Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 08, 2022

Impact of SGLT2 Inhibitors on Six-Minutes Walking Test and Its Relation to Diastolic Function in Heart Failure with Preserved Ejection Fraction: An Insight from Coronary Flow Reserve

Marwa M Gad, Ragab A Mahfouz, Mohammad Gouda, Baher Nabil

Cardiology Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: **Baher Nabil**, Email: baher.nashy@yahoo.com

ABSTRACT

Background: Improvement in symptoms and physical functions are the key therapy purposes in patients with heart failure with preserved ejection fraction (HFpEF), considering that this population has very poor health status.

Objective: To evaluate the influence of SGLT2 inhibitors on diastolic function and exercise tolerance in patients with heart failure with preserved ejection fraction (HFpEF) and the relation with microvascular function as mechanistic link.

Patients and methods: 93 patients with HFpEF were enrolled from Jan 2021 to October 2021. 47 patients were assigned to 10 mg empagliflozin (empagliflozin [+] group) were compared with 46 patients not assigned to empagliflozin (empagliflozin [-] group). They were followed-up for 6 months follow-up. Coronary flow reserve (CFR), E/e' and 6-minute walk test distance (6-MWTD) were assessed at baseline and at the end of planned follow-up.

Results: Changes in CFR, E/e' and 6-MWTD were significantly higher in empagliflozin (+) group than empagliflozin (-) group. In empagliflozin (+) and empagliflozin (-) groups, changes in 6-minute walk test distance were 73m and 29m respectively, the changes in E/e' were −8.47±0.13 and −4.4±0.09 (0.003). The changes in LAVI were 8.8±1.1vs -3.5±0.9 (<0.05) and LAMI were -10.3±2.1vs-3.3±0.7 (p<0.05). Whilst the changes in CFR were 0.81±0.05 and 0.11±0.01 (<0.001) respectively. Multivariate analysis revealed that CFR (β coefficient was [7.16]; *p*<0.001), E/e' (*p*<0.05) were independent predictors of improved 6-MWTD in HFpEF patients assigned for empagliflozin.

Conclusions. Patients with HFpEF assigned to 10 mg empagliflozin, had significant improvement in exercise tolerance, a remarkable finding which is significantly linked to improved microvascular function associated with improved diastolic function in HFpEF patients.

Keywords: SGLT2 Inhibitors, Exercise Tolerance, Heart Failure

INTRODUCTION

In heart failure with preserved ejection fraction (HFpEF) patients, improvement in symptoms and physical functions are the main goals of management, given that, this population has especially poor health status [(1).] The clinical outcomes and mortality of HFpEF are similar to those in heat failure patients with reduced ejection fraction (HFrEF) [(2,3,4)]. In contrast to HFrEF, there is no established treatment for *HFpEF*, despite the increasing its frequency and recurrent hospitalization [(5)].

Although SGLT2 inhibitors have demonstrated a reduction in heart failure adverse outcomes even in non-diabetic patients, the mechanisms of their cardiovascular benefits are still not clearly understood [(6 ,7)]. Many studies revealed that SGLT2 inhibitors have variable mechanisms of action and were shown to decrease the risk of cardiovascular mortality or worsening HF, and to improve functional status in subjects with HFrEF, irrespective of diabetes status [(8, 9, 10).]

It is known that SGLT2 expression in the normal or failed heart is insignificant and SGLT2 inhibitors do not bind to heart muscles. In addition the mechanisms mediating the usefulness of empagliflozin in subjects with HFpEF mostly remain uncertain **(11, 12)**.

We aimed to investigate the impact of SGLT2i on exercise tolerance and its association with diastolic function in patients with HFpEF and to assess their relation to improved CFR as a putative mechanistic link.

PATIENTS AND METHODS

One hundred and nine patients with or without type-2 DM and clinical diagnosis of HFpEF were enrolled for the study. LVEF $\geq$ 45% and screening for NYHA class II–IV symptoms for participants. Patients additionally had to have elevated natriuretic peptides (BNP $\geq$ 75 pg ml^{-1}; if AF, or BNP $\geq$ 100 pg ml^{-1}).

