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EDITORIAL COMMENT

Empagliflozin and HFrEF

Known and Possible Benefits of NHE1 Inhibition*

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"Where is the wisdom we have lost in knowledge?
Where is the knowledge
we have lost in information?"
—T.S. Eliot (1)

Heart failure (HF) contributes to cardiovascular morbidity and mortality in patients with diabetes (DM). Mortality and hospitalization rate, the most meaningful endpoints for prognosis in patients with HF, have a higher incidence in subjects with concomitant DM compared with DM-free patients with HF. HF and DM are highly interweaved pathological conditions. In fact, hyperglycemia predicts the risk of developing HF, whereas the latter frequently occurs in patients with DM, worsening their prognosis. Moreover, a large cohort of patients with HF has manifest or latent DM. Finally, the presence of glucose intolerance in subjects with HF increases the risk of disease progression and death from a cardiovascular accident. Thus, similar mechanisms may underlie the onset or progression of HF and DM. By extension, targeting a biochemical/molecular alteration in one condition should also benefit the other. However, although long-term measures apt to reduce glycemic levels show benefit in patients with DM, these agents do not improve cardiovascular outcomes in those with HF. Thus, one could argue that correcting hyperglycemia per se would unlikely arrest the myriad of other triggers/cofactors and subsequent unrolling of countless signaling pathways/cascades of events ultimately conducive of chronic cardiac decompensation.

At the same time, however, this failure could be the impetus for a "we don't know what we don't know" type of approach. This strategy, consisting of searching for molecular/genome signatures that distinguish, for example, one disease from another, will allow us to gain information that can be used in turn to enhance protein networks and mathematical models; these networks and models will enable us to unravel functionally meaningful interactions within complex biological systems. This in silico analysis may help to investigate, for example, the inner workings of a given drug in a specific pathological context. In essence, this approach may aid us in solving a "we do know what we don't know" type of question, such as "Why correcting high glucose levels is so beneficial in DM but not so much so in HF?" or "Is a given drug effective by modifying the same or different targets in different pathological contexts"?

In humans, sodium-glucose cotransporter-2 (SGLT2) is a protein located in the proximal part of the tubule in the kidneys, where it facilitates the reabsorption of 90% glucose, inhibiting SGLT2 results in decreased blood glucose due to glucosuria. Members of this new class of anti-type 2 DM drugs, such as empagliflozin (EMPA), increase insulin sensitivity and uptake in the muscle cells, while decreasing gluconeogenesis and improving the first phase of insulin release from pancreatic β cells. Data from EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) showed that, in patients with type 2 DM, the

