Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease

The EMPA-HEART CardioLink-6 Randomized Clinical Trial

Editorial, see p 1703

BACKGROUND: SGLT2 (sodium-glucose cotransporter 2) inhibitors lower cardiovascular events in type 2 diabetes mellitus but whether they promote direct cardiac effects remains unknown. We sought to determine if empagliflozin causes a decrease in left ventricular (LV) mass in people with type 2 diabetes mellitus and coronary artery disease.

METHODS: Between November 2016 and April 2018, we recruited 97 individuals ≥40 and ≤80 years old with glycated hemoglobin 6.5% to 10.0%, known coronary artery disease, and estimated glomerular filtration rate ≥60mL/min/1.73m^2. The participants were randomized to empagliflozin (10 mg/day, n=49) or placebo (n=48) for 6 months, in addition to standard of care. The primary outcome was the 6-month change in LV mass indexed to body surface area from baseline as measured by cardiac magnetic resonance imaging. Other measures included 6-month changes in LV end-diastolic and -systolic volumes indexed to body surface area, ejection fraction, 24-hour ambulatory blood pressure, hematocrit, and NT-proBNP (N-terminal pro b-type natriuretic peptide).

RESULTS: Among the 97 participants (90 men [93%], mean [standard deviation] age 62.8 [9.0] years, type 2 diabetes mellitus duration 11.0 [8.2] years, estimated glomerular filtration rate 88.4 [16.9] mL/min/1.73m^2, LV mass indexed to body surface area 60.7 [11.9] g/m^2), 90 had evaluable imaging at follow-up. Mean LV mass indexed to body surface area regression over 6 months was 2.6 g/m^2 and 0.01 g/m^2 for those assigned empagliflozin and placebo, respectively (adjusted difference –3.35 g/m^2; 95% CI, –5.9 to –0.81g/m^2, *P*=0.01). In the empagliflozin-allocated group, there was significant lowering of overall ambulatory systolic blood pressure (adjusted difference –6.8mmHg, 95% CI –11.2 to –2.3mmHg, *P*=0.003), diastolic blood pressure (adjusted difference –3.2mmHg; 95% CI, –5.8 to –0.6mmHg, *P*=0.02) and elevation of hematocrit (*P*=0.0003).

CONCLUSIONS: Among people with type 2 diabetes mellitus and coronary artery disease, SGLT2 inhibition with empagliflozin was associated with significant reduction in LV mass indexed to body surface area after 6 months, which may account in part for the beneficial cardiovascular outcomes observed in the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02998970.

Subodh Verma, MD, PhD*
C. David Mazer, MD*
Andrew T. Yan, MD*
Tamique Mason, MSc
Vinay Garg, MD
Hwee Teoh, PhD
Fei Zuo, MPH
Adrian Quan, MPhil
Michael E. Farkouh, MD, MSc
David H. Fitchett, MA, MB BChir, MD
Shaun G. Goodman, MD, MSc
Ronald M. Goldenberg, MD
Mohammed Al-Omran, MD, MSc
Richard E. Gilbert, MBBS, PhD
Deepak L. Bhatt, MD, MPH
Lawrence A. Leiter, MD
Peter Jüni, MD
Bernard Zinman, MD
Kim A. Connelly, MBBS, PhD*
For the EMPA-HEART CardioLink-6 Investigators

*Drs Verma, Mazer, Yan, and Connelly contributed equally.

Key Words: coronary artery disease ■ diabetes mellitus ■ SGLT2 inhibitors ■ ventricular myocardium

Sources of Funding, see page 1700

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- This was a 6-month double-blind, randomized, placebo-controlled trial of individuals with type 2 diabetes mellitus, coronary artery disease, and relatively normal left ventricular mass index.
- The empagliflozin-allocated group exhibited a significant reduction in left ventricular mass index (adjusted difference –3.35 g/m^2) compared with the placebo group.

What Are the Clinical Implications?

- The decrease in left ventricular mass associated with empagliflozin may contribute to the cardiovascular benefits observed in patients with type 2 diabetes mellitus and coronary artery disease who are treated with SGLT2 (sodium-glucose cotransporter 2) inhibitors.

SGLT2 (sodium-glucose cotransporter 2) inhibitors have been shown to reduce adverse cardiovascular outcomes in people with type 2 diabetes mellitus.[1–5] In the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, the SGLT2 inhibitor empagliflozin reduced the rates of major adverse cardiovascular events by 14%, cardiovascular death by 38%, all-cause mortality by 32%, and hospitalization for heart failure by 35% in people with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease.[1] Two other SGLT2 inhibitors, canagliflozin and dapagliflozin, have also been evaluated in large cardiovascular outcome trials in people with and without established atherosclerotic cardiovascular disease. Canagliflozin has also been assessed in a renal efficacy study that focused on participants with type 2 diabetes mellitus and established chronic kidney disease.[6] These large trials have all demonstrated cardiovascular benefits with the SGLT2 inhibitors, especially on heart failure and the composite of heart failure and cardiovascular death.[2,3]

The mechanisms underlying the benefits of these agents, particularly on reducing heart failure-associated hospitalizations and cardiovascular death, have been the subject of significant interest.[7–9] Left ventricular (LV) mass (LVM) is a strong and independent predictor of cardiovascular events, including myocardial infarction, heart failure, and mortality.[10–16] The magnitude of reduction in LVM as a result of pharmacological or surgical interventions has also been shown to correlate with the degree of cardiovascular risk reduction.[10–16] We previously found in a small preliminary study that short-term use of empagliflozin was associated with a significant reduction in LVM indexed (LVMi) to baseline body surface area. Thus, we hypothesized that the cardiovascular benefits of SGLT2 inhibition may be secondary to a reduction in LVM. To address this question, we conducted a double-blind, placebo-controlled randomized trial in a population of subjects with type 2 diabetes mellitus and coronary artery disease that was representative of the EMPA-REG OUTCOME cohort, to determine if empagliflozin promotes LVM regression as measured by the reference standard cardiac magnetic resonance imaging (cMRI).

