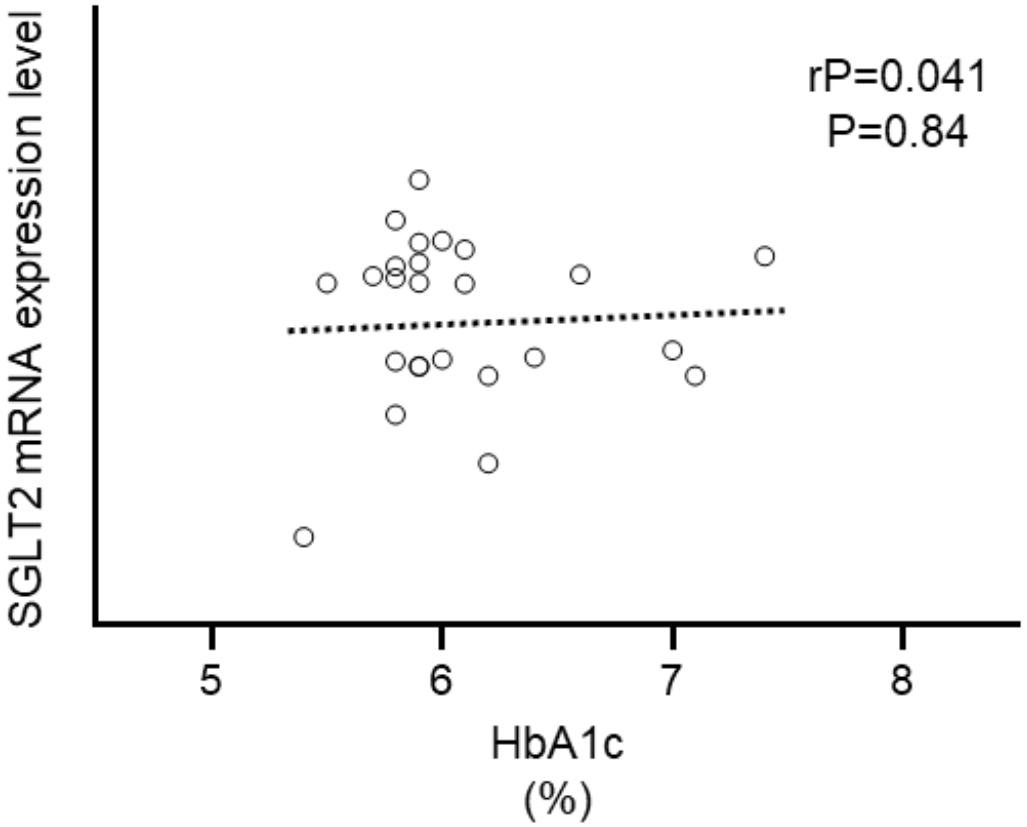
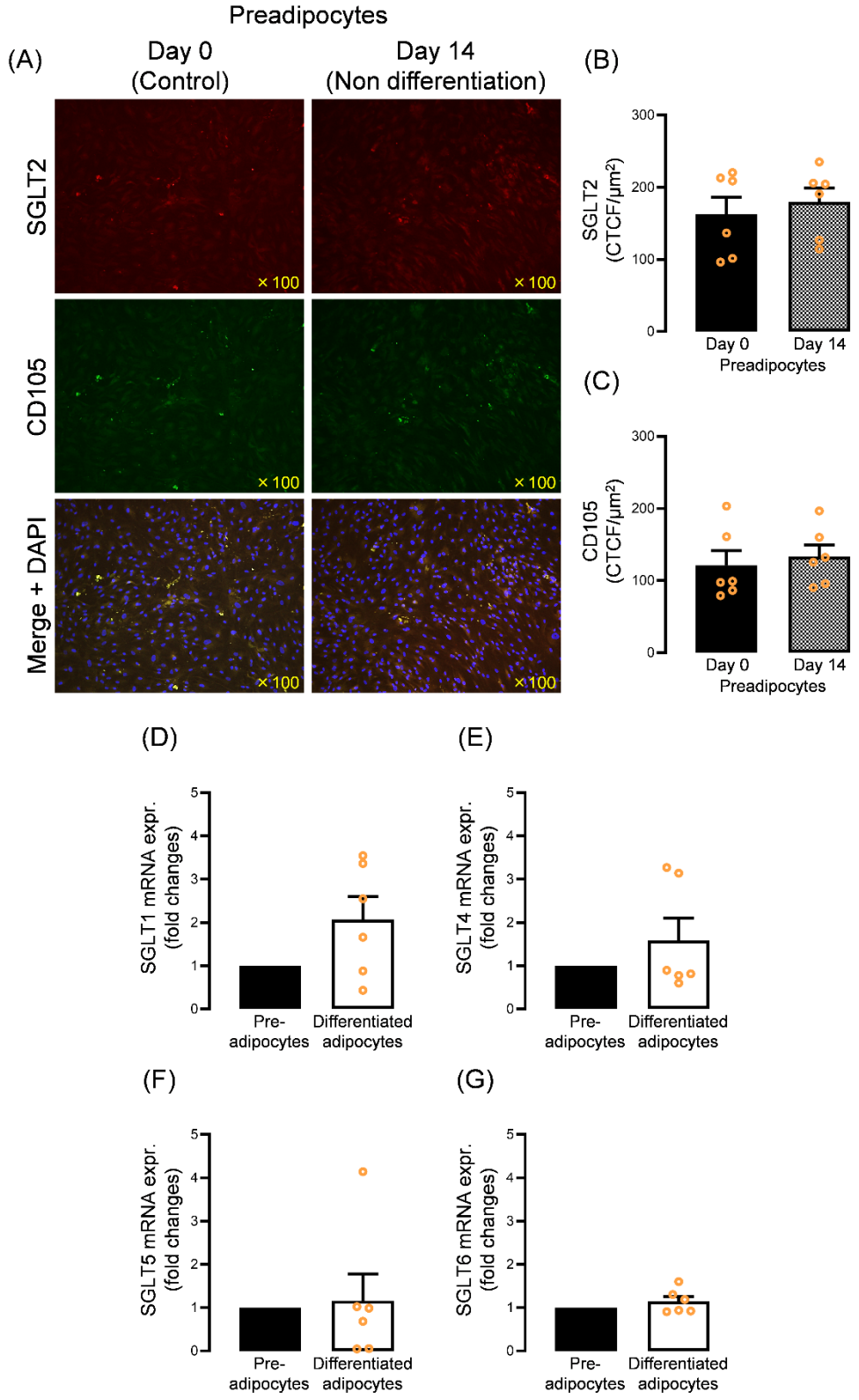
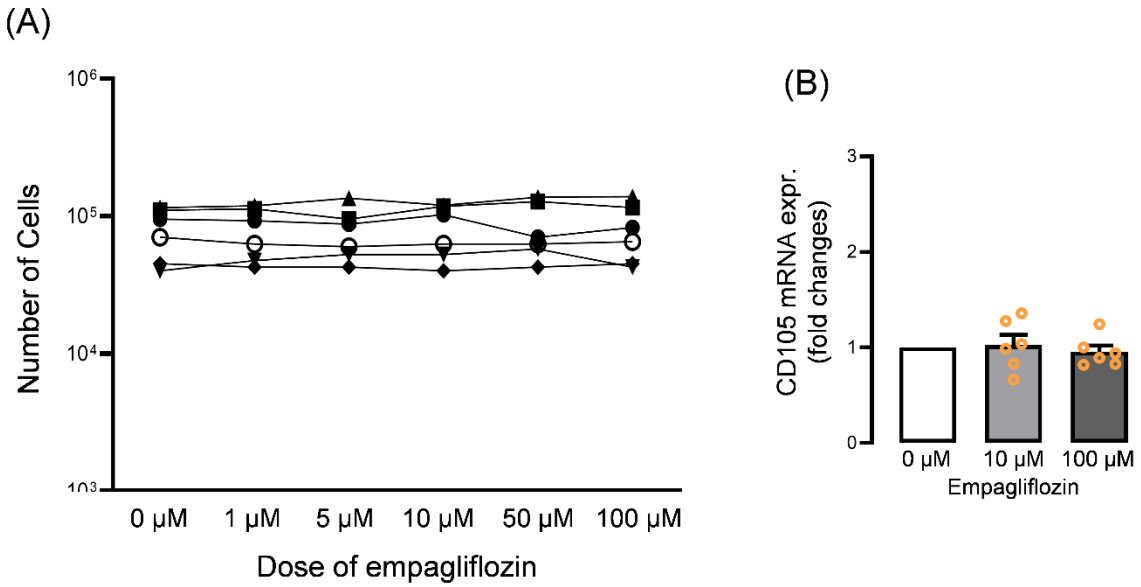
Supplemental Figure 1. There was not a significant association between *SGLT2* gene expression levels in EAT and HbA1c levels. (rP=0.041, P=0.84)