All patients thoroughly underwent a full diagnostic work-up at baseline. The diagnosis HFpEF was based on the *European Society of Cardiology* heart failure guidelines **(7)**.

Patients with acute coronary syndromes, restrictive or infiltrative cardiac disease inflammatory diseases, pulmonary hypertension and pulmonary diseases, cardiac devises, Stroke or transient ischemic attack within the last 12 weeks, acute decompensated HF or hospitalization due to decompensated HF <4 weeks prior to enrolment, eGFR <25 mL/min/1.73 m^2 (CKD-EPI formula) at registration, receiving therapy with an SGLT2 inhibitor within the last 4 weeks and type 1 diabetes or previous history of DKA were excluded from the study.

All patients underwent a physical examination, laboratory assessments, completion a 6MWT, echo-Doppler evaluation and assessment of coronary flow reserve at baseline. Based on the assigned medications at this point, subjects were stratified into the SGLT2 inhibitors [empagliflozin (+)], who assigned for their ongoing treatment group and [empagliflozin (-)] group, included patients continued their current medications.

Patients then entered a 6-months follow-up treatment period, during which patients were followed-up clinically every month. Echo-Doppler assessment, 6 MWT and reevaluation of CFR at the end of the 6 months.

Six minutes walking test

Patients underwent 6-MWT test based on a standardized protocol as described by Gyatt et al.**(13)** The purpose of the test was explained for all participants. Briefly, the patients underwent the test by crossing back and forth along a marked corridor on a hard, flat surface. The walking distance was measured after the patients had walked as far as possible in 6 minutes.

Echocardiographic examination

A full echocardiographic assessment including standard transthoracic 2D and Doppler echocardiography with the use of profound systolic and diastolic functional

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 08, 2022

indices was achieved using the VIVID 7ultrasound machine (*GE Healthcare Systems, Horten, Norway*) *with* a 2.0–3.5-MHz) according to *the American Society of Echocardiography guidelines*. [14]

Saved images were analyzed offline. Left ventricular (LV) internal dimensions and wall thickness, chamber volumes, and valvular morphology were assessed. LV mass index was obtained from LV mass measurement using standard criteria and normalized for body size (body surface area or height to the power of 1.7). Modified Simpson's method was used to calculate left ventricular ejection fraction (LVEF %). Left atrial volume index *(LAVI ml/m^2)*, E and A wave velocities of trans- mitral flow were obtained. Mitral annular velocities early (e') and late (a') velocities were obtained by Tissue Doppler imaging. Then septal and lateral E/e' ratios were calculated, and the mean E/e' ration was obtained as a marker of LV filling pressure.

Coronary flow reserve (CFR) assessment

With a high frequency transducer (5 to 7 MHz) and the guidance of color Doppler flow mapping, the distal portion of the left anterior descending artery (LAD) was imaged at modified apical 4 chamber view **(Figure 1)**. A 2.5 mm sample volume was placed on the left anterior descending coronary artery color-flow signal to obtain coronary flow spectral tracing. Doppler signal was obtained at rest and the peak diastolic velocity was recorded. Then, IV adenosine was administered (0.14 mg/kg/min) to record the hyperemic peak diastolic velocity. The average of three peak diastolic velocities was obtained of both at baseline and hyperemia. After that, we calculate the coronary flow reserve as the ratio of peak hyperemic diastolic velocity over baseline peak diastolic velocity. Coronary flow reserve ≤2.5 was considered a microvascular dysfunction. [15] To determine the reproducibility of CFR, a total of 20 randomly selected evaluations were examined twice by one investigator at a 1-week interval and once by another investigator.

