VER
Vascular & Endovascular Review

Impact of Empagliflozin on Left Ventricular Mechanics using 3-D Echocardiography in Heart Failure Patients with Reduced Ejection Fraction

Ahmed M. Alashry[1], Arafa G Ibrahim[1], Mohamed Omar[1], Wael Attia[2], Amr Abdel Aal[1]

[1]Cardiology Department, Faculty of Medicine, Helwan University, Egypt
[2]Cardiology Department, Faculty of Medicine, Al Azhar University, Egypt

***Corresponding author:** Mohamed Omar Khalifa
Email: m.omercardio@gmail.com

ABSTRACT

Background: Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated notable clinical benefits in cases with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetic status. However, underlying impacts of empagliflozin on myocardial systolic mechanics, particularly at the myocardial level, remain incompletely understood.

Method: This prospective cohort study that included non-diabetic patients with HFrEF (left ventricular ejection fraction (LVEF) ≤40%) who were naïve to empagliflozin therapy and have been on optimal guidelines directed medical treatment for a minimum of 6 months. All patients were evaluated at baseline and after 6 months from the initiation of empagliflozin. Conventional, three-dimensional, and speckle-tracking echocardiography were used to evaluate left ventricular volumes, ejection fraction, myocardial strain parameters (GLS, GCS, GAS, and GRS), and structural remodeling. Functional status was assessed using NYHA classification and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Result: A total of 150 non-diabetic patients with HFrEF were included in the study, with a mean age of 56.6 ± 9.7 years, 36% were female. After 6 months of empagliflozin therapy, patients demonstrated a significant improvement in left ventricular systolic function, with a marked increase in LVEF and significant reductions in left ventricular end-diastolic and end-systolic volumes ($p < 0.001$). In addition, significant improvements were also observed in myocardial deformation parameters, including GLS, GCS, GAS, and GRS (all $p < 0.001$). Additionally, LV mass index, left atrial volume index, and pulmonary artery systolic pressure significantly decreased. Functional capacity improved markedly, with reduction in NYHA class and significant increase in KCCQ score ($p < 0.001$).

Conclusion: These results support the myocardial-level benefits of empagliflozin beyond glycemic control and reinforce its role as a cornerstone therapy in HFrEF irrespective of diabetic status.

KEYWORDS: SGLT2 inhibitors, Heart failure with reduced ejection fraction, 3D echocardiography, Speckle-tracking strain, Ventricular remodeling.

How to Cite: Ahmed M. Alashry1, Arafa G Ibrahim1, Mohamed Omar1, Wael Attia2, Amr Abdel Aal1, (2024) Impact of Empagliflozin on Left Ventricular Mechanics using 3-D Echocardiography in Heart Failure Patients with Reduced Ejection Fraction, Vascular and Endovascular Review, Vol.7, No.1, 44-49

INTRODUCTION

About 21 million adults worldwide suffer from heart failure, which is a rapidly expanding epidemic. The disease also has a significant financial impact, with an estimated 108 billion dollars spent on it globally (1), Heart failure is the main reason of hospitalization for patients above the age of 65 years with poor prognosis as 50% of patients die within the 5 years (2).

The proximal tubule of nephron and mucosal lining of the small intestine both consist of a set of transport proteins known as sodium-glucose co-transporters (SGLT2s). The proximal convoluted tubules (PCT) contain the SGLT transporters, which are affected by SGLT2 inhibitors (3). Enhanced glucose secretion due to inhibition of SGLT2 receptors causes lowering of plasma glucose which subsequently improves HbA1C levels and enhance weight loss due to caloric loss. Through the Glut-9 transporter, glycosuria brought on by SGLT2 inhibitors may potentially mediate a uricosuric impact; with lowering of uric acid levels which was frequently linked to congestive heart failure (4).

Large clinical trials have demonstrated the beneficial effects of empagliflozin in patients with heart failure. Zinman et al., (5) showed significant reductions in cardiovascular mortality and hospitalization for heart failure among patients with type 2 diabetes treated with empagliflozin. Similarly, subsequent trials in patients with heart failure with reduced ejection fraction (HFrEF) confirmed that empagliflozin significantly reduced heart failure hospitalization and improved clinical outcomes, irrespective of diabetic status. These findings support the role of empagliflozin as an effective therapy in patients with HFrEF beyond its glucose-lowering effects. (6).

