Effect of Empagliflozin on Left Ventricular Mass and Diastolic Function in Individuals With Diabetes: An Important Clue to the EMPA-REG OUTCOME Trial?

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Amid the excitement over the results of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial (1), the potential mechanisms through which empagliflozin produced a rapid and profound reduction in hospitalization for heart failure and cardiovascular (CV) death in subjects with type 2 diabetes remain entirely unexplained. Importantly, the effects of empagliflozin on objective measures of cardiac structure and function are unknown (2). We report the first systematic analysis of echocardiograms of 10 patients with type 2 diabetes and established CV disease in whom empagliflozin 10 mg/day was initiated as per approved clinical indication, without any other concurrent changes in medications. Transthoracic echocardiograms, performed before and 3 months after initiation of empagliflozin, were analyzed by an experienced cardiac echocardiographer not involved in the clinical care of the patients and blinded to identity of the patients and the study order (pre vs. post). Informed patient consent and ethics approval were obtained.

Baseline patient characteristics were as follows: 80% were men, age was mean (SD) 67.6 (6.6) years, 40% had a previous myocardial infarction, 90% had undergone vascularization, and estimated glomerular filtration rate was 77.5 (21.3) mL/min/1.73 m^2. Background medications included the following: eight patients on metformin, five patients on dipeptidyl peptidase-4 inhibitors, one patient on a sulfonylurea, three patients on insulin, nine patients on statins, six patients on ACE inhibitors or angiotensin receptor blockers, two patients on diuretics, eight patients on β-blockers, and three patients on calcium channel blockers. Mean (SD) treatment duration was 151.8 (21.8) days. Empagliflozin treatment modestly improved glycemic control [HbA_{1c} 7.30% (0.84) [56 mmol/mol (9.3)] vs. 6.81% (0.49) [51 mmol/mol (5.4)], $P = 0.024$, and fasting blood glucose 6.3 (1.12) vs. 6.0 (0.95) mmol/L, $P = 0.668$]. There were no significant changes in blood pressure [117 (18)/68 (11) vs. 126 (13)/74 (11) mmHg, $P > 0.05$]. Body weight did not change after treatment [74.4 (9.7) vs. 74.1 (11.7) kg, $P = 0.821$].

Strikingly, short-term empagliflozin treatment was associated with a significant reduction in left ventricular (LV) mass index [mean (SD) 88 (21) vs. 75 (19) g/m^2, $P = 0.01$] (a well-established CV surrogate end point) and improved diastolic function per the early lateral annular tissue Doppler velocity [8.5 (1.6) vs. 9.6 (1.3) cm/s, $P = 0.002$ (e'; Fig. 1)]. There were numerical but not significant differences in ratio of early to late mitral inflow [0.90 (0.20) vs. 1.04 (0.20), $P = 0.101$] and early diastolic deceleration time [229.90 (45.06) vs. 205.60 (26.03) ms, $P = 0.112$]. There were no differences in LV systolic function [63% (8) vs. 66% (6), $P = 0.41$], LV end diastolic volume [47 (15) vs. 46 (15) mL/m^2, $P = 0.93$], and LV end systolic volume [18 (9) vs. 16 (7) mL/m^2, $P = 0.54$].

These observations, albeit preliminary, suggest the potential of empagliflozin to favorably promote LV reverse remodeling and improve diastolic function in subjects with type 2 diabetes and established CV disease. The rapid cardiac benefits are consistent with the early separation of the Kaplan-Meier curves for heart failure–associated hospitalization and CV mortality in the EMPA-REG OUTCOME trial (1). Whether the improvement in diastolic function is secondary to a reduction in LV mass or through another distinct mechanism remains

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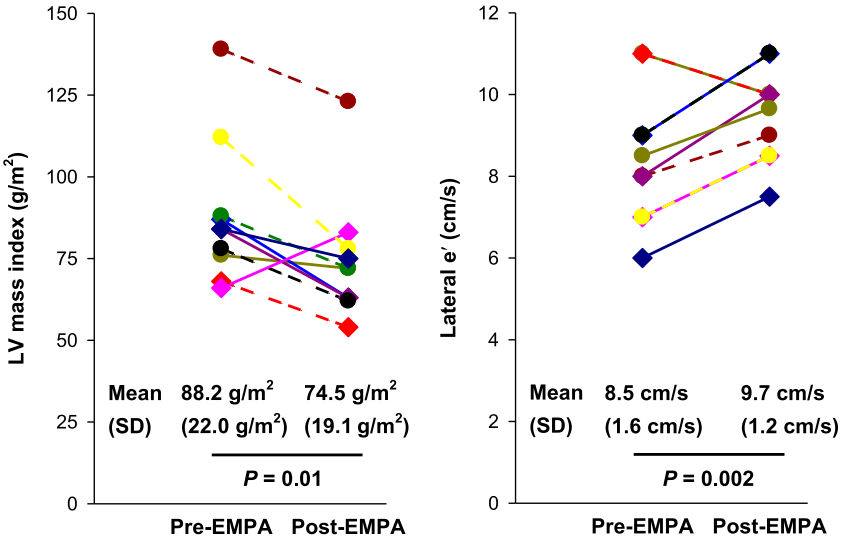

Figure 1—LV mass index and lateral e′ at baseline (Pre-EMPA) and at the 3-month follow-up (Post-EMPA). A total of 10 patients were evaluated with each patient denoted by a specific color. e′, early lateral annular tissue Doppler velocity; EMPA, empagliflozin.

unclear. Although the proportion of EMPA-REG OUTCOME patients with systolic versus diastolic dysfunction is unknown, diastolic dysfunction is present in upward of 60% of subjects with diabetes (3).

The mechanisms through which empagliflozin improves diastolic dysfunction and regresses LV mass require further elucidation. Since the human heart does not express sodium–glucose cotransporter 2 (SGLT2) receptors, it is difficult to reconcile any direct effect of the drug on the myocardium per se. However, it is possible that empagliflozin binds to myocardial receptors or substrates other than SGLT2.

The diuretic and natriuretic hypothesis (2) suggests that SGLT2 inhibitors promote sustained reductions in intravascular volume and enhance sodium excretion thereby favorably affecting myocardial loading conditions; this, coupled with an effect on arterial stiffness (4), may lead to ventricular mass regression. While the magnitude of clinical benefit relative to the small nonsignificant changes in LV volume and blood pressure we observed argues against such as the dominant mechanism, lack of power in this study remains possible. The metabolic/myocardial fuel-supply hypothesis postulates that empagliflozin, through increased ketone body production such as β-hydroxybutarate, may provide an alternative and potentially more efficient source of myocardial adenosine triphosphate (5). Changes in myocardial substrate utilization can have early and in some cases profound effects on ventricular structure and function, and therefore this tenant requires more evaluation.

In summary, we report salutary short-term changes in LV mass and diastolic function in subjects with type 2 diabetes and established CV disease after empagliflozin initiation. These data, although preliminary, hypothesis generating, and limited by the small number of patients and lack of a control group, may provide a conceptual and translational framework for the remarkable CV benefits in the EMPA-REG OUTCOME trial and open the door to exploring new potential mechanisms and therapeutic uses of SGLT2 inhibitors.

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Author Contributions. S.V. and K.A.C. drafted the manuscript. A.G. acquired the data. S.V., A.T.Y., H.T., C.D.M., and K.A.C. reviewed and interpreted the data and contributed to the discussion. K.A.C. analyzed the data. All authors critically revised the manuscript and reviewed and approved submission of the final version of the manuscript. S.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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