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Research Article

The impact of sodium-glucose cotransporter-2 inhibitors on left ventricular ejection fraction in patients after acute myocardial infarction and revascularization: the role of pharmacotherapy adherence

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Abstract

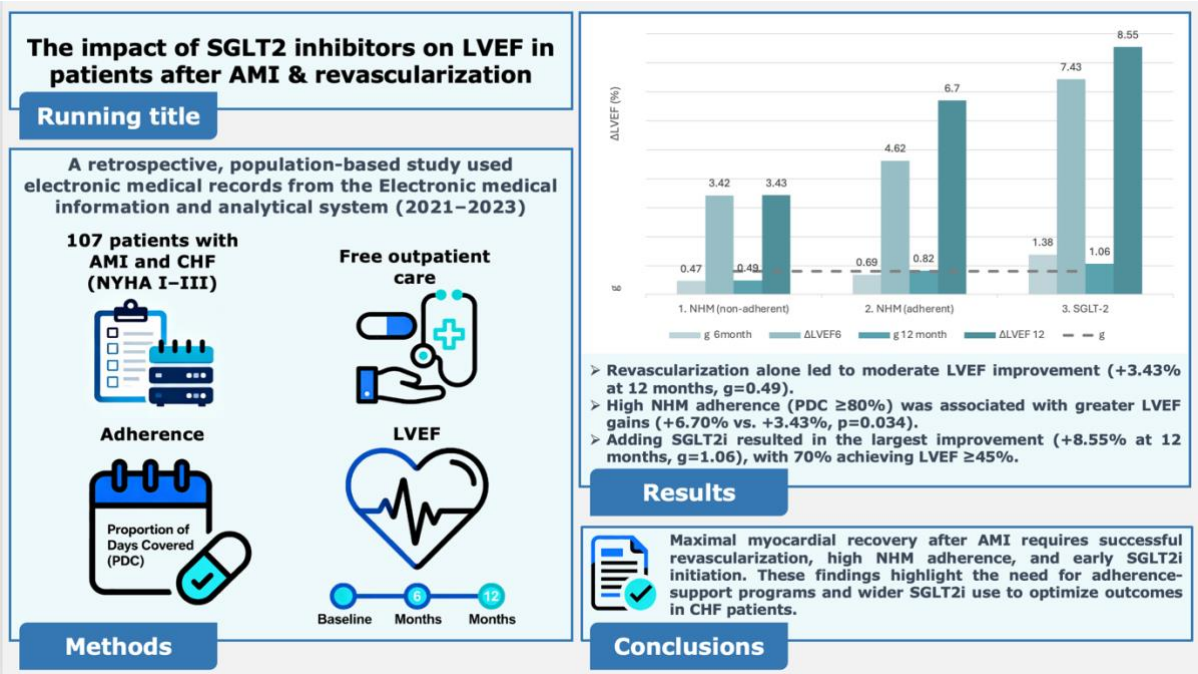
Introduction: Optimal recovery of left ventricular ejection fraction (LVEF) in chronic heart failure (CHF) patients after acute myocardial infarction (AMI) is challenging in real-world settings, where therapy adherence varies. **Aim:** This study assessed the comparative effectiveness of revascularization, neurohumoral modulator (NHM) therapy, and sodium-glucose cotransporter-2 inhibitors (SGLT2i) on LVEF dynamics, considering actual adherence.

Materials and Methods: A retrospective, population-based study used electronic medical records from the Electronic medical information and analytical system (2021–2023). 107 patients with AMI and CHF (NYHA I–III) receiving free outpatient care were included. Adherence was measured by Proportion of Days Covered (PDC). LVEF was evaluated at baseline, 6, and 12 months. Effect size was estimated using Hedges' g.

Results: Revascularization alone led to moderate LVEF improvement (+3.43% at 12 months, g=0.49). High NHM adherence (PDC ≥80%) was associated with greater LVEF gains (+6.70% vs. +3.43%, p=0.034). Only 24.3% maintained optimal adherence. Adding SGLT2i resulted in the largest improvement (+8.55% at 12 months, g=1.06), with 70% achieving LVEF ≥45%. Maximal SGLT2i effects were seen in patients with severe baseline impairment.

Conclusions: Maximal myocardial recovery after AMI requires successful revascularization, high NHM adherence, and early SGLT2i initiation. Suboptimal adherence significantly reduces efficacy. These findings highlight the need for adherence-support programs and wider SGLT2i use to optimize outcomes in CHF patients.

