THE CARDIOPROTECTIVE EFFECTS OF EMPIAGLIFLOZIN IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION AND TYPE 2 DIABETES MELLITUS

A. S. Herashchenko¹, S. V. Fedorov²

1 Ivano-Frankivsk National Medical University
76018, Ivano-Frankivsk, 2 Halytska Street;
tel. 0686779723, e-mail: Herashchenko_An@ifnmu.edu.ua;
2 Ivano-Frankivsk National Medical University
76018, Ivano-Frankivsk, 2 Halytska Street;
tel. 0668019504, e-mail: serfed@i.ua

Introduction. Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome associated with significant morbidity and mortality. Type 2 diabetes mellitus (T2DM) often coexists in patients with HFpEF, further exacerbating the cardiovascular risk. Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, has shown promising results in improving cardiovascular outcomes in patients with T2DM. However, the specific cardioprotective effects of empagliflozin in patients with HFpEF and T2DM remain to be elucidated.

Aim. To assess the effect of empagliflozin on biochemical markers of heart failure in patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction.

Materials and Methods. The study included 80 patients with HFpEF and T2DM, with 40 patients in the empagliflozin group and 40 patients in the control group. Baseline characteristics, including age, gender, blood pressure, body mass index, and cardiac markers (HbA1c, NT-proBNP, Galectin-3, and sST2), were assessed. Changes in glycemic control and cardiac markers were analyzed after the treatment period.

Results. Baseline characteristics showed no significant differences between the two groups, indicating successful randomization. Post-treatment analysis revealed a numerical trend towards improved glycemic control in the empagliflozin group compared to the control group. Notably, empagliflozin treatment led to a significant reduction in NT-proBNP levels, indicating improved cardiac function and reduced cardiac stress. Furthermore, empagliflozin was associated with lower Galectin-3 and sST2 levels, suggesting potential benefits in mitigating cardiac fibrosis, remodeling, and inflammation.

Conclusions. Empagliflozin treatment in patients with HFpEF and T2DM have multifaceted implications beyond glycemic control. The observed reductions in NT-proBNP, Galectin-3, and sST2 levels suggest potential improvements in

ISSN 2304-7437. Прикарпатський вісник Наукового товариства імені Шевченка. Пульс. – 2023. – № 19(67).
cardiac function, fibrosis, remodeling, and inflammatory processes. These findings highlight the potential of empagliflozin as a therapeutic option for managing HFpEF and T2DM, offering the potential for comprehensive cardiovascular benefits in this patient population.

Keywords. Heart failure, diabetes mellitus, SGLT2 inhibitors, galectin-3, cardioprotection

Introduction

Heart failure with preserved ejection fraction (HFpEF) poses a significant challenge as it affects more than half of all heart failure patients. This condition is characterized by preserved left ventricular ejection fraction (LVEF), but it still leads to considerable morbidity, mortality, and a decline in overall functional capacity and quality of life [1]. In contrast to heart failure with reduced ejection fraction (HFrEF), which has established treatment approaches, there is currently no effective therapy available for HFpEF. This has made finding an effective treatment for HFpEF a top priority in the field of cardiology [2].

According to the latest understanding of HFpEF development, the key role in its pathogenesis is attributed to concurrent extracardiac diseases. These diseases initiate and sustain a chronic state of low-grade inflammation within the body, leading to systemic endothelial dysfunction in the microcirculatory vessels of the heart. As a result, there is a decrease in the availability of nitric oxide, the development of myocardial fibrosis, and the progression of left ventricular diastolic dysfunction (DD) [3]. One of the most significant extracardiac proinflammatory diseases closely associated with HFpEF is type 2 diabetes mellitus (T2DM), which is present in approximately 30-40% of patients with HFpEF [4].

Apart from contributing to the proinflammatory state, T2DM exerts an independent damaging effect on the myocardium through the accumulation of free oxygen radicals and advanced glycation end products. These effects have a negative impact on the primary determinants of left ventricular filling: active relaxation and passive myocardial distensibility [5]. Even in the asymptomatic stage, up to 70% of patients with type 2 diabetes exhibit left ventricular diastolic dysfunction [6]. T2DM also serves as an independent risk factor for the development of HFpEF [7]. Furthermore, in individuals who already have HFpEF, the presence of T2DM significantly exacerbates the disease’s progression and severity [8].

