ESC HEART FAILURE
ESC Heart Failure 2025; **12**: 1620–1629
Published online 11 February 2025 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.15235

ORIGINAL ARTICLE

Burst steroid therapy and quality of life in patients with acute heart failure: Insights from the CORTAHF trial

Matteo Pagnesi[1], Gad Cotter[2,3,4], Beth A. Davison[2,3,4], Yonathan Freund[5,6], Adriaan A. Voors[7], Christopher Edwards[4], Maria Novosadova[4], Koji Takagi[4], Hamlet Hayrapetyan[8], Andranik Mshetsyan[9], Mayranush Drambyan[10], Alain Cohen-Solal[2,11], Jozine M. ter Maaten[7], Jan Biegus[12], Piotr Ponikowski[12], Gerasimos Filippatos[13], Ovidiu Chioncel[14], Malha Sadoune[2], Tabassome Simon[5], Douglas L. Mann[15], Alexandre Mebazaa[2,16] and Marco Metra[1]*

[1]*Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy;* [2]*Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France;* [3]*Heart Initiative, Durham, NC, USA;* [4]*Momentum Research, Inc, Durham, North Ccaroline, USA;* [5]*IMProving Emergency Care FHU, Sorbonne Université, Paris, France;* [6]*Emergency Department and Service Mobile d'Urgence et de Réanimation (SMUR), Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France;* [7]*University of Groningen, Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands;* [8]*Erebouni Medical Center, Yerevan, Armenia;* [9]*'Mikaelyan' Surgery Institute CJSC, Yerevan, Armenia;* [10]*'Armenia' Medical Center, Yerevan, Armenia;* [11]*Department of Cardiology, APHP Nord, Lariboisière University Hospital, Paris, France;* [12]*Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland;* [13]*National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece;* [14]*Emergency Institute for Cardiovascular Diseases 'Prof. C. C. Iliescu', University of Medicine 'Carol Davila', Bucharest, Romania;* [15]*Cardiovascular Division, Department of Medicine, Center for Cardiovascular Research, Washington University School of Medicine, St. Louis, Missouri, USA; and* [16]*Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France*

Abstract

Aims Patients hospitalized with acute heart failure (AHF) treated with a 7 day prednisone course in the CORTAHF pilot trial had a greater improvement in health-related quality of life (QoL) at Day 7 in both the overall population and in patients with baseline interleukin 6 $>$ 13 pg/mL. This post-hoc analysis examines the specific QoL domains and the relationship between clinical signs of congestion and QoL.

Methods In the CORTAHF pilot trial, patients with AHF and high-sensitivity C-reactive protein (hsCRP) $>$ 20 mg/L were randomized 1:1 to once-daily oral 40 mg prednisone for 7 days plus usual care or usual care alone. Patients completed the EQ-5D-5L, including the EQ-VAS, at baseline and Days 7 and 31. We estimated baseline-adjusted treatment effects on each of the five QoL dimensions and evaluated the interaction between baseline EQ-VAS and treatment effect on hsCRP change at Day 7 (the primary endpoint). The correlation between changes in signs of congestion and EQ-VAS were evaluated.

Results Among 100 randomized patients, the improvement in QoL at Day 7 was driven by significant effects on the EQ-5D-5L mobility [win odds 1.48, 95% confidence interval (CI) 1.05–2.12] and usual activities (win odds 1.50, 95% CI 1.05–2.20) domains. The treatment effect on 7 day hsCRP change was independent of baseline EQ-VAS (interaction $P = 0.13$). Decongestion and EQ-VAS improvement were correlated ($r = -0.528$, $P < 0.0001$).

Conclusions In patients with AHF and high hsCRP levels, 7 day burst steroid therapy improved QoL mostly by affecting the mobility and usual activities domains. QoL improvement was correlated with decongestion and may therefore not be a direct effect of steroid therapy, but mediated through improvement in HF symptoms and signs. Inflammatory activation was reduced by prednisone irrespective of baseline EQ-VAS.

Keywords acute heart failure; corticosteroids; EQ-5D-5L; EQ-VAS; inflammation; quality of life

Received: 9 January 2025; Accepted: 17 January 2025
**Correspondence to: Marco Metra, Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical specialties, Radiological sciences and Public Health, University of Brescia, Brescia, Italy. Email: metramarco@libero.it*

Introduction

Several studies have shown an association between inflammatory activation and adverse outcomes in acute heart failure (AHF).[1–3] Recently, the Effect of Short-Term Prednisone Therapy on CRP Change in Emergency Department Patients With Acute Heart Failure and Elevated Inflammatory Markers (CORTAHF) randomized pilot trial demonstrated that burst steroid therapy was associated with a reduction in inflammatory activation as measured by high-sensitivity C-reactive protein (hsCRP) at Day 7 among patients with AHF and high baseline hsCRP levels.[4] An improvement in health-related quality of life (QoL) was also reported, since the EQ-VAS, with larger values representing better QoL, increased more in patients randomized to steroid therapy at Day 7.[4] Beyond their association with other clinical outcomes such as mortality and rehospitalizations, patient-reported outcomes evaluating health-related QoL are particularly relevant in patients with heart failure (HF), as they allow an accurate evaluation of disease status and disease perception, promote a patient-centred approach and may enhance adherence to treatments.[5,6] Therefore, further assessment of the impact of novel treatment strategies for AHF on QoL is warranted.

The current analysis was designed to provide more details about the impact of burst steroid therapy on QoL in the patients with AHF and inflammatory activation enrolled in the CORTAHF trial, focusing on the different EQ-5D domains, testing the interplay between baseline EQ-VAS and steroid therapy on change in hsCRP, and evaluating the correlation between congestion and QoL.