Graphical Abstract



Keywords

heart failure, left ventricular ejection fraction, medication adherence, myocardial infarction, myocardial revascularization, neurohormonal modulating therapy, proportion of days covered (PDC), real-world clinical data, SGLT-2 inhibitors

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have opened new perspectives in the treatment of heart failure (HF), demonstrating unique cardioprotective properties independent of their hypoglycemic effect. Large randomized trials (EMPA-REG OUTCOME, DAPA-HF) have confirmed their ability to reduce the risk of hospitalization for heart failure and cardiovascular mortality by 30–35% (Novo et al. 2023; Chen et al. 2024). The mechanisms underlying these benefits remain a subject of discussion, although cardioprotective effects such as hemodynamic modulation (Adingupu et al. 2019; Filippatos et al. 2019), metabolic reprogramming (Matsumura and Sugiura 2019), and anti-inflammatory action (Filippatos et al. 2019; Novo et al. 2023) are known, which is critical for the restoration of contractile function in patients with initially reduced left ventricular ejection fraction (LVEF). The direct impact on myocardial contractile activity has not been sufficiently studied, although there are suggestions that SGLT2i enhance the effect of revascularization by modulating the energy metabolism of cardiomyocytes and suppressing post-infarction fibrosis.

Despite these impressive clinical results, the specific effects on systolic and diastolic myocardial function remain underexplored:

- Meta-analyses of randomized clinical trials (RCTs) have demonstrated a modest increase in left ventricular ejection fraction (LVEF) (+2.79%, p=0.036) (Chen et al. 2024), though without analyzing the dynamics in patients with initially reduced contractility.
- Experimental studies on ischemia models indicate suppression of fibrosis and improvements in energy metabolism; however, extrapolating these findings to clinical practice remains premature (Adingupu et al. 2019, Matsumura and Sugiura 2019).
- No studies have evaluated the interaction between SGLT2 inhibitors (SGLT2i) and revascularization effects in real-world clinical settings.

The present study is the first to systematically analyze the comparative effectiveness of three factors: (1) revascularization after acute myocardial infarction (AMI), (2) standard pharmacotherapy with neurohumoral modulators (NHM), and (3) SGLT2 inhibitor (SGLT2i) therapy – on the recovery of left ventricular contractility (LVEF). The study utilizes therapy

adherence (assessed via the Proportion of Days Covered (PDC) method) as the primary criterion for forming comparison groups.

The aim of the current study was to evaluate the contribution of revascularization, standard NHM therapy, and SGLT2i to left ventricular ejection fraction (LVEF) dynamics in post-AMI patients, using real-world clinical data while accounting for treatment adherence.

Materials and Methods

Study design

Retrospective pharmacoepidemiological population-based study. Follow-up period: 12 months.

Data source

Electronic medical records (EMRs) from the Electronic medical information and analytical system (UMIAS) for 2021–2023 were used. EMRs are completed by specialists during patient visits and contain comprehensive medical information about patients.

Data extracted from EMRs included: hospital discharge summaries, echocardiography (EchoCG) reports, data on prescribed and dispensed subsidized medications, and hospitalization records.

Study population

Study population included patients under cardiologist follow-up for 1 year after hospitalization due to acute myocardial infarction (AMI) and receiving free treatment.

The inclusion criteria for the study were: a confirmed diagnosis of acute myocardial infarction and chronic heart failure (NYHA class I–III); availability of echocardiographic (EchoCG) data at hospital discharge; the presence of active subsidized prescriptions for at least one class of neurohormonal modulators (renin-angiotensin system inhibitors (RASi), angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), beta-blockers (BB), or sodium-glucose cotransporter-2 inhibitors (SGLT2i)); and fulfillment of the subsidized electronic prescription within 14 days after hospital discharge. Patients with conditions critically affecting life prognosis were not included in the study.

Data collection

For each patient, the following were recorded: demographics (age, sex), comorbidities (coded according to the International Classification of Diseases, Tenth Revision (ICD-10)), the fact of revascularization, method (PCI/CABG), echocardiographic parameters (LVEF by Simpson's method) over time: at baseline ($LVEF_0$), at 6 months ($LVEF_6$), and at 12 months ($LVEF_{12}$), prescription data (INN of drugs, dosages, frequency, dispensing dates), and dates of hospitalizations.

Quality control of data: 10% of randomly selected EMRs were verified by two independent investigators. The data were collected correctly. All data were anonymized, and each patient was assigned a unique code. The study was conducted in accordance with ethical standards for retrospective analysis of anonymized data; approval by the Ethics Committee was not required.

