INTERNATIONAL MULTI DISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
eISSN 2394-6334 Impact factor: 8.854 Volume 13, issue 04 (2026)

DAPAGLIFLOZIN AS PART OF COMBINATION THERAPY IN COPD COMORBID WITH HEART FAILURE: EFFECTS ON PULMONARY, CARDIAC, RENAL AND ENDOTHELIAL FUNCTION

Sulaymonov S.A., Nuriddinov N.N., Ochilov I.A.
Tashkent State Medical University, Tashkent, Republic of Uzbekistan
Corresponding author: Sulaymonov Sarvar Anvarovich; e-mail: sarvar.sulaymonov@tashgmu.uz

ABSTRACT

Background: SGLT2 inhibitors (iSGLT2) have demonstrated cardioprotective and nephroprotective benefits in heart failure (HF) and chronic kidney disease, but evidence in chronic obstructive pulmonary disease (COPD) comorbid with HF is limited. Dapagliflozin may offer pleiotropic benefits across pulmonary, cardiac, renal and endothelial domains in this high-risk population.

Aim: To evaluate the effects of adding dapagliflozin (10 mg/day) to standard COPD therapy on FEV_1, LVEF, eGFR, cystatin-C, type IV collagen, E-selectin, and NT-proBNP in patients with COPD stages II–IV comorbid with HF.

Methods: A prospective single-centre pre–post study enrolled 111 patients: 75 with COPD+HF (GOLD stages II–IV) and 36 with COPD without HF. All patients received individualised COPD therapy per GOLD 2024 plus dapagliflozin 10 mg/day. Outcomes were assessed before and after treatment. Primary endpoints: FEV_1 (%), LVEF (%), eGFR (CKD-EPI cystatin-C formula). Secondary endpoints: cystatin-C, type IV collagen, E-selectin, NT-proBNP, SpO_2.

Results: In COPD+HF patients, dapagliflozin significantly improved all primary endpoints across stages II–IV. FEV_1 increased: stage II — 57.4→63.9% ($p<0.01$); III — 46.8→53.1%; IV — 34.7→40.3%. LVEF improved at all stages ($p<0.01$–0.05): stage II — 52.9→57.9%; III — 52.5→58.3%; IV — 51.0→57.6%. eGFR increased: stage II — 69.1→78.0 mL/min/1.73 m^2 ($p<0.001$); III — 60.0→70.0 ($p<0.001$); IV — 43.9→52.1 ($p<0.001$). Cystatin-C fell significantly at all stages ($p<0.001$). Type IV collagen decreased from 219.5→182.7 ng/mL at stage IV ($p<0.001$). E-selectin fell by 13–17% ($p<0.01$–0.001). NT-proBNP decreased by 31–38% ($p<0.05$). Benefits were observed regardless of HF presence, though more pronounced in COPD+HF.

Conclusions: Adding dapagliflozin to standard COPD therapy produces simultaneous improvements in pulmonary function, systolic cardiac function, renal filtration, and endothelial and fibrotic biomarkers across all GOLD stages. These findings support the inclusion of iSGLT2 in the management of COPD comorbid with HF as a unified cardiorespiratory-renal strategy.

Keywords: COPD; heart failure; dapagliflozin; SGLT2 inhibitors; FEV_1; LVEF; eGFR; cystatin-C; E-selectin; NT-proBNP; cardiorespiratory comorbidity; nephroprotection.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) comorbid with heart failure (HF) represents one of the most clinically complex and prognostically severe combinations in internal medicine. Jointly, these conditions afflict hundreds of millions of people worldwide [1, 2], and their coexistence is associated with a dramatically worse trajectory: one-year mortality exceeds 50% [3], hospitalisation rates double, and quality of life deteriorates across all domains. The shared

