JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 4, 2017

ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.07.004

EDITORIAL COMMENT

# Empagliflozin and the Prevention of Heart Failure

## Will Reverse Translation Lead to New Paradigms for the Treatment of Heart Failure?*

Douglas L. Mann, MD,[a] Daniel P. Kelly, MD[b]

Heart failure develops in more than 1 in 5 patients with diabetes mellitus (DM) older than 65 years of age and augers an extremely poor prognosis, with a median survival of approximately 4 years. The landmark EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) showed that empagliflozin significantly reduced the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio: 0.86; 95% confidence interval: 0.74 to 0.99; $p = 0.04$ for superiority) in patients with type 2 DM and established cardiovascular (CV) disease. Remarkably, empagliflozin reduced death from CV causes by 38%, hospitalization for heart failure by 35%, and progression to end-stage kidney disease in patients with type 2 DM and established CV disease (1). Notably, the improvements in primary outcomes in the EMPA-REG OUTCOMES trial occurred within the first 2 to 3 months of the trial. These striking results have raised a number of questions about the potential mechanism of action whereby empagliflozin, a renal sodium glucose transport (SGLT) inhibitor, reduces heart failure endpoints. A number of mechanisms, both cardiac and extracardiac, have been proposed including enhanced diuretic efficiency, renal protective effects, enhanced cardiac substrate metabolism, and decreased vascular stiffness. However, the specific mechanism responsible for the striking effects of empagliflozin on CV outcomes is not known (2). Accordingly, the paper by Byrne et al. (3) in this issue of *JACC: Basic to Translational Science* is of considerable interest, insofar as it suggests that empagliflozin may target the heart by a novel direct cardiac mechanism.

SEE PAGE 347

The authors subjected nondiabetic mice to either sham or transverse aortic constriction (TAC) surgery. Two to 3 weeks after TAC, mice that had a reduced left ventricular ejection fraction (LVEF) of <45% were randomly assigned to receive either vehicle (0.5% hydroxyethylcellulose [Natrosol]) or empagliflozin (10 mg/kg/day) for 2 weeks. Whereas LVEF continued to decrease ($p = 0.011$) in vehicle-treated mice, LVEF stabilized in the empagliflozin-treated mice. There were no significant differences between LV mass and LV structure in the vehicle-treated mice and those in the empagliflozin-treated mice. To determine whether the salutary effects observed in the empagliflozin-treated mice were related to extracardiac hemodynamic or metabolic factors, LV function was also assessed ex vivo in vehicle-treated and empagliflozin-treated mice by using an isolated perfused working heart system, controlling for both preload and afterload, and using identical concentrations of insulin, fatty acids, and glucose in the absence of supplemental ketone. The authors noted that empagliflozin-treated hearts exhibited significantly improved cardiac output and cardiac work ex vivo, without any

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Center for Cardiovascular Research, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and the [b]Penn Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 4, 2017
AUGUST 2017:355–7

differences in heart rate, suggesting that the effects of empagliflozin may improve intrinsic cardiac function independent of its effects of glucosuria or changes in vascular resistance.

Before discussing the clinical implications of the interesting study by Byrne et al. (3), it is helpful to discuss what is known and what is not known about SGLT in the heart. Glucose is the main source of energy in most eukaryote cells. Because glucose is a polar molecule, it is not soluble in the plasma membrane and therefore must be transported across it by carrier proteins, referred to as glucose transporters. Glucose transporters can be divided into 2 families: the facilitative diffusion glucose transporters (GLUTs) and the $Na^+$/glucose cotransporters or SGLTs. At least 2 major classes of the SGLTs have been described in human tissues thus far: SGLT1 and SGLT2 (4). Carrier protein SGLT1 serves as a high-affinity, low-capacity transporter able to transport glucose against a concentration gradient, whereas SGLT2 is a low-affinity high-capacity transporter. Empagliflozin is an SGLT2 inhibitor (SGTL2i). Quantitative studies of SGLT1 and SGLT2 gene expression in human tissue have shown that *SGLT1* expression is very high in the small intestine and that *SGLT2* expression is very high in the kidney (4). *SGLT2* mRNA is ubiquitously expressed in human tissue (including the heart) and is generally 10- to 100-fold higher than the expression of *SGLT1* in the same tissues, except for the heart, where *SGLT1* mRNA is highly expressed. Relevant to the current study, *SGLT1* mRNA and protein have been detected in cardiac myocytes (4,5), whereas (at the time of the writing) there have been no comparable studies of SGLT2 in cardiac myocytes.

