ml per minute per 1.73 m^2 and a median urinary albumin:creatinine ratio of 949 (with albumin measured in milligrams and creatinine in grams); one third of the patients did not have type 2 diabetes. The composite kidney end point was reduced (hazard ratio, 0.56; 95% CI, 0.45 to 0.68), as was all-cause mortality. Again, the beneficial effects of dapagliflozin were similar in the patients with and in those without type 2 diabetes and were independent of the presence or absence of cardiovascular disease and glucose lowering. On March 16, 2022, the EMPA-KIDNEY trial (NCT03594110) was stopped early on the basis of recommendations from the data monitoring committee because of "clear positive efficacy."[47] The trial involved more than 6000 adults, with or without diabetes, who had chronic kidney disease attributed to a wide range of underlying causes. However, it should be noted that the EMPEROR-Preserved trial, which showed the

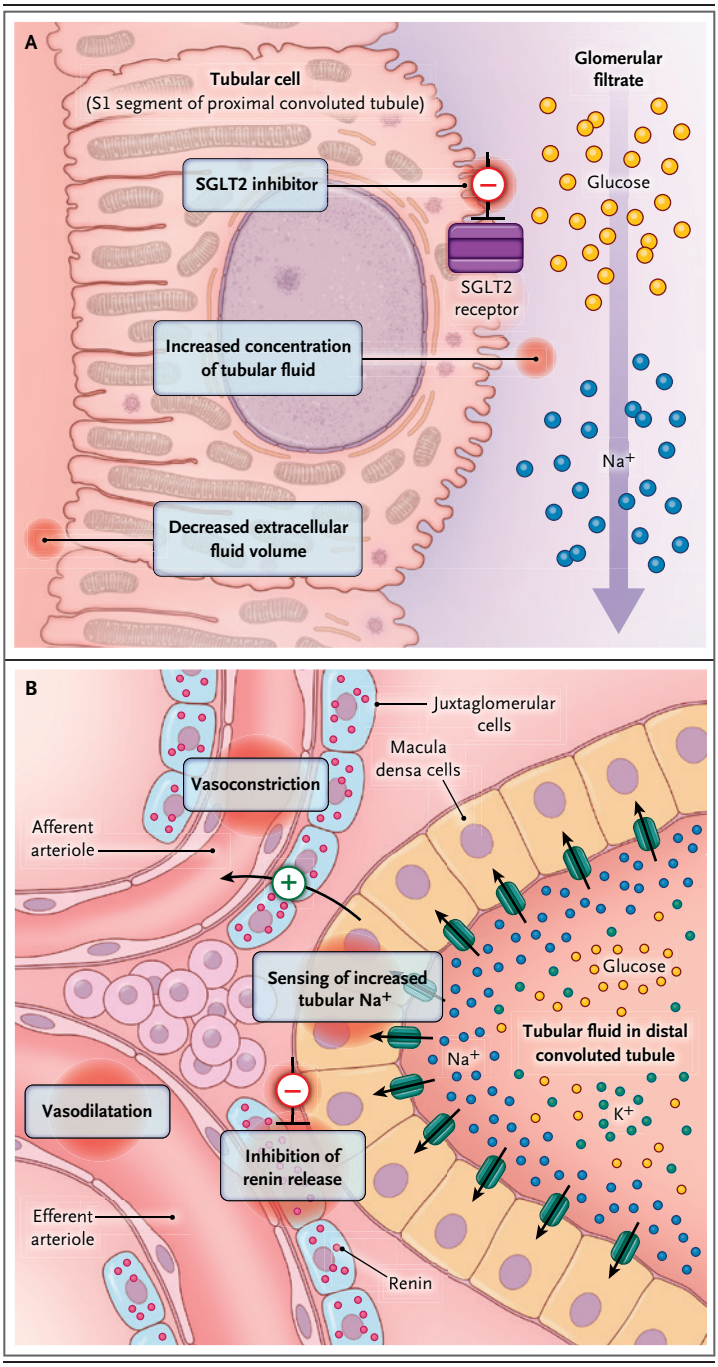

Figure 2. Effects of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibition.