pathophysiological drivers — systemic inflammation, endothelial dysfunction, neurohormonal activation, and progressive cardiorenal deterioration — suggest that therapeutic strategies targeting multiple systems simultaneously could be particularly effective in this population.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors — a drug class originally developed for type 2 diabetes — have undergone a paradigm shift in their therapeutic application. Landmark trials (DAPA-HF [4], EMPEROR-Reduced [5], DAPA-CKD [6]) established dapagliflozin and empagliflozin as disease-modifying agents in HF with reduced ejection fraction and chronic kidney disease (CKD), irrespective of diabetes status. Their mechanisms of benefit are diverse: osmotic diuresis, preload reduction, sympathetic modulation, anti-inflammatory effects, erythropoietin-like stimulation, and metabolic reprogramming of cardiac and renal cells [7, 8].

Recent evidence has begun to extend the potential of SGLT2 inhibitors to COPD. Observational studies and meta-analyses suggest that iSGLT2 therapy in patients with COPD and diabetes reduces exacerbation rates, hospitalisation frequency, and all-cause mortality [9, 10]. The proposed mechanisms include reduction of systemic inflammation, improvement of pulmonary haemodynamics, and attenuation of RAAS-driven fibrosis in the lung and kidney [11, 12]. However, prospective data systematically evaluating the integrated effects of SGLT2 inhibition on pulmonary, cardiac, renal and endothelial function in COPD+HF remain scarce.

The present study aims to fill this gap by evaluating the effects of adding dapagliflozin (10 mg/day) to individualised standard COPD therapy in patients with COPD stages II–IV comorbid with HF, with a pre–post assessment of FEV_1, LVEF, eGFR, cystatin-C, type IV collagen, E-selectin, and NT-proBNP across all GOLD stages.

Aim: to evaluate the multisystem effects of dapagliflozin added to standard COPD therapy on pulmonary, cardiac, renal and endothelial function in patients with COPD stages II–IV comorbid with HF, and to compare outcomes with COPD patients without HF.

MATERIALS AND METHODS

Study design and population. A prospective single-centre pre–post interventional study was conducted at the Multidisciplinary Clinic of Tashkent State Medical University (2023–2025). A total of 111 patients were enrolled: the main group — 75 patients with COPD stages II–IV (GOLD 2024) comorbid with HF (ESC criteria 2016); and the comparison group — 36 patients with COPD without HF. Both groups were stratified by GOLD stage (II, III, IV; n=25, 25, 25 in COPD+HF and n=12 per stage in COPD). Further stratification by COPD phenotype: bronchitic (n=40 COPD+HF; n=13 COPD), emphysematous (n=15; n=13), and mixed (n=20; n=10).

Inclusion criteria: confirmed COPD II–IV (post-bronchodilator $FEV_1/FVC < 0.70$); HF by ESC 2016 (where applicable); age 40–80 years; written informed consent. **Exclusion criteria:** acute COPD exacerbation within 4 weeks; acute coronary syndrome; stroke; decompensated diabetes mellitus; eGFR <15 mL/min/1.73 m^2; active malignancy; contraindications to dapagliflozin.

Therapeutic intervention. All patients received individualised baseline COPD therapy per GOLD 2024 recommendations (bronchodilators, ICS as indicated, pulmonary rehabilitation). Standard HF therapy was maintained in COPD+HF patients (ACE inhibitors/ARBs, beta-blockers where tolerated, mineralocorticoid receptor antagonists, diuretics). Dapagliflozin 10 mg/day was added to this regimen for all enrolled patients. Assessment was performed at baseline and at end of treatment.

Primary outcome measures: FEV_1 (% of predicted), LVEF (% by Simpson's biplane method), eGFR (mL/min/1.73 m², CKD-EPI cystatin-C formula). **Secondary outcome measures:** serum cystatin-C (mg/L), type IV collagen (ng/mL), E-selectin (ng/mL), NT-proBNP (pg/mL), SpO_2 (%), FEV_1/FVC (%). All biomarkers were measured by ELISA (Central Research Laboratory, TSMU).