Methods

Study design

The design of the CORTAHF study has been already described.[4,7,8] Briefly, CORTAHF was a multicentre, prospective, randomized, open-label pilot study enrolling patients admitted to the hospital for AHF with signs of inflammatory activation, defined as hsCRP $>$ 20 mg/L at screening. Included patients were randomized 1:1 to receive 7 day corticosteroid therapy (40 mg daily of oral prednisone) plus usual care or usual care alone. Key inclusion criteria were objective signs of congestion (at chest X-ray or lung ultrasound), systolic blood pressure $\geq$ 100 mmHg and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration $>$ 1500 pg/mL. Patients with AHF triggered by a correctable cause, such as arrhythmia, severe anaemia, acute coronary syndrome, exacerbation of chronic obstructive pulmonary disease or infection, were excluded.

The trial was originally designed to enrol 120 patients but was stopped for administrative reasons after 100 patients had been validly randomized. Moreover, the trial was originally designed to enrol patients with interleukin-6 (IL-6) $>$ 13 pg/mL, but this criterion was subsequently updated to hsCRP $>$ 20 mg/L.[4,7] At the conclusion of enrolment, blood samples obtained from enrolled patients were analysed by a central laboratory blinded to study treatment, and analyses were performed restricting the patients to those who were found to have baseline IL-6 $>$ 13 pg/mL.

The trial was approved by the appropriate ethics committees, and eligible patients gave written informed consent to participate. The study is registered in ClinicalTrials.gov (NCT05916586).

Definitions and endpoints

Details on study procedures, definitions and outcomes have been described.[4,7,8] Patients completed a linguistically validated version of the EQ-5D-5L (EuroQol) at baseline, Days 7 and 31. This standardized, self-completed questionnaire includes a five-level assessment of five health-related domains, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[9,10] Patients rank their health state in each domain on a five-point ordinal scale ranging from no problems to extreme problems.[10] This tool also includes a 20 mm vertical visual analogue scale (EQ-VAS) on which patients rate their health 'today' between 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). A composite congestion score was computed based on orthopnoea, oedema and rales scores, with overall values ranging from 0 points (i.e., no congestion) to 9 points (i.e., worst congestion), as previously described.[8]

The primary endpoint of the trial was the change in hsCRP level from baseline to Day 7, and secondary endpoints included change in EQ-VAS from baseline to Day 7 and time to first event of worsening HF, rehospitalization for HF or death through Day 91. For this secondary analysis, we further assessed the effect of prednisone burst therapy on changes in the different EQ-5D-5L domains to Day 7 and to Day 31, both in the overall population and in the pre-specified subgroup of patients with IL-6 $>$ 13 pg/mL.

Statistical analysis

Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR), categorical variables are presented as numbers and percentages. Baseline patients' characteristics were compared across baseline EQ-VAS tertiles using the following tests: Jonckheere's trend test for continuous variables, Cochran–Armitage trend test for binary variables, Cochran–Mantel–Haenszel general association for categorical variables, and Cochran–Mantel–Haenszel non-zero correlation for ordinal variables.

The treatment effect on the 7 day change in EQ-VAS, a pre-specified secondary endpoint of the trial, was estimated from the appropriate contrast from a mixed model for repeated measures (MMRM) that included the effects of centre, baseline value, treatment, baseline × visit and treatment × visit. Missing responses on the EQ-5D due to death were imputed as zero. The treatment effect on the 31 day change in EQ-VAS and on the different EQ-5D-5L domains at Days 7 and 31 were also evaluated. Treatment effects on the specific domains (i.e., ordinal outcomes) are expressed as win odds (WO) stratified by centre and adjusted for baseline response estimated using the R package 'sanon'.[11] All analyses were repeated in the pre-specified blinded subgroup of patients with IL-6 levels $>$ 13 pg/mL at baseline (n = 65).

The interaction between the treatment effect of burst steroid therapy on the primary endpoint and baseline EQ-VAS as a continuous variable was tested. Geometric mean ratio of change in CRP at Day 7 (i.e., the primary endpoint) was derived from a regression model based on baseline EQ-VAS, using a restricted cubic spline with three knots.

Correlation between EQ-VAS and congestion score was evaluated considering baseline values, changes at Day 7 and changes at Day 31. Correlation was tested both in the overall population and in the two treatments arms separately. A mixed model approach was also performed for changes in EQ-VAS and congestion score at both Days 7 and 31, accounting for correlation between repeated measures. Results of these analyses are reported as correlation coefficients (r) and P values.

All reported P values are two-sided, and a $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.3.[12]

Results

A total of 101 patients were validly randomized at 3 centres between 11 August 2023 and 15 April 2024. One patient was randomized in violation of protocol eligibility criteria and was excluded from the analyses, as already described.[4,8] One patient randomized to prednisone died from HF on Day 19, whereas all the other enrolled patients were followed to Day 91.

Baseline patients' characteristics

Baseline characteristics of included patients according to baseline EQ-VAS tertiles are reported in *Table* 1. A total of 41 patients were in the lower baseline EQ-VAS tertile (i.e., EQ-VAS $<$ 35), 25 patients were in the intermediate tertile (i.e., EQ-VAS = 35) and 34 patients were in the higher tertile (i.e., EQ-VAS $>$ 35). Patients with higher baseline EQ-VAS had lower weight and body mass index and higher oxygen saturation. These patients were also less likely to have hypercholesterolaemia and chronic lung disease and more likely to have valvular heart disease and to receive diuretic therapy as concomitant medication at baseline. No significant differences were observed across baseline EQ-VAS tertiles with respect to other comorbidities, systolic blood pressure, New York Heart Association class prior to screening and left ventricular ejection fraction. Alanine aminotransferase and aspartate aminotransferase were higher in patients with lower baseline EQ-VAS, whereas hsCRP and NT-proBNP were similar across the three EQ-VAS tertiles.