Visualization

Adherence behavior patterns were illustrated using Sankey diagrams; summarized results – via grouped histograms.

Methodological approaches

The study encountered three independent factors that each exerted a unidirectional positive effect on left ventricular ejection fraction (LVEF): revascularization (PCI/CABG), which restored coronary blood flow in nearly all patients and, by itself, led to an increase in LVEF, particularly in the first 3–6 months; standard neurohormonal therapy, involving the prescription of RAAS inhibitors, beta-blockers, and mineralocorticoid receptor antagonists in accordance with clinical guidelines; and the addition of SGLT2 inhibitors, which may provide a potential synergistic effect with neurohormonal modulation.

In accordance with the ESC 2023 position regarding the difficulty of isolating the effect of revascularization from concomitant therapy ("... difficult to separate the effect of revascularization itself from that of concomitant pharmacological treatment" (Byrne et al. 2023)), we developed a three-level analytical protocol.

1. The control group for assessing the baseline effect of revascularization was defined by the absence of SGLT2 inhibitors throughout the observation period and low adherence to neurohormonal modulation during the year (annual PDC <80% for all classes). This minimized

the medication influence when evaluating the contribution of revascularization, in line with ESC recommendations for real-world practice analysis.

2. The group for assessing the effect of neurohormonal modulation included patients without SGLT2 inhibitors and with optimal adherence to neurohormonal therapy (annual PDC ≥80% for all classes). This approach excluded the effect of SGLT2 inhibitors and the "pure" effect of revascularization (when annual PDC <80% for all neurohormonal modulators).

3. The group for evaluating the contribution of SGLT2 inhibitors was formed according to the criteria of optimal adherence to SGLT2 inhibitors (annual PDC ≥80%) and receipt of neurohormonal therapy regardless of adherence. These criteria were necessary because the combination of "adherent to SGLT2 inhibitors + adherent to neurohormonal therapy" applied to only four patients.

The stratified analysis of therapy effects is presented in Table 1.

Table 1. Characteristics of the comparison groups in the study on adherence and structure of pharmacotherapy (n=107)

Groups	Characteristics
Revascularization (n=54)	NHM PDC <80% throughout the year; no SGLT2i.
NHM (n=19)	NHM PDC ≥80% throughout the year; no SGLT2i.
NHM + SGLT2i (n=14)	SGLT2i PDC ≥80% throughout the year.

Note: PDC – Proportion of Days Covered; NGM – neurohumoral modulators (ACE inhibitors, ARBs, beta blockers, aldosterone antagonists); iNGLT-2 – type 2 sodium-glucose cotransporter inhibitors.

Method

A multistage statistical analysis was performed using Hedges' g coefficient, which makes it possible to assess not just the presence but the magnitude of the effect–serving as a 'gold standard' for comparing treatment effects in heterogeneous data settings. Key aspects of its application include:

- *Small-sample correction in real-world studies:* Hedges' g incorporates the J-factor adjustment, reducing bias in small-n estimates (Gerlach et al. 2020, Muslem et al. 2025).
- *Effect standardization*: Hedges' *g* quantifies between-group differences in standard deviation units, enabling various study comparisons (Nuzzo 2014).
- *Missing data handling:* Hedges' *g* maintains accuracy in paired data analysis even when partial exclusions occur.

Statistical analysis

Adherence

Proportion of Days Covered (PDC) was calculated with adjustments for hospitalization periods and temporary treatment discontinuations due to medical indications (excluded from the analysis) (Hess et al. 2006; NASP 2019; Fitilev et al. 2025). The start date of the next prescription was shifted to the end date of the previous one. The initial date of the calculation period was the date of the first prescription dispensing; the "refill" date was the date the medication was dispensed to the patient; the end date of the calculation period was the end of the observation period. During dose titration, a "manual management" mode was introduced for analysis using primary medical documentation data, which is a significant advantage in studies of this kind.

The medication adherence indicator (PDC) is calculated using the formula:

$$PDC = \frac{(\text{Days covered by therapy} - \text{Exception days})}{(\text{Total observation days} - \text{Exception days})} \times 100\% \quad (1),$$

Adherence was considered optimal if the PDC was at least 80% for all prescribed medication classes simultaneously. If the PDC was less than 80% for at least one class, the patient was classified as having insufficient adherence.