Panel A shows inhibition of SGLT2, with excretion of glucose and sodium ions (Na^+) in the urine. As a result of loss of Na^+, the extracellular fluid volume contracts, which may result in vasoconstriction of the afferent arterioles. Because glucose reabsorption is coupled to Na^+ absorption, the macula densa senses an increased Na^+ concentration, as shown in Panel B, increasing the activation of the tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole, which is driven primarily by adenosine-mediated signal cascades. The macula densa inhibits the release of renin from the juxtaglomerular cells, enhancing the dilatation of the efferent arteriole. Vasoconstriction of the afferent arterioles and vasodilatation of the efferent arterioles reduce the glomerular filtration rate. The reduction of intraglomerular hydrostatic pressure represents the renoprotective effect of this drug class. K^+ denotes potassium ion. Modified from Zelniker and Braunwald.[49]

beneficial effect of empagliflozin on cardiovascular end points in patients with heart failure and a preserved ejection fraction,[30] did not show a benefit with respect to kidney function.[48]

MECHANISMS OF ACTION

RENAL ACTION

In patients with type 2 diabetes, the hyperabsorption of glucose and sodium in the proximal renal tubules by SGLT2 causes afferent arteriolar vasodilatation[49] (Fig. 2), which causes glomerular hyperfiltration, leading to glomerular inflammation, fibrosis, and ultimately, diabetic kidney disease. The reduction of reabsorption of sodium increases the sodium concentration at the macula densa, specialized cells in the distal renal tubules adjacent to the glomeruli. Tubuloglomerular feedback activates adenosine receptors, which constrict the afferent glomerular arterioles. This constriction reduces glomerular hyperfiltration and thereby reduces further renal damage. SGLT2 inhibitors block the renal sodium–hydrogen exchanger 3, which enhances diuresis of sodium and glucose.[50,51] SGLT2 inhibitors also reduce tubular work and oxygen requirements; they thereby reduce the damage associated with hypoxic tubular cells and enhance renal erythropoietin production.[52]

CARDIAC ACTIONS

The fundamental mechanisms responsible for the beneficial cardiac effects of SGLT2 inhibitors are not clear; there appear to be a number of possibilities (Fig. 3). In many forms of heart failure, a reduction of cardiomyocyte ATP production is observed as a result of reduced mitochondrial glucose oxidation (Fig. 4).[50,53] SGLT2 inhibition raises circulating ketone levels, an effect that appears to improve mitochondrial function, increase the production of ATP, and enhance ventricular contractile performance.[54]

The sodium concentration in cardiomyocytes is increased in many forms of heart failure, and

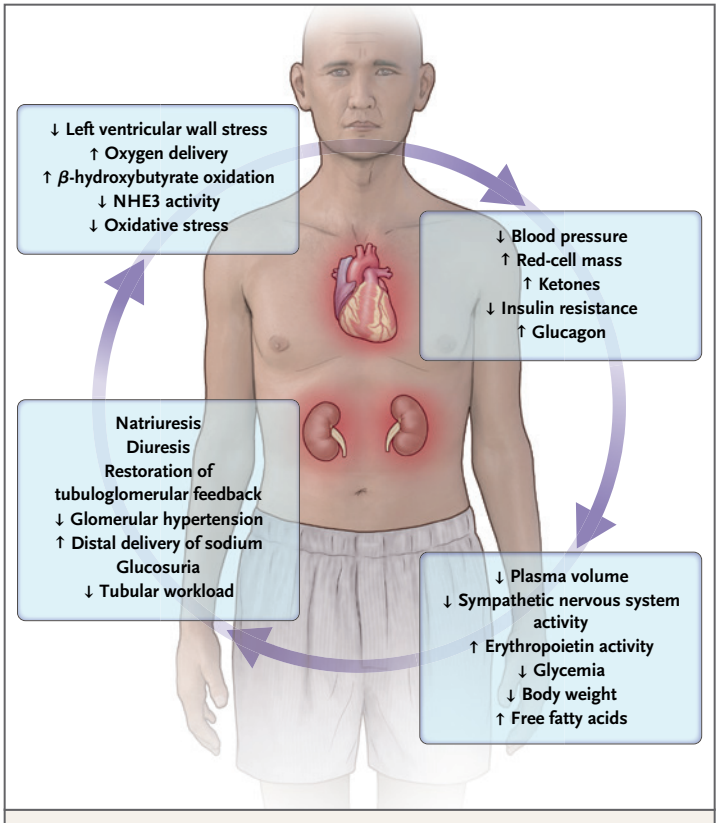

Figure 3. The Kidney–Heart Connection for Organ Protection by SGLT2 Inhibitors.