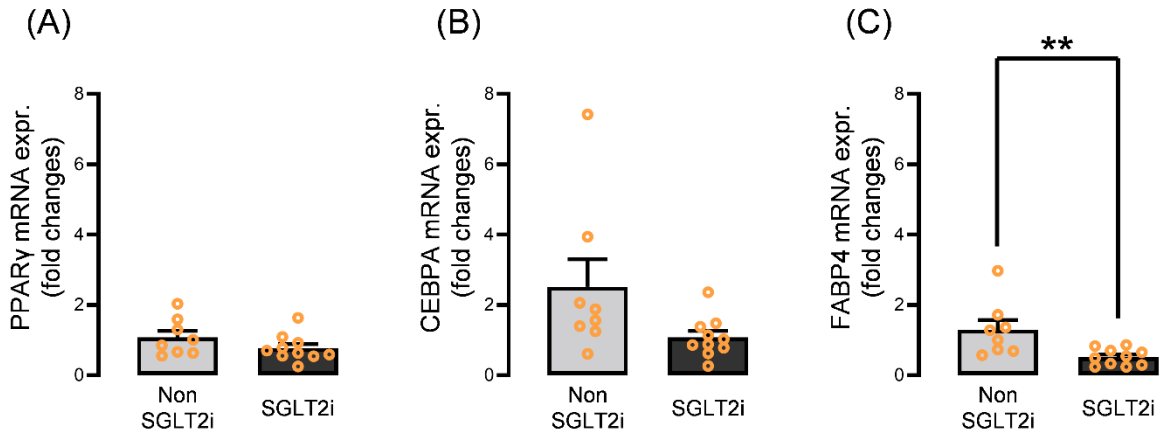
Supplemental Figure 2. (A) SGLT2 expression in preadipocyte was not decreased on day 14 without the induction of differentiation. **(B)** Quantification of SGLT2 in the preadipocyte on day 0 and day 14. **(C)** Quantification of CD105 in the preadipocyte on day 0 and day 14. *SGLT1* **(D)**, *SGLT4* **(E)**, *SGLT5* **(F)** and *SGLT6* **(G)** expression levels were not significantly reduced in the differentiated adipocyte compared with the preadipocyte. Data are presented as mean ± SD and compared using t-test.



