Supplemental Online Content

Omar M, Jensen J, Ali M, et al. Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: a substudy of the Empire HF randomized clinical trial. *JAMA Cardiol*. Published online January 6, 2021. doi:10.1001/jamacardio.2020.6827

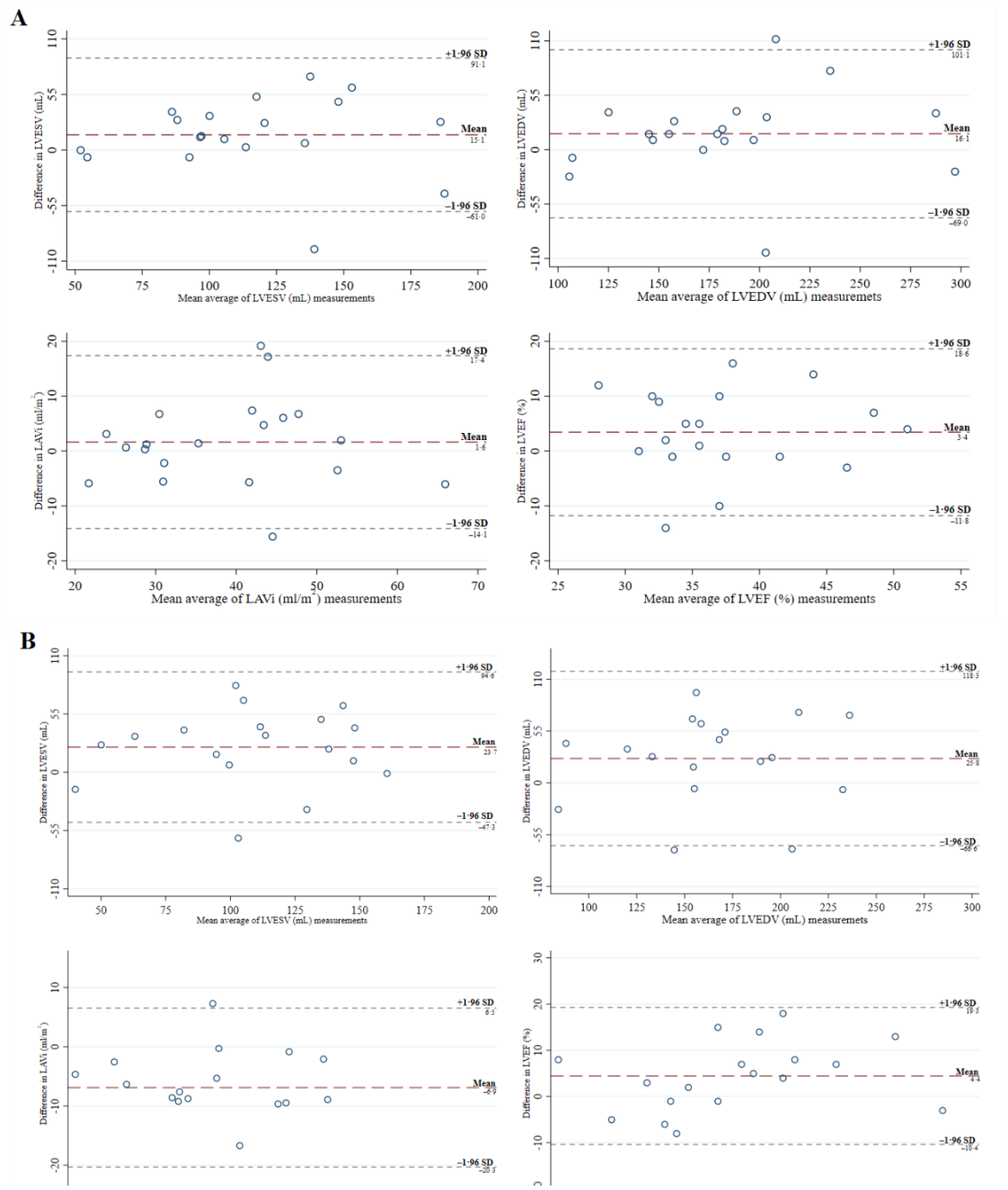
This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Intra- and inter-observer reliability on primary efficacy measures

Inter-observer and intra-observer variability of the primary and secondary outcome measurements were tested by 2 observers for 10 patients each at 2 different time points (baseline and 12 weeks) in a random order to avoid any memory of measurement between time points. All measurements were made by each observer blinded to previous measurements.