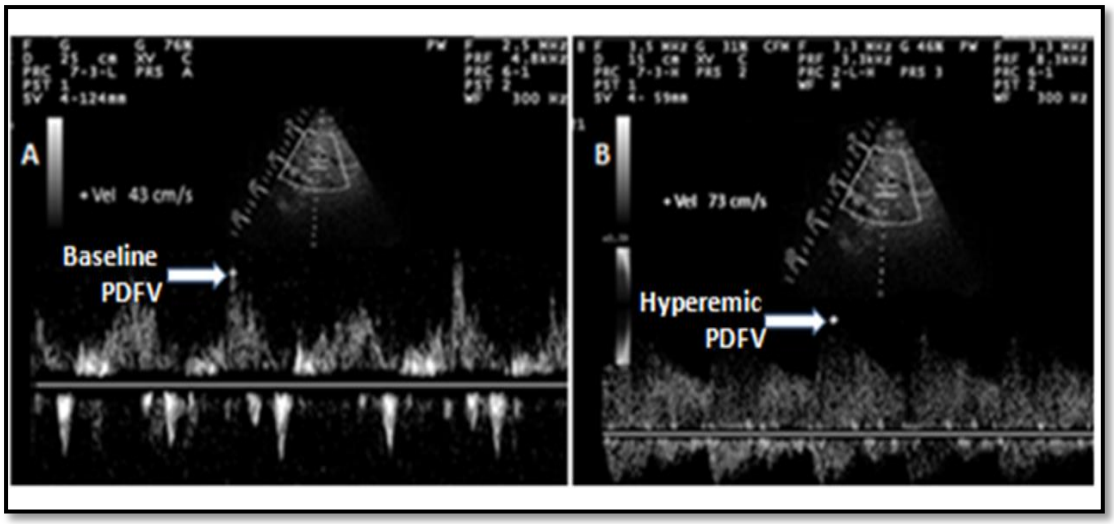

Figure (1): Spectral Doppler image with transthoracic echocardiography of coronary flow.**A-** Baseline peak Diastolic Coronary Flow Velocity (Baseline PDV). **B-**Hyperemic peak Diastolic Coronary Flow Velocity (Hyperemic PDV).

Ethical Consideration:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Mean± standard deviation was used for descriptive data, while number and percentage represent the dichotomous data. The independent–samples t-test was used for the comparison between groups, while the Kruskal–Wallis test was used for comparison of non-normally distributed variables. Spearman's correlation analysis was used to correlate the variable changes and improved exercise tolerance. Multiple regression analysis was performed to determine the independent predictors for improved exercise tolerance and reported as hazard ratio (HR) with 95% confidence interval. Analyses were achieved with software (SPSS 22, IBM, Chicago, IL). P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

One hundred and nine patients with HFpEF were enrolled, 16 patients were excluded; 9 due to inadequate image quality for CFR evaluation and 7 patients lost during follow-up. Finally, 93 patients entered the current study. 47 of them were assigned to empagliflozin 10 mg/day [Empagliflozin (+) group] and 46 patients continued treatment without empagliflozin [Empagliflozin (-)].

We did not find any significant differences in basal characteristics between both groups**.** Table 2 represents the differences between baseline data and 6 months data of both groups. The results revealed that that BMI, SBP, and TG significantly decreased in empagliflozin(+) group. On contrary, there was no significant changes in empagliflozin(-)group. Regarding echocardiographic data, as represented in table 3, we found that patients in empagliflozin(+) group had significant decrease in E/e' (p<0.01), LVMI (p<0.05), whereas CFR significantly (p<0.001) increased in empagliflozin(+) group. On the other hand, these parameters were not changed significantly in empagliflozin (-) group **(Table 1)**.

In summary, at six months assessment, the mean change in body weight was (−5.5±3.1Kg), systolic blood pressure was (18.5±7.5mmHg), diastolic blood pressure was (−9.1±3.5mmHg), Triglycerides (−40±11mg/dl), fasting glucose (−35±9mg), eGFR (22 ± 4.5ml/min) and the mean changes of 6MWT distance was (106±14m). As regard to echocardiographic data, the mean changes were as follow, E/e' ratio was (8.49±0.13), LAVI (−6.8±1.1ml/m^2), LVMI (11.3±4.1gm/m^2) and CFR was (0.86±0.05). All these mean changes were significantly higher in empagliflozin (+) group compared with the mean changes in empagliflozin (-) group **(Table 2, 3)**.