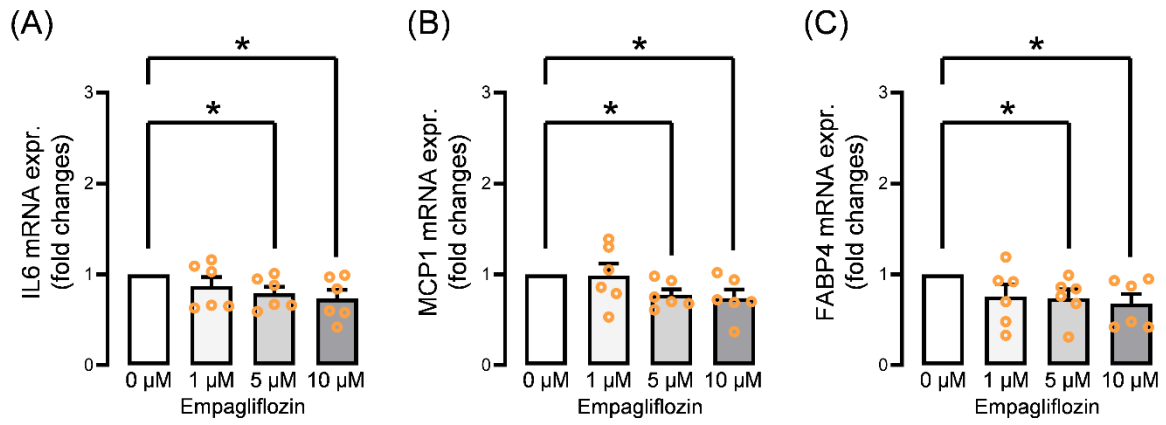
Supplemental Figure 3. (A) Proliferation of isolated human epicardial preadipocyte was not inhibited by the incubation with empagliflozin dose-dependent. **(B)** The expression of *CD105* in the preadipocyte was not affected by empagliflozin. Data are presented as mean ± SD and compared using t-test.