NHE3 denotes sodium–hydrogen exchanger 3. Modified from Tuttle et al.[39]

this increase may contribute to altered calcium handling, which in turn may lead to changes in contraction and arrhythmias. SGLT2 inhibitors reduce the activity of the sarcolemmal sodium–hydrogen exchanger 1,[55,56] the late inward sodium current,[57] and calcium–calmodulin–dependent protein kinase II, which impairs cardiomyocyte contraction and relaxation.[57]

Inflammation is frequently present in heart failure and can cause cardiac fibrosis.[58,59] SGLT2 inhibitors can attenuate activation of the nucleotide-binding domain–like protein 3, which stimulates inflammatory responses in experimental models of heart failure.[60] Carotid-artery plaques obtained at atherectomy from patients treated with an SGLT2 inhibitor show reduced inflammation and an increased collagen content.[59] Oxidative stress may impair mitochondrial function in both cardiomyocytes and endothelial cells and can cause intracellular accumulation of sodium.[61] SGLT2 inhibitors reduce free radical formation of human cardiomyocytes, thereby enhancing systolic and diastolic function.[58] By inhibiting proinflammatory–oxidative pathways, SGLT2 inhibitors improve coronary endothelial function and enhance flow-mediated vasodilatation.[62,63]

In many patients with type 2 diabetes, the aorta, coronary arteries, and ventricles are surrounded by excessive epicardial adipose tissue, which can release proinflammatory mediators that may impair ventricular function.[64] SGLT2 inhibitors reduce this adipose tissue, body weight, waist circumference, visceral and central adiposity, and extracellular volume,[65,66] reducing aortic stiffness[63] and myocardial fibrosis. It is not clear which of these several potential mechanisms are of the greatest importance in the improved cardiac performance that is observed with SGLT2 inhibitors.

CLINICAL IMPLICATIONS

ADVERSE EVENTS

The most common adverse effects of SGLT2 inhibitors are mycotic genital infections, which are related to the glucosuric action of these agents and occur more frequently in women than in men.[50] Less common adverse effects are urinary tract infections and pyelonephritis. Diabetic ketoacidosis, which is relatively uncommon, may occur, particularly in elderly patients with volume depletion. The disorder may be precipitated by an acute illness or fasting and may be accompanied by serious hypotension.[67] Diabetic ketoacidosis is characterized by an accumulation of ketone bodies, principally hydroxybutyric acid.[68] A form of ketoacidosis in patients receiving SGLT2 inhibitors is euglycemic ketoacidosis, which is not accompanied by a markedly elevated blood glucose levels.[69]

A doubling of the incidence of lower-limb amputations and an increase in bone fractures were noted with canagliflozin in the CANVAS Program.[15] However, these complications were not observed in the CREDENCE trial,[16] which also studied canagliflozin, and they have not been reported with other SGLT2 inhibitors.

OTHER CLINICAL OUTCOMES

Diabetic kidney disease accelerates atherosclerotic cardiovascular disease, hypertension, and heart failure.[13] The favorable results of SGLT2 inhibition in some patients who have chronic kidney disease in the absence of type 2 diabetes, described above, are promising.[70]

In the DECLARE–TIMI 58 trial,[17] dapagliflozin was associated with a reduction in atrial fibrilla-