Although the study by Byrne et al. (3) did not identify the mechanism(s) for the effect(s) of empagliflozin, the observation that treatment with empagliflozin exerted effects on LV function both in vivo and ex vivo argues against many of the suggested peripheral mechanisms of action of empagliflozin in preventing heart failure, including enhanced natriuresis, renoprotective effects, and decreased vascular stiffness. Although empagliflozin-mediated alterations in cardiac metabolism cannot be formally excluded, the studies by Byrne et al. (3) were conducted in nondiabetic animals, which suggests that prevention of glucotoxicity by SGLT2 inhibition is not a potential mechanism. Moreover, given that the ex vivo studies were performed in the absence of exogenous ketone substrates, the observed effects were likely not due to altered ketone metabolism, one of the metabolic mechanisms proposed for SGLT2i by empagliflozin; however, this study does not formally exclude a potential role for empagliflozin-mediated alterations in endogenous ketone metabolism. Although *SGLT2* expression is relatively low in the heart, one cannot exclude the possibility that the cardiac autonomous effects noted in this study could be due to a direct effect of glucose transport or related transport mechanisms. In this regard, it is interesting to note that empagliflozin has been shown to directly inhibit the $Na^+/H^+$ exchanger (NHE) in isolated cardiac myocytes (6). From a theoretical perspective, blocking excessive NHE activity would prevent increased intracellular $Na^+$ and a resultant decrease in $Ca^{+2}$ overload through the $Na^+/Ca^{++}$ exchanger and/or decreased generation of reactive oxygen species (7). Unfortunately, there were no studies of action potential duration, which would have addressed this possibility.

The study by Byrne et al. (3) represents an exciting example of "reverse translation (bedside to bench)," whereby the unexpected results of a clinical trial serve as the stimulus to explore novel actions of a drug that had striking effects on clinically meaningful cardiovascular outcomes. However, what is most intriguing about the reverse translation in this instance is that it suggests there is an unknown mechanism of action for a "diabetic drug" that is operative even in the absence of diabetes, at least in the experimental model used. Although the current study falls short of providing a satisfactory mechanism of action for the observed findings, it does provide the scientific basis for ongoing clinical trials in patients with established heart failure where diabetes is not the primary inclusion criterion (i.e., EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; NCT03057977]; EMPEROR-Preserved [EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction]; NCT03057951; and Dapa-HF [Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure]; NCT03036124). As with all studies, and particularly for those studies that lack a coherent biological explanation, it will be important in the future to replicate these findings in different animal models, as well as elucidate the mechanism(s) of action. It will also be important to determine whether the effects are dependent on cardiac myocyte SGLT2, using targeted loss-of-function studies. Nonetheless, the unique pharmacological profile of SGLT2 inhibitors places them at the intersection of metabolic,

hemodynamic, neurohumoral, and vascular endothelial pathways that impact the heart and the kidney, all of which are important in the treatment of heart failure, particularly heart failure with a reduced ejection fraction, for which there are no currently U.S. Food and Drug Administration-approved therapies. The exciting study by Byrne et al. (3) suggests that we still have a lot to learn about how SGLT2 inhibitors work in the heart.

**ADDRESS FOR CORRESPONDENCE:** Dr. Douglas L. Mann, Washington University, 660 South Euclid Avenue, Campus Box 8086, St. Louis, Missouri 63110. E-mail: dmann@wustl.edu.

## REFERENCES

**1.** Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.

**2.** Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. Curr Treat Options Cardiovasc Med 2017;19:23.

**3.** Byrne NJ, Parajuli N, Levasseur JL, et al. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. J Am Coll Cardiol Basic Trans Science 2017;2:347–54.

**4.** Zhou L, Cryan EV, D'Andrea MR, Belkowski S, Conway BR, Demarest KT. Human cardiomyocytes express high level of Na+/glucose cotransporter 1 (SGLT1). J Cell Biochem 2003; 90:339–46.

**5.** Banerjee SK, McGaffin KR, Pastor-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. Cardiovasc Res 2009;84:111–8.

**6.** Baartscheer A, Schumacher CA, Wust RC, et al. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia 2017; 60:568–73.

**7.** Cingolani HE, Ennis IL. Sodium-hydrogen exchanger, cardiac overload, and myocardial hypertrophy. Circulation 2007;115:1090–100.

**KEY WORDS** cardiovascular disease, diabetes mellitus, empagliflozin, SGLT, sodium glucose transport inhibitor