METHODS

The data that support the findings of this study may be available from the corresponding author upon reasonable request and in accordance with a data-sharing agreement.

Trial Design

The EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients with Type 2 Diabetes) CardioLink-6 trial (https://www.clinicaltrials.gov. Unique identifier: NCT02998970) was a double-blind, placebo-controlled, randomized investigator-initiated clinical trial that was designed and executed independent of the funder. The study design and protocol were reviewed and approved by the St. Michael's Hospital Research Ethics Board. Study enrollment took place between November 7, 2016, and April 5, 2018 (inclusive). All participants provided written informed consent before study entry.

Individuals between 40 and 80 years of age were eligible if they had a glycated hemoglobin level between 6.5% and 10.0%, known coronary artery disease (defined as a history of previous myocardial infarction or previous coronary revascularization with either percutaneous coronary intervention or coronary artery bypass graft surgery), an estimated glomerular filtration rate ≥60 mL/min/1.73m^2 (calculated using the Modification of Diet in Renal Disease equation) and had been on stable antihyperglycemic therapy for at least 2 months preceding enrollment. Key exclusion criteria were: a history of type 1 diabetes mellitus; current SGLT2 inhibitor, glucagon-like peptide 1 receptor agonist, or saxagliptin user; >4 episodes of moderate hypoglycemia per month or any episode of severe hypoglycemia within the past 12 months; undergone a percutaneous coronary intervention or coronary artery bypass graft surgery within the last 2 months; a body mass index >40 kg/m^2; an LV ejection fraction (LVEF)<30%; New York Heart Association IV symptoms of heart failure; hospitalized for decompensated heart failure within the preceding 3 months; or greater than moderate valvular disease. The detailed protocol and statistical analysis plan are available in the online-only Data Supplement.

During the baseline visit, participants underwent clinical and anthropometric assessments as well as cMRI. Blood samples were drawn for biochemical analyses and the participants were fitted with a 24-hour ambulatory blood pressure monitor device (TM-2430, A&D Company Ltd, Mississauga, ON, Canada). We used central randomization with a concealed Web-based system and computer-generated random permuted blocks of sizes of 2 and 4 to allocate participants to either 6 months of empagliflozin 10 mg/day or placebo, both

 Circulation. 2019;140:1693–1702. DOI: 10.1161/CIRCULATIONAHA.119.042375

in addition to standard of care. Three visits were arranged over the 6-month follow-up period. At each of these visits, clinical and anthropometric assessments were conducted, and blood samples drawn. The final visits also included cMRI and 24-hour ambulatory blood pressure monitoring. A Data and Safety Monitoring Board reviewed the clinical events data on an ongoing basis to ensure the safety of the study participants.

Acquisition and Analyses of the cMRI Images

All cardiovascular magnetic resonance (CMR) examinations were performed using a clinical 3T MRI scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). Scout images were obtained to plan the cardiac axis views. The segmented balanced steady-state free-precession sequence was used for the retrospective ECG-gated standard cine CMR scans of all participants, including 3 long axis views and a stack of short axis slices covering the entire heart, using the following parameters: Field of view typically 240mm; voxel dimensions 0.9 mm × 0.9 mm × 6.0 mm; TE 1.7 ms; TR 54.74 ms; echo spacing 3.9 ms; slice thickness 6 mm; flip angle 60°; bandwidth 930Hz/pixel; 25 reconstructed phases per heartbeat. All scans were performed at end-inspiratory breathhold (see the Protocol in Section 7.4 of the online-only Data Supplement).

cMRI end points were measured by level 3 readers (Drs Yan and Connelly) who were blinded to all clinical data as well as the treatment and timing of each scan, using commercially available software (cvi42®, Circle Cardiovascular Imaging Inc, Calgary, AB, Canada). LV mass (including papillary muscles), volumes and function were determined with manual tracing of the endocardial and epicardial borders.[17,18] The differences in area between the epicardial and endocardial borders in contiguous short-axis slices were multiplied by slice thickness and myocardial density before being summed to calculate LV mass. Mean 24-hour systolic blood pressure was converted to kPA and used as an approximation for end-systolic pressure.

Clinical Laboratory Tests and Biomarker Assessments

Whole blood samples were submitted directly for routine clinical testing at the St. Michael's Hospital core clinical laboratory. Plasma NT-proBNP (N-terminal pro b-type natriuretic peptide) levels were quantified on the day of collection in the same core clinical laboratory with the Cobas 6000 e601 Immunology analyzer by Roche Diagnostics (Mississauga, ON, Canada). All assays were conducted, and data analyzed, by personnel blinded to treatment group and study visit.

Study Outcomes

The primary outcome measure was the change in LVMi from baseline to 6 months. Secondary outcomes included the between-groups (empagliflozin vs placebo) baseline to 6-month changes in LV end-diastolic and end-systolic volumes (non-indexed and indexed to baseline body surface area), LVEF, and NT-proBNP.

Statistical Analyses

A total sample size of 90 individuals was estimated to be required to provide 80% power to detect a between-group difference in LVM of 10 g from baseline to 6 months at a 2-sided α of 0.05, assuming an standard deviation of 25 g and a correlation of 0.80 between LVM at baseline and 6 months. This effect size of 0.40 standard deviation units would correspond to a difference in the prespecified primary outcome of LVMi of 4 g/m^2 at a standard deviation of 10 g/m^2. The study plan was to randomize 96 participants, allowing for 5% incomplete primary outcome data, leading to 90 subjects contributing to the full analysis set.

