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Does canagliflozin decrease natriuretic peptide levels in patients with diabetes and heart failure?

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have recently been introduced as an oral antidiabetic therapy; proving to be safe and showing a reduction in the risk of cardiovascular events in patients with type 2 diabetes (T2D) [1–3], especially in terms of hospitalization for heart failure (HF). In a recent study, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial [4], in which patients with chronic HF and reduced ejection fraction with and without diabetes were included; dapagliflozin demonstrated a reduction in the composite primary outcome (hospitalization or an urgent visit resulting in intravenous therapy for HF and death from cardiovascular causes) and death from any cause. Several mechanisms have been proposed to explain the benefit of SGLT2i, such as improvement in loading conditions, cardiac metabolism and bioenergetics, inhibition of myocardial Na^+/H^+ exchange, reduction of cardiac fibrosis or alteration in adipokines and vascular function [5].

The DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction) trial [6] has suggested that the benefit of dapagliflozin in patients with chronic HF does not depend on the natriuretic peptide pathway, considering that dapagliflozin did not significantly reduce N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels over 12 weeks as compared with placebo. Nonetheless, these results have been controversial; an analysis of DAPA-HF trial has demonstrated a reduction of median NT-proBNP from baseline to 8 months with dapagliflozin (–303 pg/mL). With respect to canagliflozin, a post hoc analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program with 666 patients showed that NT-proBNP concentration did not increase in the canagliflozin group, and it did slightly in the control group over a 2-year follow-up and from a baseline median of 47 pg/mL [7].

Additionally, there are limited data of the effect of SGLT2i in patients after hospitalization for HF. In the pilot randomized study EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure) [8], patients admitted for HF with or without T2D were randomized to empagliflozin 10 mg/day or placebo and no differences were observed in NT-proBNP concentrations and other primary outcomes at 60-days follow-up.

The present study is a retrospective cohort study which included all consecutive patients with T2D admitted for HF from January 2017 to December 2019 in a single center. This study was conducted according to the Declaration of Helsinki and was approved by Local Clinical Research Ethics Committee with the code GC-15-2017-001. Excluded patients were those in whom treatment with SGLT2i was contraindicated, patients with chronic kidney disease stage 3b or higher (eGFR < 45 mL/min/1.73 m^2) and those receiving other SGLT2i than canagliflozin at discharge. All patients had received a primary diagnosis of acute decompensated HF, including signs and symptoms of fluid overload and a concentration of NT-proBNP of at least 1400 pg/mL. The addition of canagliflozin and the starting dose

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Table 1. Baseline characteristics.

Characteristic	Canagliflozin (n = 45)	Control (n = 57)	P
Age	69 ± 10	73 ± 11	0.04
Female sex	15 (33.3%)	30 (52.6%)	0.05
Body mass index [kg/m^2]	31.9 ± 5.1	30 ± 4.4	0.14
Hypertension	37 (82.2%)	48 (84.2%)	0.79
Atrial fibrillation or flutter	13 (28.9%)	20 (35.1%)	0.66
Coronary artery disease	11 (24.4%)	17 (29.8%)	0.55
Chronic obstructive pulmonary disease	11 (24.4%)	8 (14%)	0.18
Previous functional class (NYHA):			
I–II	38 (84.4%)	50 (87.7%)	0.7
III–IV	7 (15.6%)	7 (12.3%)	
Previous hospitalization for HF	15 (33.3%)	27 (47.4%)	0.15
Clinical features of HF:			
Ejection fraction ≤ 40%	26 (57.8%)	31 (54.4%)	0.73
Ischemic cause	17 (37.8%)	16 (28.1%)	0.32
Killip class on admission:			
I–II	35 (77.8%)	44 (77.2%)	0.94
III–IV	10 (22.2%)	13 (22.8%)	
Serum creatinine [mg/dL]	1.07 ± 0.3	1.1 ± 0.4	0.92
Estimated GFR [mL/min/1.73 m^2]	69.7 ± 24.4	68.6 ± 26.3	0.82
Hemoglobin [g/dL]	12.7 ± 2	12.3 ± 2.3	0.31
Glycated hemoglobin	7.4 ± 1.5	6.8 ± 2.5	0.16
Device therapy:			
ICD	1 (2.4%)	4 (8.7%)	0.21
CRT	0 (0%)	3 (6.5%)	0.1
HF treatment at hospital discharge:			
ACE inhibitor	21 (46.6%)	12 (21.5%)	0.02
ARB	17 (37.7%)	32 (56.2%)	0.16
ARN inhibitor	7 (15.6%)	8 (14%)	0.83
Beta-blocker	35 (78.8%)	45 (78.9%)	0.9
MRA	26 (57.8%)	30 (52.7%)	0.67
Loop diuretic	35 (77.7%)	46 (80.7%)	0.66
Digoxin	6 (13.3%)	14 (24.6%)	0.16
Glucose-lowering medication:			
Biguanide	35 (77.8%)	43 (75.4%)	0.78
Sulfonylurea	2 (4.4%)	4 (7%)	0.58
DPP-4 inhibitor	3 (6.7%)	12 (21.1%)	0.04
GLP-1 receptor agonist	1 (2.2%)	5 (8.8%)	0.16
Insulin	12 (26.7%)	22 (38.6%)	0.26