The mean difference between the measurements of both intra- and inter- observer were plotted against the mean of the two measurements and 95% CI limits of agreement were calculated. Differences between repeated measurements should be within a clinically acceptable limit.

eFigure 1. Bland-Altman plots comparing intra- and inter-observer agreement of LVESV, LVEDV, LAVi, and LVEF.



Panel A. Intra-observer agreement. Panel B. Inter-observer agreement.
Dashed lines represent 95% CI limit of agreement and average agreement. LVESV=Left ventricular end-systolic volume. LVEDV=Left ventricular end-diastolic volume. LAVi=left atrial volume index. LVEF=Left ventricular ejection fraction.

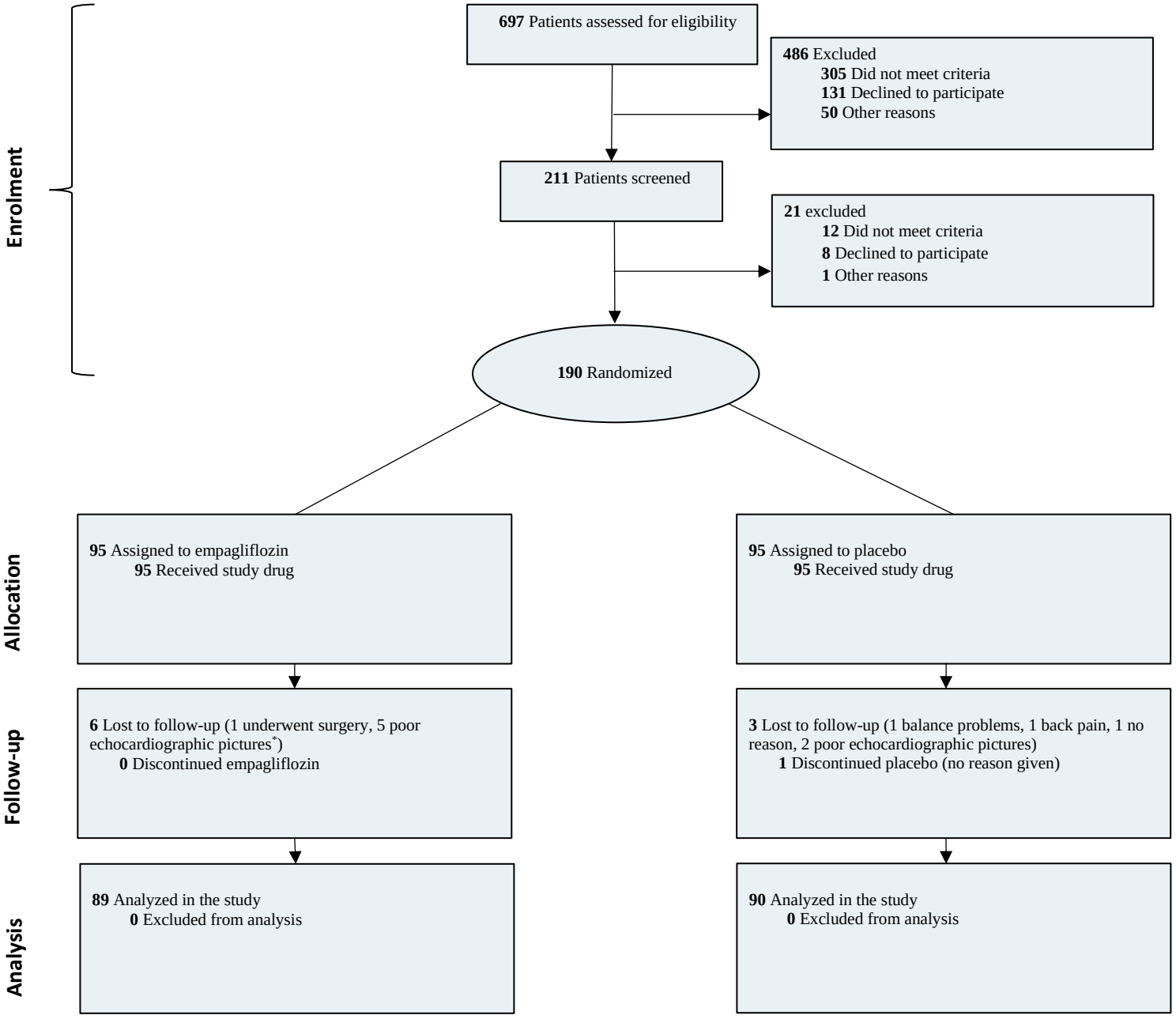
Inter-observer and intra-observer repeatability and reproducibility of echocardiographic parameters was assessed by the intraclass correlation coefficient (ICC) using two-way mixed measures analysis. ICC coefficient represent the between-pairs variance expressed as a proportion of the total variance of the observations, where ICC ranges from 0 to 1, and values > 0.6 were considered to represent substantial reliability. Moreover, a mean percentage error was calculated to describe the discrepancy between the two measurements of each variable. Investigating intra-observer variation, the overall ICC was 0.76 [$p<0.05$] and overall mean percentage error in the calculation was 8.63% for the efficacy measures. Regarding inter-observer variation, the overall ICC was 0.75 [$p<0.05$], and the overall mean percentage error was 18.0%.