Efficacy assessment

The primary endpoint of the study was the change in left ventricular ejection fraction at 6 and 12 months ($\Delta LVEF_6$, $\Delta LVEF_{12}$). All echocardiographic examinations were performed according to a unified standard approved by the Moscow Department of Health. Baseline ejection fraction values ($LVEF_0$) were obtained from hospital discharge summaries.

Statistical analysis

Descriptive statistics were presented as follows: for continuous variables with a normal distribution, the mean and standard deviation (M ± SD) were reported, while for non-normally

distributed data, the median and interquartile range (Me [IQR]) were used. Normality was assessed using the Shapiro-Wilk test at a significance level of α=0.05.

Group comparisons for paired observations ($LVEF_0 \leftrightarrow LVEF_6$, $LVEF_0 \leftrightarrow LVEF_{12}$, $LVEF_6 \leftrightarrow LVEF_{12}$) were performed using the paired Student's t-test for normally distributed differences, and the Wilcoxon test when normality was not observed. The Holm-Bonferroni method was applied to correct for multiple comparisons.

Effect size was estimated using Hedges' g coefficient with a correction for small samples, calculated as:

$$g = \left(\frac{\bar{d}}{s\_d}\right) \times \left(\frac{1 - 3}{4n - 1}\right) \qquad (2),$$

where $\bar{d}$ is the mean difference of paired observations, s_d is the standard deviation of the differences, and n is the number of pairs (Hedges 1981; Cumming 2013; Higgins et al. 2024). Ninety-five percent confidence intervals for g were calculated using the bootstrap method with 1000 iterations.

For handling missing data, the Complete Case Analysis (CCA) approach was used, including only patients with complete data at all time points in the analysis.

Software

Statistical analysis was performed using Python 3.11, with the SciPy library (v1.11) for statistical tests, Pingouin (v0.5.3) for calculating Hedges' g and confidence intervals, and Pandas (v2.1.0) for data processing. The significance level was set at a two-sided α=0.05, with results considered statistically significant at $p < 0.05$.

Results

Population characteristics and therapy adherence patterns (n=107)

Demographics

Mean age: 67.1 ± 12.2 years; male/female ratio 3:1. Revascularization was performed in 94 patients (87.9%) during hospitalization, with early revascularization in 13 (12.1%). NYHA functional class: Class I – 9 (8.4%), Class II – 88 (82.2%), Class III – 10 (9.4%). Comorbidities: arterial hypertension – 96.3%, chronic kidney disease – 34.6%, diabetes mellitus – 20.6%.

Pharmacotherapy structure

The structure of pharmacotherapy remained consistent across both semesters. Recommended prescriptions are shown in Table 2.

Table 2. The structure and adherence to pharmacotherapy in patients with AMI, depending on the phenotypes of HF (n=107)

HF Phenotype	Low LVEF, n	Moderately Reduced LVEF, n	Preserved LVEF, n	PDC, % (M ± SD)	Adherence, n (%)
RASi + BB	2	16	20	71.89± 26.26	14 (36.8)
RASi + BB + MRA	9	10	11	60.5± 29.87	4 (13.3)
RASi + BB + SGLT2i	2	3	2	78.1± 19.99	2 (28.6)
RASi + BB + MRA + SGLT2i	12	5	1	64.65± 30.66	1 (5.6)
BB	1	2	4	74.14± 26.71	3 (42.9)
BB + MRA	1	-	2	58.5± 38.16	0 (0)
RASi + MRA	1	-	-	99.0	1 (100.0)
RASi + MRA + SGLT2i	1	-	-	100.0	1 (100.0)
RASi	1	-	-	60.0	0 (0)
BB + MRA + SGLT2i	1	-	-	50.33	0 (0)
Total patients, n (%)	31 (29.0)	36 (33.6)	40 (37.4)		26 (24.3)

Note: AMI – acute myocardial infarction; HF – heart failure; HFrEF – with reduced ejection fraction, HFmrEF – with mildly reduced ejection fraction, HFpEF – with preserved ejection fraction; M±SD – mean ± standard deviation; PDC – proportion of days covered; RAASi – renin-angiotensin-aldosterone system inhibitors; BB – beta-blockers; MRA – mineralocorticoid receptor antagonists; SGLT2i – sodium-glucose cotransporter 2 inhibitors.

Patient adherence to prescribed treatment combinations over the course of a year was only 24.3%. This is a critical indicator for patients in a period crucial for their life prognosis.

Adherence patterns

We analyzed HF therapy adherence in each semester and identified 4 patient behavior patterns reflecting their adherence to recommended therapy (Fig. 1).