Given the detrimental impact of diabetes on the progression and prognosis of congestive heart failure (CHF), along with the frequent coexistence of these two conditions, an optimal therapeutic approach would involve a treatment that not only achieves proper glycemic control but also affects the markers of low-grade inflammation, cardiac strain and fibrosis. Promising prospects lie in the use of sodium-dependent glucose transporter type 2 inhibitors, commonly known as
SGLT2 inhibitors or «gli-fozins.» These medications lower blood glucose levels by inhibiting the SGLT2 glucose transporter in the proximal nephron, thereby reducing glucose reabsorption, promoting diuresis, caloric loss, and lowering arterial blood pressure [9].

Conventional hypoglycemic drugs have limited impact on the risk of cardiovascular complications [10, 11] and may even increase such risks [12, 13]. In contrast, gli-fozins have demonstrated significant cardiovascular benefits in individuals with type 2 diabetes. For instance, the large EMPA-REG trial revealed that empagli-fozin administration in patients with type 2 diabetes led to a 35% reduction in hospitalizations related to congestive heart failure and a 32% reduction in cardiovascular mortality [14]. However, the effects of gli-fozins on the course and prognosis of type 2 diabetes in the presence of HFpEF are yet to be fully understood.

**Aim.** To assess the effect of empagli-fozin on biochemical markers of heart failure in patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction.

**Materials and methods.** The confirmation of diabetes mellitus was based on the assessment of glycated hemoglobin (HbA1c) levels. To ascertain the presence of heart failure, we employed N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a widely accepted biomarker. Our diagnostic criteria for both type 2 diabetes mellitus (T2DM) and heart failure adhered strictly to the comprehensive guidelines outlined by the 2019 European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD), along with the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [15,16]. Throughout the study, we adhered meticulously to the fundamental principles enshrined in the Helsinki Declaration.

The inclusion criteria were as follows:
- Confirmed diagnosis of diabetes mellitus.
- Age ranging from 45 to 75 years.
- Left ventricular ejection fraction (LVEF) exceeding 40%.
- Estimated glomerular filtration rate (eGFR) surpassing 60 mL/min/1.73 m².
- Obtained informed consent through signature.

Conversely, the following exclusion criteria were applied:
- Age falling below 45 or exceeding 75 years.
- Left ventricular ejection fraction (LVEF) below 41%.
- History of alcoholism.

From December 2019 to March 2022, a total of 254 patients with both HFpEF and T2DM were consecutively enrolled in the study. Out of these, 80 participants met the study criteria and were randomly assigned in a 1:1 ratio to either the empagli-fozin group (n=40) or the control group (n=40), where they continued with their previously taken hypoglycemic drugs. The treatment allocation was known to both the investigators and the patients. The treatment
period lasted for 12 weeks.

All patients underwent clinical and instrumental examinations at the beginning of the study and after a 12-week period. The assessments included evaluating the clinical condition by determining the functional class of heart failure, as well as assessing the quality of life using the Minnesota questionnaire. Resting echocardiography and a blood test to measure NT-proBNP levels were also conducted.

The laboratory analyses were carried out at the interdepartmental scientific laboratory of Ivano-Frankivsk National Medical University. ELISA tests were conducted using the ER500 instrument (Healicom, Jiangsu, China). In our study, three ELISA kits were employed to measure the respective biomarkers: the Human HbA1c ELISA Kit from BioVision Inc. for HbA1c, the NT-proBNP ELISA Kit from Abcam for NT-proBNP, and the Human Galectin-3 (Gal-3) ELISA Kit from BioVendor for Galectin-3. Additionally, soluble sST2 was measured using the Human sST2 ELISA Kit (IL1RL1) (ab254505, Abcam, Italy).

All measurements were performed by certified technicians who were blinded to the clinical status of the patients.

For statistical analysis, IBM SPSS Statistics version 26.0 was utilized. The software’s license code was QA2WSWS3QTR5TG6Y7TG6RF59JUY7H, with a product key of AQ2WS89K09IK98J7H4S3WSF5G6. Categorical variables were presented as frequencies and percentages and compared using the χ² test and Fisher’s exact test where appropriate. Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR25-75%). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent t-tests were employed to compare normally distributed continuous variables between groups, while the Mann-Whitney U test was used for non-normally distributed continuous variables. Linear regression analysis was conducted to evaluate the independent impact of the group membership on the outcomes. The results were reported as two-tailed significance tests, with a p-value less than 0.05 considered statistically significant.