eTable. Primary and derived echocardiographic measurements

	Intra-observer reliability			Inter-observer reliability		
	Bias, mean (SD)	**ICC (95% CI)**	**Mean percentage error, %**	**Bias, mean (SD)**	**ICC (95% CI)**	**Mean percentage error, %**
LVESV (mL)	15.1 (38.8)	0.73 (0.30 – 0.90)	13.3 (29.3)	23.7 (36.2)	0.73 (0.15 – 0.81)	22.2 (36.8)
LVEDV (mL)	16.1 (43.4)	0.82 (0.54 – 0.93)	8.1 (22.2)	25.8 (47.2)	0.70 (0.19 – 0.89)	15.7 (30.3)
LAVi (mL/m^2)	1.6 (8.0)	0.87 (0.68 – 0.95)	3.7 (18.8)	–6.9 (6.9)	0.89 (0.70 – 0.96)	22.4 (19.1)
LVEF (%)	3.4 (7.8)	0.62 (0.002 – 0.85)	9.4 (22.0)	4.4 (7.6)	0.68 (0.42 – 0.92)	11.8 (22.3)

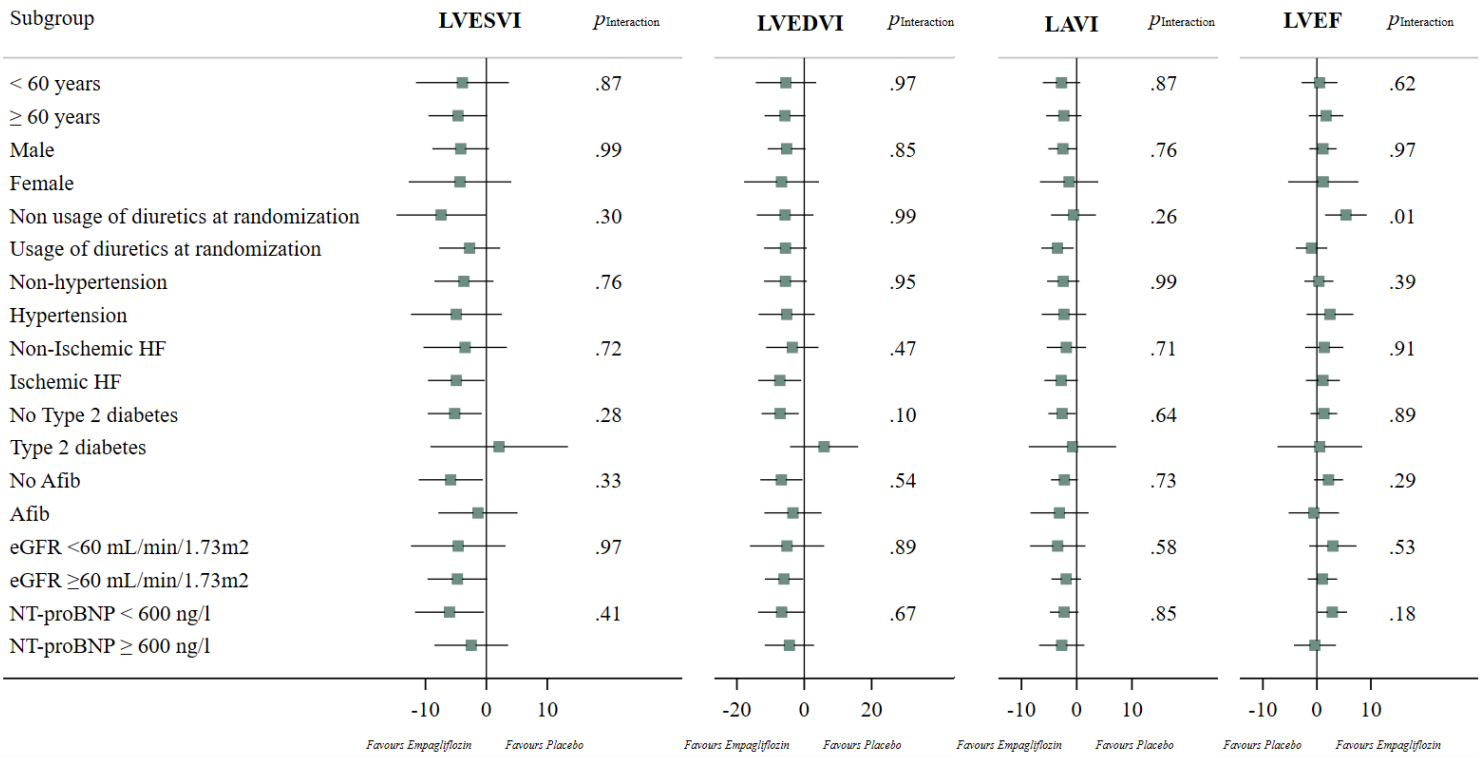
Bias are the mean differences between primary and derived measurement with (SD). ICC coefficient are the agreement between the measurements with (95% CI). ICC=Intraclass