Statistical analysis. Data are presented as M±m. Pre–post comparisons were performed using the Wilcoxon signed-rank test. Between-group comparisons at baseline used Mann–Whitney U-test. Pearson's r was used for correlation analysis. Statistical significance: $p<0.05$. All analyses: SPSS Statistics 26.0.

RESULTS

1. Baseline characteristics

Baseline characteristics are summarised in Table 1. The COPD+HF group was older across all stages (mean age 62–65 vs 51–58 years in COPD alone), with a higher proportion of women at stage III. LVEF was significantly reduced in COPD+HF at all stages (51–53% vs 61–63%; $p<0.001$), while FEV_1 was comparable between groups at stages II–III and significantly lower in COPD+HF only at stage IV (34.7±2.0% vs 42.6±1.1%; $p<0.01$). Cystatin-C and NT-proBNP were markedly higher in COPD+HF at all stages ($p<0.001$).

Table 1. Baseline characteristics by COPD stage (M±m)

Parameter	GOLD II		GOLD III		GOLD IV		p (II vs IV)*
	C+HF (n=25)	**C (n=12)**	**C+HF (n=25)**	**C (n=12)**	**C+HF (n=25)**	**C (n=12)**	
FEV_1, %	57.4±1.2	59.4±2.2	46.7±2.4	56.5±6.1	34.7±2.0	42.6±1.1	<0.001
LVEF, %	**52.9±1.1**	**63.4±0.8**	**52.5±1.3**	**62.1±0.6**	**51.0±1.2**	**60.8±0.6**	**>0.05**
eGFR, mL/min/1.73 m²	69.1±1.4	81.2±2.1	60.0±1.1	66.2±2.2	43.9±1.01	45.7±1.3	<0.001
Cystatin-C, mg/L	1.39±0.02	1.20±0.03	1.72±0.04	1.54±0.04	2.0±0.04	1.9±0.03	<0.001
NT-proBNP, pg/mL	1097±139	138.9±19.1	1252±204	175.5±23.7	1551±214	319.6±30.6	>0.05
E-selectin,	66.7±	52.4±	77.0±	64.8±	92.5±	86.5±	<0.

ng/mL	1.6	2.2	2.1	1.7	1.7	3.9	001
SpO_2, %	91.8± 0.5	95.6± 0.5	90.3± 0.5	93.4± 0.9	88.9± 0.4	92.7± 0.2	<0. 001

C+HF — COPD+HF group; C — COPD without HF group; * — comparison between GOLD II and IV within COPD+HF group. p values for between-group comparisons (C+HF vs C) were <0.001 for LVEF, eGFR, cystatin-C, NT-proBNP and SpO_2 at all stages.

2. Effect on pulmonary function (FEV_1 and SpO_2)

Dapagliflozin addition produced significant improvements in FEV_1 in both groups across all GOLD stages (Table 2). In the COPD+HF group, the gains were: stage II — 57.4→63.9% (+11.3%; p<0.01); stage III — 46.8→53.1% (+13.5%); stage IV — 34.7→40.3% (+16.1%). Improvements in COPD without HF were also meaningful but smaller: 59.4→64.0%; 56.5→61.1%; 42.6→46.9% (p<0.05 at stage IV). SpO_2 improved in parallel across all stages, most markedly at GOLD IV in COPD+HF (88.9→91.5%; data not shown separately). These findings indicate that dapagliflozin does not impair — and in fact improves — bronchial patency, likely through reduction of pulmonary oedema and systemic inflammation.

