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The Effect of Empagliflozin On Cardiac Systolic and Diastolic Functions In Patients With Type 2 Diabetes Mellitus and Hypertension

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ABSTRACT

Empagliflozin may positively affect subclinical left ventricle (LV) dysfunction. We aimed to investigate the effect of empagliflozin on cardiac systolic and diastolic functions in patients with Type 2 diabetes mellitus (DM) and hypertension.
Sixty-three patients who underwent transthoracic echocardiography between October-2019 and June-2020, receiving at least one antihypertensive pill, and started empagliflozin treatment due to Type-2 DM were included in the study. Echocardiographic parameters like global longitudinal strain (GLS), left atrial volume index (Lavi), before and 6 months after empagliflozin treatment were compared. Patient's blood pressure (BP), waist circumference, body mass index (BMI), NT-proBNP and other blood parameters were examined.
Of the 63 patients who participated in the study, 30 (47.6%) were male. There was an improvement in subclinical cardiac dysfunctions with the use of empagliflozin for 6 months. There was statistically significant difference in GLS (15±2.42 to 16.3±2.3, p<0.001), E/e' (10[8.5-11], 10.5[9-12], p:0.01), Lavi (29.6±10.5to 27.3±9.8,p<0.001) and NT-proBNP (75,65.7,p<0.001). Significant improvement in GLS was associated with baseline BMI and NT-proBNP elevation. Also, the decrease in Lavi was found to be related to the initial NT-proBNP elevation. In addition, there were significant changes in patients BP (135±7.9, 128±6.9, p-<0.001), diastolic BP (80.2±7.2, 78.6±6.6, p-value 0.012), waist circumference (107±8.9, 104±9.1,p<0.001) and BMI (33.5±5.6;30.2±4.3;p<0.001).
Empagliflozin treatment improved subclinical LV systolic and diastolic dysfunctions in patients with Type 2 DM and hypertension. The benefit of Empagliflozin may be associated with weight loss and decrease of NT-pro BNP as this improvement was more prominent in patients with high baseline BMI and NT-proBNP.

Keywords: Empagliflozin, sodium glucose co-transporter-2 inhibitor, global longitudinal strain, Left atrial volume index

Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are new types of oral antidiabetic agents that act by inhibiting glucose reabsorption in the kidney proximal tubules where glucose is reabsorbed. In recent publications, it has been shown that the use of SGLT-2i in patients with type 2 diabetes mellitus (DM) with high cardiovascular risk reduces hospitalizations due to heart failure (HF) (1, 2). SGLT-2i prevents urinary glucose reabsorption as well as induce sodium excretion. Thus, fluid excretion increases with natriuresis and causes a decrease in extravascular and intravascular volume. In this way, they provide a reduction in blood pressure (BP) and weight (3-5). Treatment with SGLT-2i in patients with type 2 DM has been shown to reduce body weight by 1.7 kg (2.4%) and systolic and diastolic BP by 4 and 2 mmHg without increasing heart rate. Although natriuresis caused by SGLT-2i is thought to be temporary, decreases in systolic (5-6 mmHg) and diastolic (1-2 mmHg) BP are considered to be continuous (1).

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As it is known, half of the HF patients are HF with low ejection fraction (HFrEF), the other half consists of HF with borderline EF and HF with preserved EF (HFpEF). Available data suggest that the clinical benefits of SGLT-2i in patients with Type 2 DM may be similar in patients with HFrEF as well as in HFpEF. Asymptomatic left ventricular (LV) systolic and diastolic dysfunction is high in patients with Type 2 DM, even in the presence of clinically undetected cardiac diseases, and is found in approximately 50-70% (6,7). In the presence of concomitant hypertension, patients with Type 2 DM do not have HF symptoms, but subclinical LV dysfunction is more frequently detected on echocardiography. SGLT-2i may positively affect subclinical LV systolic and diastolic dysfunction due to its effects such as natriuresis, diuresis, BP reduction, direct myocardial effect, hemoconcentration, effect on endothelial function and decrease in adipokine production. Our study investigates the effect of empagliflozin on subclinical cardiac dysfunction in patients with Type 2 DM and hypertension.