Analyses followed an intent-to-treat approach, where all participants randomized were included in the group to which they were originally allocated. Categorical data are reported as frequencies and percentages; continuous variables are summarized as mean and standard deviation or median and interquartile range for non-normally distributed data. The primary analysis was a superiority comparison of LVMi at the baseline and 6-month visits based on all patients with primary outcome data. Between-group comparisons of changes from baseline to 6-months for secondary and other outcomes were also based on a linear regression model adjusted for baseline values (ANCOVA). For NT-proBNP, we derived trimmed means, discarding values below the 2.5th and above the 97.5th percentile and used an ANCOVA based on robust regression with MM-type estimators.[19]

Subgroup analyses of the primary outcome were conducted to determine if the effect of empagliflozin varied according to prespecified subgroups based on baseline characteristics (see the Protocol and Statistical Analysis Plan in the online-only Data Supplement). Additional sensitivity analyses were performed to determine whether specific participant subsets based on alternative LVMi definitions (LVM indexed by height, height$^{1.7}$, and height$^{2.7}$), duration of treatment, scan quality, or presence of LV hypertrophy (see the Statistical Analysis Plan in the online-only Data Supplement) would yield similar results to the primary outcome. Analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[20] All *P* values and 95% confidence intervals are 2-sided.

RESULTS

Participant Characteristics

As shown in Figure 1, 152 individuals provided written informed consent and 97 were assigned 1:1 to receive either empagliflozin 10 mg/day (n=49) or placebo (n=48). Among those randomized, 6-month outcome data were unavailable for 7. Both baseline and 6-month cMRI images were available for 44 participants in the empagliflozin group and 46 in the placebo arm. Table 1 summarizes the demographics and baseline characteristics of the individuals who were randomized. The mean duration of type 2 diabetes mellitus in this cohort was over 10 years and 94% were on metformin with 25% taking insulin. Over 80% of the participants were taking guideline-recommended secondary prevention medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, lipid-lowering therapies, and antiplatelet therapies.

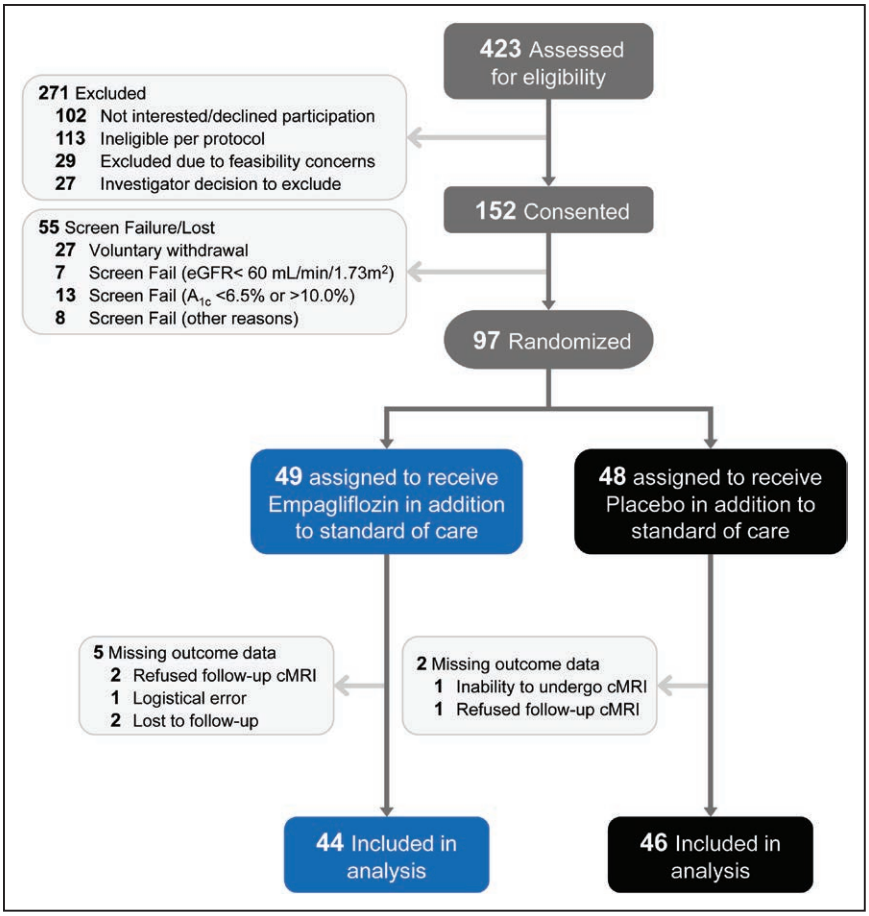

Figure 1. Flow of participants through the trial.
A_{1c} indicates glycated hemoglobin; cMRI, cardiac magnetic resonance imaging; and eGFR, estimated glomerular filtration rate.

Primary and Secondary Outcomes

Baseline LVMi was 59.3 (10.9) g/m² and 62.2 (12.8) g/m² for the groups assigned to empagliflozin and placebo respectively. The primary outcome of change in LVMi from baseline to the 6-month visit was −2.6 (7.8) g/m² for the group randomized to empagliflozin and −0.01 (5.7) g/m² for the placebo-allocated arm. The adjusted difference between groups was −3.35 g/m² (−5.9, −0.81), *P*=0.01 (Figure 2). The sensitivity analysis that considered LVM indexed by different allometric exponents revealed consistent and significant LVM regression with empagliflozin (see Table I in the online-only Data Supplement).

Table 2 summarizes the baseline, 6-month, and 6-month changes from baseline values for LV end-systolic volume, LV end-diastolic volume, and LVEF. Baseline and 6-month LV volumes, as well as the changes over 6 months, regardless of whether they were indexed to body surface area, were not different between the 2 study arms. Likewise, empagliflozin, relative to placebo, did not affect LVEF. No significant interaction was observed for the primary end point across the prespecified sub-groups except in those with a baseline LVMi >60g/m² who exhibited greater LVMi regression ($P_{interaction}$=0.007).

Clinical Measurements

Both study groups had a mean baseline glycated hemoglobin of approximately 8.0%. The mean change in glycated hemoglobin from baseline at 6-months was −0.4% (1.0%) and −0.3% (0.9%) for the empagliflozin- and placebo-assigned groups respectively (adjusted difference between groups; 95% CI, −0.2% [−0.5%, 0.2%], *P*=0.41; see Table II in the online-only Data Supplement).