Impact of burst steroid therapy on EQ-VAS

As reported previously, patients treated with prednisone reported a greater increase in EQ-VAS at Day 7 than those treated with usual care alone, with adjusted mean change from baseline of 31.86 [standard error (SE) 0.95] points in the steroid arm and 29.29 (SE 0.90) in the usual care arm [adjusted mean difference 2.57, 95% confidence interval (CI) 0.12–5.01, P = 0.040].[4] Median change from baseline was of 30.0 (IQR 22.5–38.5) in the steroid arm and 25.0 (IQR 25.0–35.0) in the usual care arm. No significant difference between treatment arms was observed with respect to change in EQ-VAS at Day 31 (adjusted mean difference 1.02, 95% CI −3.53 to 5.58, P = 0.657). Similar findings were observed at Days 7 and 31 after excluding imputation for death.

At subgroup analysis, the significant effect on EQ-VAS at Day 7 was observed only in patients with baseline IL-6 $>$ 13 pg/mL (n = 65) (adjusted mean difference 3.94, 95% CI 0.73–7.15, P = 0.017), and not in patients with baseline IL-6 $\leq$ 13 pg/mL (adjusted mean difference 0.08, 95% CI −4.15 to 4.31; P interaction = 0.141). In the subgroup of patients with baseline IL-6 $>$ 13 pg/mL, adjusted mean change and median change in EQ-VAS from baseline to Day 7 were 32.90 (SE 1.21) and 30.0 (IQR 25.0–40.0), respectively, in the steroid arm, and 28.96 (SE 1.31) and 25.0 (IQR 25.0–30.0), respectively, in the usual care arm. No significant difference between treatment arms was observed with respect to change in EQ-VAS at Day 31 in the subgroup of patients with IL-6 $>$ 13 pg/mL (adjusted mean difference 3.26, 95% CI −3.25 to 9.78, P = 0.321). However, after excluding imputation for death, a significantly greater increase in EQ-VAS was observed in the steroid arm versus usual care arm both at Day 7 (adjusted mean difference 3.92, 95% CI 0.70–7.13, P = 0.018) and at Day 31 (adjusted mean difference 5.23, 95% CI 0.70–9.76, P = 0.024).

Table 1 Patients' characteristics by baseline EQ-VAS tertiles.

Parameter	EQ-VAS < 35(*N* = 41)	EQ-VAS = 35(*N* = 25)	EQ-VAS > 35(*N* = 34)	Trend*P* value[a]
Demographics				
Age, years	64.3 (8.57)	67.7 (9.24)	68.1 (8.21)	0.0855
Male sex	25 (61.0%)	18 (72.0%)	20 (58.8%)	0.8874
Vital signs				
Weight, kg	95.1 (20.73)	88.0 (16.77)	84.4 (14.27)	0.0168
BMI, kg/m^2	32.8 (6.30)	30.4 (4.98)	29.4 (4.43)	0.0083
Systolic blood pressure, mmHg	141.8 (33.98)	143.4 (33.04)	139.2 (19.66)	0.4763
Oxygen saturation, %	79.9 (7.41)	82.7 (8.53)	85.4 (7.25)	0.0037
Medical history				
Diabetes	19 (46.3%)	12 (48.0%)	10 (29.4%)	0.1488
Hypertension	36 (87.8%)	20 (80.0%)	30 (88.2%)	0.9947
Hypercholesterolaemia	40 (97.6%)	23 (92.0%)	19 (55.9%)	<0.0001
Malignancy	1 (2.4%)	1 (4.0%)	0	0.6578
Chronic lung disease	7 (17.1%)	2 (8.0%)	0	0.0127
Renal disease/history of dialysis	1 (2.4%)	0	0	0.7500
Ischaemic heart disease	36 (87.8%)	24 (96.0%)	28 (82.4%)	0.5118
Myocardial infarction	32 (78.0%)	19 (76.0%)	24 (70.6%)	0.4619
Stroke				0.3882
CVA	1 (2.4%)	0	2 (5.9%)	
TIA	0	1 (4.0%)	2 (5.9%)	
Valvular disease	14 (34.1%)	11 (44.0%)	21 (61.8%)	0.0175
Severe mitral regurgitation	0	0	0	0.9999
Moderate mitral regurgitation	14 (34.1%)	11 (44.0%)	19 (55.9%)	0.0593
Severe tricuspid regurgitation	0	0	0	0.9999
Moderate tricuspid regurgitation	14 (34.1%)	9 (36.0%)	10 (29.4%)	0.6771
Severe aortic stenosis	0	0	0	0.9999
Moderate aortic stenosis	0	0	2 (5.9%)	0.1133
Moderate or severe mitral stenosis	0	0	0	0.9999
Moderate or severe tricuspid stenosis	0	0	0	0.9999
Atrial fibrillation	8 (19.5%)	6 (24.0%)	12 (35.3%)	0.1243
Sustained ventricular tachycardia or ventricular fibrillation	0	0	0	0.9999
ICD/CRT implant	0	1 (4.0%)	2 (5.9%)	0.1897
HF history				
NYHA class prior to screening				0.1570
Class I	0	0	0	
Class II	8 (19.5%)	3 (12.0%)	5 (14.7%)	
Class III	24 (58.5%)	20 (80.0%)	29 (85.3%)	
Class IV	9 (22.0%)	2 (8.0%)	0	
Most recent LVEF, %	28.3 (8.66)	28.3 (7.86)	29.1 (9.56)	0.7933
Laboratory findings				
Sodium, mmol/L	141.8 (3.55)	142.3 (3.38)	140.3 (2.71)	0.0661
Potassium, mmol/L	4.4 (0.64)	4.3 (0.57)	4.2 (0.46)	0.0519
Glucose, mmol/L	7.8 (3.60)	7.5 (2.56)	7.6 (2.98)	0.7645
AST, U/L	28.2 (18.90)	22.1 (8.76)	20.3 (8.90)	0.0338
ALT, U/L	35.2 (40.21)	23.8 (12.14)	20.6 (15.36)	0.0180
Total bilirubin, μmol/L	13.8 (6.53)	14.8 (7.93)	12.3 (6.92)	0.2345
Haemoglobin, g/L	139.5 (19.90)	135.8 (19.98)	131.9 (19.58)	0.0795
Urea/BUN, mmol/L	8.8 (2.72)	8.0 (2.50)	8.4 (2.33)	0.1891
Creatinine, μmol/L	105.1 (15.28)	105.1 (21.55)	109.4 (25.00)	0.8733
eGFR, mL/min/1.73m^2	61.0 (11.44)	62.1 (11.57)	58.9 (13.82)	0.7790
Troponin T*, ng/mL	0.035 (0.023, 0.044)	0.041 (0.022, 0.049)	0.033 (0.024, 0.046)	0.8977
Troponin I*, ng/mL	0.021 (0.017, 0.030)	0.019 (0.011, 0.028)	0.023 (0.015, 0.042)	0.8540
hsCRP*, mg/L	33.5 (28.0, 41.4)	27.8 (24.3, 33.0)	30.0 (25.9, 44.6)	0.5748
WBC, 10^9/L	8.8 (2.55)	8.1 (2.36)	10.2 (3.25)	0.1168
Lymphocytes, %	21.3 (10.93)	22.1 (5.85)	19.5 (8.41)	0.6624
NT-proBNP*, pg/mL	4391.0 (2481.0, 9357.0)	4182.0 (2840.0, 6275.0)	5480.0 (2300.0, 10256.0)	0.9492
IL-6*, pg/mL	16.6 (9.7, 32.5)	21.9 (15.1, 29.0)	15.6 (7.1, 26.8)	0.9517
IL-17*, pg/mL	0.52 (0.18, 1.16)	1.10 (0.50, 1.78)	0.93 (0.62, 1.60)	0.0219
PRC*, pg/mL	2.0 (2.0, 11.6)	2.0 (2.0, 24.4)	2.0 (2.0, 23.9)	0.8036
NEP activity*, nmol/uL/min	0.33 (0.22, 0.74)	0.33 (0.11, 0.69)	0.25 (0.10, 0.65)	0.0893
Concomitant medications at baseline				
ACEI, ARB or ARNI	28 (68.3%)	20 (80.0%)	19 (55.9%)	0.2883
Beta-blocker	23 (56.1%)	17 (68.0%)	20 (58.8%)	0.7766
Diuretic	28 (68.3%)	19 (76.0%)	15 (44.1%)	0.0387
Thiazide diuretic	8 (19.5%)	4 (16.0%)	2 (5.9%)	0.0999