Table (1): Baseline characteristic of study patients

Variable	Empagliflozin (+) (n=47)	Empagliflozin (-) (n = 46)	P value
Age, years	59.1 ± 5.9	59.8 ± 6.3	0.65
Male, n (%)	31(66)	28(61)	0.81
Body mass index, kg/m2	26.8 ± 4.2	27.3 ± 4.4	0.33
Diabetes, n (%)	18(38)	16(35)	0.85
Hypertension, n (%)	33(70)	32(69.5)	0.97
Smoking habit, n (%)	19(40.4)	20(43.5)	0.91
Dyslipidemia, n (%)	22(47)	24(52)	0.65
Coronary artery disease, n (%)	11(23.4)	13(28.3)	0.45
History of HF or systolic LV dysfunction, n (%)	0(0)	0(0)	1.00
LV hypertrophy, n (%)	26(55.3)	23(50)	0.75
Functional class			
NYHA Class II, n (%)	30 (63.8)	32 (69.6)	0.78
NYHA Class III/IV, n (%)	17(36.2)	14 (30.4)	0.46
ACE inhibitors/ARBs, n (%)	37(78.7)	38(82.6)	0.96
Diuretics, n (%)	29(61.7)	30(65.2)	0.87
Calcium channel blockers, n (%)	15(32)	13(28.3)	0.88
Beta blocker, n (%)	16(34)	18(39)	0.87
Statins, n (%)	20(42.6)	22(47.8)	0.93
Anti-platelets, n (%)	16(34)	17(36.9)	0.97

Table (2): Comparison of variables change between baseline and 6 months in empagliflozin (+) group versus empagliflozin (-)

Variables	Empagliflozin (+) N= 47		Empagliflozin (-) N= 46		P value
	Baseline	At 6 months	Baseline	At 6 months N= 46	
Body weight (kg)	59.7±11.5	54.0±8.3*	60.5±11.2	59.5±11.0	
Δ		−5.5±3.1		−0.9±0.1	<0.05
SBP (mmHg)	139.8±17.5	121.5±10.3**	140.3±19.6	132.8±14.5*	
Δ		−18.5±7.5		−8.4±6.3	<0.01
DBP (mmHg)	81.5±9.5	73.5±7.3*	80.2±10.3	76.0±8.9*	
Δ		−9.1±3.5		−4.6±2.2	>0.05
TC (mg/dL)	231±29	168±22	239±25	199±27	
Δ		−63 ±15		−41 ±15	>0.05
LDL-C (mg/dL)	117±19	108±12	115±16	109±15	
Δ		−9±4		-6±2	>0.05
HDL-C (mg/dL)	58±10	58±9	60±11	60±8	
Δ		−1.0±0.10		−1.0±0.2	>0.05
TG (mg/dL)	248±71	207±40*	243±67	239±60	
Δ		−40±11		4±3	<0.05
FPG (mg/dL)	146±31	110±17**	142±31	139±29	
Δ		−35±9		−3±3.0	<0.03
BNP (pg/mL)	217±35	205±31	209±29	198±20	
		-12±4		−10±4	0.71
Creatinine, mg/dl	1.29 ± 0.3	0.93 ± 0.2*	1.21 ± 0.3	1.17 ± 0.2	
Δ		-0.37 ± 0.1		-0.05 ± 0.01	
eGFR (ml/min/1.73 m^2)	75.7 ± 12.5	98.5 ± 18.0*	77.5 ± 15.8	79.6±17.5	
Δ		22 ± 4.5		2.1 ± 1.4	<0.05
6-MWTD	255±23	361±37**	268±20	285±26	
Δ		106±14		18±5	<0.001

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 08, 2022

Table (3): Comparison of echo-parameters between baseline and 6 months in empagliflozin (+) group versus placebo group