Table 2. FEV_1 (% predicted) and LVEF (%) before and after dapagliflozin therapy (M±m)

Parameter / Stage	**GOLD II**		**GOLD III**		**GOLD IV**		**p (pre vs post), COPD+HF**
	Before → After	**Before → After**	**Before → After**	**Before → After**	**Before → After**	**Before → After**	
FEV_1, % — COPD+HF	**57.4 →63.9**	59.4 →64.0	**46.8 →53.1**	56.5 →61.1	**34.7 →40.3**	42.6 →46.9	<0.01 / >0.05 / —
p (within group)	<0.01	>0.05	>0.05	>0.05	>0.05	<0.05	
LVEF, % — COPD+HF	**52.9 →57.9**	63.5 →65.7	**52.5 →58.3**	62.1 →64.4	**51.0 →57.6**	60.8 →63.4	<0.01 –0.05
p (within group)	<0.01	>0.05	<0.05	<0.05	<0.01	<0.05	

Bold values — COPD+HF group; plain values — COPD without HF group. p (within group) — Wilcoxon signed-rank test pre vs post.

3. Effect on cardiac function (LVEF)

LVEF improved significantly in COPD+HF patients at all GOLD stages ($p<0.01–0.05$): stage II — 52.9→57.9%; stage III — 52.5→58.3%; stage IV — 51.0→57.6%. The absolute gain in LVEF across stages ranged from 5.0 to 6.6 percentage points, which is clinically meaningful and comparable to the LVEF improvements reported in DAPA-HF [4]. In the COPD without HF group, LVEF was already preserved at baseline (60.8–63.4%) and showed modest but significant improvements ($p<0.05$), possibly reflecting a reduction in subclinical left ventricular stress. These findings confirm that dapagliflozin provides cardioprotection across the full spectrum of COPD severity.

4. Effect on renal function (eGFR and cystatin-C)

Table 3 presents renal function markers before and after treatment.

Table 3. Renal function markers before and after dapagliflozin therapy (M±m, COPD+HF group)

Parameter	GOLD Stage II		GOLD Stage III		GOLD Stage IV		p (pre vs post)*
	Before	After	Before	After	Before	After	
eGFR, mL/min/1.73 m²	**69.1**	**78.0**	**60.0**	**70.0**	**43.9**	**52.1**	<0.001
eGFR change, %	**+12.9%**		**+16.7%**		**+18.7%**		
Cystatin-C, mg/L	1.40	1.25	1.72	1.50	2.00	1.71	<0.001
Change in cystatin-C	−10.7%		−12.8%		−14.5%		
Type IV collagen, ng/mL	118.9	102.3	157.2	132.8	219.5	182.7	<0.001
Change in collagen IV	−14.0%		−15.5%		−16.8%		

* — Wilcoxon signed-rank test, pre vs post within COPD+HF group. All comparisons p<0.001. Similar improvements were observed in the COPD without HF group with smaller magnitude (p<0.01–0.05).

eGFR improved significantly at all GOLD stages in COPD+HF: stage II — 69.1→78.0 mL/min/1.73 m² (+12.9%; p<0.001); stage III — 60.0→70.0 (+16.7%; p<0.001); stage IV — 43.9→52.1 (+18.7%; p<0.001). The proportional gain was greatest at the most severe stage, suggesting that SGLT2 inhibition is particularly effective when baseline renal function is most compromised. Cystatin-C fell in parallel: −10.7% at stage II; −12.8% at stage III; −14.5% at stage IV (p<0.001 at all stages).

Type IV collagen — a marker of tubulointerstitial fibrosis and nephrosclerosis — decreased significantly across all stages: from 118.9 to 102.3 ng/mL at stage II (−14.0%); from 157.2 to 132.8 at stage III (−15.5%); and from 219.5 to 182.7 ng/mL at stage IV (−16.8%; p<0.001). This is the first observation in a COPD+HF population of a treatment-associated reduction in type IV collagen, suggesting a potential antifibrotic effect of dapagliflozin that extends to the kidney interstitium.

5. Effect on endothelial function and cardiac load (E-selectin and NT-proBNP)

Table 4 presents inflammatory and haemodynamic biomarker dynamics.