(*Continues*)

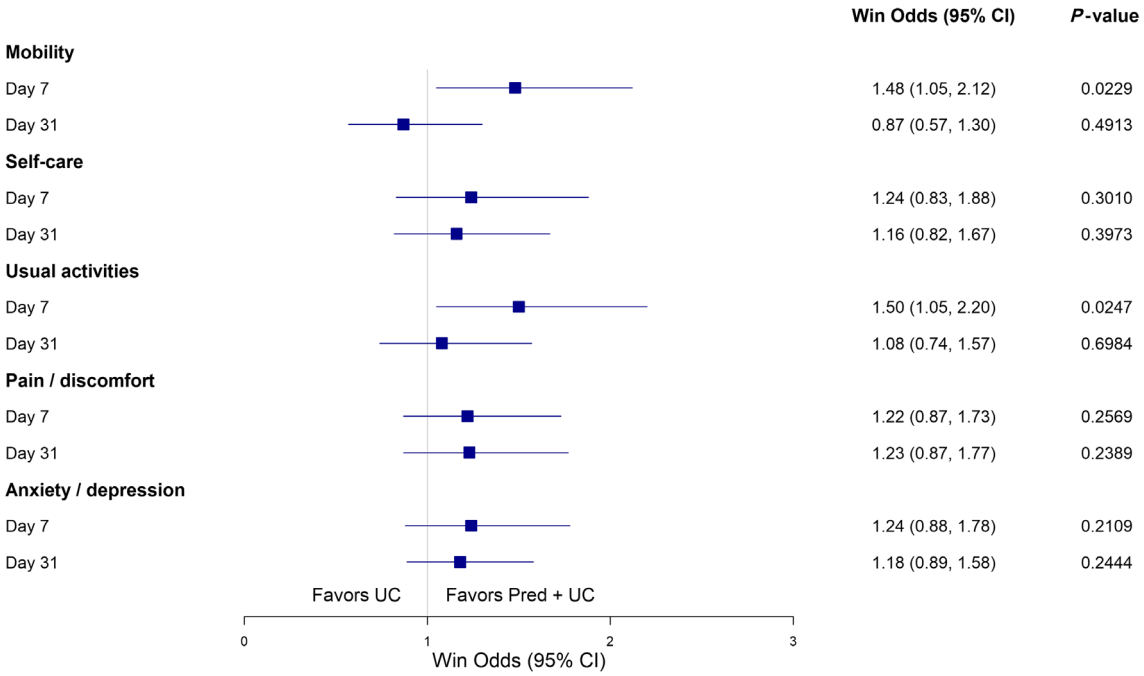
DOI: 10.1002/ehf2.15235

Table 1 (continued)

Parameter	EQ-VAS < 35(*N* = 41)	EQ-VAS = 35(*N* = 25)	EQ-VAS > 35(*N* = 34)	Trend*P* value[a]
SGLT2 inhibitor	7 (17.1%)	6 (24.0%)	2 (5.9%)	0.2598
Nitrates	1 (2.4%)	0	0	0.7500
Calcium channel blocker	15 (36.6%)	8 (32.0%)	8 (23.5%)	0.2263
Digoxin	5 (12.2%)	3 (12.0%)	2 (5.9%)	0.4482
Antiplatelet	28 (68.3%)	17 (68.0%)	25 (73.5%)	0.6310