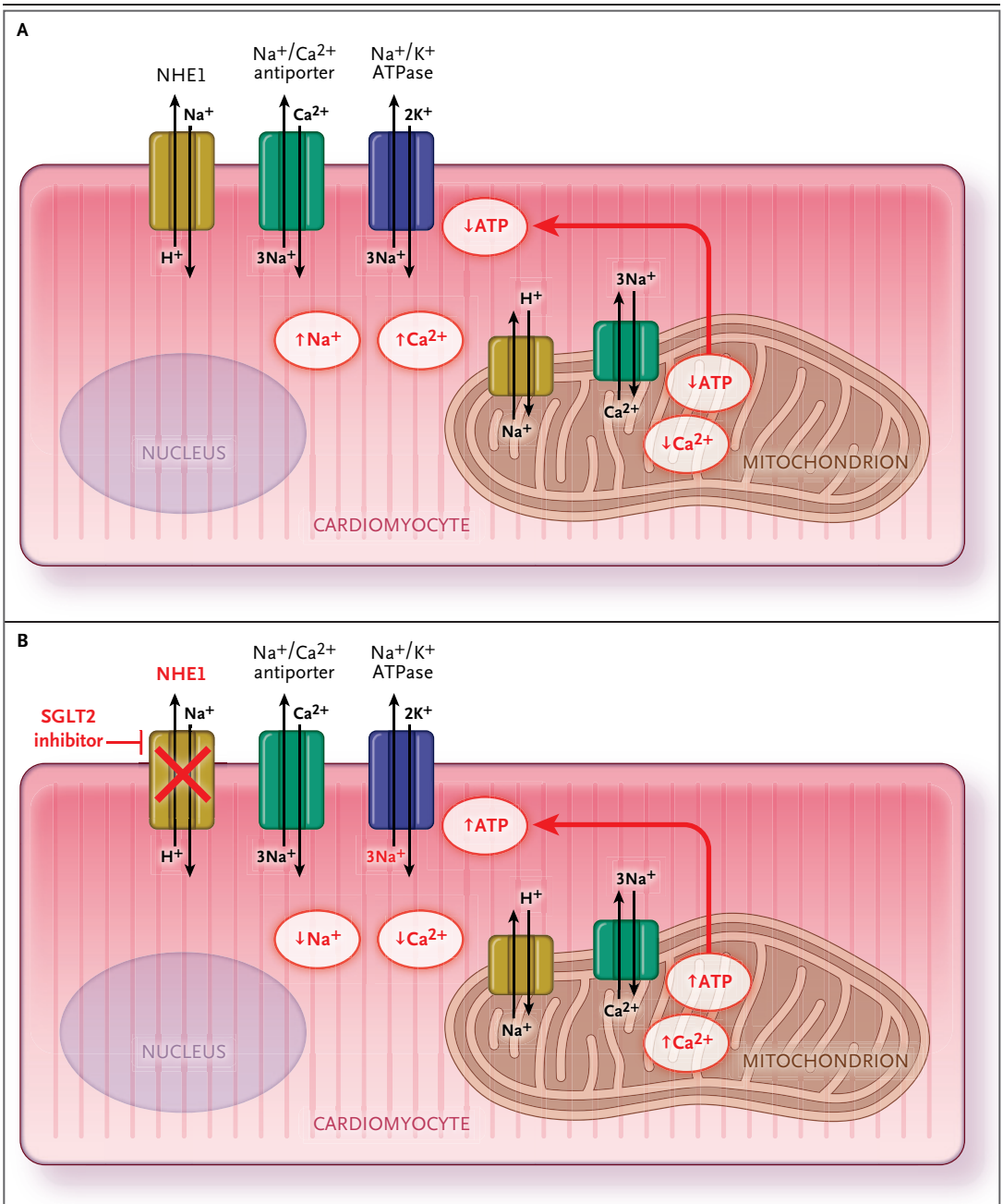

Figure 4. Direct Effects of SGLT2 Inhibitors on the Cardiomyocyte.

