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EDITORIAL COMMENT

The Growing Case for Use of SGLT2i in Heart Failure

Additional Benefits of Empagliflozin in a HFpEF Rodent Model*

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Heart disease associated with diabetes mellitus (DM) continues to be the leading cause of death worldwide. However, with the development of renal sodium glucose transport inhibitors (SGLTi) there appears to be new hope. Specifically, the use of SGLTi as a treatment for type 2 diabetes (T2D) leads to lower blood glucose levels by inhibiting SGLT2, which accounts for ~90% of glucose reabsorption in the kidney proximal convoluted tubule. At this point, a number of SGLT2i have been approved for treatment of T2D, namely: empagliflozin (1), canagliflozin (2), and dapagliflozin (3), which have each shown improvement in cardiovascular outcomes in clinical trials. These gliflozins have demonstrated cardiovascular beneficial effects including reduced mortality from cardiovascular causes (1-3), and decreased hospitalization from heart failure (1,3). The mechanisms of these successes in clinical trials have begun to be worked out by multiple groups that recently found improvements in cardiac function by administering empagliflozin to *db/db* diabetic mice (4,5). In these studies, Verma et al. (4) found that ATP production and cardiac function was improved following 4 weeks of empagliflozin administration to *db/db* mice compared with vehicle treatment. This effect is associated with preserved cardiac glucose and lipid metabolism (4). Additionally, in female *db/db* mice, Habibi et al. (5) showed that 5 weeks of empagliflozin treatment improved diastolic function, myocardial fibrosis, and mitochondrial expansion. On the other hand, the effect of empagliflozin on pressure overload-induced heart failure resulting from transverse aortic constriction (TAC), in the absence of diabetes, also had protective effects. In this study, Byrne et al. (6) found that 2 weeks of oral administration of empagliflozin after TAC improved cardiac systolic function as measured in vivo or ex vivo. However, there were no changes in remodeling of cardiac mass, left ventricle structure, cardiac fibrosis, and immune cell infiltration into the cardiac tissue (6). In either case, both the human trials and these mechanistic studies in rodent models that show encouraging results of SGLT2i therapy in either diabetes or pressure overload-induced heart failure suggests that these agents should be examined for treatment of additional heart failure etiologies.

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One area of cardiovascular disease that has proven exceptionally resistant to current therapy options is that of heart failure with preserved ejection fraction (HFpEF). These patients have symptoms suggestive of heart failure, but with normal left ventricular ejection fraction. This disease is associated with age, female sex, hypertension, obesity, renal dysfunction, and atrial fibrillation (7). It has complex pathophysiology in addition to diastolic dysfunction. The current treatment options available have been able to relieve volume overload and alleviate other concurrent chronic diseases in patients to reduce or prevent hospitalizations (8). This limitation of therapeutic options for HFpEF appears to be coming to an end

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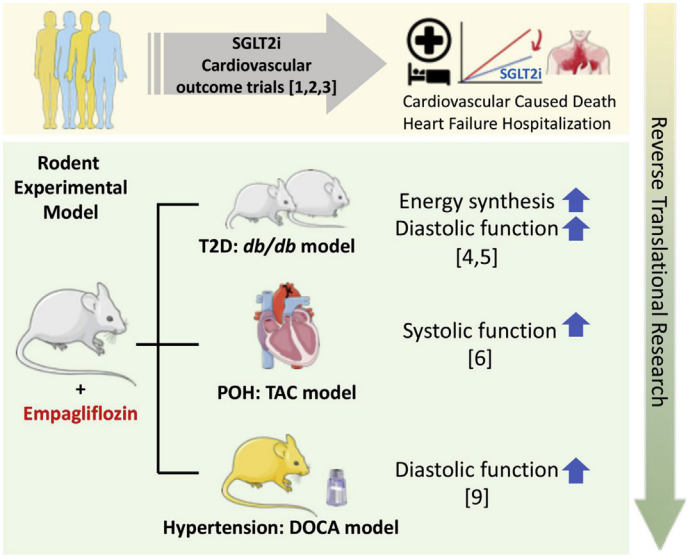
with the paper by Connelly et al. (9) in this issue of *JACC: Basic to Translational Science*.