Note: Data are presented as *n* (%), mean (*SD*) or *median (IQR).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; EQ-VAS, EuroQol visual analogue scale; hsCRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IL, interleukin; IQR, interquartile range; LVEF, left ventricular ejection fraction; NEP, neutral endopeptidase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PRC, plasma renin concentration; *SD*, standard deviation; SGLT2, sodium-glucose cotransporter 2; TIA, transient ischaemic attack; WBC, white blood cell.
[a]Jonckheere's trend test for continuous variables, Cochran–Armitage trend test for binary variables, Cochran–Mantel–Haenszel general association for categorical variables and Cochran–Mantel–Haenszel nonzero correlation for ordinal variables.

Figure 1 Treatment effect on the different EQ-5D-5L domains in the overall population. Win odds and 95% confidence intervals (CIs) comparing treatment groups (burst steroid therapy plus usual care vs. usual care only), stratified by centre and adjusted for baseline response, are plotted for each EuroQol 5-Dimension 5-Level (EQ-5D-5L) domain at Visit 4 (i.e., Day 7) and Visit 5 (i.e., Day 31).



Impact of burst steroid therapy on QoL domains

The impact of steroid therapy vs. usual care on the different EQ-5D-5L domains at Day 7 and at Day 31 in the overall population is shown in *Figure* 1 and fully reported in *Tables* S1–S10. At Day 7, significant treatment effects were observed on mobility (stratified adjusted WO 1.48, 95% CI 1.05–2.12, *P* = 0.023; *Table* S1) and usual activities (stratified adjusted WO 1.50, 95% CI 1.05–2.20, *P* = 0.025; Table S5). No significant differences between treatment arms were observed at Day 7 in the self-care (stratified adjusted WO 1.24, 95% CI 0.83–1.88, *P* = 0.301; Table S3), pain/discomfort (stratified adjusted WO 1.22, 95% CI 0.87–1.73, *P* = 0.257; Table S7) and anxiety/depression domains (stratified adjusted WO 1.24, 95% CI 0.88–1.78, *P* = 0.211; Table S9). The significant effects on mobility and usual activities domains at Day 7 were confirmed in the subgroup of patients with baseline IL-6 > 13 pg/mL (*Figure* S1), with

stratified adjusted WO of 1.79 (95% CI 1.18–2.86, P = 0.005) for mobility and of 1.62 (95% CI 1.03–2.69, P = 0.037) for usual activities.

No significant differences between treatment arms were observed at Day 31 in the mobility (Table S2), self-care (Table S4), usual activities (Table S6), pain/discomfort (Table S8) and anxiety/depression domains (Table S10).

Treatment effect on the primary endpoint by baseline self-rated health status

The effect of burst steroid therapy plus usual care versus usual care alone on change in hsCRP from baseline to Day 7 (i.e., trial primary endpoint) across the entire spectrum of baseline EQ-VAS is reported in *Figure* 2. The treatment effect did not vary significantly across baseline EQ-VAS as a continuous variable (P value for interaction = 0.128).

Correlation between QoL and congestion

In the overall population, a significant correlation between baseline EQ-VAS and baseline congestion score was observed, with higher congestion score values associated with lower EQ-VAS ($r = -0.744$, $P < 0.0001$; Figure S2). In both treatment arms, change in EQ-VAS was also significantly correlated with change in congestion score both at Day 7 (Figure S3) and at Day 31 (Figure S4), with more effective decongestion associated with higher improvement in EQ-VAS. In the overall population, a significant correlation was confirmed between change in EQ-VAS and change in congestion score at both timepoints, with higher improvement in EQ-VAS associated with a higher reduction in congestion score ($r = -0.528$, $P < 0.0001$; *Figure* 3). This overall correlation at both timepoints was confirmed in both treatment arms when evaluated separately (Figure S5).

Discussion

In the CORTAHF trial, 7 day burst steroid therapy added to usual care was associated with a significant improvement in health-related QoL as measured by EQ-VAS at Day 7 in patients with AHF. This improvement in EQ-VAS was particularly evident among patients with baseline IL-6 > 13 pg/mL and was driven by significant effects on the EQ-5D-5L mobility and usual activities domains. Steroid therapy reduced inflammatory activation (i.e., change in hsCRP at day 7) independently from baseline QoL. A significant correlation was also observed between increased decongestion and improvement in EQ-VAS at Days 7 and 31.

Assessment of health-related QoL is of paramount importance in patients with HF.[6,13,14] In particular, the EQ-5D-5L questionnaire allows a careful evaluation of patient-reported QoL and its excellent psychometric properties have been demonstrated in different populations, settings and conditions,[15] including cardiovascular diseases and more specifically HF.[16–18] This questionnaire asks patients to rate their health status 'today', unlike other QoL tools with longer recall periods that are commonly used in HF, thus is particularly useful in the setting of our study where AHF patients were assessed at baseline and after 7 and 31 days.[19] In CORTAHF, patients with better QoL at baseline assessment had lower weight and higher oxygen saturation and were less likely to

Figure 2 Treatment effect on the primary endpoint by baseline EQ-VAS in the overall population. The treatment effect of burst steroid therapy plus usual care versus usual care alone on the primary endpoint [i.e., change in C-reactive protein (CRP) from baseline to Day 7], is shown across the spectrum of baseline EuroQol visual analogue scale (EQ-VAS). Geometric mean ratio of change in CRP at Day 7 with 95% confidence interval was derived from a regression model based on baseline EQ-VAS, using a restricted cubic spline with three knots. The P value for interaction between treatment effect and baseline EQ-VAS is also reported.