Materials and Methods

This study was designed as a retrospective, non-randomized, observational single-center study. A total of 63 patients who underwent transthoracic echocardiography between October 2019 and June 2020 and started empagliflozin treatment due to Type 2 DM were included in the study. Inclusion criteria were as follows: age between 18–80 years; confirmed diagnosis of Type 2 DM; preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2); preserved left ventricular ejection fraction (LVEF ≥ 50%); and the use of at least one antihypertensive medication.

Exclusion criteria included clinical symptoms or signs of heart failure (e.g., peripheral edema, exertional dyspnea), diagnosis of type 1 diabetes mellitus, moderate-to-severe aortic or mitral valve disease, atrial fibrillation, congenital heart disease, uncontrolled hypertension (BP > 160/100 mmHg), active malignancy, and morbid obesity (BMI > 40 kg/m^2). The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Koşuyolu Training and Research Hospital ; all enrolled patients gave written informed consent. However, lifestyle modifications (e.g., diet, physical activity) and other concurrent medical interventions during the 6-month empagliflozin therapy were not standardized or controlled for due to the retrospective design of the study.

Blood Tests and Clinical Features: Blood samples, Full Blood Count and other biochemical parameters were evaluated at the time of admission and after 6 months of empagliflozin treatment. Fasting plasma glucose level ≥ 126 mg/dl or a random plasma glucose level ≥ 200 mg/dl plus diabetic symptoms, or a second-hour plasma glucose level ≥ 200 mg/dl in oral glucose tolerance test, or HbA1c level ≥ 6.5 were accepted in favor of DM diagnosis.

The BP was measured by trained clinical personnel with an automatic oscillometric measuring device and in standardized procedures (8). BP measurement requirements included measuring BP early in the visit and not following the stressful exam. After 5 minutes of rest, average BP of 3 measurements was taken which was measured at 1-minute intervals. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m), (kg/m^2) Body surface area was calculated with the Mosteller formula (m2 = [height (cm) × weight (kg)/3600]1/2). Waist circumference was assessed at the level of the umbilicus. Changes in concurrent antihypertensive, antidiabetic (excluding empagliflozin), and lipid-lowering medications during the follow-up period were not systematically recorded or controlled for due to the retrospective nature of the study.

Echocardiography: Baseline transtorasic echocardiography during the enrolment, and 6th month control echocardiography after empagliflozin treatment were recorded in accordance with the guidelines of the American Society of Echocardiography (9), and were compared after the patients enrolment completed. A complete transthoracic echocardiogram (TTE) study, with a frame rate of more than 60 frames/s was performed using the GE Vivid E95 ultrasound system. All data were transferred to a workstation for further offline analysis (EchoPAC PC; GE Vingmed Ultrasound AS). LV,EF was calculated using the biplane Simpson's method (10). The area-length method was used to calculate left atrial volume (Lav). The calculated volume was indexed to Body Surface Area (BSA) to obtain Lavi. The LV inflow was evaluated with tissue doppler imaging. Early (E) and late (A) waves and the E/A ratio were measured with a mitral inflow profile. The E/Em ratio was calculated with the help of the septal and lateral measurements and the mean values were

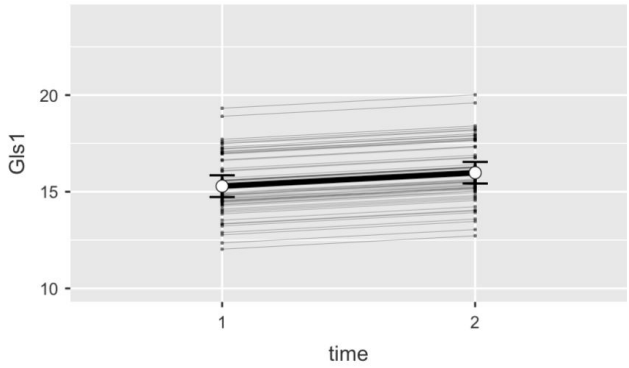

Fig. 1. Global Longitudinal Strain value graph before and after treatment

determined. Speckle tracking echocardiography (STE) analysis was performed offline and by one investigator for myocardial assessment. Using a dedicated software package (Echopac, GE Vingmed) 2D strain was measured as previously described (11). For Speckle tracking analysis, 3 cycles with a frame rate of ≥45 fps were taken and the average value was calculated. The software automatically determined LV endocardial borders with the help of three manually selected landmark points (lateral and septal mitral annulus and LV apex). LV Global longitudinal strains (GLS) were obtained for standard apical four-chamber, three-chamber, and two-chamber views. All speckle-tracking echocardiographic analyses, including GLS measurements, were performed offline by a single experienced cardiologist. Intra and interobserver variability analyses were not performed, which constitutes a methodological limitation of the study.