Mean overall ambulatory blood pressure at baseline was 139/80 mmHg for the group randomized to empagliflozin and 138/78 mmHg for that allocated to placebo. Empagliflozin exposure for 6 months was associated with a mean 7.9 (13.5) mmHg reduction in systolic blood pressure and a 3.1 (7.5) mmHg decrease in diastolic blood pressure. In contrast, in the placebo group, the mean ambulatory systolic and diastolic blood pressure readings at 6 months were comparable to those measured at baseline. The adjusted differences between groups (95% CI) was −6.8 (−11.2, −2.3) mmHg, *P*=0.003 and −3.2 (−5.8, −0.6) mmHg, *P*=0.016 for systolic and diastolic blood pressure respectively.

The mean baseline hematocrit was 42.6% (4.2%) for the group taking empagliflozin and 41.3% (3.4%) for the placebo-allocated group. The

Table 1. Baseline Demographics, Anthropometric Characteristics and Clinical, and Pharmacotherapy History*

	N (%)			
	Empagliflozin 10 mg (n=49)		Placebo (n=48)	
Men	44	(90)	46	(96)
Age, median (IQR), y	64	(57, 69)	64	(56, 72)
BMI, median (IQR), kg/m^2	26.7	(24.5, 30.2)	26.6	(24.4, 29.3)
BSA, median (IQR), m^2	2.0	(1.8, 2.1)	1.9	(1.8, 2.1)
Duration of T2DM, median (IQR), y	10.0	(4.0, 15.0)	10.0	(5.0, 15.0)
A_{1c}, median (IQR), %	7.9	(7.5, 8.4)	7.9	(7.3, 8.7)
Glucose (random), median (IQR), mg/dL	138.6	(118.8, 219.6)	162.0	(120.6, 226.8)
Overall BP, median (IQR), mmHg				
Systolic	128	(120,143)	134	(125, 146)
Diastolic	74	(69, 82)	77	(71, 81)
Cholesterol (random), median (IQR), mg/dL	123	(114, 138)	121	(107, 140)
LDL-C, median (IQR), mg/dL	55	(41, 71)	48	(39, 65)
HDL-C, median (IQR), mg/dL	38	(35, 42)	38	(33, 46)
Triglyceride, median (IQR), mg/dL	170	(122, 219)	156	(112, 185)
eGFR, median (IQR), mL/min per 1.73 m^2	87	(78, 98)	88	(75, 101)
Creatinine, median (IQR), mg/dL	0.9	(0.8, 1.0)	0.9	(0.8, 1.0)
Hemoglobin, median (IQR), g/dL	14.1	(13.1, 15.2)	13.8	(12.8, 15.0)
Hematocrit, median (IQR), %	0.42	(0.40, 0.46)	0.42	(0.39, 0.44)
LVMi, median (IQR), g/m^2	58	(51, 64)	60	(54, 70)
NT-proBNP, median (IQR), pg/mL	97	(46, 188)	116	(62, 227)
Previous myocardial infarction	19	(39)	21	(44)
PCI >2 months before screening	26	(53)	19	(40)
CABG surgery >2 months before screening	28	(57)	27	(56)
Heart failure	2	(4)	4	(8)
Hypertension	45	(92)	43	(90)
Nephropathy	0	(0)	2	(4)
Stroke or TIA	8	(16)	6	(13)
Peripheral artery disease	2	(4)	3	(6)
Smoking history	20	(41)	22	(46)
Medications				
Metformin	47	(96)	44	(92)
Insulin	12	(25)	12	(25)
Statin	47	(96)	46	(96)
ACEi/ARB	40	(82)	41	(85)
Diuretic	2	(4)	6	(13)
β-blocker	38	(78)	39	(81)
Calcium channel blocker	6	(12)	15	(31)
ASA/P2Y$_{12}$ Inhibitor	40	(82)	41	(85)

SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert creatinine values to μmol/L, multiply by 88.4. A_{1c} indicates glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure, CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVMi, left ventricular mass indexed to body surface area; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; and TIA, transient ischemic attack.

*Intention-to-treat population.

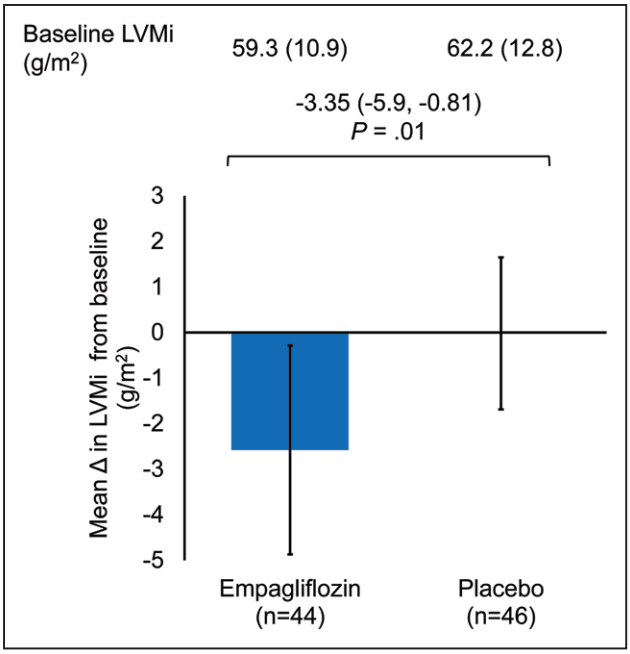

Figure 2. Empagliflozin exposure for 6 months is associated with a decrease in LVMi as assessed by cardiac magnetic resonance imaging. Baseline and 6-month data were available for 44 individuals who were assigned to empagliflozin 10 mg/day and 46 who were allocated placebo. The mean change in left ventricular mass indexed to body surface area (LVMi) is presented as mean (95% CI), and the adjusted difference between groups datum is shown with 95% CI for the intention-to-treat population. The data were analyzed using ANCOVA adjusting for baseline values.

6-month hematocrit in the empagliflozin group was 2.4% (3.0%) higher than the corresponding baseline measurement; a 0.4% (2.8%) increase was noted in the placebo group over the same observation window. These changes yielded an adjusted difference between groups of 2.3% (1.1%, 3.6%), *P*=0.0003.