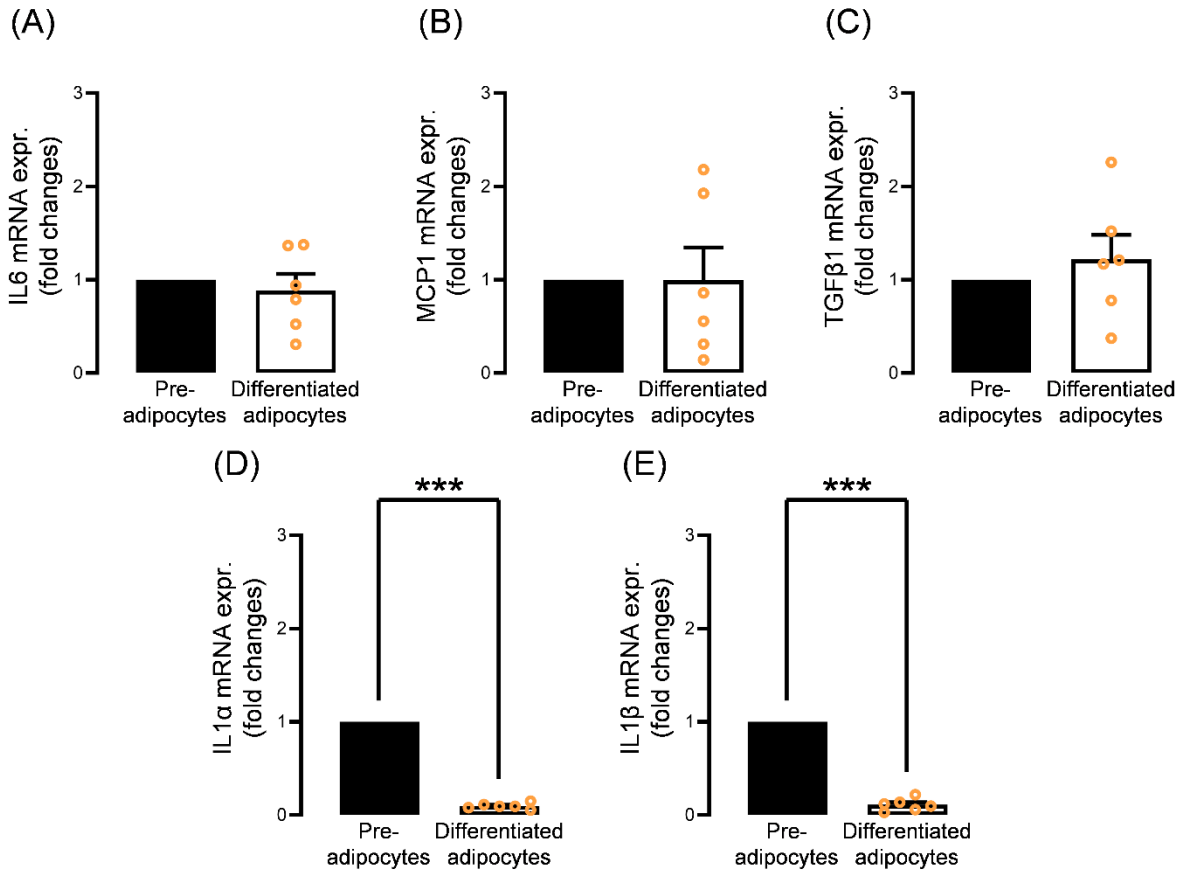
Supplemental Figure 4. Gene expression levels of *PPARγ* **(A)** and *CEBPA* **(B)** were not significantly affected, while those of *FABP4* **(C)** was significantly lower in patients receiving SGLT2 inhibitors than in patients receiving other anti-diabetic agents in the human EAT. Data are presented as mean ± SD and compared using Mann-Whitney *U*-test. **p<0.01.



