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Short Term Use of Empagliflozin Does Not Improve Left Ventricular Function in Non-Diabetic Hypertensive Patients: Results from a Non-Randomised Controlled Trial

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Abstract

Background: A selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), empagliflozin, has demonstrated its effects in reducing cardiovascular mortality and hospitalization rates for heart failure in type 2 diabetes patients. However, the cardiac-intrinsic mechanism for this cardiovascular benefit has not been sufficiently studied. We therefore aimed to investigate the effect of empagliflozin on left ventricular function in a group of patients with grade I hypertension. **Methods:** We carried out a single-arm non-randomized clinical trial at the National Obesity Centre in Yaoundé over a period of 8 months (October 2016 to May 2017), where patients were assigned to receive 25 mg of empagliflozin once daily. Cardiac ultrasound, 24-hour ambulatory blood pressure measurement, resting electrocardiography and biological assessment were carried out at baseline and at the end of a 6-week treatment period with empagliflozin. The primary outcome was the improvement of the left ventricular relaxation evaluation criteria. Ethical approval was obtained from the Centre Regional Ethics Committee in Yaoundé, Cameroon. **Results:** A total of 11 patients were treated (median observation time, 6 weeks). We noted a non-significant improvement in the early lateral annular velocity from 9.7 [9.2 - 11.4] cm/s to 9.1 [8.8 - 10.2] cm/s, p = 0.21. We also noted a non-significant improvement of the mitral profile (E/A) from 0.71 [0.63 - 0.78] cm/s to 0.81 [0.58 - 0.88] cm/s, p = 0.08. There were no differences in E/E'

ratio, 5.0 [4.1 - 6.3] vs 5.6 [4.9 - 7.4], p = 0.07. There was a non-significant drop in both systolic (p = 0.06) and diastolic (p = 0.09) blood pressure. We also observed on ECG a drop of the PR interval from 200 [157 - 200] ms to 160 [143 - 186] ms, p = 0.04. **Conclusion:** Short-term treatment with empagliflozin does not show an improvement of the left ventricular function in grade I hypertensive patients with diastolic dysfunction. **Trial registration:** This study was retrospectively registered on Clinical Trial Registry with ClinicalTrials.gov Identifier: NCT04203914.

Keywords

Empagliflozin, Cardiovascular Mortality, Mitral Velocity E', ABPM, ECG

1. Introduction

The cardiovascular safety of novel anti-diabetic agents has increasingly become center-stage in clinical diabetes management [1]. The sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin when compared with placebo in the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study demonstrated significant cardiovascular benefits including significant reduction in cardiovascular death and hospitalization for heart failure by 38% and 35% respectively [2]. This significant benefit on heart failure on SGLT2 inhibition was also confirmed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program [3]. The underlying mechanisms to explain the cardiovascular benefits of SGLT2 inhibitors are not very well-understood but are thought to be attributed to their ability to alter vascular function and reductions in both systolic and diastolic blood pressure [4] [5] [6].

Reduction in blood pressure in patients taking SGLT2 inhibitors has been observed in individuals with and without diabetes in other studies, and so does not showcase a mere reversal of kidney or vascular pathology [7] [8] commonest in patients with diabetes. Therefore vascular function and blood pressure reduction may not explain the overall cardiovascular benefits of SGLT2 inhibitors. Given that in the EMPA-REG OUTCOME study, other cardiovascular outcomes such as coronary events and stroke were not significantly altered, it is important to explore other markers of cardiovascular factors which may have explained the significant benefit of heart failure. SGLT2 inhibitors are thought to improve ventricular loading conditions due to the reduction of preload (via their diuretic and natriuretic effects) [9], but little is known on how left ventricular filling pressure is affected by this drug.

Left ventricular filling pressure has proven to be an early marker and predictor of outcomes in cardiovascular diseases assessment and a number of echocardiographic measurements are used to estimate left ventricular pressure parameters [10]. The early lateral annular velocity (E'), the mitral profile (E/A) and the

mitral annular early diastolic velocity (E/E') are commonly used for the evaluation of diastolic function by way of non-invasive echocardiographic assessment [11]. The way SGLT2 inhibitors affect cardiac diastolic function generally and specifically ventricular filling pressures may provide insights into additional mechanisms which could possibly explain the reduction in the incidence of heart failure and heart failure hospitalization noted with the usage of these drugs. We therefore aimed to investigate the effects of empagliflozin on left ventricular function in non-diabetic hypertensive (grade I) patients with initial diastolic dysfunction.