Statistical Analysis: Descriptive data are presented as mean ± standard deviation. If not normally distributed, the median was given as the interquartile range. The patients were divided into two groups as before and 6 months after empagliflozin use. Paired-T test and Wilcoxon test were used to compare the difference between groups. Changes in hemodynamic and echocardiographic parameters over time were evaluated using a linear mixed model with an unstructured covariance model and time as a constant variable. This analysis gives the estimation of each parameter and the significance of this estimation relative to the baseline assessment of repeated measurements. GLS increase and pro-BNP decrease were used to evaluate the improvement in subclinical LV systolic dysfunction, which we accepted as the endpoint. An increase in the E' parameter and a decrease in the E/E' and Lavi parameters were used to evaluate the improvement in diastolic functions. As this was a retrospective observational study, a priori power analysis was not performed. However, post-hoc evaluation of the sample size indicated adequate statistical power (>80%) to detect clinically significant differences in primary echocardiographic parameters such as GLS and NT-proBNP.

Results

Among 63 patients, 33 (52.4%) were male and their age was 56.7±8.6. Coronary artery disease (CAD) was present in 21 (33.3%) patients; 6 (9.5%) had a history of cerebrovascular events , and 41 (65.1%) patients were smokers. Regarding antihypertensive treatment, 60 (95.2%) patients were using angiotensin-converting enzyme inhibitor (ACEi) or AT1 receptor blocker (ARB), 19 (30.2%) calcium channel blockers, 18 (28.6%) diuretics, and 23 (36.5%) patients were using beta-blockers. The basal characteristic values of the patients are presented in Table 1.

Anthropometric measurements of the patients were significantly decreased after empagliflozin treatment, the values before and after treatment for weight, waist circumference and BMI. Systolic and diastolic BP were significantly reduced after 6 months.

Regarding blood parameters, hemoglobin and hematocrit were significantly increased, In addition, fasting blood glucose, HbA1c and NT-proBNP levels were significantly decreased after 6-month empagliflozin treatment. Baseline and 6th-month anthropometric, hemodynamic and blood parameters are presented in Table 2.

Systolic and diastolic echocardiographic parameters were also improved with empagliflozin. Left atrial diameter and Lavi were significantly decreased. There was a significant increase in e and a significant decrease in E/e. There is no statistical significance in the E, A, E/A, and deceleration time parameters. GLS values were also improved from 15±2.42 to 16.3±2.3, p<0.001, as shown in Figure-1. The 6-month echocardiographic changes of the patients are shown in Table 3.

When GLS increase was added to the statistical model as a covariate, statistically significant changes were observed in BMI (beta coefficient -0.10, p-value p:0.007) and log (Pro-BNP) (beta coefficient: -0.51, p-value <0.001). The values of other variables obtained when GLS was added to the model as a covariate are presented in Table-4.

Table 1: Clinical Characteristics of The Patients

Age, years (mean±SD)	56.7±8.6
Male sex n (%)	30 (%47.6)
CAD n (%)	21 (%33.3)
CVO n (%)	6 (%9.5)
Smoker n (%)	41 (%65.1)
ACEi / ARB n (%)	60 (%95.2)
Calcium channel blockers n (%)	19 (%30.2)
Diuretics n (%)	18 (%28.6)
Beta-blockers n (%)	23 (%36.5)

***Table footnote:** CAD: Ischaemic heart disease, CVO: Ischaemic cerebrovascular disease ACEi: angiotensin converting enzyme inhibitor, ARB: AT1 receptor blocker