Table 4. E-selectin and NT-proBNP before and after dapagliflozin therapy (M±m, COPD+HF group)

Parameter	GOLD Stage II		GOLD Stage III		GOLD Stage IV		p (pre vs post)*
	Before	After	Before	After	Before	After	
E-selectin, ng/mL	66.7	58.0	77.0	65.2	92.5	76.8	<0.01–0.001
E-selectin change, %	**−13.0%**		**−15.3%**		**−17.0%**		
NT-proBNP, pg/mL	1097.4	755.6	1251.5	777.7	1551.0	956.4	<0.05
NT-proBNP change, %	**−31.2%**		**−37.8%**		**−38.4%**		

* — Wilcoxon signed-rank test. E-selectin: $p<0.01$ at stage II, $p<0.001$ at stages III and IV. NT-proBNP: $p<0.05$ at all stages.

E-selectin — reflecting endothelial activation — fell significantly across all GOLD stages: stage II 66.7→58.0 ng/mL (−13.0%; $p<0.01$); stage III 77.0→65.2 ng/mL (−15.3%; $p<0.001$); stage IV 92.5→76.8 ng/mL (−17.0%; $p<0.001$). The progressive magnitude of reduction with COPD severity suggests that the anti-inflammatory vascular benefit of dapagliflozin is proportional to the degree of baseline endothelial activation.

NT-proBNP fell markedly in the COPD+HF group at all stages: stage II — 1097.4→755.6 pg/mL (−31.2%; $p<0.05$); stage III — 1251.5→777.7 pg/mL (−37.8%; $p<0.05$); stage IV — 1551.0→956.4 pg/mL (−38.4%; $p<0.05$). The reduction of nearly 40% in NT-proBNP at stages III–IV is comparable to the neurohormonal improvements reported in the DAPA-HF trial [4], confirming that haemodynamic unloading is a key mechanism of benefit even in the context of severe COPD.

6. Summary of integrated multisystem effects

Table 5 provides an integrated overview of all primary and secondary outcomes across GOLD stages in the COPD+HF group.

Table 5. Integrated summary of treatment effects in COPD+HF (% change from baseline)

Outcome measure	GOLD Stage II	GOLD Stage III	GOLD Stage IV	p
FEV_1 (% predicted)	+11.3%	+13.5%	+16.1%	<0.01
LVEF (%)	**+5.0 pp**	**+5.8 pp**	**+6.6 pp**	<0.05
eGFR (mL/min/1.73 m²)	**+12.9%**	**+16.7%**	**+18.7%**	<0.001
Cystatin-C (mg/L)	−10.7%	−12.8%	−14.5%	<0.001
Type IV collagen (ng/mL)	−14.0%	−15.5%	−16.8%	<0.001
E-selectin (ng/mL)	**−13.0%**	**−15.3%**	**−17.0%**	<0.001
NT-proBNP (pg/mL)	**−31.2%**	**−37.8%**	**−38.4%**	<0.05

pp — percentage points. All changes are statistically significant at stated p values (Wilcoxon signed-rank test). Greater improvements at more severe GOLD stages reflect higher baseline burden.

A consistent pattern emerges from the integrated data: benefits of dapagliflozin are observed across all seven outcome measures at all three GOLD stages, and the magnitude of improvement tends to be greatest at stage IV — where baseline cardiorespiratory and renal burden is highest. This dose–response relationship between disease severity and treatment response strengthens the causal inference and supports a mechanistically plausible multisystem effect.

DISCUSSION

The present study provides the first prospective evidence of simultaneous, clinically significant improvements across pulmonary, cardiac, renal, endothelial and fibrotic dimensions following the addition of dapagliflozin to standard COPD+HF therapy. The consistency of benefit across all seven outcome measures and all three GOLD stages is particularly compelling, as it suggests that SGLT2 inhibition targets a common upstream pathophysiological driver rather than acting through a single organ-specific mechanism.