eFigure 2. Trial profile



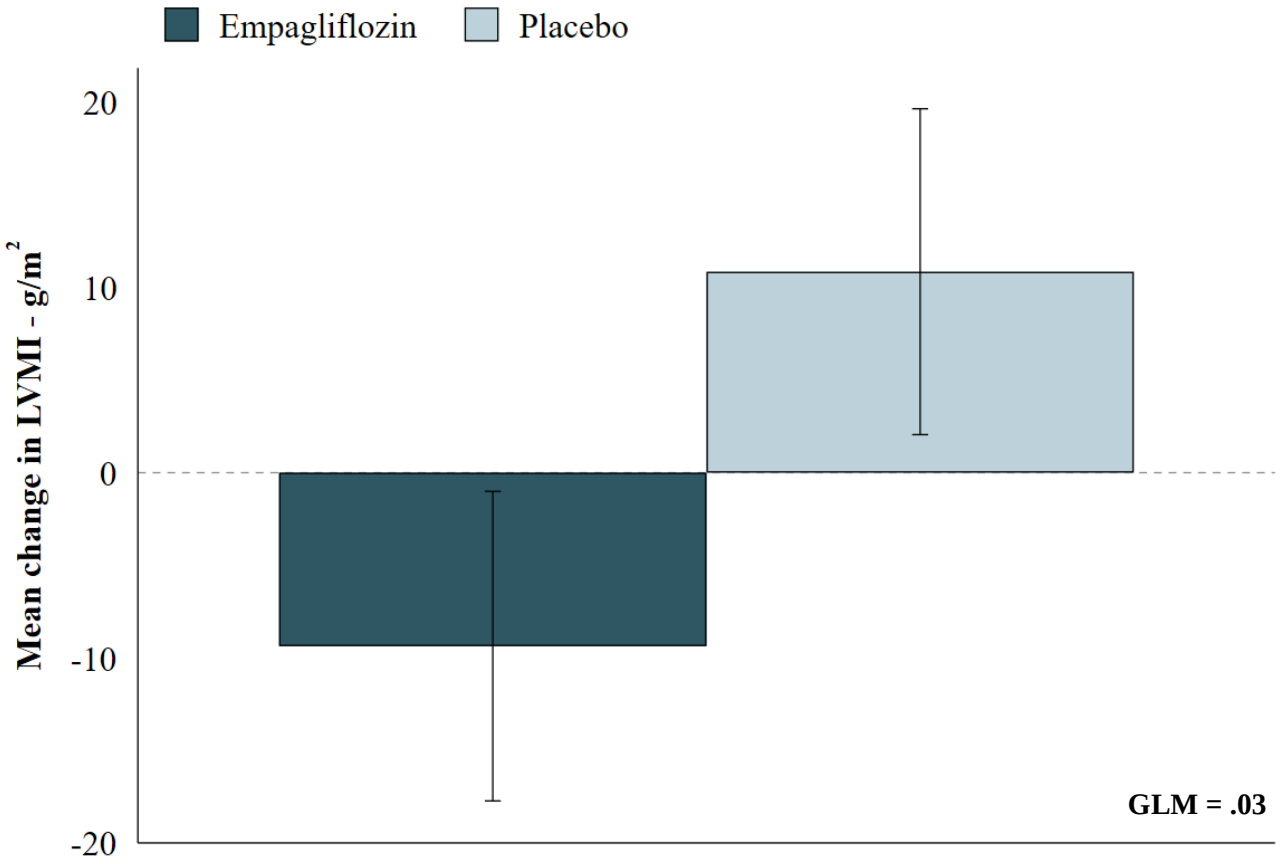
* Patients who participated at follow-up visit and underwent an echocardiography, image quality was too poor to allow estimations of left ventricular volumes and ejection fraction.