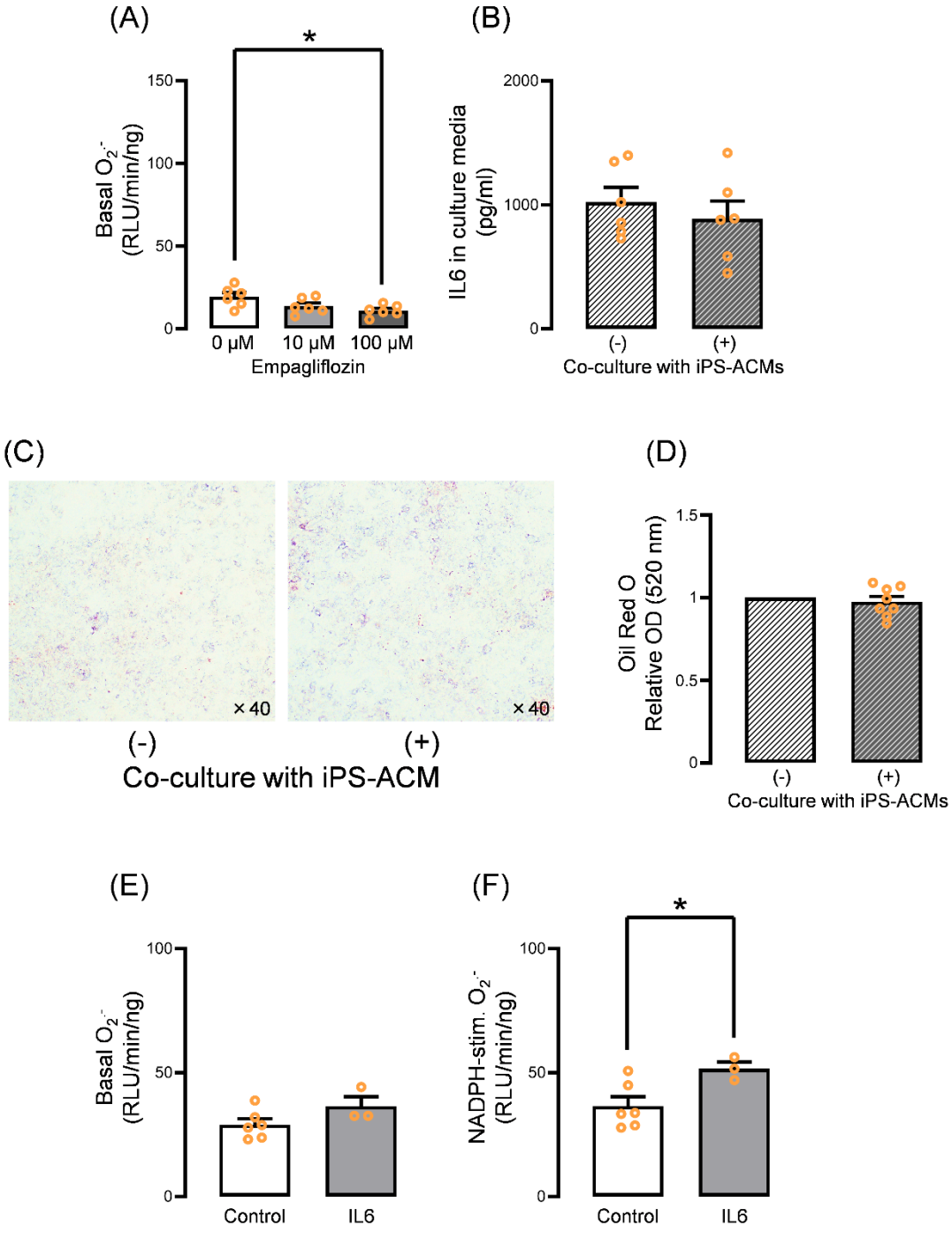
Supplemental Figure 5. Adipocytes incubated with lower doses of empagliflozin (1 μM, 5 μM, 10 μM) before differentiation showed dose-dependent downregulations of *IL6* **(A)**, *MCP1* **(B)** and *FABP4* **(C)**. The incubation with 5 μM or 10 μM empagliflozin significantly reduced *IL6*, *MCP1,* and *FABP4* mRNA expression. Data are presented as mean ± SD and compared using t-test. *p<0.05.



