Int J Heart Fail. 2024 Oct;6(4):176-178
https://doi.org/10.36628/ijhf.2024.0018
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Letter

The Impact of the Novel Sodium-Dependent Glucose Cotransporter 2 Inhibitor, Enavogliflozin, on Cardiac Reverse Remodeling in Heart Failure Patients With Type 2 Diabetes Mellitus: A Case Series

Taeil Yang, MD[1,*], Youngwoo Jang, MD[2,3,*], and Wook-Jin Chung, MD, PhD, FACC[2,3]

[1]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine, Seoul, Korea
[2]Gachon Cardiovascular Research Institute, Gachon University, Incheon, Korea
[3]Division of Cardiovascular Disease, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

Received: Mar 21, 2024
Revised: Oct 22, 2024
Accepted: Oct 23, 2024
Published online: Oct 28, 2024

Correspondence to
Wook-Jin Chung, MD, PhD, FACC
Gachon Cardiovascular Research Institute, Gachon University and Division of Cardiovascular Disease, Department of Internal Medicine, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea.
Email: heart@gilhospital.com

*Taeil Yang and Youngwoo Jang contributed equally to the manuscript.

INTRODUCTION

Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors have changed the landscape of heart failure (HF) therapy. Multiple randomized controlled trials have shown effectiveness of SGLT2 inhibitors in treating HF patients, regardless of left ventricular ejection fraction (LVEF).[1] To this end, current HF guidelines recommend SGLT2 inhibitors as a first-line treatment for HF.[2] However, there are only three SGLT2 inhibitors - dapagliflozin, empagliflozin, and sotagliflozin - approved by the U.S. Food and Drug Administration as a treatment option for HF. Enavogliflozin is a new SGLT2 inhibitor currently approved by the Ministry of Food and Drug Safety for type 2 diabetes mellitus (DM) patients within Korea.[3] Accordingly, we set out to explore its efficacy in HF patients with DM, as SGLT2 inhibitors are generally known for its class effect on HF.[4] Herein, we report 5 cases of HF patients who had DM, who underwent echocardiographic evaluation before and after enavogliflozin therapy.

CASE

This is a single-center, retrospective case series study conducted between January 2023 and January 2024 (GDIRB2024-035). HF patients with type 2 DM in the outpatient clinic setting at Gachon University Gil Medical Center, prescribed with enavogliflozin for at least 30 consecutive days were enrolled. HF was defined as those who were previously diagnosed and treated for HF or de novo patients who had typical symptoms with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[5] Echocardiograms were analyzed before and after enavogliflozin administration. The primary endpoint was the relative change in NT-proBNP and secondary endpoints included the median % change in left ventricular (LV) and left atrial (LA) remodeling parameters such as LVEF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), and LA volume index (LAVI). Paired sample nonparametric tests (Wilcoxon signed rank test) were performed to compare pre- and post-treatment echocardiographic and laboratory data. All statistical analyses were carried out using SPSS 26.0 statistical software (released

2019, IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, USA).

Median age was 67 years (interquartile range [IQR], 52 to 75), where males constituted the majority (n=4, 80%) (**Supplementary Table 1**). Median body mass index was 26.7 kg/m^2 and LVEF was 48.2%. There was one de novo HF patient. Of the 5 patients, 2 patients were diagnosed with HF with preserved ejection fraction, one with HF with improved EF (HFimpEF), and one patient with HF with mildly reduced ejection fraction and one with HF with reduced ejection fraction (HFrEF). One patient had previously received another SGLT2 inhibitor (case 1 of **Supplementary Table 1**) for DM and HF. Enavogliflozin (0.3 mg daily) was administered for 72.4±16.7 days.

Laboratory findings and echocardiographic characteristics pre- and post-enavogliflozin medication are shown in **Supplementary Table 2**. Baseline mean NT-proBNP and hemoglobin A1c (HbA1c) were 558±478 pg/mL and 7.7±0.6% respectively. Median LVEF, LVEDVI, LVESVI, LAVI, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity decrease (E/E′), and maximal tricuspid regurgitation velocity were 52% (IQR, 33 to 62), 39.2 mL/m^2 (IQR, 33.1 to 70.9), 18.7 mL/m^2 (IQR, 12.7 to 47.9), 34.6 mL/m^2 (IQR, 26.7 to 38.6), 10.2 (IQR, 6.8 to 15.8), and 2.4 m/s (IQR, 2.3 to 2.9), respectively. After enavogliflozin treatment, the absolute change of median NT-proBNP and HbA1c was −352 pg/mL (p=0.043) and −0.7% (p=0.279), respectively. The follow-up echocardiography demonstrated a significant reduction in median LVEDVI (−9.6 mL/m^2, p=0.043), LVESVI (−1.6 mL/m^2, p=0.043), and LAVI (−7.4 mL/m^2, p=0.043) (**Figure 1**). There was a trend of LVEF absolute increase by 2.0% (p=0.176) and an absolute reduction of E/E′ by −2.3 (p=0.225). The administration of enavogliflozin was also associated with significant % median (IQR) reduction in NT-proBNP (−64.5% [−77.0 to −21.4]; p=0.043), LVEDVI (−26.3% [−28.9 to −7.7]; p=0.043), LVESVI (−17.2% [−31.0 to −16.9]; p=0.043), and LAVI (−13.2% [−30.6 to −6.3], p=0.043).