Variables	Empagliflozin (+) N= 47		placebo group N= 46		P value
	Baseline	At 6 months	Baseline	At 6 months	
EF%	54.6±3.9	55.6±4.1	54.9±3.8	55.5±3.5	
Δ		0.7±0.5		0.9±0.4	>0.05
Mean E/e'	15.60±2.37	7.15±1.65**	15.25±2.59	10.95±1.90*	
Δ		−8.47±0.13		−4.4±0.09	<0.003
LAVI,mL/m^2	32.5 ± 6.1	23.8 ± 4.3*	32.9 ± 6.5	29.5± 6.05	
Δ		-8.8±1.1		-3.5±0.9	<0.05
LVMI (g/m^2)	98.7 ± 20.5	89.1± 14.2**	97.5 ± 20.3	94.3± 25.5	
Δ		-10.3±2.1		-3.3±0.7	<0.05
Resting Diastolic PV, m/s	31.5 ± 11.5	31.2 ± 13.0	32.1 ± 10.0	31.7 ± 11.4	
Δ					<0.05
Hyperemic Diastolic PV, m/s	50.9 ± 17.1	73.9 ± 23.5	51.2 ± 10.7	55.8 ± 12.5	
Δ					<0.001
CFR	1.62±0.07	2.41±0.21**	1.60±0.06	1.73±0.08	
Δ		0.81±0.05		0.11±0.01	<0.001

EF: Ejection fraction, LAVI: left atrial volume index, LVMI: Left ventricular mass index, PV: Peak velocity, CFR: Coronary flow reserve.

Interestingly, 6 months empagliflozin prescription increased 6MWTD significantly. This improvement in 6MWTD was significantly associated with the Δmean E/e' (r=-0.33; p<0.03), LAVI (r=-0.39; p<0.03) and ΔCFR (r=−0.61; p<0.001) **(Table 4)**.

Furthermore, the E/e' inversely correlated with the CFR (−r=0.57; p<0.001) **(Figure 2)**.

On performing multiple regression analysis, we found that improved exercise tolerance in HFpEF Empagliflozin (+) group was influenced significantly by increased CFR (95% CI: 3.51-10.85; p<0.001), decreased E/e' (95% CI: −5.23 to 1.65, p<0.03) **(Table 5)**.

Table (4): Correlation between the changes of variables and exercise tolerance in patients with HFpEF assigned for Empagliflozin

Variables	r	P value
Δ Body weight	0.19	0.40
Δ Systolic blood pressure	0.25	<0.05
Δ E/e′	0.31	<0.03
Δ LAVI	0.39	<0.03
Δ LVMI	0.15	0.47
Δ Coronary flow reserve	0.63	<0.001

LAVI: left atrial volume index, LVMI: Left ventricular mass index.

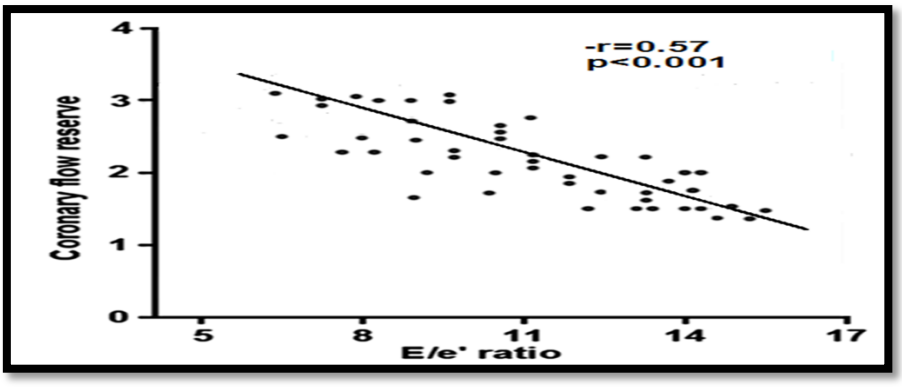

Figure (2): Correlation between E/e' ratio and Coronary Flow Reserve

Table (5): Multiple regression analysis for the association of 6MWTD after 6 months administration of empagliflozin

Variables	Standardized coefficient β	95% CI	P-value
Δ Body mass index	−1.92	−4.30- 0.59	0.45
Δ Systolic blood pressure	−1.89	−4.21 to 0.55	0.31
Δ E/e'	−3.59	−5.23 to 1.65	<0.03
Δ LAVI	− 1.93	−2.79 - 1.46	0.16
Δ LVMI	−1.34	−1.03-1.52	0.57
Δ CFR	7.16	3.51-10.85	<0.001

LAVI: left atrial volume index, LVMI: Left ventricular mass index.