2. Methods

Study Oversight and Ethical Considerations: The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine and Biomedical Sciences (University of Yaoundé 1, Cameroon) and the Centre Regional Ethics Committee for Research in Human Health (0454/CRERSHC/2017). All study procedure was done in accordance with the 2013 revised Helsinki Declaration. This study was also retrospectively registered on Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT04203914.

Study Design: This was a single arm non-randomized clinical trial to assess the effect of once-daily empagliflozin (at a dose of 25mg) on left ventricle relaxation in adults with hypertension and diastolic dysfunction receiving standard care. The study was conducted over a period of 8 months (October 2016 to May 2017) which each patient completing the drug treatment phase in 6 weeks with evaluations done before and after the treatment with empagliflozin. Eleven (11) patients completed the trial.

Study Setting and Patients: The study was carried out at the National Obesity Centre at the Yaounde Central Hospital in Cameroon which is a tertiary diabetes care unit in Cameroon. Eligible patients were adults (≥21 years) with grade I hypertension, with an estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73m^2 who had not changed their anti-hypertensive treatment for at least 12 weeks before the trial. We screened all eligible patients and included only those with diastolic dysfunction (defined as E/A less than 1). We excluded patients with diabetes.

Study Procedure: Eligible patients underwent a two-week, run-in period in which background antihypertensive therapy was unchanged. Patients meeting the inclusion criteria then received 25 mg of empagliflozin once daily. The patients were monitored 1 week after the initiation of the therapy and every 2 weeks until the 6th week. They also received weekly phone calls to monitor for the occurrence of side effects. Cardiac ultrasound, resting ECG and 24-hour Ambulatory Blood Pressure Measurement (ABPM) were done before and also at the end of the trial. When necessary, the patients who required an adjustment of their background antihypertensive treatment were excluded. **Figure 1** shows the flow diagram for recruitment and study procedure.

Study Outcomes: The primary outcome was the left ventricular relaxation

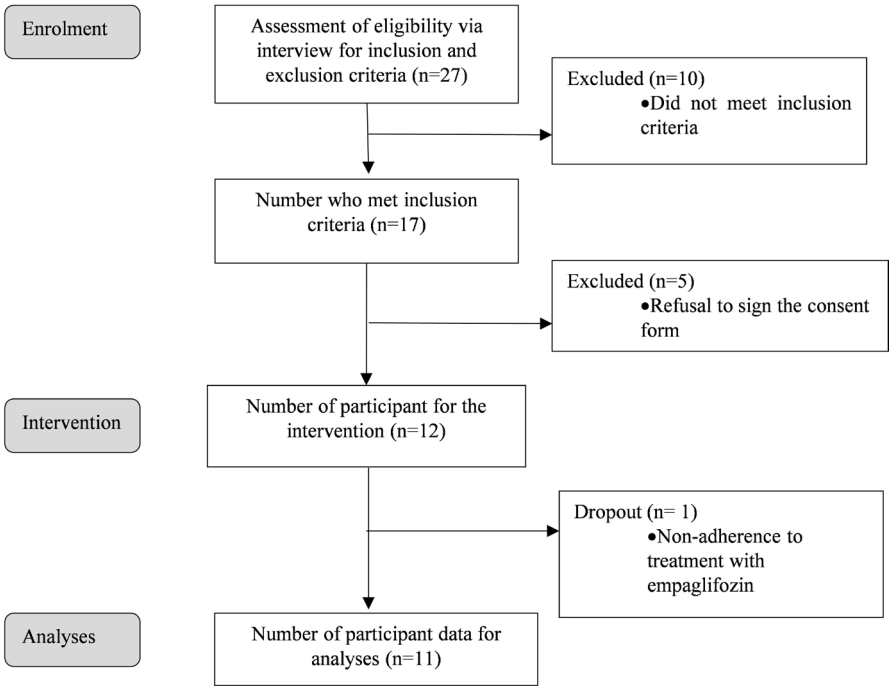

Figure 1. Study flow diagram of participants through the study.

evaluation criteria; early lateral annular velocity, E', the mitral profile (E/A ratio) and the E/E' ratio. Secondary outcome variables were the blood pressure profile on Ambulatory Blood Pressure Measurement (ABPM) and the QT interval on electrocardiography (ECG). Safety was assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of a study drug.

Statistical Analysis: The sample size was calculated based on 13% improvement of the primary outcome (E' velocity) before and after empagliflozin treatment [12]. Considering power of 80%, a minimum sample size of 15 participants was obtained. Data were analyzed using StataSE 15 and paired analyses were used to assess differences before and after the intervention. The level of significance was set at 5%.