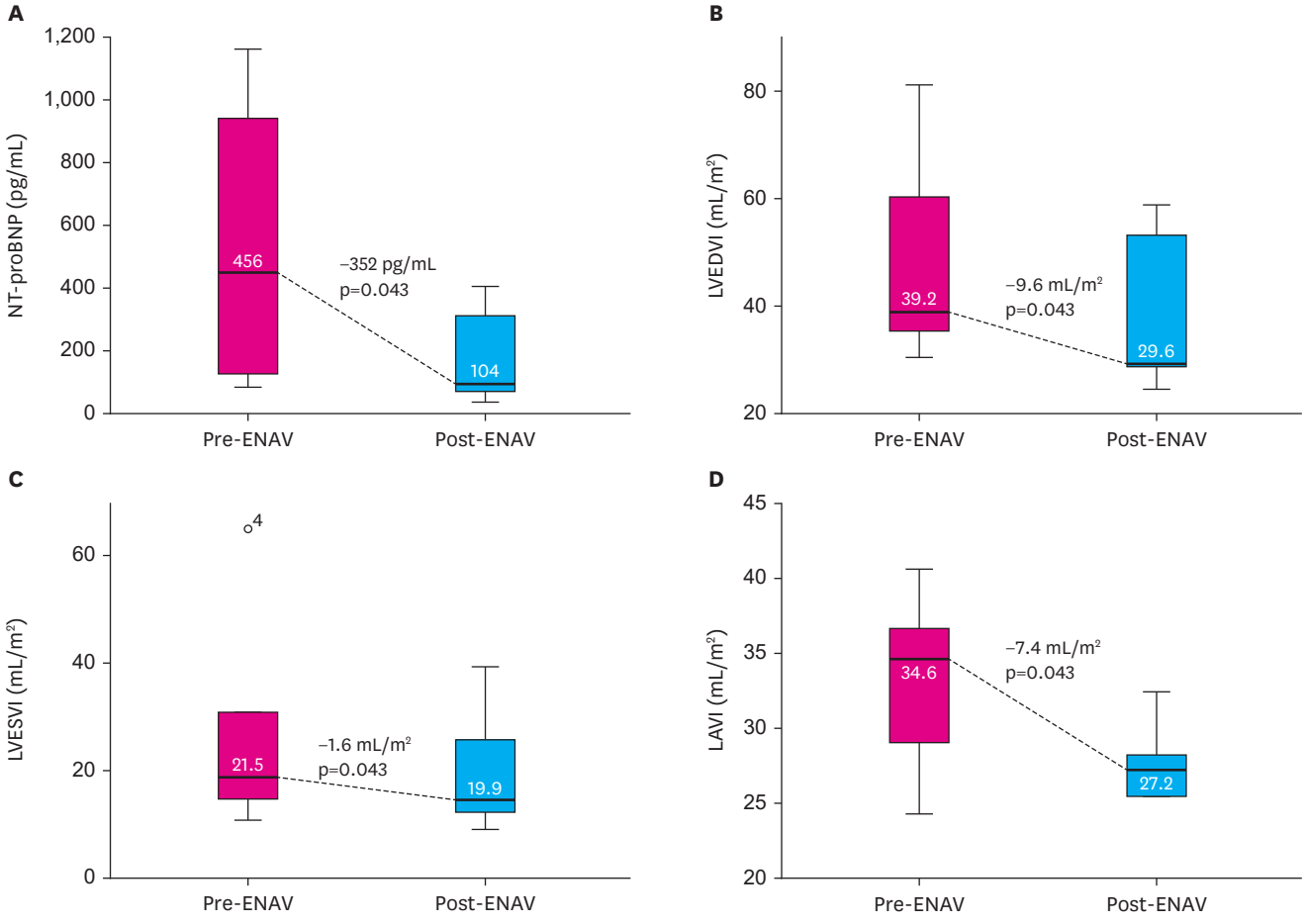

Figure 1. Absolute change of echocardiographic left ventricular and left atrial remodeling indices pre- and post-ENAV treatment.
(A) NT-proBNP, (B) LVEDVI, (C) LVESVI, and (D) LAVI of pre- and post-ENAV treatment.
ENAV = enavogliflozin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LAVI = left atrial volume index.