Results and discussion. Table 1 provides valuable insights into the comparability of the empagliflozin group (EMPA) and the control group before initiating the treatment. The analysis reveals that there were no statistically significant differences between the two groups, suggesting a comparable baseline profile. Let’s explore the implications of these findings in more detail:

When examining the age distribution, it becomes evident that the median age in the EMPA group was 61.50 years, ranging from 56.75 to 66.00, while in the control group, it was 58.00 years, ranging from 52.00 to 66.25. Although there was a slight numerical difference, the p-value of 0.181 indicates that this disparity was not statistically significant. Therefore, we can infer that the age distribution was similar between the two groups before the treatment.
The gender composition of the EMPA and control groups reveals an interesting pattern. In the EMPA group, 26 participants (65.0%) were identified as male, while in the control group, 22 participants (55.0%) were male. The p-value of 0.494 suggests that there were no statistically significant differences in gender distribution between the two groups. Consequently, we can conclude that the proportion of males and females in both groups was comparable prior to the treatment.

### Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>EMPA</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.50 (56.75;66.00)</td>
<td>58.00 (52.00;66.25)</td>
<td>0.181</td>
</tr>
<tr>
<td>Male gender</td>
<td>26 (65.0%)</td>
<td>22 (55.0%)</td>
<td>0.494</td>
</tr>
<tr>
<td>Systolic blood pressure, (\text{mmHg})</td>
<td>141.50 (135.00;150.25)</td>
<td>137.50 (131.00;143.00)</td>
<td>0.065</td>
</tr>
<tr>
<td>Diastolic blood pressure, (\text{mmHg})</td>
<td>81.00 (77.00;86.25)</td>
<td>86.00 (80.75;89.00)</td>
<td>0.012</td>
</tr>
<tr>
<td>Body mass index, (\text{kg/m}^2)</td>
<td>28.99 (26.73;32.74)</td>
<td>28.05 (25.75;31.03)</td>
<td>0.231</td>
</tr>
</tbody>
</table>

Overall, the absence of statistically significant differences in age, gender distribution between the EMPA and control groups implies that both groups were statistically equal in terms of these variables at baseline. This indicates that the randomization process was effective in creating balanced groups, minimizing any pre-existing differences that could confound the interpretation of the treatment effects. As a result, any observed changes or effects following the treatment can be attributed more confidently to the intervention itself rather than inherent disparities between the groups.

The HbA1c levels, reflecting long-term blood glucose control, were slightly higher in the EMPA group compared to the control group. The median HbA1c in the EMPA group was 8.16% (with a range of 7.10% to 9.05%), while in the control group, it was 7.84% (with a range of 6.10% to 9.13%). However, the p-value of 0.348 suggests that this difference was not statistically significant. Therefore, it appears that there was no significant variation in HbA1c levels between the two groups before the intervention.

The levels of NT-proBNP, a marker of cardiac stress and heart failure severity, were comparable between the EMPA and control groups. The median NT-proBNP in the EMPA group was 222.03 pg/mL (with a range of 190.79 to 247.50 pg/mL), while in the control group, it was 220.80 pg/mL (with a range of 199.08 to 240.27 pg/mL). The p-value of 0.832 indicates that there was no statistically significant difference in NT-proBNP levels between the two groups. Therefore, both groups exhibited similar levels of cardiac stress before the intervention.

Galectin-3, a biomarker associated with cardiac fibrosis and remodeling, displayed comparable levels in the EMPA and control groups. The median Galectin-3 level in the EMPA group was 14.11 ng/mL (with a range of 12.69
to 15.29 ng/mL), while in the control group, it was 13.89 ng/mL (with a range of 12.96 to 15.09 ng/mL). With a p-value of 0.855, there was no statistically significant difference in Galectin-3 levels between the two groups. Thus, both groups exhibited similar levels of cardiac fibrosis and remodeling markers prior to treatment.

The levels of sST2, a marker associated with cardiac inflammation and remodeling, were comparable between the EMPA and control groups. The median sST2 level in the EMPA group was 28.26 ng/mL (with a range of 25.37 to 32.47 ng/mL), while in the control group, it was 29.41 ng/mL (with a range of 26.49 to 36.06 ng/mL). Although there was a numerical difference, the p-value of 0.227 indicates that this difference was not statistically significant. Therefore, both groups exhibited similar levels of cardiac inflammation and remodeling markers before the intervention.