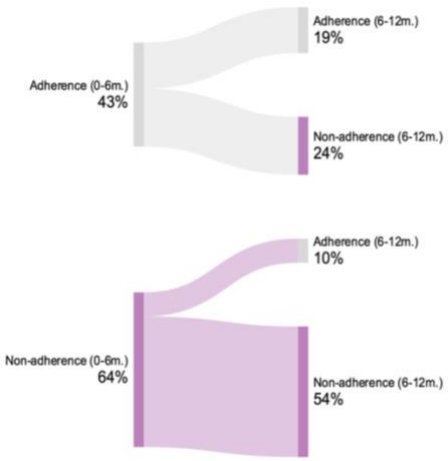


Figure 1. Patient behavior patterns regarding recommended HF therapy within 1 year after AMI.

Four behavioral groups were identified in the first and second half-year periods with respect to the administered treatment: adherent/adherent – 19 patients (17.8%), adherent/non-adherent – 24 patients (22.4%), non-adherent/adherent – 10 patients (9.3%), and non-adherent/non-adherent – 54 patients (50.5%). These findings indicate a persistent trend of patients neglecting prescribed therapy during the critical post-infarction period.

Subsequently, the impact of revascularization on the dynamics of left ventricular ejection fraction (LVEF) was assessed in patients who remained consistently non-adherent to therapy throughout the year and did not receive SGLT2 inhibitors, as well as the effectiveness of neurohormonal modulation (NHM) therapy in patients with optimal NHM adherence over the year who did not receive SGLT2 inhibitors either, during the 12 months following acute myocardial infarction and revascularization. The results of both analyses are presented in Table 3.

It should also be clarified that the analysis included only patients with at least two echocardiographic reports. The number of paired data points for comparison, as presented in the tables (Tables 3, 4, 5), may not coincide with the total number of patients in each study group, which is typical for longitudinal studies.

Clinical interpretation of effects based on Hedges' g coefficient was performed according to established criteria: g = 0.2 for a small effect, g = 0.5 for a medium effect, and g ≥ 0.8 for a large effect.

Table 3. Impact of adherence to neurohumoral modulators on LVEF dynamics over 1year post-AMI with revascularization in HF patients (n=73)

Parameter	**Non-adherent** (n=54) PDC_{0-6}<80% PDC_{6-12}<80%	***p*-value**	**Adherent** (n=19) PDC_{0-6}≥80% PDC_{6-12}≥80%	***p*-value**
$LVEF_0$ (M±SD)	46.35 ± 7.40 (n=31)	–	47.87 ± 6.59 (n=15)	–
$LVEF_6$ (M±SD)	49.46 ± 8.15 (n=26)	–	51.85 ± 5.00 (n=13)	0.266
$LVEF_{12}$ (M±SD)	50.43 ± 6.31 (n=14)	–	56.80 ± 6.96 (n=10)	0.034
$\Delta LVEF_6$ (M±SE)	+3.42 ± 1.37 (26 pairs)	0.019	+4.62 ± 1.76 (13 pairs)	0.022
$\Delta LVEF_{12}$ (M±SE)	+3.43 ± 1.75 (14 pairs)	0.072	+6.70 ± 2.27 (10 pairs)	0.027
Hedges' g (95% CI)				
$LVEF_6$ vs $LVEF_0$	0.47 (0.088, 0.86)	–	0.69 (0.15–1.35)	–
$LVEF_{12}$ vs $LVEF_0$	0.49 (−0.038, 1.02)	–	0.82 (0.05–1.59)	–

***Note*:** AMI – acute myocardial infarction; HF – heart failure; LVEF (EF) – left ventricular ejection fraction; PDC – proportion of days covered; M±SD – mean ± standard deviation; M±SE – mean ± standard error; g – Hedges' g effect size, 95% CI – 95% confidence interval; Within-group comparisons were performed using the Wilcoxon test, effect size calculated by Hedges' g.

The effect of revascularization in patients with low adherence to neurohormonal modulators over both half-year periods showed a moderate increase in ejection fraction at 6 months (+3.42±1.37; p=0.0195), while at 12 months the effect persisted but was not statistically significant (+3.43±1.75; p=0.072). The effect size (g) did not reach the medium level

(0.47→0.49). The proportion of patients with LVEF >50% was initially 41.9%, rising to 53.8% at 6 months and 64.3% at 12 months.