The empagliflozin-assigned group had a mean baseline heart rate of 75 (9) beats per minute while that for the placebo-allocated group was 70 (9) beats per minute. At the 6-month time point, the mean heart rate change in the empagliflozin group was 0.3 (8.2) beats per minute lower than that at baseline in contrast to an elevation of 2.6 (7.5) beats per minute in the placebo group. There was, however, no difference in the adjusted difference between groups (–0.42 [–3.54 to 2.7], *P*=0.79).

Biomarker Outcomes

Median (interquartile range) values of NT-proBNP at baseline were 97.0 (46.3, 188.3) pg/mL and 115.5 (61.8, 226.8) pg/mL for the empagliflozin and placebo groups, respectively. At 6 months, median (interquartile range) values were 102 (58.5, 201.0) pg/mL and 99 (62.0, 169.0) pg/ml for the empagliflozin and placebo groups. An adjusted difference of 7.4 pg/mL (95% CI, –10.3, 25.1; *P*=0.42) was detected for the empagliflozin group as compared with placebo.

Adverse Events

Empagliflozin was well tolerated with no significant excess of adverse effects, study discontinuations or clinical events relative to the placebo group (see Table III in the online-only Data Supplement). No clinical cardiovascular events or any deaths occurred during the 6-month follow-up.

DISCUSSION

The EMPA-HEART CardioLink-6 trial demonstrated that compared with placebo, the addition of empagliflozin to standard antihyperglycemic treatment in people with type 2 diabetes mellitus and coronary artery disease was associated with a significant reduction in LVMi as measured by cMRI. The use of empagliflozin was also associated with a significant lowering of ambulatory systolic blood pressure with no impact on the circulating levels of NT-proBNP.

Proposed mechanisms to explain the reduction of heart failure outcomes of SGLT2 inhibitors include natriuresis, osmotic diuresis, a reduction in preload and afterload, inhibition of the cardiac sodium-hydrogen exchanger, and improved myocardial bioenergetics.[7,9,21,22] However, whether these mediators alter cardiac structure and function remains an important and unanswered clinical question. Although experimental data and clinical case reports have suggested that SGLT2 inhibitors may improve cardiac structure and function,[23,24] this is the first trial to provide randomized clinical data in humans demonstrating that the SGLT2 inhibitor empagliflozin promotes LV mass regression. Given that LVM regression is an important and causal determinant of cardiovascular events and mortality, these data provide potential translational insights into the biology of SGLT2 inhibitors and their cardioprotective outcome benefits.

It is noteworthy that the beneficial effects on LVMi in the current study were observed early, over a 6-month treatment period. This is in keeping with the early separation of the Kaplan–Meier curves for cardiovascular death and hospitalization for heart failure that were noted in the EMPA-REG OUTCOME trial. Additionally, a reduction in LVM was observed in a stable secondary prevention population with normal LVMi at baseline and with relatively well controlled blood pressure, in the context of background therapy with renin-angiotensin inhibitors.

LVM is directly related to both LV volume and LV wall thickness across all myocardial segments, which is reflected by the endocardial and epicardial contours across the entire LV on CMR measurements. Consequently, a reduction in LV mass in the absence of concurrent reduction in LV volumes reflects an overall reduction in wall thickness. Importantly, the magnitude of LV

Table 2. Changes in Cardiac Parameters After Exposure to Empagliflozin 10 mg/day or Placebo for 6 Months as Assessed by cMRI*

	Empagliflozin 10 mg (n=44)			Placebo (n=46)			Adjusted Difference Between Groups (95% CI)		*P* Value
	Baseline	6-Month	Δ from Baseline	Baseline	6-Month	Δ from Baseline			
LVMi, g/m²†	59.3 (10.9)	56.7 (9.2)	−2.6 (7.8)	62.2 (12.8)	62.1 (11.7)	−0.01 (5.7)	−3.35	(−5.9, −0.8)	0.01
LVM, g	116.5 (26.3)	111.8 (25.0)	−4.7 (15.4)	120.9 (33.0)	120.2 (30.3)	−0.39 (10.8)	−5.0	(−10.2, 0.2)	0.06
LVEDV, mL	124.1 (33.0)	120.6 (31.1)	−2.9 (17.7)	138.4 (39.1)	134.0 (39.4)	−4.3 (19.3)	−0.9	(−8.5, 6.7)	0.81
LVESV, mL	53.0 (20.8)	50.4 (21.5)	−1.9 (10.0)	62.5 (26.0)	62.9 (29.4)	0.3 (13.0)	−2.2	(−7.3, 2.8)	0.38
LVESVi, mL/m²	27.1 (10.5)	25.7 (10.6)	−1.0 (5.1)	32.3 (11.8)	32.5 (13.4)	0.0 (6.6)	−1.2	(−3.8, 1.4)	0.36
LVEDVi, mL/m²	63.3 (15.5)	61.3 (13.7)	−1.6 (8.8)	71.4 (15.4)	69.3 (16.5)	−2.1 (9.7)	−1.2	(−5.0, 2.7)	0.55
LVEF, %	58.0 (7.5)	59.1 (8.6)	0.72 (5.1)	55.5 (8.7)	54.3 (8.9)	1.0 (6.5)	2.2	(−0.2, 4.7)	0.08

Data are expressed as mean (SD) and analyzed using ANCOVA adjusting for baseline values. LV indicates left ventricular; LVEDV(i), LV end-diastolic volume (indexed to body surface area); LVEF, LV ejection fraction; LVESV(i), LV end-systolic volume (indexed to body surface area); and LVM(i), LV mass (indexed to body surface area).

*Intention-to-treat population.

†Primary outcome.

mass regression was greatest in those with the highest baseline LVMi. Indeed, among the participants with a baseline LVMi >60 g/m², a −7.3 g/m² reduction in LVMi was observed. The exact mechanisms underlying the reduction in wall thickness remain to be elucidated, and may either represent a decrease in cardiomyocyte mass, or may relate to changes in interstitial water content, or both. Further detailed tissue characterization using CMR is required to dissect which mechanisms may have contributed to the observed reduction in LVM.