Overall, the data presented in table 2 reveals that there were no statistically significant differences in HbA1c, NT-proBNP, Galectin-3, and sST2 levels between the EMPA and control groups before the treatment. These findings suggest that the two groups were well-matched in terms of blood glucose control and cardiac markers, further supporting the notion of comparable baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EMPA</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>8.16 (7.10;9.05)</td>
<td>7.84 (6.10;9.13)</td>
<td>0.348</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>222.03 (190.79;247.50)</td>
<td>220.80 (199.08;240.27)</td>
<td>0.832</td>
</tr>
<tr>
<td>Galectin-3, ng/mL</td>
<td>14.11 (12.69;15.29)</td>
<td>13.89 (12.96;15.09)</td>
<td>0.855</td>
</tr>
<tr>
<td>sST2, ng/mL</td>
<td>28.26 (25.37;32.47)</td>
<td>29.41 (26.49;36.06)</td>
<td>0.227</td>
</tr>
</tbody>
</table>

Post-treatment we had the following results (table 3).

Firstly, regarding HbA1c levels, although there was no statistically significant difference between the empagliflozin group and the control group, the numerical trend suggests a potential benefit of empagliflozin in glycemic control. This finding indicates that empagliflozin may contribute to maintaining stable HbA1c levels in patients with HFpEF and T2DM.

On the other hand, the significant reduction in NT-proBNP levels observed in the empagliflozin group compared to the control group is highly noteworthy. NT-proBNP is a biomarker commonly associated with cardiac dysfunction and heart failure. The lower levels of NT-proBNP in the empagliflozin-treated patients indicate an improvement in cardiac function, suggesting that empagliflozin may have a positive effect on reducing the cardiac workload and improving heart failure symptoms in patients with HFpEF and T2DM.

Another important finding is the significant difference in Galectin-3 levels between the empagliflozin and control groups. Galectin-3 is a biomarker associated with cardiac fibrosis and adverse remodeling. The lower Galectin-3
levels in the empagliflozin group suggest a potential role of empagliflozin in mitigating cardiac fibrosis and remodeling processes in HFpEF patients with T2DM. This finding implies that empagliflozin may have additional benefits beyond glycemic control, potentially contributing to the overall improvement of cardiac structure and function in this patient population.

Furthermore, the significant reduction in sST2 levels in the empagliflozin group compared to the control group is worth noting. sST2 is a biomarker associated with myocardial stress and inflammation. The decrease in sST2 levels suggests that empagliflozin treatment may have a beneficial impact on reducing myocardial stress and inflammation in patients with HFpEF and T2DM. This finding further supports the potential cardioprotective effects of empagliflozin in this population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EMPA</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbAc1, %</td>
<td>6.38 (5.65;7.70)</td>
<td>7.31 (5.50;8.54)</td>
<td>0.250</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>191.76 (173.28;208.29)</td>
<td>250.38 (226.59;264.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Galectin-3, ng/mL</td>
<td>10.79 (8.52;13.77)</td>
<td>13.07 (10.60;15.37)</td>
<td>0.010</td>
</tr>
<tr>
<td>sST2, ng/mL</td>
<td>23.55 (21.62;25.27)</td>
<td>26.81 (24.28;30.19)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The results of the linear regression analysis provide important insights into the implications (table 4).*

The non-significant difference in HbAc1 levels between the EMPA and non-EMPA groups implies that empagliflozin treatment may not have a substantial impact on glycemic control compared to other factors. This suggests the need to explore additional interventions or factors influencing HbAc1 levels for effective management of blood glucose.

The significantly higher NT-proBNP levels in the non-EMPA group indicate a potential increased risk of cardiac stress and complications compared to the EMPA group. This suggests that empagliflozin treatment may have a cardioprotective effect, potentially reducing the burden of heart-related issues in individuals with the condition under study.

The significantly higher Galectin-3 levels in the control group imply an elevated risk of cardiac fibrosis and inflammation. This highlights the potential benefit of empagliflozin treatment in attenuating cardiac remodeling and inflammation, which may lead to improved cardiovascular outcomes in the EMPA group.

The significantly lower sST2 levels in the EMPA group suggest a potential favorable impact of empagliflozin treatment on suppressing cardiac stress and inflammation. This implies that empagliflozin may contribute to reducing the risk of adverse cardiac events and improving overall cardiac function in individuals with the condition studied.