The effect of neurohormonal modulators in patients with optimal adherence demonstrated a significant increase in LVEF at 6 months (+4.62±1.7; p=0.022), which further strengthened at 12 months (+6.70±2.27; p=0.027). The effect size (g) increased from moderate to high (0.69→0.82). The proportion of patients with LVEF >50% rose from 40% at baseline to 50% at 6 months and 80% at 12 months.

Clinically meaningful differences between adherent and non-adherent patients were observed: adherence to therapy increased the annual LVEF gain by +6.37% (p=0.034). The effect size (g) was substantially higher in the adherent group (0.82 vs 0.42). After one year, the proportion of patients with LVEF >50% reached 80% in the adherent group compared to 64% in the non-adherent group.

The final stage of the study examined the effect of SGLT2 inhibitors against the background of standard therapy. Initially, it was planned to assess the contribution of SGLT2 inhibitors to LVEF improvement in patients who were adherent to neurohormonal modulators throughout the year, but only four such patients were identified. Therefore, we evaluated the contribution of SGLT2 inhibitors in patients receiving neurohormonal modulators regardless of adherence to standard heart failure therapy. The results of this comparison are presented in Table 4.

Table 4. Impact of SGLT2 inhibitors on LVEF dynamics in patients during 1 year after AMI with revascularization on the background of standard HF therapy with neurohumoral modulators (n=82)

Parameter	**+SGLT2i** (n=14) PDC_{0-6}≥80% PDC_{6-2}≥80%	***p*-value**	**NHM** (n=68) PDC_{0-6}1-100% PDC_{6-12}1-100%	***p*-value**
$LVEF_0$ (M±SD)	40.0 ± 6.75 (n=14)	–	47.37 ± 6.83 (n=68)	0.002
$LVEF_6$ (M±SD)	47.4 ± 6.90 (n=14)	–	51.15 ± 6.90 (n=59)	0.082
$LVEF_{12}$ (M±SD)	48.4 ± 7.12 (n=11)	–	52.94 ± 6.70 (n=36)	0.079
$\Delta LVEF_6$ (M±SE)	+7.43 ± 1.36 (14 pairs)	<0.001	+4.15 ± 0.84 (59 pairs)	<0.0001
$\Delta LVEF_{12}$ (M±SE)	+8.55 ± 2.25 (11 pairs)	0.004	+5.25 ± 1.25 (36 pairs)	0.0002
Hedges' g (95% CI)				
$LVEF_6$ vs $LVEF_0$	1.38 (0.84–1.93)	–	0.69 (0.15–1.35)	–
$LVEF_{12}$ vs $LVEF_0$	1.06 (0.44–1.69)	–	0.82 (0.05–1.59)	–

Note: AMI – acute myocardial infarction; EF – left ventricular ejection fraction; PDC – proportion of days covered; NHM – neurohumoral modulators (ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists); SGLT2i – sodium-glucose cotransporter 2 inhibitors; M±SD – mean ± standard deviation; M±SE – mean ± standard error; p-value – significance level of difference between compared parameters; Hedges' g, 95% CI – effect size (g) and confidence interval; Within-group comparisons were performed using the Wilcoxon test, effect size calculated by Hedges' g.

The effect of adding SGLT2 inhibitors to standard heart failure therapy was marked by a significant increase in ejection fraction at 6 months (+7.43; SE=1.36; p<0.001), with the effect stabilizing at a high level by 12 months (+8.55; SE=1.36; p=0.004). The effect size (g) reached its maximum and then plateaued (1.38→1.06). The proportion of patients with LVEF ≥40% was 78.6% at 6 months and 81.8% at one year.

Clinically meaningful differences were observed between the effects of SGLT2 inhibitors (in adherent patients) and neurohormonal modulators (regardless of adherence). Initially, the ejection fraction in the SGLT2 inhibitor group was significantly lower (40.0 ± 6.75 vs 47.37 ± 6.83; p=0.002). At 6 months, the addition of SGLT2 inhibitors provided an additional increase in ejection fraction of +3.28 compared to neurohormonal modulators (p=0.051), and at 12 months the difference was +3.30 (p=0.217). The effect size (g) at 6 months was higher for SGLT2 inhibitors (1.38 vs 0.69), as well as at 12 months (1.06 vs 0.82).

Summary of results

A clear illustration of the data is provided in Figure 2.