https://doi.org/10.36628/ijhf.2024.0018

DISCUSSION

Our data demonstrates that, although the sample size is small, enavogliflozin may have promising effects on decreasing NT-proBNP and might provoke LV and LA reverse remodeling in HF patients with DM, regardless of LVEF. This trend appears to be similar with other SGLT2 inhibitors used in HF therapy.[6]

The change in remodeling indices appeared to be most dramatic in the HFrEF patient (case 1), despite switching from another SGLT2 inhibitor, empagliflozin 10 mg, due to poorly controlled blood glucose levels. The HFrEF patient had already received guideline-directed medical therapy, including an angiotensin receptor/neprilysin inhibitor, beta blocker, mineralocorticoid receptor antagonist, and SGLT2 inhibitor for 1 year. The patient's LVEF increased by 13%, along with reductions in LV and LA remodeling indices, after switching to the SGLT2 inhibitor. Other patients also received proper HF medication, and none of the medications or dosages, including loop diuretics, were changed during the follow-up period.

The improvement was most modest in the patient with HFimpEF (case 2). The patient showed relatively less improvement in echocardiogram and serum laboratory tests compared to other cases, likely because he had already achieved substantial improvement through appropriate standard-of-care therapy for HF. However, LV remodeling indices such as LVEDVI, LVESVI, and LAVI, were reduced in all patients regardless of HF subtype or LVEF after the administration of enavogliflozin, suggesting the drug's effect on cardiac reverse remodeling.

Due to the small sample size of this study, however, further large, randomized clinical trials are required to prove the effect of enavogliflozin on patients with HF and DM. Preclinical studies are also required to evaluate the effect of the drug in patients with HF without DM.

This is the first study to report a case series of HF patients with type 2 DM treated with enavogliflozin. NT-proBNP was significantly reduced after enavogliflozin administration. Reductions in absolute value and % median change of LVEDVI, LVESVI, and LAVI were also demonstrated. These findings suggest a positive effect of enavogliflozin in cardiac reverse remodeling for HF.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics of total patients

Supplementary Table 2

Absolute change of echocardiogram parameters pre- and post-enavogliflozin medication

ORCID iDs

Taeil Yang
https://orcid.org/0009-0003-3744-7084
Youngwoo Jang
https://orcid.org/0000-0002-8802-268X
Wook-Jin Chung
https://orcid.org/0000-0002-9767-7098

Funding

This study was supported by Gachon University Gil Medical Center (FRD2023-09, FRD2022-05-02, FRD2020-11), Gachon University, College of Medicine (grant number: 202309730001), and by the "Korea National Institute of Health" (KNIH) research project (project No. 2024ER0902-00, 2021-ER0902-00, 2021-ER0902-01, 2021-ER0902-02, and 2018-ER6304-00, 2018-ER6304-01, 2018-ER6304-02) and the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (project No. 9991006834, RS-2020-KD000164).

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Jang Y, Chung WJ. Data curation: Yang T, Jang Y. Formal analysis: Yang T, Jang Y. Funding acquisition: Jang Y, Chung WJ. Methodology: Jang Y. Validation: Chung WJ. Writing - original draft: Yang T, Jang Y. Writing - review & editing: Yang T, Jang Y, Chung WJ.

REFERENCES

1. Talha KM, Anker SD, Butler J. SGLT-2 inhibitors in heart failure: a review of current evidence. Int J Heart Fail 2023;5:82-90. PUBMED | CROSSREF
2. Youn JC, Kim D, Cho JY, et al. Korean Society of Heart Failure guidelines for the management of heart failure: treatment. Int J Heart Fail 2023;5:66-81. PUBMED | CROSSREF
3. Kwak SH, Han KA, Kim KS, et al. Efficacy and safety of enavogliflozin, a novel SGLT2 inhibitor, in Korean people with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, placebo-controlled, phase III trial. Diabetes Obes Metab 2023;25:1865-73. PUBMED | CROSSREF
4. Giugliano D, Esposito K. Class effect for SGLT-2 inhibitors: a tale of 9 drugs. Cardiovasc Diabetol 2019;18:94. PUBMED | CROSSREF
5. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089-98. PUBMED | CROSSREF
6. Dhingra NK, Mistry N, Puar P, et al. SGLT2 inhibitors and cardiac remodelling: a systematic review and meta-analysis of randomized cardiac magnetic resonance imaging trials. ESC Heart Fail 2021;8:4693-700. PUBMED | CROSSREF