3. Results

General characteristics of study participants: We enrolled 15 participants, and only 11 completed the trial and were included for analysis representing 73.3% completion rate. Reasons for drop out were poor adherence to treatment and loss to follow-up (see **Figure 1**). The study population consisted of 2 men and 9 women, with a median age of 59 [56 - 61] years. The median duration of treatment with empagliflozin was 6 weeks. Calcium channel blockers were the most common drugs used in 8 participants, followed by diuretics and beta blockers in 6 participants, angiotensin converting enzyme inhibitors (ACEIs) in 3 participants and Angiotensin II receptor antagonists (ARA II) in 2 participants. The median BMI was 29.5 [25.1 - 31.5] kg/m^2 meaning the majority of

participants would have been overweight and with a total median fat mass at 37.1 [33.0 - 41.5] grams. The median systolic and diastolic blood pressure values were 133 [112 - 147] and 87 [71 - 93] mmHg respectively. The blood glucose level was normal as shown by a fasting blood glucose at 84 [76 - 95] mg/dl with a corresponding glycated hemoglobin (HbA1c) level at 4.9 [4.6 - 5.5] percent. Table 1 shows the baseline characteristics of the study participants.

Table 1. Table showing baseline characteristics of study participants.

Characteristics	Baseline Assessment
Age, years	59 [56 - 61]
Gender	
Male	2
Female	9
Anti-hypertensive treatment	
Diuretics	6
Angiotensin Converting Enzyme inhibitors (ACEIs)	3
Angiotensin II Receptor Blockers (ARA-II)	2
Calcium channel blockers	8
Beta blockers	6
Monotherapy	3
Bitherapy	4
Triple therapy and/or more	4
Anthropometric characteristics	
Weight (kg)	78.7 [71.6 - 85.1]
BMI (kg/m^2)	29.5 [25.1 - 31.5]
Fat mass (g)	37.1 [33.0 - 41.5]
Abdominal circumference (cm)	96.0 [93.0 - 105.0]
SBP (mmHg)	133 [112 - 147]
DBP (mmHg)	87 [71 - 93]
Biological characteristics	
Fasting blood glucose (mg/dl)	84 [76 - 95]
Glycated hemoglobin (HbA1c, %)	4.9 [4.6 - 5.5]
ALAT (IU/mL)	17 [8.6 - 32.1]
Total-Cholesterol (mg/dl)	190 [160 - 210]
LDL-Cholesterol (mg/dl)	120 [80 - 140]
HDL-Cholesterol (mg/dl)	40 [40 - 50]
Triglyceride (mg/dl)	150 [90 - 190]
eGFR, MDRD (mL/min/1.73m^2)	66.0 [58.5 - 91.5]

Results are displayed in frequency and in median [interquartile range].

Table 2. Table showing effect of Empagliflozin after 6 weeks of treatment.

Characteristics	Before Empagliflozin treatment	After Empagliflozin treatment	Absolute difference	P value
Echocardiographic parameters				
E' velocity, cm/sec	9.7 [9.2 - 11.4]	9.1 [8.8 - 10.2]	0.6	0.21
E/A	0.71 [0.63 - 0.78]	0.81 [0.58 - 0.88]	0.1	0.08
E/E'	5.0 [4.1 - 6.3]	5.6 [4.9 - 7.4]	0.6	0.07
24-hour blood pressure profile				
Systolic blood pressure, mmHg	133 [112 - 147]	121 [107 - 124]	9.02	0.06
Diastolic blood pressure mmHg	87 [71 - 93]	71 [68 - 81]	18.39	0.09
Diurnal systolic blood pressure, mmHg	126 [120 - 135]	115 [111 - 128]	8.7	0.25
Diurnal diastolic blood pressure, mmHg	78 [70 - 82]	71 [67 - 79]	9	0.48
Nocturnal systolic blood pressure, mmHg	116 [103 - 127]	115 [102 - 121]	0.9	0.29
Nocturnal diastolic blood pressure, mmHg	68 [62 - 77]	66 [59 - 75]	2.9	0.72
ECG findings				
Sokoloff index (SV1 + RV5) mm	21 [16 - 28]	21 [17 - 28]	0	0.59
Corrected QT interval (QTc), msec	411 [396 - 431]	397 [381 – 411]	14	0.11
PR interval (msec)	200 [157 - 200]	190 [175 - 200]	1	0.674

Results are displayed as median [interquartile range].