LV myocardium consists of three distinct myocardial layers that contract simultaneously in different directions. Right ventricular (RV) myocardial fibers have a complex 3D arrangement (a superficial circumferential layer, a deep longitudinal layer, and a

poorly developed mid-wall circumferential layer) with longitudinal orientation. Hence, the accurate assessment of cardiac function requires 3D analysis (7)

In this context, three-dimensional echocardiography and speckle-tracking imaging offer significant advantages over conventional two-dimensional assessment in the evaluation of left ventricular systolic function. Three-dimensional echocardiography enables accurate quantification of left ventricular volumes and ejection fraction without geometric assumptions, thereby reducing measurement variability and foreshortening errors. In addition, speckle-tracking echocardiography allows angle-independent assessment of myocardial deformation, providing sensitive detection of subtle changes in myocardial mechanics through strain analysis. Parameters such as global longitudinal, circumferential, radial, and area strain reflect intrinsic myocardial contractility and can identify early systolic dysfunction and reverse remodeling before detectable changes in ejection fraction occur. Accordingly, the combined use of 3D echocardiography and speckle-tracking offers a comprehensive and reproducible evaluation of left ventricular systolic performance and myocardial mechanics, particularly in patients with heart failure (7).

Despite the established clinical benefits of empagliflozin in reducing heart failure hospitalizations and improving survival, data regarding its direct effects on myocardial systolic function and reverse left ventricular remodeling, particularly in non-diabetic patients with HFrEF, remain limited. Understanding these myocardial-level effects is essential to clarify the mechanisms underlying the clinical benefits of empagliflozin. Therefore, this study was designed to evaluate the impact of empagliflozin on left ventricular systolic function myocardial mechanics and functional status in non-diabetic patients with HFrEF, aiming to provide further insight into its role beyond glycemic control.

METHODS

Study population.

From January 2022 to January 2024, non-diabetic patients diagnosed with heart failure with reduced EF (HFrEF) were recruited and followed-up for 6 months.

Inclusion Criteria were:

1) LVEF is < 40%
2) Age ≥ 18 years
3) Minimum of six months of optimal guideline-based medical therapy for HF.
4) New York Heart Association (NYHA) functional class I–III
5) No previous exposure to SGLT 2 inhibitors

Exclusion Criteria included:

1) Diabetes mellitus defined according to American Diabetes Association criteria
2) Significant valvular heart disease
3) History of recent revascularization or acute coronary syndrome
4) CKD with eGFR <20mL/min/1.73m2 and/or on regular hemodialysis

All patients were subjected to history taking, general and cardiac examination and laboratory work-up. Echocardiographic and clinical evaluations were carried out at baseline a six months later.

A detailed and informed written consent was obtained from all the eligible patients.
And An approval from the Research Ethics Committee of Helwan faculty of medicine was obtained (number, REC-FMHU 147-2021, date. 10-12-2021).

Echocardiographic Assessment

Transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid E95, GE Healthcare, Horten, Norway) in accordance with established standard operating procedures. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were assessed using two- and three-dimensional echocardiography whenever feasible, following the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (8). All echocardiographic examinations were performed by experienced echocardiographers who were blinded to clinical data.

Apical 3D full volume was determined as follows: 4R wave-triggered sub-volumes were acquired for 4 consecutive cardiac cycles during breath-holding to form a larger pyramidal volume including the entire LV. The 3D dataset was then stored for offline analysis. The software displayed the apical 4, 2, and 3 chambers and short-axis views. In each image, manual adjustment of the axis was used to obtain the best orientation of the apical views and avoid LV foreshortening. After manual identification of the mitral valve plane and the apex with 2 reference points on the end-diastolic and end-systolic frames, the software identified the endocardial border in each frame, an LV 3D model was then generated, and LV volumes and LEVEF were then calculated (9). Data analysis was performed offline using the original raw data from all 3DE data sets on an Echo PAC software workstation (Vivid GE 95) for semiautomated endocardial surface detection.

Speckle tracking was evaluated by recording three consecutive end-expiratory cardiac cycles using high frame rate (80–100 frames/s) and harmonic imaging was acquired in the apical four-, two-chamber views as well as long axis views for quantification of peak systolic strain by automated function imaging speckle tracking analysis. GLPSS for the complete LV was provided by the software using a 17-segment model in a ‘bull's eye’ plot calculated as the average of a longitudinal peak systolic strain of

each view and the mean of the three views the normal value of longitudinal peak systolic strain was -20%. Global Area strain (GAS) was calculated as the percentage variation in the surface area defined by the longitudinal and circumferential strain vectors (10).