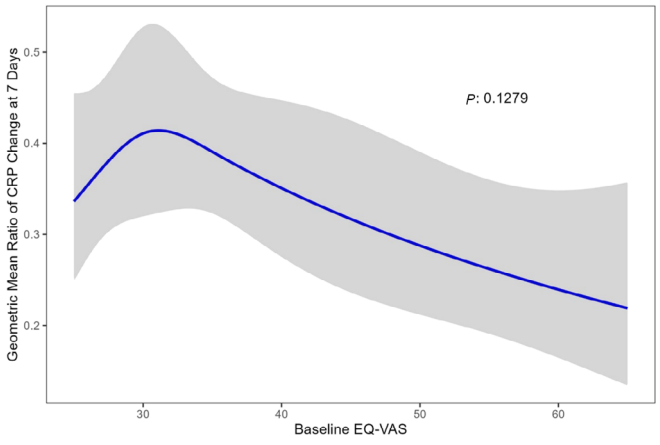
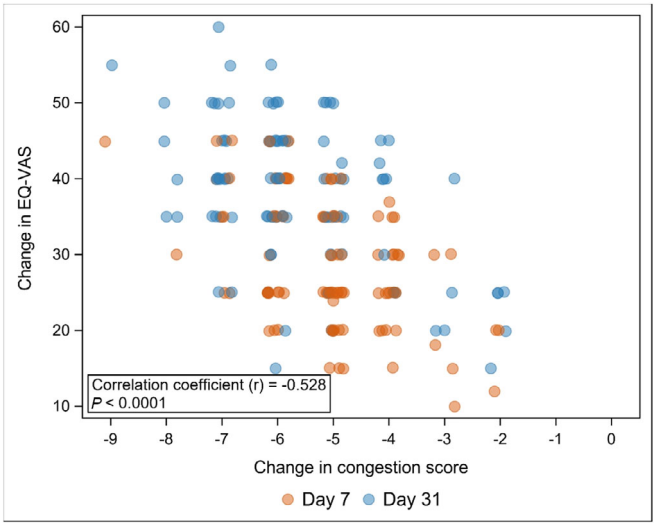


Figure 3 Correlation between change in EQ-VAS and congestion score at Days 7 and 31 in the overall population. The figure shows the correlation between change in EQ-VAS and change in congestion score at Days 7 and 31 in the overall population. Red dots represent changes at Day 7; blue dots represent changes at Day 31. The overall correlation coefficient (*r*) is based on a mixed model approach for changes in EQ-VAS and congestion score at both timepoints, accounting for correlation between repeated measures.



have chronic lung disease and more likely to have valvular disease and to receive diuretic therapy before randomization. However, hsCRP and NT-proBNP were similar, and there were not significant differences with respect to other comorbidities across the baseline EQ-VAS tertiles.

Previous studies investigated the potential role of steroid therapy in improving QoL in different non-cardiovascular settings and conditions.[20–24] These studies have not demonstrated any improvement, and in some case, they showed worsening of QoL following steroid therapy initiation.[20–24] This finding contrasts with common wisdom that suggests that steroids would improve QoL through their euphoric effects, which however promptly attenuate after cessation of steroid therapy.[25] Thus, further assessment of the impact of burst steroid therapy on HF-related QoL is of particular interest in the context of the CORTAHF trial enrolling patients with AHF and pro-inflammatory activation. Notably, no significant interaction was observed in our study between baseline EQ-VAS as a continuous variable and the effect of burst steroid therapy versus usual care with respect to the primary endpoint of the trial, that is, change in hsCRP from baseline to Day 7. Therefore, the effect of prednisone in reducing inflammatory activation among patients with AHF does not seem to vary by the patient's own perceived health status at the time of therapy initiation because this effect seems maintained in both patients with poor or moderately reduced baseline EQ-VAS that were enrolled in CORTAHF.

As previously described, burst steroid therapy significantly improved EQ-VAS at Day 7 as compared with usual care alone.[4] This effect was particularly evident in the pre-specified subgroup of patients with baseline IL-6 $>$ 13 pg/mL, which was centrally measured in a blinded manner after enrolment was completed. In these patients, the adjusted mean difference between treatment arms in EQ-VAS change at Day 7 was 3.94 (95% CI 0.73–7.15), and significant improvement in EQ-VAS at Day 31 was also observed after excluding imputation for death. Of note, a 5-point difference in median EQ-VAS change from baseline to Day 7 was observed between treatment arms in both the overall population and the pre-specified subgroup with IL-6 $>$ 13 pg/mL. This difference is higher than a 3-point threshold that has been considered clinically meaningful according to previous HF studies.[26] The improvement in EQ-VAS at Day 7 was driven by significant effects of burst steroid therapy on the EQ-5D-5L mobility and usual activities domains, that were observed in both the overall population and the subgroup of patients with IL-6 $>$ 13 pg/mL. The mobility and usual activities domains are closely associated with HF, as also demonstrated by previous studies in both chronic HF and AHF, showing that these two domains are those with the most patient-reported limitations.[16,27] Interestingly, a recent analysis of the Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial showed that the effects of high-intensity care versus usual care were more pronounced on the EQ-5D-5L mobility, usual activities and anxiety/depression domains,[16] similar to CORTAHF and thus suggesting an AHF-specific effect.