Table 2: The Effects of Empagliflozin on Anthropometric and Laboratory Data

Variables	Before treatment	6 months after treatment	Mean difference	p
BW (kg)	84.3±13,2	81.3±13.1	2.96	<0.001
Waist circumference (cm)	107±8.9	104±9.1	2.66	<0.001
BMI(kg/m2)	33.5±5.6	30.2±4.3	3.1	<0.001
Systolic BP(mmHg)	135±7.9	128±6.8	6.99	<0.001
Diastolic BP(mmHg)	80.2±7.2	78.6±6.6	1.51	0.012
Hemoglobin (gr/dl)	13.5±1.8	14.1±1.4	-0.62	<0.001
Hematocrit %	41.0±5.3	42.5±4.2	-1.56	0.002
Plt (*103 /µL)	264±110	244±56	19.8	0.10
Creatinine (mg/dl)	0.75±0.17	0.76±0.17	-0.01	0.53
AST (U/L) *	23.5(18-31.8)	23(18-28)	1.80	0.21
ALT (U/L) *	21.8(17-40.3)	22(17.4-29)	3.80	0.05
Total Cholesterol mg/dl)	215±54.6	194±52	19.5	0.02
LDL-C(mg/dl)	131±48.6	111±39.6	18.7	0.01
HDL-C(mg/dl)	45±9.9	47.1±9.4	-2.31	0.05
Triglyceride (mg/dl)	197±96.8	180±99.2	14.5	0.23
Fasting glucose level (mg/dL) *	153(140-202)	134(122-167)	20	<0.001
HbA1c (%)	8.6±1.4	7.7±1.1	0.9	<0.001
NT-proBNP (pg/ml)*	75(23.9-284)	67.7(27.1-234)	30.08	<0.001

***Table footnote:** A1c: glycated hemoglobin, BMI: body mass index, BP: blood pressure, BW: body weight; HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro b-type natriuretic peptide.
Parameters marked with * were evaluated with Wilcoxon and other parameters by Paired-T test

When the reduction of Lavi was added to the statistical model as a covariate, a statistically significant change was observed in log (pro-BNP) (beta coefficient 1.66, p-value 0.002). No statistical significance was observed in age, gender, BMI, systolic BP, and HbA1c. This data is presented in Table 5.

Discussion

In this study, the anthropometric, hemodynamic, and echocardiographic data of patients with Type 2 DM and hypertension were evaluated before and after empagliflozin treatment; it was observed that patient's weight , BMI, systolic and diastolic BP and NT-proBNP values were significantly

Table 3: The Effects of Empagliflozin on Echocardiographic Parametres

Variables	Before treatment	6 months after treatment	Mean difference	p
LaD (cm)	3.77±0.42	3.64±0.46	0.13	<0.001
Lavi(mL/m2)	29.6±10.5	27.3±9.8	2.3	<0.001
LvEDD(cm)	4.87±0.38	4.80±0.40	0.07	0.11
LvESD(cm)	2.96±0.51	2.89±0.46	0.07	0.14
E (cm/s)	80.9±29.1	78.3±30.9	2.64	0.14
A (cm/s)	92.7±21.6	88.9±21.0	3.74	0.05
e' (cm/s)*	10(8.5-11)	10.5(9-12)	-0.75	<0.001
E/A*	0.80(0.66-0.94)	0.83(0.69-0.94)	-0.03	0.15
E/e'*	7.88(6.28-9.05)	6.95(5.91-8.24)	0.58	0.01
DT(msn)	145±35.8	155±36.9	-7.0	0.07
TAPSE (cm)	1.99±0.34	2.09±0.38	-0.1	0.08
LvEDV(ml)	80.2±25	83.1±25.6	-2.87	0.12
LvESV (ml)	34.3±12.5	34±12.1	0.20	0.81
EF%	58.8±4.8	59.2±5.8	-0.46	0.068
GLS	15±2.42	16.3±2.3	-1.29	<0.001

***Table footnote:** LaD: Left Atrial Diameter, Lavi: Left atrial volume index, LvEDD: Left ventricular end-diastolic diameter, LvESD: Left ventricular end-systolic diameter LvEDV: Left ventricul end-diastolic volume, LvESV: Left ventricul end-systolic volume, DT: deceleration time GLS: global longitudinal strain, EF left ventricular ejection fraction, E early ventricular filling velocity

Table 4: The Values of The Variables Obtained By Adding GLS Covariate to The Linear Mixed Model

Variables	Beta	CI	P
Time	-0.69	-1.26, -0.12	0.02
Age	0.03	-0.03, 0.09	0.35
BMI	-0.10	-0.18, 0.03	0.007
Systolic BP	-0.02	-0.08, 0.05	0,59
HbA1c	0.10	-0.027, 0.048	0.58
Log (NT-proBNP)	-0.51	-0.81, 0.21	<0.001

***Table footnote:** BMI: body mass index, BP: blood pressure, CI: Confidence Interval

decreased, echocardiographic parameters such as the GLS, E/E', E', and Lavi are statistically significantly improved whereas no significant change revealed in M, M/A, DT, EF, LvEDC, LvESC, LvEDV, and LvESV.