Numeric values are expressed as median (interquartile range) or number (percentage, %). ACE —angiotensin-converting enzyme; ARB — angiotensin receptor blocker; ARN — angiotensin receptor neprilysin; CRT — cardiac resynchronization therapy; DPP-4 — dipeptidyl peptidase 4; GFR — glomerular filtration rate; GLP-1 — glucagon-like peptide 1; HF — heart failure; ICD — implantable cardioverter-defibrillator; MRA — mineralocorticoid receptor antagonist; NYHA — New York Heart Association

were left to criteria of the treating physician. NT-proBNP concentrations were collected at 3 months, 6 months, and 1 year after hospitalization from laboratory records if available.

The aim of this study was to compare mean NT-proBNP levels at hospital discharge and at 3, 6 and 12 months of follow-up in patients treated with and without canagliflozin.

Table 2. N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels during follow-up period according to canagliflozin.

Group	Admission	Discharge	3 months	6 months	12 months	P*
Canagliflozin (n = 45)	6279 ± 5446 (3110–7884)	4406 ± 3341 (1317–7031)	1376 ± 1266 (491–1638)	1350 ± 1246 (359–1927)	1612 ± 1891 (400–1856)	
Control (n = 57)	6969 ± 7753 (2052–10197)	5587 ± 5358 (2364–6117)	3223 ± 3201 (846–4650)	4106 ± 5011 (733–5040)	4702 ± 6036 (1346–5426)	
P**	**0.692**	**0.258**	**0.001**	**0.001**	**0.003**	**0.004**

NT-proBNP levels are expressed as mean ± standard deviation and interquartile range (IQR 25–75). *Comparing p-value of NT-proBNP levels between the canagliflozin group and the control group during follow-up period (repeated-measures ANOVA analysis). **Comparing p-value of NT-proBNP levels between the canagliflozin group and the control group por each period of follow-up (Student t-test).

This study was conducted according to the Declaration of Helsinki and was approved by Local Clinical Research Ethics Committee (Hospital Universitario Reina Sofía). Written informed consent was obtained from all patients.

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range: IQR 25–75) and were compared using the Student t-test or the Mann–Whitney U test, according to the distribution, which was tested by the Saphiro-Wilk test.

Categorical variables are presented as counts and percentages and were compared using the χ^2 test or the Fisher exact test, as appropriate. Changes in NT-proBNP concentration during follow-up were compared with repeated-measures ANOVA analysis. A value of $p < 0.05$ was considered statistically significant.