In our study, a significant correlation was observed between higher congestion score and worse QoL (i.e., lower EQ-VAS) at baseline. Moreover, in both treatment arms, increased decongestion was correlated with higher improvement in EQ-VAS at both Days 7 and 31. This was confirmed

in an analysis evaluating both timepoints together in the overall population (overall correlation coefficient = −0.528, $P < 0.0001$). This confirms the close relationship between worse AHF clinical presentation and/or trajectory, i.e., worse congestion at baseline and/or suboptimal decongestion, and worse QoL. Therefore, the effects of AHF-specific treatments, including neurohormonal therapies, sodium-glucose cotransporter inhibitors and anti-inflammatory therapies, may simultaneously favour decongestion and improve QoL.[16,28,29] Because previous studies investigated the potential effect of steroid therapy on QoL in non-cardiovascular settings,[20–24] our findings suggest the interesting possibility that congestion represents a key determinant of QoL in AHF and the effects of burst steroid therapy in improving QoL in AHF may be indeed mediated by enhanced decongestion.[4,8]

Limitations

CORTAHF was a small pilot trial with 100 randomized patients; thus, larger prospective randomized studies are needed to confirm its findings. The trial was open label, and both treating physicians and patients who completed the QoL questionnaires were aware of the assigned treatment, thus potentially introducing some bias. Moreover, other anti-inflammatory therapies might have provided slightly different or enhanced biological effects than oral 40 mg prednisone.

Conclusions

In the CORTAHF pilot study enrolling patients with AHF and high hsCRP levels, 7 day burst steroid therapy reduced inflammatory activation independently from baseline patient-reported health status and was associated with improved health-related QoL at Day 7, especially among patients with baseline IL-6 > 13 pg/mL. Improvement in QoL was driven by significant effects on the EQ-5D-5L mobility and usual activities domains, that is, those most closely associated with HF. QoL improvement was correlated with decongestion and may therefore not be a direct effect of steroid therapy, but mediated through improvement in HF symptoms and signs.

Acknowledgements

Open access publishing facilitated by Universita degli Studi di Brescia, as part of the Wiley - CRUI-CARE agreement. [Correction added on 15 February 2025, after first online publication: CRUI-CARE funding statement has been added.]

Conflict of interest statement

M. P. has received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. G. C. and B. A. D. are directors of Heart Initiative, a non-profit organization. G. C., B. A. D., C. E., M. N., and K. T. are employees of Momentum Research, which has received grants for research from the Heart Initiative, Corteria, Windtree, Echosens and 4teen4. The employer of A. A. V. received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche diagnostics and SalubrisBio. H. H. has nothing to declare. D. M. is on the scientific advisory board of Tenaya therapeutics, HAYA Therapeutics and Cardurion Therapeutics and is a consultant from Novo holdings and Tourmaline Therapeutics. A. C. S. has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott and Boehringer Ingelheim. J. M. t. M. reports speaker and/or consultancy fees to institution from Novartis, Boehringer Ingelheim, Moderna, Roche and Novo Nordisk and receiving grants from Netherlands Heart Foundation and Netherlands Organization for Scientific Research (NWO) outside the submitted work. J. B. has received honoraria from Bayer, Boehringer Ingelheim and AstraZeneca for lectures. G. F. has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic and Amgen. O. C. serves on an advisory board for Boehringer Ingelheim. D. L. M. is on the scientific advisory board for Tenaya Therapeutics, HAYA Therapeutics, Cardurion Therapeutics and is a consultant from Novo holdings and Tourmaline Therapeutics. A. M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4 and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4 and Adrenomed; and is a coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. M. M. has received personal fees since January 2021 from Actelion, Amgen, Livanova and Vifor Pharma as a member of executive or data monitoring committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences and Novartis for participation in advisory boards or for speaking at sponsored meetings. All other authors have nothing to disclose.

Funding

The study was sponsored by the Heart Initiative (Durham, NC, USA).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Changes in the EQ-5D-5L mobility domain from randomization to day 7 by treatment group in the overall population.
Table S2: Changes in the EQ-5D-5L mobility domain from randomization to day 31 by treatment group in the overall population.
Table S3: Changes in the EQ-5D-5L self-care domain from randomization to day 7 by treatment group in the overall population.
Table S4: Changes in the EQ-5D-5L self-care domain from randomization to day 31 by treatment group in the overall population.
Table S5: Changes in the EQ-5D-5L usual activities domain from randomization to day 7 by treatment group in the overall population.
Table S6: Changes in the EQ-5D-5L usual activities domain from randomization to day 31 by treatment group in the overall population.
Table S7: Changes in the EQ-5D-5L pain/discomfort domain from randomization to day 7 by treatment group in the overall population.
Table S8: Changes in the EQ-5D-5L pain/discomfort domain from randomization to day 31 by treatment group in the overall population.
Table S9: Changes in the EQ-5D-5L anxiety/depression domain from randomization to day 7 by treatment group in the overall population.
Table S10: Changes in the EQ-5D-5L anxiety/depression domain from randomization to day 31 by treatment group in the overall population.
Figure S1: Treatment effect on the different EQ-5D-5L domains in the subgroup of patients with IL-6 $>$ 13 pg/mL.
Figure S2: Correlation between EQ-VAS and congestion score at baseline in the overall population.
Figure S3: Correlation between change in EQ-VAS and congestion score at day 7 by treatment arm.
Figure S4: Correlation between change in EQ-VAS and congestion score at day 31 by treatment arm.
Figure S5: Correlation between change in EQ-VAS and congestion score at day 7 and day 31 by treatment arm.