Supplemental Figure 6. There are no significant differences in *IL6* **(A)**, *MCP1* **(B)** and *TGFβ* **(C)** between the preadipocytes and differentiated adipocytes, while the *IL1α* **(D)** and *IL1β* **(E)** gene expression levels were significantly reduced in the differentiated adipocytes. Data are presented as mean ± SD and compared using t-test. ***p<0.001.



Supplemental Figure 7. (A) Lucigenin-enhanced chemiluminescence revealed that co-culture with empagliflozin-treated adipocytes reduced basal $O_2^{\cdot-}$ level generation in a dose-dependent manner. **(B)** IL6 protein levels in the supernatant from the adipocyte before and after the co-culture with iPS-ACM were not significantly different. Incubation of human iPS-ACM with IL6 showed increased basal $O_2^{\cdot-}$ **(C)** Co-incubation with cardiomyocyte did not affect the morphology and lipid content of the mature adipocytes (Oil-red O staining). **(D)** Oil-red O dye measured using spectrophotometer with an absorbance of 520 nm was not significantly changed after co-incubation with cardiomyocyte. **(E)** and NADPH-stimulated $O_2^{\cdot-}$ **(F)** measured using luminometry compared with the control. Data are presented as mean ± SD and compared using t-test or ANOVA. *p<0.05.



Supplemental Table 1. Demographic characteristics of the study participants in Study 2.

	Non-SGLT2i	SGLT2i	P value
Patients, n	14	15	
Age (year)	69.5 (66.5–5)	69 (66.5–74.5)	0.70
Male sex	11 (79.6%)	12 (80.0%)	0.93
BMI (kg/m^2)	22.94±3.94	24.03±2.63	0.39
Surgery (combined)			
AVR / AS, AR	3	4	
MVR / MS, MR	1	4	
CABG / AP, OMI	10	8	
Other / TAA, AAA	4	3	
Hypertension	9 (64.3%)	13 (86.7%)	0.18
Dyslipidemia	13 (92.9%)	13 (86.7%)	0.60
T2DM	14 (100%)	13 (86.7%)	0.16
NYHA functional classification			
I	3 (21.4%)	2 (13.3%)	
II	10 (71.4%)	9 (60.0%)	
III	1 (7.1%)	3 (20.0%)	
IV	0	1 (6.7%)	
Laboratory data			
TG (mg/dl)	113.14±53.71	135.20±78.49	0.38
HDL-C (mg/dl)	54.04±18.08	48.29±12.81	0.34
LDL-C (mg/dl)	83.58±17.43	103.92±37.45	0.073
FBS (mg/dl)	135.43±52.06	140.79±46.61	0.78
HbA1c (%)	7.00±0.94	7.04±0.99	0.92
Ccr (ml/min/1.73 m^2)	58.45±20.90	63.61±26.75	0.68
NT-proBNP (pg/ml)	457.5 (227.75–1033.425)	955 (174.5–2166.5)	0.40
Medication			
ACE inhibitor/ARB	11 (78.6%)	11 (73.3%)	0.75
β-blocker	2 (14.3%)	12 (80.0%)	<0.001
CCB	6 (42.9%)	6 (40.0%)	0.88