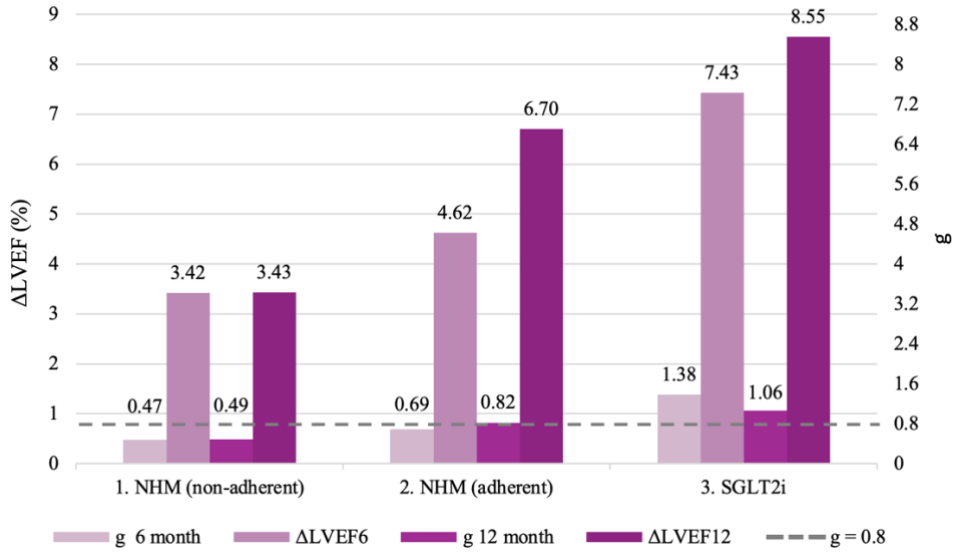


Figure 2. Summary data on the dynamics of left ventricular ejection fraction, Hedges' g coefficient depending on adherence to neurohumoral modulator therapy, as well as the addition of SGLT2 inhibitors to this therapy during the first and second halves of the year in patients after AMI with revascularization (n=107). ***Note:*** LVEF – left ventricular ejection fraction; Hedges' g – effect size (g); NHM – neurohumoral modulators (ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists); SGLT2i – sodium-glucose cotransporter-2 inhibitors; 1. NHM (non-adherent) – control group for evaluating the baseline effect of revascularization defined by criteria: no SGLT2i throughout observation and low NHM adherence during the year (PDCyear <80% for all classes); 2. NHM (adherent) – group for evaluating NHM effect included patients without SGLT2i and with optimal NHM adherence (PDCyear ≥80% for all classes); 3. SGLT2i – group for assessing SGLT2i contribution formed by criteria: optimal SGLT2i adherence (PDCyear ≥80%) and receiving NHM regardless of adherence.

1. The baseline effect of revascularization was observed as a moderate effect at 6 months (ΔLVEF = +3.42±1.37; p=0.0195; g=0.47), with stabilization at a similar level by 12 months (ΔLVEF = +3.43±1.75; p=0.072; g=0.49).

2. The added value of adherence to neurohormonal modulator therapy was reflected in a moderate effect at 6 months (ΔLVEF = +4.62±1.76; p=0.022; g=0.69) and a high effect at 12 months (ΔLVEF = +6.70±2.27; p=0.027; g=0.82).

3. The added value of SGLT2 inhibitors was characterized by a maximal effect at 6 months (ΔLVEF = +7.43±1.36; p<0.001; g=1.38) with a baseline $LVEF_0$ of 40.0±6.75%. By 12 months, the maximal effect reached a plateau (ΔLVEF = +8.55±2.25; p=0.004; g=1.06), with 78.6% of patients achieving LVEF ≥40% at 6 months and 81.8% at one year.

Discussion

This study is the first in Russian clinical practice to perform a comprehensive population-based analysis of left ventricular ejection fraction (LVEF) dynamics in patients with chronic heart failure (CHF) following acute myocardial infarction (AMI) and revascularization, while accounting for real-world adherence to standard neurohumoral modulator (NHM) therapy and sodium-glucose cotransporter-2 inhibitors (SGLT2i).

Effect of revascularization and standard therapy

Our data confirm that coronary blood flow restoration alone provides moderate improvement in myocardial systolic function: LVEF increased by +3.42% (Hedges' g = 0.47, p<0.05) at 6 months and +3.43% (g = 0.49, p<0.05) at 12 months, with the primary effect achieved within the first post-AMI months. This aligns with contemporary concepts of myocardial remodeling dynamics after successful revascularization, where functional recovery peaks during the early post-infarction period (Khademi et al. 2024; Kuzheleva et al. 2024; Ndrepepa et al. 2024).