References

1. Garofalo M, Corso R, Tomasoni D, Adamo M, Lombardi CM, Inciardi RM, *et al*. Inflammation in acute heart failure. *Front Cardiovasc Med* 2023;**10**:1235178. doi:10.3389/fcvm.2023.1235178
2. Cotter G, Pagnesi M, Davison B. C-reactive protein, inflammation and short-term mortality in acute heart failure. *Eur J Heart Fail.* 2024;**26**:1759-1761. doi:10.1002/ejhf.3361
3. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:1324-1340. doi:10.1016/j.jacc.2020.01.014
4. Cotter G, Davison BA, Freund Y, Voors AA, Edwards C, Novosadova M, *et al*. Burst steroid therapy for acute heart failure: the CORTAHF randomized, open-label, pilot trial. *Eur J Heart Fail.* 2024; doi:10.1002/ejhf.3452
5. Savarese G, Lindenfeld J, Stolfo D, Adams K, Ahmad T, Desai NR, *et al*. Use of patient-reported outcomes in heart failure: from clinical trials to routine practice. *Eur J Heart Fail* 2023;**25**:139-151. doi:10.1002/ejhf.2778
6. Zannad F, Alikhaani J, Alikhaani S, Butler J, Gordon J, Jensen K, *et al*. Patient-reported outcome measures and patient engagement in heart failure clinical trials: multi-stakeholder perspectives. *Eur J Heart Fail* 2023;**25**:478-487. doi:10.1002/ejhf.2828
7. Cotter G, Davison B, Freund Y, Mebazaa A, Voors A, Edwards C, *et al*. Corticosteroid burst therapy in patients with acute heart failure: design of the CORTAHF pilot study. *ESC Heart Fail* 2024;**11**:2672-2680. doi:10.1002/ehf2.14930
8. Biegus J, Cotter G, Davison BA, Freund Y, Voors AA, Edwards C, *et al*. The effects of burst steroid therapy on short-term decongestion in acute heart failure patients with pro-inflammatory activation: a post hoc analysis of the CORTAHF randomized, open-label, pilot trial. *J Card Fail* 2024; doi:10.1016/j.cardfail.2024.09.002
9. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med.* 2001;**33**:337-343. doi:10.3109/07853890109002087
10. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727-1736. doi:10.1007/s11136-011-9903-x
11. Kawaguchi A, Koch G. Sanon: an R package for stratified analysis with nonparametric covariable adjustment. *J Stat Softw* 2015;**67**:1-37. doi:10.18637/jss.v067.i09
12. R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2023 https://www.R-project.org/ (accessed July 2024).
13. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, *et al*. Health-related quality of life and mortality in heart failure: the global congestive heart failure study of 23 000 patients from 40 countries. *Circulation* 2021;**143**:2129-2142. doi:10.1161/CIRCULATIONAHA.120.050850
14. Moons P, Norekval TM, Arbelo E, Borregaard B, Casadei B, Cosyns B, *et al*. Placing patient-reported outcomes at the centre of cardiovascular clinical practice: implications for quality of care and management. *Eur Heart J* 2023;**44**:3405-3422. doi:10.1093/eurheartj/ehad514
15. Feng YS, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res* 2021;**30**:647-673. doi:10.1007/s11136-020-02688-y
16. Celutkiene J, Cerlinskaite-Bajore K, Cotter G, Edwards C, Adamo M, Arrigo M, *et al*. Impact of rapid up-titration of guideline-directed medical therapies on quality of life: insights from the STRONG-HF Trial. *Circ Heart Fail* 2024;

17:e011221. doi:10.1161/CIRCHEARTFAILURE.123.011221
17. Boczor S, Daubmann A, Eisele M, Blozik E, Scherer M. Quality of life assessment in patients with heart failure: validity of the German version of the generic EQ-5D-5L. *BMC Public Health* 2019;**19**:1464. doi:10.1186/s12889-019-7623-2
18. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;**8**:13. doi:10.1186/1477-7525-8-13
19. Bansback N, Sun H, Guh DP, Li X, Nosyk B, Griffin S, *et al*. Impact of the recall period on measuring health utilities for acute events. *Health Econ* 2008;**17**:1413-1419. doi:10.1002/hec.1351
20. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Qual Life Res* 2017;**26**:1037-1058. doi:10.1007/s11136-016-1435-y
21. Berthon BS, Gibson PG, McElduff P, MacDonald-Wicks LK, Wood LG. Effects of short-term oral corticosteroid intake on dietary intake, body weight and body composition in adults with asthma—a randomized controlled trial. *Clin Exp Allergy* 2015;**45**:908-919. doi:10.1111/cea.12505
22. Judson MA, Chaudhry H, Louis A, Lee K, Yucel R. The effect of corticosteroids on quality of life in a sarcoidosis clinic: the results of a propensity analysis. *Respir Med.* 2015;**109**:526-531. doi:10.1016/j.rmed.2015.01.019
23. Jacobs JW, Geenen R, Evers AW, van Jaarsveld CH, Kraaimaat FW, Bijlsma JW. Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. *Ann Rheum Dis.* 2001;**60**:61-64. doi:10.1136/ard.60.1.61
24. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, *et al*. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013;**309**:2223-2231. doi:10.1001/jama.2013.5023
25. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc.* 2006;**81**:1361-1367. doi:10.4065/81.10.1361
26. Flynn KE, Lin L, Ellis SJ, Russell SD, Spertus JA, Whellan DJ, *et al*. Outcomes, health policy, and managed care: relationships between patient-reported outcome measures and clinical measures in outpatients with heart failure. *Am Heart J.* 2009;**158**:S64-S71. doi:10.1016/j.ahj.2009.07.010
27. Ravera A, Santema BT, Sama IE, Meyer S, Lombardi CM, Carubelli V, *et al*. Quality of life in men and women with heart failure: association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire. *Eur J Heart Fail* 2021;**23**:567-577. doi:10.1002/ejhf.2154
28. Biegus J, Mebazaa A, Davison B, Cotter G, Edwards C, Celutkiene J, *et al*. Effects of rapid uptitration of Neurohormonal blockade on effective, sustainable decongestion and outcomes in STRONG-HF. *J Am Coll Cardiol* 2024;**84**:323-336. doi:10.1016/j.jacc.2024.04.055
29. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, *et al*. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J* 2023;**44**:41-50. doi:10.1093/eurheartj/ehac530