Using 24-hour ambulatory blood pressure monitoring, we found a marked reduction in both systolic and diastolic blood pressure with empagliflozin use. The observed reduction in systolic and diastolic blood pressure was significant during both daytime and nighttime. These findings are in keeping with the SACRA (SGLT2 Inhibitor and ARB Combination Therapy in Patients With Diabetes and Uncontrolled Nocturnal Hypertension) study which demonstrated a similar reduction in overall, daytime, and nocturnal blood pressure.[25] While one might postulate that the reduction in LVM was mediated by the antihypertensive effect of empagliflozin, further exploratory analyses suggest that the observed reduction in LVMi was independent of blood pressure changes. Although we found a positive and significant correlation between systolic blood pressure and LVMi at baseline, the change in 24-hour ambulatory blood pressure was not associated with the change in LVM over the 6-month observation window (Pearson's Correlation 0.08; 95% confidence limits, −0.14, 0.29). These observations suggest that mechanisms other than blood pressure reduction may be involved in the LVMi regression noted after empagliflozin exposure. That said, a decrease in blood pressure cannot, for now, be definitively ruled out as a contributory mechanism of action. In keeping with this line of thought, while LVM regression is often associated with the lowering of blood pressure, LVM reductions occurring in the absence of blood pressure changes have also been reported.[15,26] In the LIFE (Losartan Intervention for Endpoint Reduction) study, LVM regression (as assessed by electrocardiogram analyses), independent of treatment assignment and blood pressure, was associated with a reduction in all-cause mortality, cardiovascular death, sudden cardiac death, myocardial infarction, new heart failure, new atrial fibrillation, and stroke.[15] Furthermore, losartan (compared with atenolol) was associated with a greater decrease in LVM and cardiovascular events even though blood pressure control did not differ substantially between the 2 strategies.[15] Sacubitril/valsartan (compared with olmesartan) has been associated with greater declines in blood pressure and LVMi.[27] Importantly, in a prespecified subgroup analysis, we observed a greater reduction in LVMi among participants with a higher LVMi at baseline who were assigned to empagliflozin. This finding is consistent with a recent post hoc subgroup analysis of the EMPA-REG OUTCOME trial which demonstrated that patients with echocardiogram evidence of LV hypertrophy derived a greater reduction in major adverse cardiac events from empagliflozin,[28] and further supports the notion that LVM regression might contribute to the beneficial cardiovascular effects of empagliflozin.

In accord with the EMPA-REG OUTCOME trial, we observed a significant increase in hematocrit in the empagliflozin group as compared with the placebo group. Although the mediation analysis from the EMPA-REG OUTCOME trial[29] suggested that changes in hematocrit and hemoglobin accounted for approximately 50% of the observed clinical benefit, it is noteworthy that LV volumes, LVEF, LVM, and cardiac biomarkers were not assessed and therefore excluded from the mediation analysis. Furthermore, we did not find any significant correlation between changes in hematocrit and LVMi (Pearson's Correlation 0.02; 95% confidence limits, −0.23, 0.19). Moreover, there were no significant differences in NT-proBNP, indexed LV end-systolic volume, or indexed LV end-diastolic volume between the 2 study

arms. Two important points should be noted. Firstly, the EMPA-HEART population demonstrated normal volumes (end-diastolic volume and end-systolic volume) as well as NT-proBNP at baseline. NT-proBNP is released in response to increase wall stretch, the best surrogate of which is preload or end-diastolic volume. The current study did not demonstrate elevated end-diastolic volume at either baseline or at end study, hence NT-proBNP would not be expected to change. Secondly, the natriuretic or osmotic effect of SGLT2 inhibitors remains one mechanism by which these antihyperglycemic agents produce their benefits, through reducing intravascular volume and therefore preload. We did not, however, observe any changes in ventricular volumes with empagliflozin although this does not preclude a potential effect in individuals with elevated volumes at baseline. cMRI has been shown to accurately detect changes in end-systolic volume and end-diastolic volume of as little as 5 and 10 mL respectively; therefore, the lack of change cannot be ascribed to insensitive measurement tools.

The EMPA-HEART CardioLink-6 trial has strengths and limitations that merit consideration. First, we used cMRI which provides a direct measure of LV mass independent of geometric assumptions. Second, like many clinical trials, most of the participants were male, although other studies have not identified a sex difference in outcomes with SGLT2 inhibitors or in LVM regression with other therapies. Third, owing to the nature of study, the overall sample size was small and the follow-up brief. Fourth, people with evidence of chronic kidney disease and those with known/recent heart failure were excluded from this trial. Fifth, 29 EMPA-HEART trial participants had a change in either dose, frequency, or type of any concomitant medications over the course of the study, 53.2% of which involved medications not listed in Table 1. Whether these medication changes may have affected the outcomes in this cohort is unknown. Sixth, because the baseline characteristics of the population were similar to that of the EMPA-REG OUTCOME cohort and a high proportion of both study populations were on secondary prevention therapies, it remains to be determined if empagliflozin exposure would also promote LVM regression in individuals with type 2 diabetes mellitus but without established atherosclerotic cardiovascular disease. Seventh, the lack of any changes in ventricular volume and the biomarkers measured may reflect the participants enrolled. Notably, reductions in NT-proBNP have been demonstrated previously with another SGLT2 inhibitor canagliflozin.[30] Finally, it has been suggested that SGLT2 inhibitors may afford greater benefits in people with reduced ejection fraction relative to those with preserved ejection fraction[31–33] and we note that the EMPA-HEART CardioLink-6 trial not only did not recruit individuals with heart failure per se but also excluded those with significant LV dysfunction.

Conclusions

The EMPA-HEART CardioLink-6 trial has demonstrated that SGLT2 inhibition with empagliflozin leads to significant reduction in LVMi in patients with type 2 diabetes mellitus and coronary artery disease. These benefits are observed in individuals who were well treated with background therapies and appear to occur early (within 6 months). These data may provide insights into the cardiovascular benefit of empagliflozin observed in larger outcome studies.

ARTICLE INFORMATION

Received June 22, 2019; accepted October 11, 2019.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.119.042375.