Effect of empagliflozin on Left ventricle function and other cardiovascular parameters: There was an overall non-significant improvement in the E' velocity from 9.7 [9.2 - 11.4] cm/s to 9.1 [8.8 - 10.2] cm/s (p = 0.21) after 6 weeks of empagliflozin treatment as shown in Table 2. In sub-analysis, four participants with an initial altered E' velocity showed improvement from 8.2 [7.0 - 9.5] cm/s to 10.0 [9.4 - 10.2] cm/s, p = 0.07. The 7 other patients without an E' initial trouble passed from 10.9 [9.9 - 12.0] cm/s to 8.9 [7.7 - 9.5]. We also noted a non-significant improvement of the mitrial profile (E/A) from 0.71 [0.63 - 0.78] cm/s to 0.81 [0.58 - 0.88] cm/s (p = 0.08). The E/e' ratio did not show any specific changes; 5.0 [4.1 - 6.3] before intervention to 5.0 [4.1 - 6.3] after intervention (p = 0.07).

The total systolic blood pressure at ABPM dropped to −9 mmHg (p = 0.25), the diastolic to −6 mmHg (p = 0.35), the mean to −7 mmHg (p = 0.42). There was no significantly variation in the nocturnal blood pressure. The diurnal diastolic blood pressure dropped to 7 mmHg, the diastolic and the mean blood pressure to 9 mmHg. The pulsed blood pressure dropped to 4 mmHg.

There were no significant changes on ECG findings 6 weeks after empagliflozin treatment. The Sokoloff index (SV1 + RV5) did not change; 21 [16 - 28] mm before intervention to 21 [17 - 28] mm after the intervention (p = 0.59). The corrected QT interval (QTc) reduced from 411 [396 - 431] msec to 397 [381 -

411] msec, p = 0.11. The PR interval also showed a non-significant reduction from 200 [157 - 200] msec to 190 [175 - 200] msec, p = 0.674.

Safety and Adverse Events: We did not observe any serious adverse events that have been routinely reported with empagliflozin treatment (genital mycotic infection, hypoglycemic events, acute renal failure, urinary tract infection, thromboembolic events, and bone fracture).

4. Discussion

This study showed that a 6-week oral intake of empagliflozin 25 mg/day in patients with grade I hypertension does not improve their left ventricular function as measured by the early lateral annular velocity (E') and ratio of early to late mitral inflow (E/A) and the mitral annular early diastolic velocity (E/E'). Although improvement in left ventricular function was not demonstrated in this study, it remains an important clinical entity in hypertensive patients who are already prone to have diastolic dysfunction even in the presence of seemingly normal systolic function [13]. The short duration (6 weeks) of the trial may have limited the demonstration of any relevant changes in the left ventricular pressure parameters.

Verma *et al.* [12] found a global improvement of the early lateral annular velocity E' [8.5 (1.6) vs. 9.6 (1.3) cm/s, p = 0.002] after 12 weeks of treatment with empagliflozin 10 mg per day. Their treatment duration was twice the duration in our study and all their participants had an initial lower baseline early lateral annular velocity. Similarly to our findings, their study did not show significant differences in E/A ratio [0.90 (0.20) vs. 1.04 (0.20), p = 0.101]. However this drop in early to late mitral inflow (E/A) may be due to the drop of the preload associated with empagliflozin treatment or a specific intra-myocardiac action. Also given that our patients did not have diabetes, these actions may be a specific action of empagliflozin on the left ventricular pressure independent of glycosuria which may be seen in those with diabetes.

Our study also showed a non-significant drop in both systolic and diastolic blood pressure values including a drop in diurnal and nocturnal blood pressure parameters on ambulatory blood pressure measurement. SGLT2 inhibitors are not antihypertensive agents but have been associated with sustained lowering of both systolic and diastolic blood pressure parameters in other studies [5] [6]. This has commonly been attributed to sustained reduction in plasma volume seen in SGLT2 inhibition. In our study, the short duration of treatment probably was not sufficient to observe any significant reduction in these blood pressure parameters.

This study has several limitations. The small sample size and the absence of a control group may have limited the effect size on the primary outcome parameters, the generalizability of these results and the possibility to allude any changes noted to the direct effect of empagliflozin respectively. The trial duration was short compared to similar studies but provides preliminary data on whether

short-term treatment with empagliflozin may be beneficial or not.

5. Conclusion

Empagliflozin 25 mg did not show any significant improvement of left ventricular function in non-diabetic patients with grade I hypertension after 6 weeks of treatment. Hence, short-term treatment with empagliflozin may not be clinically relevant and so the cardiovascular benefits seen with this drug may be as a result of long term treatment.

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Authors' Contributions

ES, LMK designed the study. KE was involved in patient recruitment, data collection and analysis. LMK, KE, JCK were involved in drafting the manuscript. LMK, JCK, ES and JCM reviewed the manuscript. All authors approved this final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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