that involves metabolic reprogramming. This is a novel alternative treatment that adds to the armamentarium of heart failure management. More work is needed to define the exact role of SGLT2 inhibitors and expand the treatment options for heart failure. Nonetheless, the article by Mann and Lehrke opens up an intriguing pathway that can serve

as a springboard for other potentially important metabolic interventions for heart failure.

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See Article page 895.

Commentary: SGLT2 inhibitors reduce mortality and heart failure in patients with type 2 diabetes mellitus—is metabolic reprogramming the mechanism for these favorable outcomes?

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In patients undergoing coronary artery bypass graft surgery, the use of intravenous insulin infusions to maintain serum glucose <180 mg/dL has been shown to decrease mortality, deep sternal wound infections, atrial and ventricular arrhythmias, the need for inotropic support, and intensive care unit and hospital length of stay.¹⁻³ Maintaining serum glucose <180 mg/dL in the perioperative period following coronary artery bypass graft surgery is now a class I recommendation in the Society of Thoracic Surgeons guidelines for glycemic control during cardiac surgery.⁴ However, recent studies have shown that tight glycemic control with intensive insulin therapy in the absence of myocardial ischemia may not be beneficial for all patients with diabetes, especially those with type 2 diabetes mellitus (T2DM), and may even be harmful.⁵ Insulin resistance, hyperglucagonemia, incretin

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Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Feb 28, 2021; revisions received Feb 28, 2021; accepted for publication March 2, 2021; available ahead of print March 5, 2021.

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J Thorac Cardiovasc Surg 2022;164:901-4
0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2021.03.005>

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CENTRAL MESSAGE

Metabolic reprogramming may be the mechanism by which SGLT2 inhibitors reduce mortality and heart failure in patients with type 2 diabetes mellitus.

deficiency or resistance, and increased renal glucose reabsorption have all been linked to the increased incidence of cardiovascular disease following insulin therapy in patients with T2DM.⁶ Older, noninsulin glucose-lowering therapies have been associated with weight gain, hypertension, the risk of hypoglycemia, and edema due to the retention of salt and water.⁷ This has prompted the development of newer glucose-lowering medications targeting novel pathways to reduce cardiovascular and renal events in patients with T2DM.

One of these new diabetic agents is the sodium glucose transporter 2 inhibitor (SGLT2i). In patients with T2DM, there is an increased upregulation of sodium-glucose co-transporter-2 (SGLT2) transporters in the proximal renal tubule, which increases the reabsorption of glucose.⁸ When serum glucose exceeds 200 to 250 mg/dL, sodium-glucose linked transporters (SGLTs) become saturated, and glucose is excreted in the urine. The inhibition of SGLT2 using SGLT2i lowers this threshold so that less glucose is reabsorbed. Since the glucose-lowering effects

of SGLT2i are partially dependent on the serum glucose concentration, the risk of hypoglycemia, unlike insulin, is very low.

Several large-scale trials were undertaken to determine the safety of this new class of glucose-lowering agents. Unexpectedly, these studies also found that SGLT2i reduced the incidence of adverse cardiovascular outcomes. The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial studied the effects of the SGLT2 inhibitor empagliflozin in 7020 patients with T2DM and established atherosclerotic cardiovascular disease.⁹ Patients who received empagliflozin had a 14% reduction ($P = .04$) of the composite end point of myocardial infarctions (MIs), strokes, and cardiovascular death, with a 38% reduction in cardiovascular death, a 32% reduction in all-cause death, and a 32% reduction in the incidence of hospitalization for heart failure (HF). A post-hoc analysis of this trial revealed that patients randomized to empagliflozin had a decreased incidence of cardiovascular events irrespective of a history of HF, MIs, stroke, or left ventricular hypertrophy.¹⁰

In the CANVAS (Canagliflozin Cardiovascular Assessment Study) study, the SGLT2 inhibitor canagliflozin decreased the risk of hospitalization for HF by 32%, cardiovascular death by 17%, and all death by 15%.¹¹ In the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in MI 58) trial, dapagliflozin significantly ($P = .005$) reduced the composite risk of cardiovascular death and hospitalization for HF primarily by lowering the rate of hospitalization for HF by 27%.¹² A meta-analysis of these 3 trials showed that the beneficial effects of SGLT2i were confined to patients who already had established atherosclerotic cardiovascular disease.¹³ Patients with worse baseline renal function tended to derive greater reductions in HF with SGLT2i agents. Surprisingly, SGLT2i agents had only a modest glucose-lowering effect (0.5%-1% reduction in HbA1c), and a slight reduction in body weight (2-3 kg) and systolic blood pressure (3-5 mm Hg).^{9,11,14}

Two additional SGLT2i trials targeted specific T2DM patient populations. In the CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trial, involving 4402 patients with T2DM, canagliflozin decreased the composite end point of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death by 30%.¹⁵ There was a 22% reduction in cardiovascular death ($P = .05$) and a 31% reduction in the composite end point of cardiovascular death and hospitalization for HF ($P < .001$). In the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, the effects of dapagliflozin were studied in 4744 patients with HF with and without T2DM.¹⁶ Dapagliflozin significantly reduced the risk of cardiovascular death and HF by 26% ($P < .0001$), with an 18% reduction in

cardiovascular death ($P = .029$). This treatment effect was consistent irrespective of whether there was a history of T2DM. In 2605 patients with HF and no T2DM, dapagliflozin reduced the risk of cardiovascular death or HF by 27%. These results were achieved in patients with HF who were well treated with angiotensin-converting enzyme inhibitors, beta-blockers, mineral corticoid-receptor antagonists, and neprilysin inhibitors. A pooled analysis of 4 SGLT2i trials also showed that these agents reduced major renal complications, including the need for dialysis, transplantation, and provided protection against acute kidney injury.¹⁷ In summary, these trials demonstrated that SGLT2i reduces the risk of hospitalization for HF and the incidence of MIs, strokes, cardiovascular, and all deaths in patients with established atherosclerotic cardiovascular disease. The favorable effects of SGLT2i appeared to occur independent of glucose lowering.