DISCUSSION:

The results of the current study indicate that exercise tolerance, assessed in terms of 6 MWTD for patients with HFpEF with or without DM, had significantly improved 6 months after the addition of 10 mg of empagliflozin to their ongoing treatment. We noted a significant association between improved exercise tolerance and diastolic function. Intriguingly, CFR significantly increased in HFpEF patients assigned for SGLT2 inhibitor [empagliflozin (+)] compared with [empagliflozin (-)], an important finding of improving microvascular function, which could explain improved diastolic parameters and exercise tolerance in patients with HFpEF with or without diabetes mellitus after the addition of SGLT2 inhibitors to their current medications.

Zinman, et al. [16] reported that SGLT2i had direct physiologic evidence support the clinical significance of SGLT2 inhibitors cardiovascular diseases. Shah, et al. [17] demonstrated that in HFpEF patients without coronary artery disease, coronary flow reserve was correlated with peripheral endothelial function. Furthermore, **Buus, et al.** [18] reported that endothelial dependent and independent functions are important determinants of coronary microvasculature function; in addition, they found that coronary flow reserve improved as L-arginine/ADMA ratio improved.

Patients with HFpEF have a considerable reduced exercise tolerance as evaluated with physical function tests, even with stable compensated status. [19]

Noticeably, limited physical activity is an independent predictor of unfavorable outcome including rehospitalization, poor quality of life, failure of independence and death [(20)].

In the present study, at the end of 6 months follow-up, there was significant reduction in body weight and systolic blood pressure, in addition to improved CFR, reduction in the mean E/e', and LAVI. These observed SGLT2 inhibitors benefits could be suggested potential mechanisms translate to improvements in exercise tolerance in HFpEF patients.

Nassif, et al. (21) reported that SGLT2 inhibitors have been shown to decrease pulmonary artery pressure, which decreases congestion. Furthermore, several studies stated that SGLT2 inhibitors improve systemic microvascular and systemic endothelial function; reduce systemic inflammation and oxidative stress; and improve insulin sensitivity and activate fatty acid oxidation in the skeletal muscle. [(22, 23)]

Van Heerebeek, et al. [(24)] stated that coronary microvascular endothelial dysfunction is an important determinant in HFpEF. Besides, in HFpEF, impaired coronary microvasculature endothelial function ambitions left ventricular remodeling and dysfunction by reducing the bioavailability myocardial nitric oxide and protein kinase-G activity.

Recent data from an animal model (ob/ob−/− animals) has demonstrated that SGLT2 inhibitors tend to improve coronary microvascular function and contractile performance. [(25)]

In HFpEF, sympathetic nerve activity enhanced significantly, associated with significant reduction in the baroreceptor reflux response through negative feedback, which results in vasoconstriction, accelerated heart rate and water retention. Administration of SGLT2 inhibitors to HFpEF patients may suppress this pathway. [(26)]

SGLT2 inhibition increases L-arginine/ADMA ratio resulted in improved coronary microvascular function via improved NO-dependent endothelial function. Formerly, Westergren, et al. [(27)] demonstrated that plasma levels of L-arginine in ob/ob$^{-/-}$ mice is lower compared to lean mice, signifying nitric oxide pathway dysfunction.

Study Limitations:

First, single center study. Second, a relatively small number of patients recruited for the study. Third, relatively short –term follow-up period.