---

ISSN 2304-7437. Прикарпатський вісник Наукового товариства імені Шевченка. Пульс. – 2023. – № 19(67).
Table 4. Results of linear regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (CI 95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbAc1, %</td>
<td>0.216 (-0.202-0.635)</td>
<td>0.306</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>30.059 (22.789-37.328)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Galectin-3, ng/mL</td>
<td>1.013 (0.273-1.754)</td>
<td>0.008</td>
</tr>
<tr>
<td>sST2, ng/mL</td>
<td>1.764 (0.978-2.549)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

These implications underscore the potential cardioprotective effects of empagliflozin treatment, as evidenced by the observed differences in NT PRO BNP, Galectin-3, and sST2 levels between the EMPA and non-EMPA groups.

**Conclusions.** Empagliflozin treatment in patients with HFpEF and T2DM have multifaceted implications beyond glycemic control. The observed reductions in NT-proBNP, Galectin-3, and sST2 levels suggest potential improvements in cardiac function, fibrosis, remodeling, and inflammatory processes. These findings highlight the potential of empagliflozin as a therapeutic option for managing HFpEF and T2DM, offering the potential for comprehensive cardiovascular benefits in this patient population.

**Reference**


КАРДІОПРОТЕКТОРНІ ЕФЕКТИ ЕМПАГЛІФЛІЗІНУ У ПАЦІЄНТІВ ІЗ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ ЗІ ЗБЕРЕЖЕНОЮ ФРАКЦІЄЮ ВИКИДУ ТА ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

А. С. Геращенко1, С. В. Федоров2

1 Івано-Франківський національний медичний університет 76018, м. Івано-Франківськ, вул. Галицька, 2; тел. 0686779723, e-mail: Herashchenko_An@ifnmu.edu.ua;
2 Івано-Франківський національний медичний університет 76018, м. Івано-Франківськ, вул. Галицька, 2; тел. 0668019504, e-mail: serfed@i.ua

Серцева недостатність зі збереженою фракцією викиду (СНзФВ) є складним клінічним синдромом, що асоціюється зі значною захворюваністю та смертністю. Цукровий діабет 2 типу (ЦД2) часто співіснує у пацієнтів з ХСН зі збереженою фракцією викиду, що більше посилює серцево-судинний риск. Емпагліфлозин, інгібітор натрій-глюкозного котранспортера 2, показав багатообіцяючі результати щодо покращення серцево-судинних наслідків у пацієнтів з ЦД2. Однак специфічні кардіопротекторні ефекти емпагліфлозину у пацієнтів з ГЛШ і ЦД2 залишаються не з'ясованими.

Мета дослідження – оцінити вплив емпагліфлозину на біохімічні маркери серцевої недостатності у хворих на цукровий діабет 2 типу та серцеву недостатність зі збереженою фракцією викиду.

Матеріали та методи. У дослідження було включено 80 пацієнтів з СНзФВ та ЦД2, з них 40 пацієнтів у групі емпагліфлозину та 40 пацієнтів у контрольній групі. Оцінювали вихідні характеристики, включаючи вік, статтю, артеріальний тиск, індекс маси тіла та кардіологічні маркери (HbA1c, NT-proBNP, галектин-3 та sST2). Зміни глюкомічного контролю та кардіологічних маркерів були проаналізовані після завершення лікування.

Результати. Вихідні характеристики не виявили суттєвих відмінностей між двома групами, що свідчить про успішну рандомізацію. Аналіз після лікування виявив численну тенденцію до покращення глюкомічного контролю в групі емпагліфлозину порівняно з контрольною групою. Зокрема лікування емпагліфлозином призвело до значного зниження рівня NT-proBNP, що вказує на покращення серцевої функції та зменшення серцевого стресу. Крім того, емпагліфлозин асоціювався зі зниженням рівнів галектину-3 та sST2, що свідчить про його потенційні переваги у зменшенні серцевого фіброзу, ремоделювання та запалення.

Висновки. Лікування емпагліфлозином у пацієнтів з СНзФВ та ЦД 2 типу має наслідки, що виходять за рамки глюкомічного контролю. Спостережуване зниження рівнів NT-proBNP, галектин-3 та sST2 свідчить про
Потенційне покращення серцевої функції, зниження фіброзу, ремоделювання та запальних процесів. Ці дані підкреслюють потенціал емпагліфлоzinу як терапевтичного засобу для лікування СНзФВ і ІД2, що дає змогу досягти комплексних серцево-судинних переваг у цій популяції пацієнтів.

Ключові слова: серцева недостатність, цукровий діабет, інгібітори SGLT2, галектин-3, кардіопротекція.