Our findings demonstrate that without optimal adherence to NHM (RASi, BB, MRA), the benefits of revascularization are attenuated: non-adherent patients exhibited significantly lower

annual LVEF gains compared to adherent counterparts ($\Delta LVEF_{12}$: +3.43% vs. +6.70%, p=0.034). This highlights NHM therapy's critical role in sustaining long-term myocardial recovery, aligning with international evidence linking guideline-directed pharmacotherapy to improved CHF outcomes (Saito et al. 2024).

Role of therapy adherence

The study revealed a persistent decline in adherence during the second six-month period, leading to stagnation or regression of treatment effects. Only 24.3% of patients maintained optimal adherence (PDC ≥80%) over 12 months, while 50% remained consistently non-adherent. This pattern mirrors challenges observed in international registries and underscores the gap between clinical guidelines and real-world practice (El-Zein et al. 2024). Patients with high adherence had a markedly greater increase in LVEF and higher proportion of cases of achieving target LVEF values (>50%). Patients with PDC <80% lose 2.08% of potential increase in EF (p=0.034).

SGLT2i effect

The pronounced remodeling effect of SGLT2 inhibitors on the myocardium is associated with their ability to reduce intracellular sodium and calcium overload, thereby diminishing cardiomyocyte hypertrophy and fibrosis. This is supported by evidence of reduced proinflammatory activity and decreased intercellular matrix expansion. The use of SGLT2 inhibitors improves coronary microvascular function and myocardial relaxation through enhancement of energy metabolism, particularly by increasing the utilization of ketone bodies and fatty acids by myocardial cells. Additionally, decreased sympathetic nervous system activity and reduced vascular wall tension have been observed, potentially limiting the adverse effects of chronic neurohormonal activation. Clinical studies have shown that these mechanisms are associated with reduced cardiac chamber dilatation and hypertrophy and contribute to the recovery of left ventricular systolic function after acute injury (Mkrtumyan et al. 2021; Ignatova et al. 2024; Kurochkina et al. 2024; Saipudinova et al. 2024).

For the first time in a Russian cohort, adding SGLT2 inhibitors (SGLT2i) to standard neurohumoral modulator (NHM) therapy in patients with initially reduced LVEF (38.7% ± 7.1%) demonstrated significant contractility improvement: $\Delta LVEF_6$: +7.43% (Hedges' g = 1.38, p<0.001) and $\Delta LVEF_{12}$: +8.55% (g = 1.06, p<0.001). Effects plateaued after 6 months, with 84% achieving LVEF ≥40% by 6 months and 70% reaching LVEF ≥45% at 1 year. These findings align with global data linking SGLT2i to reduced heart failure (HF) hospitalizations and enhanced post-infarction remodeling (Zhu et al. 2023; Idowu et al. 2024).

It is particularly important that the maximal effect of SGLT2 inhibitors was observed in patients with initially more severe impairment of contractility, which underscores their unique role in contemporary heart failure therapy (Idowu et al. 2024).

Methodological aspects

The use of standardized effect size (Hedges' g) allowed for objective comparison of clinical significance across interventions in real-world settings, effectively minimizing biases inherent to small-sample studies and missing data. This approach aligns with ESC recommendations for analyzing heterogeneous observational data, ensuring robust interpretation of results despite non-randomized design limitations.

The methodological isolation of a stable non-adherent cohort (PDC <80% for all NHM classes, no SGLT2i) to assess revascularization's "pure" effect significantly enhanced result validity. By excluding confounding pharmacological influences, this strategy provided a clearer understanding of coronary flow restoration's intrinsic contribution to LVEF recovery, addressing a key challenge highlighted in ESC 2023 guidelines.

Some limitations of our research should be also acknowledged. Key limitations include progressive attrition of patients with complete echocardiography data at 12 months (typical for real-world longitudinal studies) and unaccounted variability in standard therapy dosages.

Conclusion

Results of the study demonstrate that in real clinical practice only combination of successful revascularization, high adherence to standard therapy and addition of SGLT-2 provides maximal restoration of myocardial contractility in patients with CHF after AMI. Suboptimal adherence significantly reduces treatment efficacy. These findings emphasize the need for adherence-support programs and broader SGLT2i adoption in this population.

The study bridges the critical gap between RCT evidence and real-world practice, demonstrating that revascularization, NHM adherence, and early SGLT2i use synergistically maximize myocardial recovery.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

Data corroborating the results of this study may be acquired by the corresponding author upon reasonable request.

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