The EMPA-HEART CardioLink-6 study, showed that empagliflozin caused a significant decrease in LV mass index in patients with Type 2DM and CAD (12). However, contrary to our results, no significant difference was observed in the NT-proBNP levels in this study. Since our patient group consisted of patients with hypertension, baseline NT-proBNP levels showed a wider distribution compared to this study. Because systolic and diastolic BP elevations, together with an increase in LV filling pressure, cause an increase in tension in the LV myocardium and cause an increase in NT-proBNP levels. In addition, our patient group has a higher BMI when compared to EMPA-HEART CardioLink-6. So, our study supports that the decrease in NT-proBNP, which was previously shown in canagliflozin, may also have been observed with empagliflozin (13). However, both studies showed no significant change in LV end-diastolic and end-systolic volumes. In addition, the significant decrease observed in Lavi is consistent with the decrease in NT-proBNP. This comparative interpretation, especially with the EMPA-HEART CardioLink-6 trial, enhances the contextual relevance of our findings within the existing body of literature. Although a reduction in LV filling pressures and wall stress is the primary driver of NT-proBNP reduction, other mechanisms such as improved myocardial metabolism, reduced oxidative stress, and direct myocardial effects of empagliflozin (e.g., modulation of intracellular sodium and calcium homeostasis) may also

Table 5: The Values of The Variables Obtained by Adding The Lavi Decrease As A Covariate to The Linear Mixed Model

Variables	Beta	CI	P
Time	2.14	0.4, 3.85	0.02
Age	-0.16	-0.4, 0.10	0.22
Sex	2.05	-2.61, 6.70	0.39
BMI	0.03	-0.21, 0.27	0.81
Systolic BP	-0.17	-0.47, 0.12	0.24
HbA1c	1.57	-3.30, 0.15	0.08
log (NT-proBNP)	1.66	0.62, 2.67	0.002

***Table Footnote:** BMI: Body Mass Index, BP: Blood Pressure, CI: Confidence Interval

contribute. These multifactorial effects are particularly relevant in patients with subclinical myocardial dysfunction, as in our cohort.

Myocardial assessment with STE is a sensitive tool for the assessment of ventricular function in early myocardial disease. As in our patient group EF>50%, GLS with STE is an important finding in the follow-up of subclinical LV dysfunction. A statistically significant improvement was observed in the GLS of the patients due to the same reasons as the decrease in tension on the LV wall, which may lead to a decrease in NT-proBNP value, and the decrease in end-diastolic pressures. Because when GLS improvement is added to the statistical model as a covariate, there is a statistical significance with the initial NT-proBNP elevation. Besides, the high initial BMI of the patients is also statistically significant in the improvement of GLS. This may suggest that the clinical benefit is greater in patients with high BMI. Obese hypertensives present increased value systemic vascular resistance SVR in comparison with non-obese patients(15). Moreover, the decrease in SVR with weight loss may be responsible for the decrease in systolic and diastolic BP in patients, as well as improvement in GLS and a decrease in NT-proBNP levels.

Obesity and high BMI have been associated with a subclinical decrease in LV systolic and diastolic function and deterioration in GLS, as shown in previous studies (16,17). The decrease in BMI may be responsible for the increase in GLS due to the weight-reduction effect of empagliflozin, which was seen in our patient group and known from previous studies. The fact that the improvement in GLS was associated with the initial elevated BMI, in our statistical model supports this. It is well-known that high systolic BP is associated with poor GLS. It has also been shown that worsening GLS in hypertensive patients can accurately predict subclinical LV systolic dysfunction. The significant reduction BP in our patient group after 6 months may also be associated with the improvements in GLS. As seen in Table 4, while the initial systolic BP elevation was associated with the worsening of GLS, it was not found to be statistically significant. Larger studies are needed on this subject.

