See Article page 895.

Commentary: Benefits of SGLT2 inhibition in heart failure: A bellwether for importance of other metabolic pathways

Victor A. Ferraris, MD, PhD

In this issue of the *Journal*, Mann and Lehrke¹ present an intriguing review of the pathways responsible for maintaining myocardial cell metabolism in patients with heart failure. The authors focus their review on changes and potential interventions that relate to glucose uptake and utilization of ketones and free fatty acids in the failing myocardium. They introduce the potential beneficial effects of SGLT2 inhibitors as a means of shifting metabolism away from depleted glucose metabolic pathways toward use of ketones and fatty acid substrates for preserving metabolic needs of failing myocardial cells.

Readers of the *Journal* might not be familiar with the class of drugs encompassed by SGLT2 inhibitors. It is surprising that there are no fewer than 7 SGLT2 inhibitors approved for human use, including familiar trade names like Jardiance and Farxiga. Most SGLT2 inhibitors are approved for use in patients with type 2 diabetes and renal dysfunction. The beneficial mechanism relates to reduced glucose reabsorption in the distal tubules, especially in patients with volume overload. The fact that these drugs are already approved for human use in patients with type 2 diabetes stimulates investigation into other indications for these drugs and favors the pursuit of this class of drugs in patients with volume overload from heart failure.

When this article was subjected to expert review, it became clear that the manuscript was simplified to

Drugs that inhibit SGLT2 pathways.

CENTRAL MESSAGE

The benefits of SGLT2 inhibitors in heart failure with reduced ejection fraction are intriguing and may set the stage for other metabolic treatments in patients with heart failure.

emphasize one important step in a very complex process of myocardial cell metabolism in heart failure. It is likely that the mechanisms encompassed by this article relate to heart failure with reduced ejection fraction. Other forms of heart failure, including heart failure with preserved ejection fraction, have uncertain responses to SGLT2 inhibitors.

Readers of this expert opinion by Mann and Lehrke must be intrigued about the possible role of the class of drugs encompassed by SGLT2 inhibitors in patients with heart failure. Some readily apparent questions surface, such as:

- Since this class of drugs is already approved for human use, should clinical trials in heart failure be the next step in addressing benefits for patients with CHF?
- Does a relevant animal model exist to test potential interventions for modifications of SGLT2 pathways?
- How important is SGLT2 inhibitor therapy when considering the global picture of heart failure, including other metabolic pathways that are likely relevant in heart failure patients?
- How should studies of metabolic pathways in heart failure be prioritized?
- Can drugs that target various other metabolic pathways in heart failure be combined with SGLT2 inhibitors?

Mann and Lehrke provide a focused review of a potentially important pathway in the progression of heart failure

From the Division of Cardiothoracic Surgery, Department of Surgery, University of Kentucky and Lexington VA Medical Center, Lexington, Ky.

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 March 21, 2021; revisions received March 21, 2021; accepted for publication March 23, 2021; available ahead of print March 27, 2021.

Address for reprints: Victor A. Ferraris, MD, PhD, Division of Cardiothoracic Surgery, University of Kentucky & Lexington VA Medical Center, A301, Kentucky Clinic, 740 South Limestone, Lexington, KY 40536-0284 (E-mail: ferraris@uky.edu).

J Thorac Cardiovasc Surg 2022;164:900-1
0022-5223/\$36.00

Copyright © 2021 by The American Association for Thoracic Surgery
<https://doi.org/10.1016/j.jtcvs.2021.03.073>

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.

Reference

1. Mann PA, Lehrke M. Cardiac substrate utilization in heart failure: where is the relevance of SGLT2 inhibition? *J Thorac Cardiovasc Surg.* 2022;164:895-9.

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?

Harold L. Lazar, MD

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

From the Division of Cardiac Surgery, Boston University School of Medicine, Boston, Mass.

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.

Address for reprints: Harold L. Lazar, MD, Division of Cardiac Surgery, Boston University School of Medicine, 80 East Concord St, Boston, MA 02118 (E-mail: harold.l.lazar@gmail.com).

J Thorac Cardiovasc Surg 2022;164:901-4

0022-5223/\$36.00

Copyright © 2021 by The American Association for Thoracic Surgery

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

Harold L. Lazar, MD

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