A total of 102 patients were included: 45 patients (starting dose: 57.8%, 100 mg/day and 42.2%, 300 mg/day) in the canagliflozin group and 57 patients in the control group. No serious adverse events among patients who received canagliflozin were detected. Three patients discontinued canagliflozin during follow-up, two of them due to hypotension and one by medical criteria. Table 1 summarizes the baseline clinical characteristics of the patients. There were no significant differences in clinical characteristics and comorbidities in both groups, except for age; slightly lower in the canagliflozin group (69.2 ± 10.3 vs. 73.2 ± 11.1; $p = 0.04$). Treatment at discharge was also similar, patients in the control group received more dipeptidyl peptidase-4 inhibitors (21.1% vs. 6.7%; $p = 0.04$). Few patients received sacubitril-valsartan (15.6%) in the canagliflozin group and 14% in the control group. More than a half of the patients in both groups had HF with reduced ejection fraction, 26 (57.8%) in the canagliflozin group and 31 (54.4%) in the control group.

Table 2 shows the results of the analysis of NT-proBNP concentration levels at admission, discharge and at 3, 6 and 12 months of follow-up. Mean levels of peptides were similar in both groups at hospital admission and discharge. During the first 3-month period, a decrease in NT-proBNP concentration was observed in both groups. This decrease was more pronounced in the canagliflozin group ($p < 0.001$). At 6 and 12 months, NT-proBNP levels remained stable in patients treated with canagliflozin, in contrast with patients in the control group, in whom mean levels increased. Consequently, after a year of follow-up, the difference in NT-proBNP levels between groups was more evident ($p = 0.003$), with a reduction from baseline of 64.3% in the canagliflozin group and of 15.8% in control group ($p = 0.004$). There were no differences in patients according to the ejection fraction group.

Notwithstanding, the limitations inherent to the observational study design, we observed an early significant reduction in NT-proBNP levels that was sustained for at least 12 months after discharge. In addition, this reduction was equally observed in patients with reduced and preserved ejection fraction HF.

Since the diuretic effect of SGLT2i does not seem to be enough to explain these differences and the other multiple cardiovascular benefits, ongoing studies are trying to elucidate the potential mechanisms involved: improved myocardial energetics and ionic homeostasis, adipokine regulation, cardiac remodeling, etc. [9]. All these cardiac mechanisms and the increasingly accounted for protective renal effects could be related to the observed reduction in NT-proBNP levels during follow-up.

The present findings support the controversial idea that SGLT2i reduces NT-proBNP levels in patients with HF; and may contribute to building the growing knowledge about SGLT2i mechanisms.

In conclusion, a canagliflozin prescription at discharge in patients with HF and T2D was associated with a reduction in NT-proBNP concentration at follow-up. Future clinical randomized trials should be performed to confirm these findings.

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References

1. Zinman B, Wanner C, Lachin J, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Eng J Med. 2015; 373(22): 2117–2128, doi: 10.1056/nejmoa1504720.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377(7): 644–657, doi: 10.1056/NEJMoa1611925, indexed in Pubmed: 28605608.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380(4): 347–357, doi: 10.1056/NEJMoa1812389, indexed in Pubmed: 30415602.
4. McMurray JJV, Solomon SD, Inzucchi SE. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(20): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
5. Packer M, Anker SD, Butler J, et al. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol. 2017; 2(9): 1025–1029, doi: 10.1001/jamacardio.2017.2275, indexed in Pubmed: 28768320.
6. Nassif ME, Windsor SL, Tang F, et al. 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, doi: 10.1161/CIRCULATIONAHA.119.042929, indexed in Pubmed: 31524498.
7. Januzzi JL, Butler J, Jarolim P, et al. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. J Am Coll Cardiol. 2017; 70(6): 704–712, doi: 10.1016/j.jacc.2017.06.016, indexed in Pubmed: 28619659.
8. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020; 22(4): 713–722, doi: 10.1002/ejhf.1713, indexed in Pubmed: 31912605.
9. Garg V, Verma S, Connelly K. Mechanistic insights regarding the role of SGLT2 inhibitors and GLP1 agonist drugs on cardiovascular disease in diabetes. Prog Cardiovasc Dis. 2019; 62(4): 349–357, doi: 10.1016/j.pcad.2019.07.005, indexed in Pubmed: 31381891.