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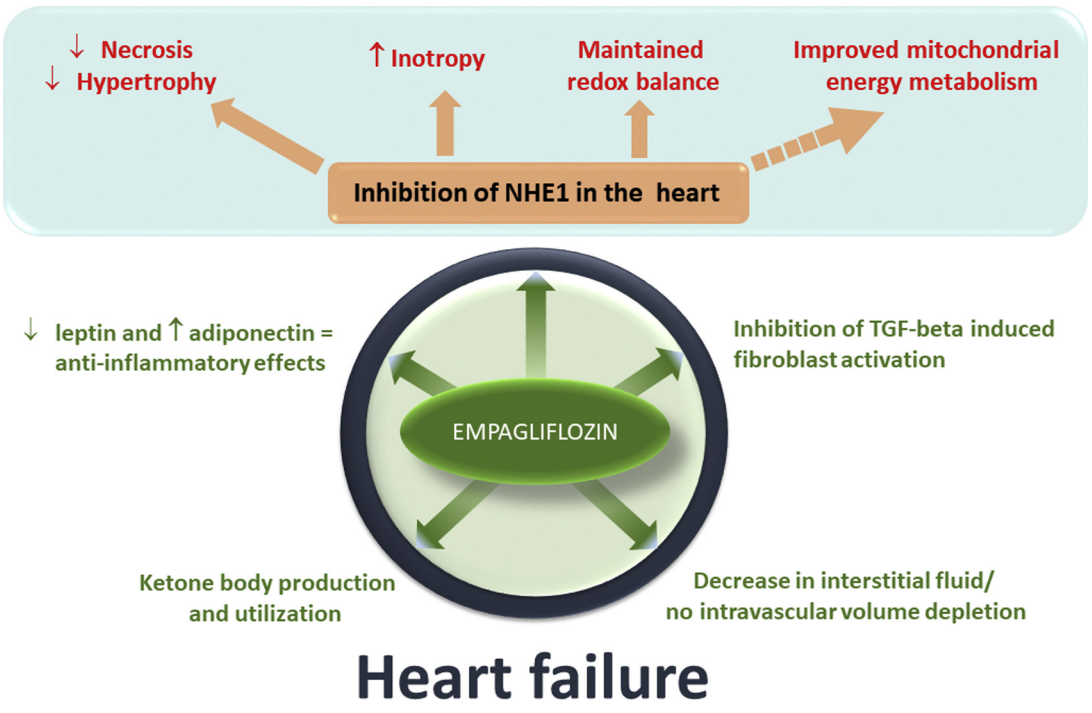
administration of empagliflozin led to lower rates of death from cardiovascular causes, nonfatal myocardial infarction (MI), or stroke, as well as HF-related hospitalizations, compared with those patients receiving a placebo. It is particularly relevant that beneficial effects of empagliflozin on cardiovascular outcomes emerged early and remained sustained throughout the observation period. However, we still need to fully uncover the potential, as well as the underlying mechanisms, of empagliflozin as an anti-HF measure. EMPA-REG OUTCOME has shown that it is unlikely that these benefits stem from the reduction or prevention of atherothrombotic events such as MI or stroke. Moreover, HF and mortality diverged early during treatment, suggesting that EMPA can benefit cardiovascular function via glucose-independent mechanisms, a hypothesis currently tested in the EMPA-TROPISM (Safety and Efficacy of Empagliflozin versus Placebo on Top of Guideline-directed Medical Therapy in Heart Failure Patients with Reduced Ejection Fraction without Diabetes) trial.

SEE PAGE 831

In this issue of *JACC: Basic to Translational Science*, Iborra-Egea et al. (2) posed precisely this question: through what mechanisms does empagliflozin benefit the failing heart, with or without DM? To answer this question, the investigators designed a complex experimental matrix, including the emerging tool of machine learning, with a family of algorithms that correspond to artificial neural networks. In brief, they used in-depth learning analysis (integrating massive, publicly available databases) to investigate how empagliflozin eventually improves outcomes in patients with HF and reduced ejection fraction (HFrEF) with or without DM. The information gathered from this in silico approach (i.e., the empagliflozin-predicted mechanism of action that explains the connection between a model's input and output data) was then validated in rats in which HFrEF was induced by MI, either in the absence or presence of empagliflozin. The machine learning approach allowed them to identify the activation of the sodium-hydrogen exchanger-1 (NHE1) cotransporter as the most robust mechanism of action that was similar for diabetic and nondiabetic patients, thus suggesting a DM-independent mechanism. With the same in silico (mathematical model) design, they determined that, in the absence of empagliflozin, NHE1 is activated, prompting the induction of baculoviral 1AP repeat-containing protein 2. This event, in turn, induces the degradation of the proteasome-mediated X-linked inhibitors of apoptosis (XIAP) and baculoviral 1AP repeat-containing protein 5 (BIRC5), thus fueling HFrEF progression. These changes were absent in empagliflozin-treated rats with MI, thus accounting for the halted HF progression. In the hearts of rats with MI, the investigators then validated these in silico findings by assessing the messenger ribonucleic acid levels of XIAP and BIRC5 as the end-effectors of the proposed pathway, in the absence and presence of empagliflozin. They found that the drug counteracted the reduction in gene expression of both XIAP and BIRC5, thus preserving their antiapoptotic effects. In essence, empagliflozin can benefit the failing heart even in the absence of overt diabetic conditions and very likely countering NHE1-triggered myocyte apoptosis.