Correspondence

Subodh Verma, MD, PhD, Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, 8th Floor, Bond Wing, 30 Bond Street, Toronto, ON, Canada, M5B 1W8; or Kim A. Connelly, MBBS, PhD, Division of Cardiology, St. Michael's Hospital, University of Toronto, 7th Floor, Bond Wing, 30 Bond Street, Toronto, ON, Canada, M5B 1W8. Email Subodh.Verma@unityhealth.to or Kim.Connelly@unityhealth.to

Affiliations

Division of Cardiac Surgery (S.V., T.M, V.G., H.T., A.Q.), Division of Cardiology (A.T.Y., D.H.F., S.G.G., K.A.C.), Division of Endocrinology and Metabolism (H.T., R.E.G., L.A.L.), Division of Vascular Surgery (M.A.O.), Department of Anesthesia (C.D.M.), and Applied Health Research Centre (F.Z., P.J.), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada. Department of Surgery (S.V., M.A.O.), Department of Pharmacology and Toxicology (S.V., T.M., V.G., M.A.O.), Department of Anesthesia (C.D.M.), Department of Physiology (C.D.M., K.A.C.), Department of Medicine (A.T.Y., V.G., M.E.F., D.H.F., S.G.G., R.E.G., L.A.L., P.J., B.Z., K.A.C.), Department of Nutritional Sciences (L.A.L.), Heart and Stroke Richard Lewar Centre (S.V., A.T.Y., M.E.F., K.A.C.), and Institute of Health Policy, Management, and Evaluation (P.J.), University of Toronto, Ontario, Canada. Division of Cardiology, Peter Munk Cardiac Centre, Toronto General Hospital/Mount Sinai Hospital, Ontario, Canada (M.E.F.). Canadian Heart Research Centre, Toronto, Ontario (S.G.G.). Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research Centre, University of Alberta, Edmonton (S.G.G.). LMC Diabetes & Endocrinology, Concord, Ontario, Canada (R.M.G.). Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA (D.L.B.). Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada (B.Z.).

Acknowledgments

This work was presented in part as a Late Breaking Clinical Trial at the American Heart Association Scientific Sessions 2018, November 10–12, 2018, Chicago, IL.

Sources of Funding

This trial was supported by an unrestricted investigator-initiated study grant from Boehringer Ingelheim to Drs Verma and Zinman. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or decision to submit the manuscript for publication. The database for the study was located, and the data analyses were conducted, at the not-for-profit academic research organization Applied Health Research Centre (AHRC), which is integrated with the Li Ka Shing Knowledge Institute of St. Michael's Hospital, and not shared with the funder. The manuscript was modified after consultation with the co-authors. The authors had unrestricted rights to publish the results and the final decision on content was exclusively retained by the authors.

Disclosures

Dr Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery, reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, NovoNordisk, Sanofi, Servier and Valeant, and is also the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr Mazer holds a Merit Award from the Department of Anesthesia at the University of Toronto and reports receiving honoraria from Amgen, Boehringer Ingelheim, and OctaPharma. Dr Yan reports receiving research support from AstraZeneca. Ms Mason was the recipient of a Boehringer Ingelheim Diabetes and Cardiovascular Disease Scholarship. Dr Teoh reports receiving honorarium from Boehringer Ingelheim and writing fees for unrelated diabetes mellitus-related manuscripts from Merck and Servier. Dr Farkouh reports receiving research support from Amgen and NovoNordsk. Dr Fitchett reports receiving honoraria for CME activities and fees for consultation from AstraZeneca, Boehringer Ingelheim, and Eli Lilly and membership on the steering committee of the EMPA-REG OUTCOME trial. Dr Goodman reports receiving grants and/or honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, NovoNordisk, Sanofi, and Duke Clinical Research Institute/Duke University, outside the submitted work. Dr Goldenberg reports receiving research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, and Sanofi, serving on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, and Sanofi. serving on speaker bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, and Sanofi, and serving as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, and Sanofi. Dr Gilbert holds a Canada Research Chair in Diabetes Complications and reports receiving research grants to the institution from AstraZeneca and Boehringer Ingelheim, serving on advisory panels for AstraZeneca, Boehringer Ingelheim, and Janssen. as well as receiving CME speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, and Janssen. Dr Bhatt is on the advisory board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences, the Board of Directors of Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; chairs the American Heart Association Quality Oversight Committee, Data Monitoring Committees, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; receives honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); the following relationships, Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); and received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company; receives royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); is the site co-investigator for Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; a trustee of the American College of Cardiology; and has performed unfunded research for FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. Dr Leiter reports grants and/or honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier, and GSK outside the submitted work. Dr Jüni holds a Canada Research Chair in Clinical Epidemiology of Chronic Diseases, reports receiving research grants to the institution from AstraZeneca, Biosensors International, Biotronik, Eli Lilly, and The Medicines Company, and serves as an unpaid member of the steering group of trials funded by AstraZeneca, Biosensors International, Biotronik, St. Jude Medical, and The Medicines Company. Dr Zinman reports receiving research support from Boehringer Ingelheim and serving as a consultant for AstraZeneca, Eli Lilly, Janssen, Merck, NovoNordisk, and Sanofi. Dr Connelly holds a New Investigator Salary Award from the Canadian Institutes of Health Research and an Early Researcher Award from the Ontario Ministry of Research and Innovation, is listed as an inventor on a patent application by Boehringer Ingelheim on the use of dipeptidyl peptidase-4 inhibitors in heart failure, and reports receiving research grants to his institution from AstraZeneca and Boehringer Ingelheim. support for travel to scientific meetings from Boehringer Ingelheim, and honoraria for speaking engagements and ad hoc participation in advisory boards from AstraZeneca, Boehringer Ingelheim, and Janssen. The remaining authors report no conflicts.