ARNI	0	0	n/a
Statin	12 (85.7%)	13 (86.7%)	0.94
Diuretic	2 (14.3%)	8 (53.3%)	0.026
SGLT2i	0	15 (100%)	n/a
DPP4i	14 (100%)	0	n/a
Insulin	0	0	n/a
Other anti-diabetics	3 (21.4%)	0	n/a
Steroid	0	0	n/a

BMI: Body mass index; AVR: Aortic valve replacement; AS: Aortic stenosis; AR: Aortic regurgitation, MVR: Mitral valve replacement; MS: Mitral stenosis; MR: Mitral regurgitation; CABG: Coronary artery bypass grafting; AP: Angina pectoris; OMI: Old myocardial infarction; TAA: Thoracic aortic aneurysm; AAA: Abdominal aortic aneurysm; T2DM: Type 2 diabetes mellitus; NYHA: New York Heart Association (functional classification); TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBS: Fasting blood sugar; HbA1c: hemoglobin A1c; Ccr: Creatinine clearance; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; ARNI: angiotensin receptor neprilysin inhibitor; SGLT2i: Sodium–glucose cotransporter two inhibitor; DPP4i: dipeptidyl peptidase four inhibitor. n/a: not applicable; n/a: not applicable; Values are presented as numbers (percentage), median [25th-75th percentiles] or mean ± standard deviation.

Supplemental Table 2. Demographic characteristics of the study participants in Study 3.

	Non-AF	AF	P value
Patients, n	19	19	
Age (year)	73 (71–74.5)	72 (69.5–76)	0.79
Male sex	8 (42.1%)	15 (79.0%)	0.020
BMI (kg/m^2)	23.20±3.92	23.08±2.80	0.92
Surgery (combined)			
AVR / AS, AR	9	9	
MVR / MS, MR	3	14	
CABG / AP, OMI	6	1	
Other / TAA, AAA	7	3	
Hypertension	16 (84.2%)	9 (47.4%)	0.016
Dyslipidemia	12 (63.2%)	7 (36.8%)	0.11
T2DM	0	0	n/a
NYHA functional classification			
I	4 (21.1%)	3 (15.8%)	
II	12 (63.2%)	11 (57.9%)	
III	3 (15.8%)	5 (26.3%)	
IV	0	0	
$CHADS_2$ score			
0–2	14	15	
3–4	5	4	
5–6	0	0	
Laboratory data			
TG (mg/dl)	135.95±62.50	85.16±41.68	0.006
HDL-C (mg/dl)	53.12±15.70	57.76±11.65	0.31
LDL-C (mg/dl)	110.17±30.13	100.02±36.44	0.36
FBS (mg/dl)	97.28±12.04	102.05±20.56	0.39
HbA1c (%)	5.92±0.41	5.81±0.46	0.42
Ccr ($ml/min/1.73\ m^2$)	69.87±39.27	59.49±25.26	0.34
NT-proBNP (pg/ml)	230 (136–485)	1373 (887.5–2083)	<0.001