CONCLUSION:

We suggested that SGLT2 inhibitors might improve exercise tolerance and diastolic function in HFpEF patients with or without DM. Furthermore, SGLT2 inhibitors increased CFR significantly, an important finding, which could explain the improved exercise tolerance in patients with HFpEF, assigned for SGLT2 inhibitors.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally in the study.

REFERENCES:

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251–59.

2. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT. Systolic and diastolic heart failure in the community. JAMA 2006; 296: 2209–16.

3. Berry C, Hogg K, Norrie J, Stevenson K, Brett M, McMurray J. Heart failure with preserved left ventricular systolic function: A hospital cohort study. Heart 2005; 91: 907–13.

4. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260–69.

5. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP. Get with the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. Circulation 2012; 126: 65–75.

6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.

7. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.

8. Nassif, M. E., Windsor, S. L., Tang, F., Khariton, Y., Husain, M., Inzucchi, S. E.. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation, (2019); 140(18), 1463-1476.

9. McMurray, J. J., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Langkilde, A. M. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine, 2019; 381(21),1995-2008.

10. **Cowie, M. R. & Fisher, M.** SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat. Rev. Cardiol. 2020; 17, 761–72.

11. **Di Franco, A., Cantini, G., Tani, A., Coppini, R., Zecchi-Orlandini, S., Raimondi, L., Mannucci, E.** Sodium-dependent glucose transporters (SGLT) in human ischemic heart: a new potential pharmacological target. International journal of cardiology, 2017;243, 86-90.

12. Ghezzi C, et al. Dapagliflozin binds specifically to sodium-glucose cotransporter 2 in the proximal renal tubule. J Am Soc Nephrol. 2017;28(3):802–10.

13. Guyatt GH, Sullivan MJ, Thompson PJ. The 6-min walk test: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985, 132:919–23.

14. **Nagueh SF, Smiseth OA, Appleton CP, et al.** Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

15. **Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman A.** Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. JACC Cardiovasc Interv 2015; 8: 1445–53.

16. **Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.

17. **Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan R-S, Beussink-Nelson L, Ljung Faxén U, Fermer ML, Broberg MA, et al.** Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018;39(37):3439–50.

18. **Buus NH, Bottcher M, Hermansen F, Sander M, Nielsen TT, Mulvany MJ.** Influence of nitric oxide synthase and adrenergic inhibition on adenosine-induced myocardial hyperemia. Circulation. 2001; 104(19):2305–10.

19. **Wolsk, E. et al.** Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction. Eur. J. Heart Fail. 20, 715–22 (2018).

20. **Juni, R. P. et al.** Cardiac microvascular endothelial enhancement of cardiomyocyte function is impaired by inflammation and restored by empagliflozin. JACC Basic Transl. Sci. 4, 575–91 (2019).

21. **Nassif, M. E. et al.** Empagliflozin effects on pulmonary artery pressure in patients with heart failure. Circulation 143, 1673–86 (2021).

22. **Shah, S. J. et al.** Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur. Heart J. 39, 3439–50 (2018).

23**. Nambu, H. et al.** Empagliflozin restores lowered exercise endurance capacity via the activation of skeletal muscle fatty acid oxidation in a murine model of heart failure. Eur. J. Pharmacol. 866, 172810 (2020).

24. **Van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, et al.** Diastolic stiffness of the failing diabetic heart: Importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation 2008; 117: 43–51.

25. **Damilola D. Adingupu, Sven O. Göpel, Julia Grönros; et al.** SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic ob/ob−/− mice. Cardiovasc Diabetol 18, 16 (2019).

26. **Sano M**. Hemodynamic effects of sodium-glucose cotransporter 2 inhibitors. J Clin Med Res 2017; 9: 457–60.

27. **Westergren HU, Gronros J, Heinonen SE, Miliotis T, Jennbacken K, Sabirsh A, Ericsson A, Jonsson-Rylander AC, Svedlund S, Gan LM.** Impaired coronary and renal vascular function spontaneously in type 2 diabetic leptin-deficient mice. PLoS ONE. 2015;10(6):e0130648.