REFERENCES

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi: 10.1056/NEJMoa1611925
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357. doi: 10.1056/NEJMoa1812389
4. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, George JT, Zinman B. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation*. 2018;137:405–407. doi: 10.1161/CIRCULATIONAHA.117.032031
5. Verma S, Mazer CD, Fitchett D, Inzucchi SE, Pfarr E, George JT, Zinman B. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME® randomised trial. *Diabetologia*. 2018;61:1712–1723. doi: 10.1007/s00125-018-4644-9
6. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. doi: 10.1056/NEJMoa1811744
7. Verma S, McMurray JJV, Cherney DZI. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol*. 2017;2:939–940. doi: 10.1001/jamacardio.2017.1891
8. Chin KL, Ofori-Asenso R, Hopper I, von Lueder TG, Reid CM, Zoungas S, Wang BH, Liew D. Potential mechanisms underlying the cardiovascular benefits of sodium glucose cotransporter 2 inhibitors: a systematic review of data from preclinical studies. *Cardiovasc Res*. 2019;115:266–276. doi: 10.1093/cvr/cvy295
9. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108–2117. doi: 10.1007/s00125-018-4670-7
10. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol*. 1998;32:1454–1459. doi: 10.1016/s0735-1097(98)00407-0
11. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol*. 2008;52:2148–2155. doi: 10.1016/j.jacc.2008.09.014
12. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114:345–352. doi: 10.7326/0003-4819-114-5-345
13. Abdi-Ali A, Miller RJH, Southern D, Zhang M, Mikami Y, Knudtson M, Heydari B, Howarth AG, Lydell CP, James MT, et al. LV mass independently predicts mortality and need for future revascularization in patients undergoing diagnostic coronary angiography. *JACC Cardiovasc Imaging*. 2018;11:423–433. doi: 10.1016/j.jcmg.2017.04.012
14. Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, Bosch J, Sussex B, Probstfield J, Yusuf S; Heart Outcomes Prevention Evaluation (HOPE) Investigators. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation*. 2001;104:1615–1621. doi: 10.1161/hc3901.096700
15. Devereux RB, Dahlöf B, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris KE, Edelman JM, Wachtell K. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losar-

tan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation*. 2004;110:1456–1462. doi: 10.1161/01.CIR.0000141573.44737.5A
16. Gardin JM, Arnold A, Gottdiener JS, Wong ND, Fried LP, Klopfenstein HS, O'Leary DH, Tracy R, Kronmal R. Left ventricular mass in the elderly. The Cardiovascular Health Study. *Hypertension*. 1997;29:1095–1103. doi: 10.1161/01.hyp.29.5.1095
17. Riffel JH, Schmucker K, Andre F, Ochs M, Hirschberg K, Schaub E, Fritz T, Mueller-Hennessen M, Giannitsis E, Katus HA, et al. Cardiovascular magnetic resonance of cardiac morphology and function: impact of different strategies of contour drawing and indexing. *Clin Res Cardiol*. 2019;108:411–429. doi: 10.1007/s00392-018-1371-7
18. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, Plein S, Tee M, Eng J, Bluemke DA. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:29. doi: 10.1186/s12968-015-0111-7
19. Koller M. *Simulations for Sharpening Wald-type Inference in Robust Regression for Small Samples. Vignette of robustbase: Basic Robust Statistics, R package version 0.7-0*. 2011
20. R Core Team. *R: A language and environment for statistical computing*. 2018. R Foundation for Statistical Computing, Vienna, Austria.
21. Connelly KA, Bhatt DL, Verma S. Can we DECLARE a victory against cardio-renal disease in diabetes? *Cell Metab*. 2018;28:813–815. doi: 10.1016/j.cmet.2018.11.010
22. Lopaschuk GD, Verma S. Empagliflozin's fuel hypothesis: not so soon. *Cell Metab*. 2016;24:200–202. doi: 10.1016/j.cmet.2016.07.018
23. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, Sabongui A, Teoh H, Mazer CD, Connelly KA. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care*. 2016;39:e212–e213. doi: 10.2337/dc16-1312
24. Byrne NJ, Parajuli N, Levasseur JL, Boisvenue J, Beker DL, Masson G, Fedak PWM, Verma S, Dyck JRB. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. *JACC Basic Transl Sci*. 2017;2:347–354. doi: 10.1016/j.jacbts.2017.07.003
25. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, Uchiyama K, Niijima Y, Katsuya T, Urata H, et al. 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation*. 2019;139:2089–2097. doi: 10.1161/CIRCULATIONAHA.118.037076
26. Xing F, Chen J, Zhao B, Jiang J, Tang A, Chen Y. Real role of β-blockers in regression of left ventricular mass in hypertension patients: Bayesian network meta-analysis. *Medicine (Baltimore)*. 2017;96:e6290. doi: 10.1097/MD.0000000000006290
27. Schmieder RE, Wagner F, Mayr M, Delles C, Ott C, Keicher C, Hrabak-Paar M, Heye T, Aichner S, Khder Y, et al. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. *Eur Heart J*. 2017;38:3308–3317. doi: 10.1093/eurheartj/ehx525
28. Verma S, Mazer CD, Bhatt DL, Raj SR, Yan AT, Verma A, Ferrannini E, Simons G, Lee J, Zinman B, et al. Empagliflozin and cardiovascular outcomes in patients with type 2 diabetes and left ventricular hypertrophy: a subanalysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2019;42:e42–e44. doi: 10.2337/dc18-1959
29. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, Schmoor C, Ohneberg K, Johansen OE, George JT, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41:356–363. doi: 10.2337/dc17-1096
30. Januzzi JL Jr, Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M, Davies MJ. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol*. 2017;70:704–712. doi: 10.1016/j.jacc.2017.06.016
31. Figtree GA, Rådholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Matthews DR, Shaw W, Neal B. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes mellitus. *Circulation*. 2019;139:2591–2593. doi: 10.1161/CIRCULATIONAHA.119.040057
32. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, Kuder J, Murphy SA, Bhatt DL, Leiter LA, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. *Circulation*. 2019;139:2516–2527. doi: 10.1161/CIRCULATIONAHA.119.039996
33. Verma S, McMurray JJV. The serendipitous story of SGLT2 inhibitors in heart failure. *Circulation*. 2019;139:2537–2541. doi: 10.1161/CIRCULATIONAHA.119.040514