Echocardiography			
LAD (mm)	38.0±6.5	49.4±5.3	<0.001
LVEF (%)	62.1±12.1	56.0±11.1	0.11
Medication			
ACE inhibitor/ARB	7 (36.8%)	12 (63.2%)	0.19
β-blocker	6 (31.6%)	13 (68.4%)	0.023
CCB	12 (63.2%)	5 (26.3%)	0.022
ARNI	0	0	n/a
Statin	11 (57.9%)	3 (15.8%)	0.006
Diuretic	1 (5.3%)	10 (52.6%)	0.001
SGLT2i	0	0	n/a
DPP4i	0	0	n/a
Insulin	0	0	n/a
Other anti-diabetics	0	0	n/a
Steroid	0	0	n/a

BMI: Body mass index; AVR: Aortic valve replacement; AS: Aortic stenosis; AR: Aortic regurgitation, MVR: Mitral valve replacement; MS: Mitral stenosis; MR: Mitral regurgitation; CABG: Coronary artery bypass grafting; AP: Angina pectoris; OMI: Old myocardial infarction; TAA: Thoracic aortic aneurysm; AAA: Abdominal aortic aneurysm; T2DM: Type 2 diabetes mellitus; NYHA: New York Heart Association (functional classification); TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBS: Fasting blood sugar; HbA1c: hemoglobin A1c; Ccr: Creatinine clearance; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; LAD: Left atrial diameter; LVEF: Left ventricular ejection fraction; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; ARNI: angiotensin receptor neprilysin inhibitor; SGLT2i: Sodium–glucose cotransporter 2 inhibitor; DPP4i: dipeptidyl peptidase 4 inhibitor; n/a: not applicable; Values are presented as numbers (percentage), median [25th-75th percentiles] or mean ± standard deviation.

Supplemental Table 3. Demographic characteristics of the study participants in Supplemental Figure 1.

Patients, n	25
Age (year)	72 (69–74)
Male sex	15 (60.0%)
BMI (kg/m^2)	22.67±3.00
Surgery (combined)	
AVR / AS, AR	11
MVR / MS, MR	11
CABG / AP, OMI	6
Other / TAA, AAA	8
Hypertension	15 (60.0%)
Dyslipidemia	15 (60.0%)
T2DM	7 (28.0%)
NYHA functional classification	
I	5 (20.0%)
II	16 (64.0%)
III	4 (16.0%)
IV	0
Laboratory data	
TG (mg/dl)	109.12±69.42
HDL-C (mg/dl)	57.40±14.80
LDL-C (mg/dl)	110.98±39.09
FBS (mg/dl)	108.29±26.96
HbA1c (%)	6.09±0.49
Ccr (ml/min/1.73 m^2)	59.59±19.58
NT-proBNP (pg/ml)	1299 (214–1488)
Medication	
ACE inhibitor/ARB	12 (48.0%)
β-blocker	11 (44.0%)

CCB	10 (40.0%)
ARNI	0
Statin	11 (44.0%)
Diuretic	9 (36.0%)
SGLT2i	2 (8.0%)
DPP4i	0
Insulin	0
Other anti-diabetics	0
Steroid	0

BMI: Body mass index; AVR: Aortic valve replacement; AS: Aortic stenosis; AR: Aortic regurgitation, MVR: Mitral valve replacement; MS: Mitral stenosis; MR: Mitral regurgitation; CABG: Coronary artery bypass grafting; AP: Angina pectoris; OMI: Old myocardial infarction; TAA: Thoracic aortic aneurysm; AAA: Abdominal aortic aneurysm; T2DM: Type 2 diabetes mellitus; NYHA: New York Heart Association (functional classification); TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBS: Fasting blood sugar; HbA1c: hemoglobin A1c; Ccr: Creatinine clearance; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; ARNI: angiotensin receptor neprilysin inhibitor; SGLT2i: Sodium–glucose cotransporter 2 inhibitor; DPP4i: dipeptidyl peptidase 4 inhibitor. Values are presented as numbers (percentage), median [25th-75th percentiles] or mean ± standard deviation.