While these clinical trials clearly demonstrated the significant reduction in mortality and major adverse cardiovascular events with SGLT2i agents, the mechanisms for these improved outcomes remain unknown. Several mechanisms have been proposed:

1. Improved hemodynamics and oxygenation. SGLT2i stimulates diuresis and glycosuria, which reduces intravascular volume, thereby lowering cardiac preload and afterload, which improves cardiac output. This may lead to decreased arterial stiffness and improved diastolic and endothelial function, which ultimately contributes to decreased left ventricular mass and hypertrophy.¹⁸ In the EMPA-REG trial, SGLT2i increased hematocrit and hemoglobin levels and normalized production of erythropoietin, resulting in improved oxygenation.¹⁹
2. Reduction of epicardial adipose tissue. Canagliflozin has been shown to reduce epicardial adipose tissue, which has been linked to coronary atherogenesis.²⁰ A clinical trial examining dapagliflozin and epicardial adipose tissue is currently ongoing (NCT02235298).
3. Stimulation of ketogenesis and reduction of serum uric acid. SGLT2i agents increase free fatty acid oxidation and stimulate ketogenesis. This increases ATP production and ultimately improves myocardial performance.²¹ SGLT2i reduces serum uric acid levels by 10% to 15%. Elevated serum uric acid has been associated with adverse cardiovascular events.²²
4. Reduction of inflammatory mediators. Dapagliflozin has been found to decrease interleukin-6, activator protein-1, and nuclear factor κ B plasma levels.^{23,24} Blocking the reabsorption of glucose from renal tubular cells by SGLT2i may attenuate the production of these proinflammatory mediators, thereby contributing to decrease vascular inflammation and improved endothelial function.

5. Improved efficiency of cardiac mitochondrial function. SGLT2i inhibits the cardiac Na⁺/hydrogen exchanger, thus lowering cytosolic Na⁺ and Ca²⁺ concentrations and increasing mitochondrial Ca²⁺ concentration.²⁵ Inhibition of sodium–hydrogen exchanger activity has been associated with decreased myocardial arrhythmias and reductions in myocardial hypertrophy, fibrosis, and adverse remodeling—all of which lead to HF.^{26,27}

In this edition of the *Journal*, Mann and colleagues²⁸ propose several additional explanations for the beneficial effects seen with SGLT2i. They hypothesize that the reduced insulin signaling that occurs with SGLT2i alters myocardial substrate use and results in “metabolic reprogramming,” which is an integral component of the pathogenesis of HF. In the early stages of HF, glucose oxidation is augmented to increase the supply of ATP to meet the increased workload of the failing myocardium. Ultimately, mammalian target of rapamycin complex 1 (mTORC1), a regulator of cell growth, metabolic control, and autophagy, is activated, which promotes cellular protein synthesis needed to meet the increased demands of the hypertrophied myocardium. However, this increase in mTORC1 activity stresses the endoplasmic reticulum and results in apoptotic cell death.^{29,30} The inhibition of mTORC1 has been shown to prevent adverse cardiac remodeling and preserves left ventricular function in animal models of cardiomyopathy.^{31,32} Increased glucose uptake with insulin therapy in the hypertrophied myocardium is an indicator of left ventricular stress and has been associated with a poor prognosis in HF trials.³³ The reduction of serum insulin and glucose levels by SGLT2i may explain some of the benefits of these drugs. However, as Mann and colleagues have noted, it is not known whether the increased uptake of glucose by the failing myocardium is only an indication of myocardial stress or whether it by itself contributes to the progression of the cardiomyopathy.

Mann and colleagues suggest that shifting the failing myocardium away from glucose metabolism to other fuel sources may be an important factor of SGLT2i to correct the “mitochondrial dysfunction” seen in patients with HF. They note that SGLT2i also increases the cardiac expression of PGC-1α, which is involved in increasing myocardial fatty acid oxidation and ultimately ATP content.^{34,35} In the ischemic myocardium, myocardial oxidative metabolism is impaired and insulin increases glucose uptake to generate extra sources of ATP to enhance myocardial performance. However, in the myopathic myocardium, insulin-induced uptake of glucose may ultimately contribute to decreased ventricular function and HF. Mann and colleagues suggest that the “metabolic reprogramming” induced by SGLT2i may be an important component in the treatment of the myopathic myocardium.

The unexpected favorable results of SGLT2i in decreasing mortality and HF hospitalization in patients

with and without T2DM has prompted the initiation of new clinical trials to determine the mechanisms for these beneficial outcomes. Understanding the mechanisms of these noninsulin agents on both the myocardium and the kidney will be crucial to unlock new therapies to both treat and prevent cardiomyopathies and end-stage renal disease.

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