LVMI was measured in the short axis view at end diastole by subtracting the epicardial volume from the endocardial volume multiplted by myocardial density divided by body surface area (BSA). LVM= myocardial volume X density (1.05). LVMI= LVM/BSA **(11).** PASP was estimated by the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation and then adding to this value an estimated right atrial pressure that measured by inferior vena caval diameter & its collapsibility. Degree of mitral regurgitation was evaluated in different views to assess the severity of MR (mild, moderate and severe) by measurement of vena contracta and jet area in case of eccentric jet **(12).** LA volume was measured from standard apical 4- and 2- chamber views at end-systole just before mitral valve opening. LA borders were traced using planimetry in control and study subjects. The borders consisted of the walls of the left atrium excluding pulmonary veins and left atrial appendage. The biplane method of disks was used to calculate LA volume. LAVi was calculated by dividing LA volume by body surface area of subjects **(11).**

Clinical and Functional Assessment

The functional status was assessed utilizing the NYHA classification. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was employed to evaluate health-related life quality at baseline and subsequently at six months. Clinical response to treatment was considered to be demonstrated by enhancements in functional class and KCCQ score (13).

Study Outcomes

Changes in metrics of left ventricular systolic function (LVEDV, LVESV, and LVEF), changes in global longitudinal peak systolic strain, global area strain & circumferential strain were the primary outcome. Changes in KCCQ scores and NYHA functional class were the Secondary outcome during follow-up period.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0. Quantitative data were expressed as mean ± SD or median (IQR) as appropriate, while qualitative data were presented as numbers and percentages. Group comparisons were performed using Chi-square or Fisher's exact test for qualitative variables, and independent t-test or Mann–Whitney test for quantitative variables. Correlations, ROC curve analysis, and univariate and multivariate logistic regression were applied to identify predictors of mortality. $P \leq 0.05$ was considered statistically significant, and $P \leq 0.001$ was considered highly significant.

RESULTS

Over course of 24 months, from January 2022 to January 2024, 150 cases were gathered from the cardiology department of Badr University Hospital at Helwan University for this cohort study.36% of patients were female, and the study population's mean age was 56.61±9.71 years. Demographic data are presented in (Table 1). Hypertension was present in 41.3%, ischemic heart disease in 16%, and dyslipidemia in 33.3% of the studied patients

Table (1): Demographic data of the studied patients

		Total no.= 150
Sex	**Female**	54 (36%)
Age	**Mean ± SD**	56.61 ± 9.71
Weight	**Mean ± SD**	85.27 ± 10.51
Height	**Mean ± SD**	166.13 ± 5.03
BSA	**Mean ± SD**	1.98 ± 0.13
BMI	**Mean ± SD**	30.95 ± 3.95

Functional baseline assessment showed that 6.7%, 62% and 31.3% of patients were classified as NYHA functional class I, II and III, respectively (Table 2)

Table 2 : Baseline NYHA class and KCCQ

Baseline Data		**Total no.= 150**
NYHA	**I**	10 (6.7%)
	II	93 (62%)
	III	47 (31.3%)
KCCQ	**Mean ± SD**	41.78 ± 10.4

Baseline echocardiographic measurements and characteristics of the study group are demonstrated in table (3).

Table (3): Baseline ECHO parameters of the studied patients

Baseline Data		Total no.= 150
LVEDV(ml)	Mean ± SD	183.98 ± 52.39
LVESV(ml)	Mean ± SD	120.93 ± 34.55
EF(%)	Mean ± SD	33.06 ± 4.89
GLS(%)	Mean ± SD	-6.57 ± 1.44
GCS(%)	Mean ± SD	-11.41 ± 1.56
GRS(%)	Mean ± SD	27.51 ± 1.99
LVMI	Mean ± SD	72.61 ± 19.12
LAVI	Mean ± SD	39.67 ± 3.12
MR severity	Mild	31 (20.7%)
	Moderate	69 (46%)
	Severe	50 (33.3%)
PASP	Mean ± SD	50.31 ± 8.36

Follow-up

The percentage of cases with NYHA class III was significantly reduced after 6 months 15 (10%) vs. 47 (31.3%) (p-value <0.001). Also, the KCCQ was significantly raised after 6 months 47.71 ± 10.76 vs. 41.78 ± 10.4 (p-value <0.001) (Table 4).