Panel A shows that conditions such as heart failure and type 2 diabetes mellitus increase the expression of sodium–hydrogen exchanger 1 (NHE1) and result in increased cytosolic Na^+ and calcium ion (Ca^{2+}) concentrations but reduced mitochondrial Ca^{2+} and mitochondrial ATP generation. Panel B shows that SGLT2 inhibition of cardiac NHE1 reduces cytoplasmic Na^+ and Ca^{2+} levels and increases mitochondrial Ca^{2+} levels, resulting in improved mitochondrial respiration (as well as increased ATP production) and viability of cardiomyocytes. Modified from Uthman et al.[53] and Zelniker and Braunwald.[50]

tion or atrial flutter (hazard ratio, 0.81; 95% CI, 0.68 to 0.95).[71] In the DAPA-HF trial,[24] dapagliflozin was associated with a reduction in ventricular arrhythmias, resuscitated cardiac arrest, or sudden death (hazard ratio, 0.73; 95% CI, 0.63 to 0.99).[72] In a meta-analysis of 34 randomized, controlled trials, SGLT2 inhibitors were also associated with significant reductions in atrial

arrhythmias (odds ratio, 0.81; 95% CI, 0.69 to 0.95) and sudden cardiac death (odds ratio, 0.72; 95% CI, 0.54 to 0.97).[73]

In a meta-analysis of 43 randomized, placebo-controlled trials involving 22,528 patients with type 2 diabetes, randomized assignment to an SGLT2 inhibitor was associated with modest but significant reductions in arterial pressure (by an average of 2.5 mm Hg systolic and 1.5 mm Hg diastolic), with no increase in heart rate.[74] Another reported benefit of SGLT2 inhibitors is the mitigation of anemia (presumably through stimulation of erythropoiesis), which improves oxygen delivery to the heart[75]; empagliflozin has also been reported to reduce the risk of obstructive sleep apnea.[76]

SGLT2 Inhibitors Combined with Other Drugs

Glucagon-like peptide 1 receptor agonists are effective hypoglycemic agents with beneficial cardiovascular effects.[77] A meta-analysis of five placebo-controlled trials showed that these drugs reduced the composite end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke among patients with established atherosclerotic cardiovascular disease (hazard ratio, 0.88; 95% CI, 0.84 to 0.94). However, these agents did not consistently reduce hospitalization for heart failure.[78] The combination of an SGLT2 inhibitor and a glucagon-like peptide receptor agonist appears to be safe and has an additive action in reducing glycated hemoglobin levels and possibly other end points as well.[79,80] However, the current cost of this drug combination may limit its use. In the DAPA-HF[24] and EMPEROR-Reduced[30] trials, the combination of an SGLT2 inhibitor with sacubitril–valsartan was associated with additive effects and acceptable adverse-event rates.[81,82]

Practice Guidelines

In 2022, for patients with type 2 diabetes and established arteriosclerotic cardiovascular disease, multiple risk factors, or diabetic kidney disease, the American Diabetes Association recommended treatment with an SGLT2 inhibitor, a glucagon-like peptide 1 receptor agonist, or both to reduce the risk of a major adverse cardiovascular event.[83] The 2021 guidelines of the European Society of Cardiology[84] and the 2022 guidelines of the American Heart Association[85] for the treatment of heart failure made similar recommendations.

The FDA has approved empagliflozin to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, irrespective of the ejection fraction.[86] The FDA's approval of dapagliflozin was similar but was limited (at the time of this writing) to patients with a reduced ejection fraction. Canagliflozin has been approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. A detailed review has identified SGLT2 inhibitors as early first-line therapy in patients with newly diagnosed heart failure and a reduced ejection fraction.[87] Dapagliflozin and canagliflozin have also been approved by the FDA for reducing the risk of end-stage kidney disease.

ClincialTrials.gov lists more than 20 ongoing phase 3 trials of SGLT2 inhibitors. These include studies of empagliflozin (NCT04509674) and dapagliflozin (NCT04564742) after myocardial infarction.

Conclusions

SGLT2 inhibitors are responsible for major paradigm shifts in the care of patients with or at high risk for heart failure, progression of chronic kidney disease, or both. SGLT2 inhibition improves cardiovascular outcomes in patients with heart failure over a wide range of ejection fractions, regardless of whether the patients have type 2 diabetes. In addition to having glucosuric and natriuretic properties, these agents also reduce the risk of end-stage kidney disease in patients with type 2 diabetes and chronic kidney disease.

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