The E/E' ratio is an echocardiographic parameter with a high correlation with LV filling pressures (18, 19). In addition, the E/E' ratio has prognostic significance in diastolic dysfunction and HF (9). In our study, a significant increase in E/E' was observed in the 6 months, indicating the improvement in LV diastolic functions. This may imply a reduction in total cardiovascular risk.

Mitral annular E' wave originating from TDI pulsed-wave doppler is less affected by preload and heart rate than E wave and E/A ratio in evaluating diastolic dysfunction. The E' wave is useful in the assessment of afterload-related myocardial relaxation (20,21). In our study, it was shown that the use of empagliflozin for 6 months caused a significant increase in E' wave velocity. This is indicative of improvement in diastolic dysfunction and reduction of LV afterload.

Lavi measured by the biplane method is one of the early indicators of diastolic dysfunction. Lavi may also indicate diastolic dysfunction in the absence of obvious myocardial disease. In our study, Lavi decreased statistically significantly in the 6 months after drug use. This may be associated with decreased end-diastolic pressures and LV wall tension. Because elevation in NT-proBNP at baseline values was associated with decreased Lavi (Table-5).

Patients with high Lavi have a higher risk of developing new Af (22). Therefore, patients with Af were excluded from our study. As it is known,

Af is an important cause of mortality and morbidity in diabetic or hypertensive patients. The reduction in Lavi within 6 months may also reduce the risk of a newly developing Af with normal sinus rhythm population. Larger and randomized controlled studies are needed on this subject.

In addition, we observed a significant increase in Hct and Hgb values when the 6-month blood values of patients were compared. It is known that his hemoconcentration is not only due to the diuretic effect. There was also an increase in endogenous erythropoietin synthesis (23,24). In the analysis performed in the EMPA-REG OUTCOME study, the increase in Hct and Hgb values is thought to account for approximately 50% of the observed clinical benefit (25). This rise in hemoglobin and hematocrit may improve oxygen-carrying capacity and tissue perfusion, potentially contributing to the reduction in symptoms and subclinical myocardial stress. Moreover, these changes may reflect improved renal erythropoietin signaling, which has been proposed as one of the pleiotropic benefits of SGLT-2 inhibitors beyond glycemic control.

The relationship between BMI and hyperlipidemia is known (26). Controlling hyperlipidemia with lifestyle changes and medical treatment reduces the risk of atherosclerotic cardiovascular disease (27,28). When the 6-month changes were examined in our patient group, a significant decrease in total cholesterol (p-value: 0.01) and LDL (p-value: 0.02), as well as an increase in HDL (p-value: 0.05) was observed. This may be associated with a reduced risk of long-term cardiovascular disease in the patient group. However, changes in hematocrit level and lipid parameters were not associated with echocardiographic variables or nNT-proBNP in our study.

It is important to acknowledge that several patients in our cohort were receiving background cardiovascular therapies, including ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and diuretics. These medications are known to independently influence both systolic and diastolic cardiac function, as well as NT-proBNP levels. Although the distribution of these therapies was stable and typical for a hypertensive diabetic population, we cannot completely exclude their potential confounding effects on the observed improvements in echocardiographic and biomarker outcomes. Future prospective studies with stratified analyses based on background medical therapy would be valuable in addressing this limitation.

Limitations: Although our study has high statistical power, it is a short-term, retrospective and relatively small study. Some patients were on multiple antihypertensive therapy for many years, while others were on single antihypertensive therapy for a relatively shorter period. In addition, since we selected patients with EF>50%, it was observed that some patients may have HF with preserved EF and therefore NT-proBNP values were in a wide range. Since our study was not a prospective study, the compliance of patients with lifestyle changes and treatment could not be evaluated clearly. Although BP measurements were performed by trained clinical staff using an automatic oscillometric device and within standardised procedures, patient-based personal factors may have led to differences between measurements. Furthermore, as the retrospective design inherently limits the ability to establish causality, future prospective and randomized controlled studies are warranted to validate our findings and better assess the long-term cardiovascular benefits

In our study showed that subclinical cardiac dysfunctions were improved with the use of empagliflozin for 6 months in patients diagnosed with Type 2 DM with hypertension. In addition, the benefit of empagliflozin was more prominent in patients with large BMI and high baseline NT-proBNP values.

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