Empagliflozin has cardiac and extracardiac protective actions, including enhanced diuretic efficiency, renal protection, augmented cardiac substrate metabolism (i.e., enhanced ketone formation and utilization), and decreased vascular stiffness. Moreover, empagliflozin can inhibit transforming growth factor-beta-induced fibroblast activation, collagen deposition, and fibrosis, as well as reduce production of the proinflammatory adipokine leptin and increase production of the anti-inflammatory adipokine adiponectin. In terms of empagliflozin's primary cardiac effects, an essential study by Byrne et al. (3), conducted in mice with pressure overload-induced HF, revealed that empagliflozin-treated hearts exhibited significantly improved cardiac output and cardiac work ex vivo, with no differences in heart rate; these findings suggest improved cardiac contractility independent of and in addition to changes in vascular resistance. However, mechanisms accounting for these primary cardiac effects remained unclear. Among its other merits, the current research by Iborra-Egea et al. (2) contributes to filling this gap by confirming and expanding previous evidence attesting that NHE1 is a primary target of empagliflozin in the heart. Baartscheer et al. (4) had already reported that empagliflozin reduces $[Na^+]$ and $[Ca^{2+}]$ in isolated ventricular myocytes, independently from the presence of glucose but in a manner sensitive to the NHE1 inhibitor cariporide, thus suggesting that empagliflozin inhibits this antiporter. More recently, Bertero et al. (5) advanced the "sodium hypothesis" according to which "…empagliflozin may reduce intracellular sodium (Na^+) load observed in failing cardiac myocytes by inhibiting the sarcolemmal Na^+/H^+ exchanger. Because elevated intracellular Na^+ hampers mitochondrial Ca^{2+} handling and thereby, deteriorates energy supply and demand matching and the mitochondrial antioxidative defense systems, empagliflozin may positively affect cardiac function by restoring mitochondrial function, and redox state

FIGURE 1 Empagliflozin and Heart Failure



Some mechanisms that explain the benefits afforded by empagliflozin to patients with heart failure and reduced ejection fraction, and cardiac effects already attributed to the inhibition of NHE1 activity. The **dotted line** represents additional yet to be verified salutary actions.
TGF = transforming growth factor.

in the failing heart." Accordingly, the long-term ablation of NHE1 activity enhances the myocyte redox potential and mitigates high-fat diet-induced myocardial stress and fatty liver disease, leading to better-preserved insulin sensitivity, while potentially altering both cardiac and systemic metabolic substrate handling in mice (6).

In aggregate, the study by Iborra-Egea et al. (2), as well as earlier reports, imply that by reducing intercellular Na^+ and Ca^{2+}, SGLT-2 inhibitors such as empagliflozin can not only modulate myocyte mechanical function by affecting Ca^{2+} handling/cycling but also afford myocardial protection by maintaining proper myocardial redox balance, and possibly mitochondrial energy metabolism (**Figure 1**). In-depth future studies shall evaluate whether empagliflozin helps in maintaining mitochondrial energetic and redox assets in HFrEF and other cardiac disorders.

Sarcolemmal NHE activity of human ventricular myocytes stems from the NHE1 isoform, and its expression is significantly higher in recipient hearts with chronic end-stage HF than it is in unused donor hearts. Moreover, inhibiting NHE1 can attenuate cardiomyocyte injury, remodeling, and systolic dysfunction. Along with the fact that empagliflozin is a well-tolerated drug that can be administered once daily with a lower risk of inducing hypoglycemia, these facts provide a solid mechanistic ground for repurposing empagliflozin as an anti-HF drug, at least for HFrEF treatment, which is the major translational message emanating from the studies performed by Iborra-Egea et al. (2). Among the additional questions raised by their contribution is whether NHE1 expression/activity is altered also in patients with heart failure with preserved ejection fraction. Is NHE1 upregulated under this condition too? Would features of HF with preserved ejection fraction such as diastolic dysfunction and left ventricular hypertrophy be effectively corrected by empagliflozin? Another important pending issue comes from the evidence that aldosterone stimulates NHE1 in the heart and vasculature; therefore, would empagliflozin be able to obviate or attenuate cardiac and vascular stigmata brought by any conditions linked to hyperaldosteronism? This has self-evident implications when we are in the need of attenuating the neurohormonal overdrive typical of many cardiovascular disorders.

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Thanks to the present study (2) and other contributions, we are no longer outside, looking in, regarding the role of NHE1 in HF pathogenesis. Moreover, the multifaceted and complex approach adopted herein by Iborra-Egea et al. reiterates that gathering more information/predictions (integrating big data with computer modeling) increases our wisdom, namely our acuity in orienting ourselves when facing a "we don't know what we don't know" type of issue. One may argue, however, that despite the excellent help offered by machine learning, sometimes human ingenuity/intuition gets it first.

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