Connelly et al. (9) examined the hypothesis that SGLT2i may have beneficial effects in nondiabetic HFpEF, extending what was previously observed in patients with diabetes (1,10) and experimental models of pressure overload-induced heart failure model (6). The complex nature of hypertension, which results from various factors including genetic, lifestyle, and autonomic nerve systems, can limit modeling of HFpEF. A growing number of researchers have used a deoxycorticosterone acetate (DOCA)-salt model to replicate an overactive sympathetic nervous and renin-angiotensin system. DOCA leads to a renal sodium imbalance, resulting in hypervolemia (11). The addition of 0.6% to 1% NaCl to drinking water or uninephrectomy intensifies the hypertension. The DOCA model more accurately replicates multiple physiological connections to neurological, cardiovascular, renal circulation, and immune system changes in addition to the cardiac blood pressure outcome. Connelly et al. (9) used a rat model of uninephrectomy with DOCA and 1% NaCl water to induce HFpEF. Then in these or control animals a subset were treated with empagliflozin-containing chow. The resulting 4 groups were followed and assessed systemically in metabolic cage, for biochemical endpoints, cardiac function by echocardiography and cardiac catherization, cardiac remodeling by histopathology, and molecularly. The authors found that empagliflozin attenuated cardiac hypertrophy, preserved lung weight, and ameliorated diastolic dysfunction. However, empagliflozin had no effect on systolic blood pressure, cardiac fibrosis, and fibrosis-related gene expression. This partially improved cardiac function, but had no effect on fibrosis similar to results previously reported for empagliflozin-treated experimental diabetic and pressure-overload rodent models (5,6). Although a specific mechanism is not fully elucidated, the authors point out, "potential pathophysiological mechanisms that underlie these salutary changes are likely multifactorial." Despite this limitation, the continued successes of multiple groups to show protection via empagliflozin treatment of heart failure resulting from diverse etiologies is promising. This strongly supports the need for continued mechanistic work to define the regulated pathways and help elucidate the possibility and efficacy of this drug class for future use. One important distinction of this study and the TAC study mentioned in the previous text is that the mechanism may be independent of other known beneficial effects of SGLT2i, such as lowering glucose in diabetes. However, because this may not be related to calcium-channel expression or fatty acid oxidation-related gene expression, as suggested by Connelly et al. (9), other interesting possibilities remain.

It is noteworthy that the effects of empagliflozin have similar patterns to the prior reports with a T2D model (4,5) and that of other heart disease models without diabetes, such as TAC (6) and now HFpEF (9) (**Figure 1**). However, a number of limitations concerning the specific mechanisms, such as changes in circulating metabolites, improved hemodynamics through natriuresis, osmotic diuresis, neurohormonal changes, or immune system adaptation, must be accounted for when considering SGLT2i as a therapeutic option for heart failure treatment. In addition to the specific physiological mechanisms, SGLT2i for heart failure should be fully defined in the current model by measuring energy production efficiency in heart muscle (12), gene regulation, and post-translational protein modifications, which are in

FIGURE 1 Schematic of Clinical Observations, Promises, and the Future of SGLT2i



Patient trials of SGLT2i for the treatment of diabetes have revealed improved cardiovascular outcomes, reduced mortality, and better quality of life as it pertains to hospitalization **(top)** (1–3). Rodent studies have revealed cardiac benefits in either diabetes or pressure overload which is expanded to HFpEF in the study published by Connelly et al. (9) **(lower)** (4–6). The figure was produced using images modified from Servier Medical Art (smart.servier.com). DOCA = deoxycorticosterone acetate; POH = pressure overload-induced heart failure; SGLT2i = sodium/glucose cotransporter 2 inhibitor; T2D = type 2 diabetes; TAC = transverse aortic constriction.

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part regulated by sensing of energy status, the difference in contractility caused by the effect of calcium flux control in the process of regulating sodium reabsorption, or changes in the mitochondrial environment around the cardiac sarcomeres. Many questions remain regarding SGLT2i's efficacy in the failing heart, but the study by Connelly et al. (9) extends our knowledge on the potential benefits of SGLT2i on myocardial function and applicable disease etiologies.

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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. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.

3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.

4. Verma S, Rawat S, Ho KL, et al. Empagliflozin increases cardiac energy production in diabetes: Novel translational insights into the heart failure benefits of SGLT2 inhibitors. J Am Coll Cardiol Basic Trans Science 2018;3:575–87.

5. Habibi J, Aroor AR, Sowers JR, et al. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. Cardiovasc Diabetol 2017;16:9.

6. 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;2:142.

7. Andersen MJ, Borlaug BA. Heart failure with preserved ejection fraction: current understandings and challenges. Curr Cardiol Rep 2014;16:501.

8. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1868–77.

9. Connelly KA, Zhang Y, Visram A, et al. Empagliflozin improves diastolic function in a nondiabetic rodent model of heart failure with preserved ejection fraction. J Am Coll Cardiol Basic Trans Science 2019;4:27–37.

10. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015;38:420–8.

11. Basting T, Lazartigues E. DOCA-salt hypertension: an update. Curr Hypertens Rep 2017;19:32.

12. Lopaschuk Gary D, Verma S. Empagliflozin's fuel hypothesis: not so soon. Cell Metabolism 2016;24:200–2.

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