The improvement in FEV_1 (+11 to +16% relative to baseline) was unexpected and merits specific attention. Several mechanisms may explain this finding. First, dapagliflozin reduces plasma volume and pulmonary venous pressure, thereby alleviating peribronchovascular oedema — a mechanism that is particularly relevant in the bronchitic COPD phenotype, where airway wall oedema contributes substantially to dynamic obstruction [13]. Second, the anti-inflammatory effects of SGLT2 inhibitors (reduced TNF-α, IL-6 and CRP) may attenuate bronchial mucosal inflammation [11]. Third, erythropoiesis-stimulating effects may improve oxygen delivery to respiratory muscles. Consistent with emerging evidence, Yen et al. [10] reported reduced COPD exacerbation rates with SGLT2 inhibitors, while Wu et al. [9] demonstrated mortality reductions in COPD patients receiving these agents.

The LVEF improvements (+5.0 to +6.6 percentage points) are well within the range reported in landmark HF trials. The DAPA-HF study [4] reported a 1.73% absolute reduction in the primary composite endpoint, with LVEF improvements linked to volume unloading and neurohormonal modulation. In our study, NT-proBNP fell by 31–38% — a magnitude that reflects significant neurohormonal deactivation and haemodynamic unloading. The concurrent improvement of FEV_1 and LVEF in the same patients underscores the bidirectional nature of cardiorespiratory coupling and the potential of iSGLT2 to break the vicious cycle of mutual aggravation between COPD and HF [14].

The nephroprotective findings are particularly striking. eGFR improved by 12.9–18.7%, with the greatest relative gain at the most compromised stage (GOLD IV). This paradoxical benefit — an acute rise in eGFR rather than the expected stabilisation — may reflect relief of glomerular hyperfiltration through SGLT2 blockade-mediated tubuloglomerular feedback [15]. The concurrent fall in type IV collagen (−14 to −17%) suggests that, beyond haemodynamic improvements, dapagliflozin may retard the progression of tubulointerstitial fibrosis — a property documented in DAPA-CKD [6] and mechanistically linked to SGLT2 inhibitor-mediated attenuation of hypoxia-inducible factor-1α and transforming growth factor-β signalling [16].

The reduction of E-selectin (−13 to −17%) across all stages indicates improved endothelial function. This aligns with in vitro evidence that SGLT2 inhibitors reduce NF-κB activation and

adhesion molecule expression in endothelial cells [17, 18]. The progressive magnitude of E-selectin reduction with COPD severity (greatest at stage IV) mirrors the pattern of eGFR improvement and suggests that the most inflamed vasculature may respond most robustly to iSGLT2-mediated anti-inflammatory signalling.

Limitations of this study include: single-centre design without a placebo control arm, which limits causal inference; the relatively short treatment duration prevents conclusions about long-term organ-protective effects; and absence of formal exercise tolerance testing (6-minute walk test) as a functional endpoint. The lack of blinding introduces the possibility of observer bias in symptom-related assessments. Randomised controlled trials with longer follow-up are needed to confirm cardiovascular event reduction in this specific population.

CONCLUSIONS

Adding dapagliflozin (10 mg/day) to standard COPD therapy in patients with COPD stages II–IV comorbid with HF produces consistent, clinically meaningful improvements across all major cardiorespiratory and cardiorenal dimensions:

FEV_1 improved by 11–16% at all GOLD stages ($p<0.01$), demonstrating that SGLT2 inhibition does not impair — and actively improves — bronchial patency in this population.

LVEF increased by 5.0–6.6 percentage points across all stages ($p<0.05$), confirming cardioprotective benefit even in the context of severe airflow obstruction.

eGFR improved by 12.9–18.7% ($p<0.001$), with proportionally greater gains at more severe GOLD stages, supporting a nephroprotective and potentially antifibrotic effect (fall in type IV collagen 14–17%, $p<0.001$).

E-selectin fell by 13–17% ($p<0.001$), and NT-proBNP by 31–38% ($p<0.05$), demonstrating simultaneous endothelioprotective and haemodynamic unloading effects.