eFigure 3. Forest plot of subgroup analysis



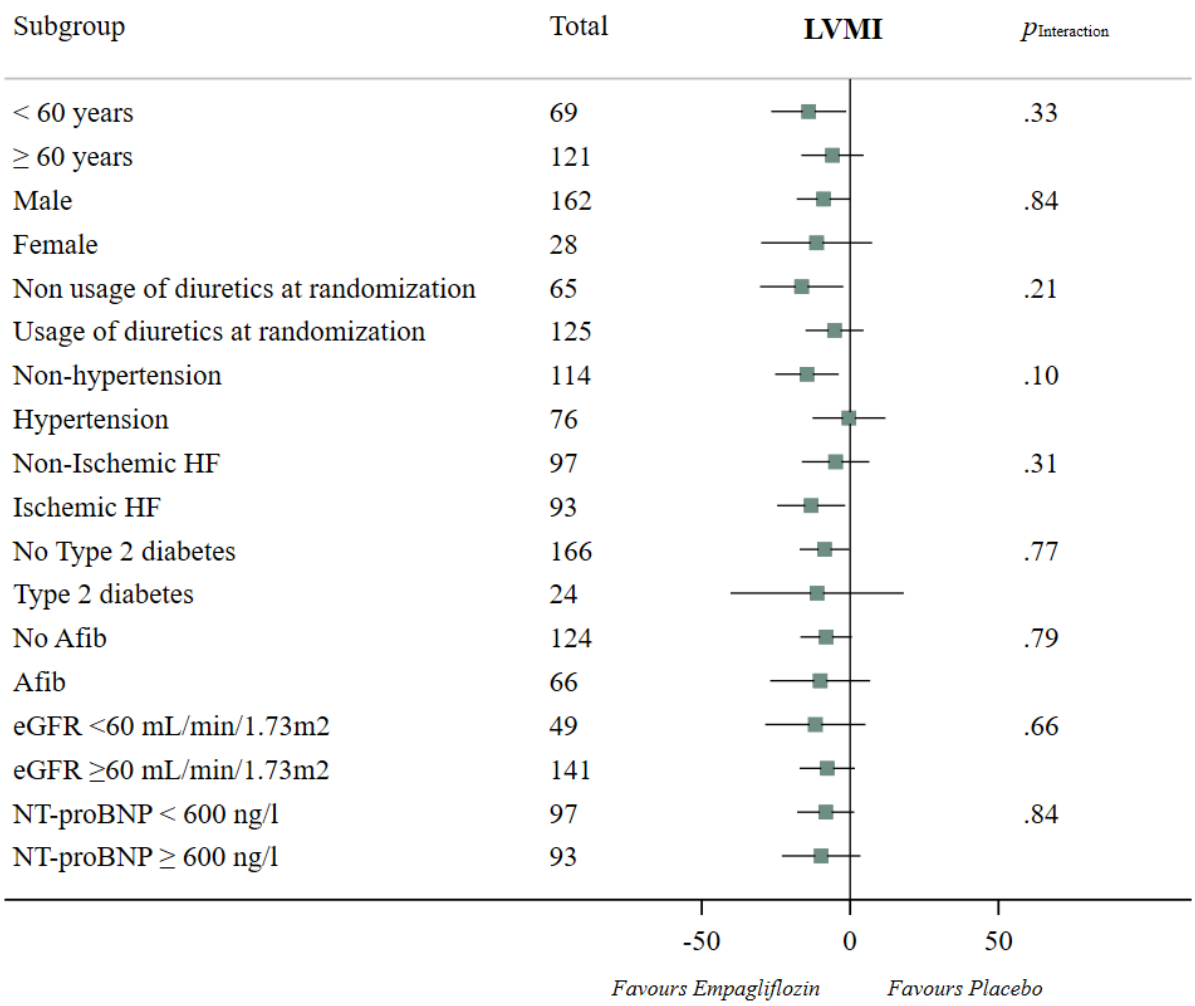
P values represents subgroups comparison correspond to test for interaction.
Abbreviations: LVESVI, Left ventricular end-systolic volume index (mL/m2); LVEDVI, Left ventricular end-diastolic volume index (mL/m2); LAVi, Left atrial volume index (mL/m2); LVEF, Left ventricular ejection fraction (%); HF, Heart failure; eGFR, Estimated glomerular filtration rate (mL/min/1.73m2); NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.

eFigure 4. Empagliflozin exposure for 12 weeks is associated with a decrease in LVMI assessed by echocardiographic imaging



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 for the intention-to-treat population after 12 weeks of treatment with empagliflozin.
The data were analyzed using General linear mixed-effect model (GLM), adjusted for baseline values, age, gender, hypertension and atrial fibrillation.

eFigure 5. LVMi outcome, according to pre-specified subgroup



P-values represents subgroups comparison correspond to test for interaction.
Treatment differences for LVMi g/m^2 from baseline to follow-up were computed using linear mixed-effect model adjusting for the corresponding baseline values of each outcome variable.
LVMi= Left ventricular mass index, HF=Heart failure, eGFR= estimated glomerular filtration rate, mL/min/1.73m^2, NT-proBNP=N-terminal fragment of the prohormone brain natriuretic peptide.