Table (4): Comparison between symptoms at baseline and after 6 months among the studied patients

Symptoms		Baseline Data	After 6 months	Test value	P-value	Sig.
NYHA	I	10 (6.7%)	31 (20.7%)	27.886*	0.000	HS
	II	93 (62%)	104 (69.3%)			
	III	47 (31.3%)	15 (10%)			
KCCQ	Mean ± SD	41.78 ± 10.4	47.71 ± 10.76	-15.414•	0.000	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant, *: Chi-square test; •: Paired t-test

Echocardiographiv follow-up showed marked impreovement in LV diemnsions, EF, LVMI and LAVI measured by 2D echocardiogrpahy. Also, speckle tracking showed improvement in GLS, GCS, GAS and GRS (Table 5)

Table (5): Comparison between ECHO at baseline after 6 months among the studied patients

Echocardiographic parameters		Baseline Data	After 6 months	Test value	P-value	Sig.
LVEDV(ml)	Mean ± SD	183.98 ± 52.39	166.15 ± 43.88	6.943•	0.000	HS
LVESV(ml)	Mean ± SD	120.93 ± 34.55	103.05 ± 29.73	10.180•	0.000	HS
EF(%)	Mean ± SD	33.06 ± 4.89	37.89 ± 5.7	-11.995•	0.000	HS
GLS(%)	Mean ± SD	-6.57 ± 1.44	-8.99 ± 2.83	12.064•	0.000	HS
GCS(%)	Mean ± SD	-11.41 ± 1.56	-13.89 ± 2.68	16.279•	0.000	HS
GAS(%)	Mean ± SD	-17.4 ± 1.6	-19.9 ± 2.7	16.4•	0.000	HS
GRS(%)	Mean ± SD	27.51 ± 1.99	29.28 ± 2.85	-12.330•	0.000	HS
LVMI	Mean ± SD	72.61 ± 19.12	69.7 ± 18.83	13.652•	0.000	HS
LAVI	Mean ± SD	39.67 ± 3.12	36.55 ± 3.51	16.330•	0.000	HS
MR severity	Mild	31 (20.7%)	43 (28.7%)	3.086*	0.213	NS
	Moderate	69 (46%)	67 (44.7%)			
	Severe	50 (33.3%)	40 (26.7%)			
PASP	Mean ± SD	50.31 ± 8.36	49.15 ± 8.77	3.841•	0.000	HS
	Range	23 – 70	23 – 70			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant, *: Chi-square test; •: Paired t-test

DISCUSSION

Our study showed that the use of empagliflozin in non-diabetic patients with HFrEF is associated with significant improvement LV systolic function as reflected by marked increase of EF and improvement in global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS) and global area stain (GAS), in addition to reduction of LV volumes and LVMI. These findings demonstrate the positive remodeling effect of empagliflozin on left ventricular mechanics, and myocardial contractility which is independent from its beneficial glycemic effect.

Heart failure (HF) is a complex and potentially life-threatening disorder related to considerable mortality and morbidity, significant healthcare costs, and reduced functional capacity and quality of life. Globally, almost 64 million individuals suffer from heart failure. Although heart failure (HF) incidence has stabilized and seems to be decreasing in developed nations, its prevalence is growing because of factors as an aging population, improved management and survival outcomes of ischemic heart

disease, along with increased availability of effective evidence-based treatments that extend lives of HF cases (14).Despite the proofed clinical efficacy of Empaglflozin in patients with HFrEF in several randomized studies, pivotal trials like EMPA-REG didn't fully explain the mechanistic basis of Empagliflozin's cardiovascular benefits, specially, its impacts on myocardial function at the structural level in non-diabetic patients

In contrast to our study, Jensen et al. (15) reported no statistically significant effect of empagliflozin on left ventricular global longitudinal strain (LV-GLS), with an adjusted mean absolute change of 0.7% compared to placebo. Similarly, there was no significant difference was in LVEF, where the adjusted mean absolute change between empagliflozin and placebo was 2.2%. The differences in findings between the two studies are due to variations in methodology, patient populations, and measured parameters. Jensen et al. (16) focused on assessing the effect of empagliflozin LV-GLS using low-dose dobutamine stress echocardiography in a 12-week trial, which may not have been long enough to capture long-term changes. Their primary outcome was LV global longitudinal strain (LV-GLS) under stress conditions. In contrast, our study evaluated multiple echocardiographic parameters over six months, showing significant improvements in LV mechanics and functional capacity.

Our findings are consistent with previous randomized clinical trials demonstrating the beneficial effects of empagliflozin on cardiac structure and function. The reduction in left ventricular volumes observed in our study aligns with results from the SUGAR-DM-HF trial, which reported significant decreases in left ventricular end-systolic and end-diastolic volume indices following empagliflozin therapy (17).