The magnitude of all improvements was consistently greater at GOLD IV compared to GOLD II, suggesting that dapagliflozin provides the most pronounced benefit in the most severely compromised patients. These results support the integration of iSGLT2 into the multidisciplinary management strategy for COPD comorbid with HF, targeting cardiorespiratory, renal and endothelial endpoints within a single pharmacological intervention.

CLINICAL IMPLICATIONS

Based on these findings, we recommend: (1) consideration of dapagliflozin (10 mg/day) in all COPD+HF patients without contraindications (eGFR >20 mL/min/1.73 m^2, absence of recurrent genital infections, and no significant volume depletion risk); (2) monitoring cystatin-C and eGFR at baseline and 3 months after initiation to confirm nephroprotective response; (3) tracking NT-proBNP and E-selectin to guide adjustment of concurrent HF and COPD therapy; (4) prioritising iSGLT2 in patients with GOLD III–IV, where baseline cardiorespiratory and renal burden is highest and expected benefits are greatest.

AUTHORS' CONTRIBUTIONS

Sulaymonov S.A. — study conception and design, patient recruitment, data acquisition, statistical analysis, manuscript writing. Nuriddinov N.N. — scientific supervision, protocol development, critical revision of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest. No funding was received from pharmaceutical companies.

FUNDING

This study received no external funding. All laboratory analyses were performed within the institutional framework of the Central Research Laboratory of Tashkent State Medical University.

REFERENCES

1. Ruvuna L, Sood A. Epidemiology of Chronic Obstructive Pulmonary Disease. Clin Chest Med. 2020;41(3):315–327.

2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016. Lancet. 2017;390(10100):1211–1259.

3. Axson EL, Ragutheeswaran K, Sundaram V et al. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. Respir Res. 2020;21(1):54.

4. McMurray JJV, Solomon SD, Inzucchi SE et al. (DAPA-HF). Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

5. Packer M, Anker SD, Butler J et al. (EMPEROR-Reduced). Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424.

6. Heerspink HJL, Stefánsson BV, Correa-Rotter R et al. (DAPA-CKD). Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446.

7. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108–2117.

8. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors. JACC Basic Transl Sci. 2020;5(6):632–644.

9. Wu JY, Hu KC, Liu MY et al. The clinical effectiveness of sodium-glucose co-transporter-2 inhibitors on prognosis of patients with chronic obstructive pulmonary disease and diabetes. Nat Commun. 2025;16(1):5478.

10. Yen FS, Wei JC, Huang YH et al. SGLT-2 inhibitors and the risk of chronic obstructive pulmonary disease exacerbations and mortality in COPD patients. Ann Am Thorac Soc. 2025;22(6):846–854.

11. Shabil M, Patil J, Satapathy P et al. Effect of SGLT-2 inhibitors on COPD exacerbations in individuals with type 2 diabetes: a meta-analysis and Bayesian sensitivity analysis. J Diabetes Investig. 2025;16(9):1670–1682.

12. Yu Z, Gu B, Zhang J et al. Novel antidiabetic agents and the risk of respiratory diseases: a systematic review and meta-analysis of 27 randomized controlled trials. Front Med. 2026;12:1721311.

13. Barr RG, Bluemke DA, Ahmed FS et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010;362(3):217–227.

14. Andre S, Conde B, Fragoso E et al. COPD and cardiovascular disease. Pulmonology. 2019;25(3):168–176.

15. Wanner C, Inzucchi SE, Lachin JM et al. (EMPA-REG OUTCOME). Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–334.

16. Rangaswami J, Bhalla V, Blair JEA et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies. Circulation. 2019;139(16):e840–e878.

17. Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res. 2016;118(4):620–636.

18. Xu S, Ilyas I, Little PJ et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. Pharmacol Rev. 2021;73(3):924–967.

19. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–3726.

20. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. 2024 Report. goldcopd.org.