The decline in left atrial volume index (LAVI) and pulmonary artery systolic pressure (PASP) demonstrated by our study, reflects the reduction in left atrial and pulmonary congestion, supporting the decongestive role of Empagliflozin in the management of heart failure. This is consistent with findings of the EMBRACE-HF trial (16), which showed that Empagliflozin in patients with HF irrespective of their EF and diabetic status, significantly reduced pulmonary artery diastolic pressure, with effects becoming evident as early as week 1 and intensifying over time as evident by monitoring of previously implanted pulmonary artery pressure sensors

In addition to echocardiographic improvements, our study showed significant functional and symptomatic improvement, as reflected by better NYHA functional class and increased KCCQ scores. These findings support the clinical relevance of myocardial remodeling and functional recovery associated with empagliflozin treatment (18). Our findings are in contrast to that reported by Lee et al. (16), where they showed no notable difference in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score in patients who received Empagliflozin.

In agreement with our findings, the EMPEROR-Reduced trial demonstrated that empagliflozin significantly improved functional status and health-related quality of life in patients with heart failure and reduced ejection fraction, as reflected by improvements in NYHA functional class and Kansas City Cardiomyopathy Questionnaire scores. These findings further support the beneficial impact of empagliflozin on functional capacity and patient-reported outcomes beyond its effects on cardiac structure and hemodynamics (19).

LIMITATIONS

This study was conducted at a single center with a relatively limited sample size, which may restrict the generalizability of the results. The absence of a randomized control group and the relatively short follow-up period limit causal inference and assessment of long-term outcomes. The results of our study is applicable only on Empagliflozin and further studies is required to proof the same outcome in other SGLT2 inhibitors In addition, advanced imaging techniques such as cardiac magnetic resonance imaging were not utilized to further characterize myocardial tissue.

CONCLUSIONS

In non-diabetic patients with heart failure and reduced ejection fraction, empagliflozin therapy was associated with significant improvement in left ventricular systolic function, evidenced by increased ejection fraction and favorable reverse ventricular remodeling. These echocardiographic improvements were accompanied by significant functional and symptomatic benefits, including improved NYHA functional class and enhanced health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire. The findings of this study support the role of empagliflozin as an effective therapeutic option in patients with HFrEF, extending its benefits beyond glycemic control and reinforcing its use as a cornerstone therapy irrespective of diabetic status.

REFERENCES

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017 Apr;3(1):7-11. doi: 10.15420/cfr.2016:25:2.
2. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized failure: rates and long-term mortality. J Card Fail. 2004 Oct;10(5):374-9. doi: 10.1016/j.cardfail.2004.02.003.
3. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017; 24(1):73-9. doi: 10.1097/MED.0000000000000311.
4. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZ. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136(17):1643-58. doi: 10.1161/CIRCULATIONAHA.117.030012.

5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373:2117–28. doi:10.1056/NEJMoa1504720.
6. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-57. doi: 10.1056/NEJMoa1812389.
7. Nabeshima Y, Seo Y, Takeuchi M. A review of current trends in three-dimensional analysis of left ventricular myocardial strain. Cardiovasc Ultrasound 2020;18:1-21.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1–39.e14. doi:10.1016/j.echo.2014.10.003.
9. Mostafa S. Assessment of right ventricular systolic function in heart failure with preserved, reduced and mid-range ejection fraction. Indian Heart J 2019;71:406-11.
10. Moustafa S, Elrabat K, Swailem F, Galal A. The correlation between speckle tracking echocardiography and coronary artery disease in patients with suspected stable angina pectoris. Indian Heart J 2018;70:379-86.
11. Bhambhani A, John N, Mathew A. Real-time three-dimensional echocardiographic left heart parameters in healthy Indian adults. Indian Heart J 2018;70:642-48.
12. Kalogeropoulos AP, Siwamogsatham S, Hayek S, Li S, Deka A, Marti CN, et al. Echocardiographic assessment of pulmonary artery systolic pressure and outcomes in ambulatory heart failure patients. J Am Heart Assoc 2014;3:e000363.
13. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology. 2000;35(5):1245–1255. doi:10.1016/S0735-1097(00)00531-3.
14. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272-87. doi: 10.1093/cvr/cvac013.
15. Jensen J, Omar M, Ali M, Frederiksen PH, Kistorp C, Tuxen C, et al. The effect of empagliflozin on contractile reserve in heart failure: Prespecified sub-study of a randomized, double-blind, and placebo-controlled trial. Am Heart J 2022;250:57-65.
16. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation. 2021; 143(6):516-25. doi: 10.1161/CIRCULATIONAHA.120.052186.
17. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation. 2018;137(2):119-29. doi: 10.1161/CIRCULATIONAHA.117.028268.
18. Nassif ME, Qintar M, Windsor SL, Jermyn R, Shavelle DM, Tang F, et al. Empagliflozin effects on pulmonary artery pressure in patients with heart failure. Circulation 2021;143:1673-86.
19. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021;143(4):326-36. doi: 10.1161/CIRCULATIONAHA.120.051783.