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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

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ABSTRACT

Background: The effect of steroids on congestion in patients with acute heart failure (AHF) is not known.

Methods and Results: Patients with AHF, NT-proBNP levels > 1500 pg/mL and high-sensitivity C-reactive protein (hsCRP) levels > 20 mg/L were randomized to once-daily oral 40 mg prednisone for 7 days or usual care. In this post hoc analysis, congestion score was calculated on the basis of orthopnea, edema and rales (0 reflecting lack of congestion, and 9 maximal congestion) at each time point. Among 100 eligible patients randomized, those assigned to prednisone had a greater improvement in congestion score at day 31 (win odds for the prednisone group compared to usual care at day 31 was 1.77 (95% CI 1.17–2.84; $P = 0.0066$) in all patients and 2.41 (95% CI 1.37–5.05; $P = 0.0016$) in patients with IL-6 > 13 pg/mL at baseline. In patients with congestion scores ≥ 7 at baseline, the effects of prednisone therapy on the EQ-5D visual analog scale score were 4.30 (95% CI 0.77-7.83) points at day 7 and 5.40 (0.51–10.29) points at day 31, accompanied by lower heart rate and respiratory rate and higher oxygen saturation compared to usual care.

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Conclusions: In patients with AHF and inflammatory activation, 7-day steroid therapy was associated with reduction in signs of congestion up to day 31. These results need confirmation in larger studies examining potential effects of steroids on congestion, diuresis, fluid redistribution and vascular permeability as well as clinical effects in AHF. (*J Cardiac Fail 2025;31:354–366*)

Key Words: Acute heart failure, inflammation, decongestion, HF events.

Introduction

Inflammation has been shown to be activated in patients with heart failure (HF), especially in the setting of acute HF (AHF).[1-4] Interestingly, the first evidence that elevated C-reactive protein (CRP) was associated with more severe HF and signs of congestion in patients with HF appeared 70 years ago for AHF[5] and was subsequently reconfirmed by using various inflammatory markers.[6-11] Proinflammatory activation in HF has many potential adverse effects, such as worsening cardiac contractility, stimulation of fibrosis, renal and vascular dysfunction, fluid retention/redistribution, disruption of the endothelial barrier with increased capillary permeability, and neurohormonal activation, all of which may promote congestion development.[4,12,13] The potential link between inflammatory drive and congestion has been recently documented by Pandhi et al.,[14] who have found overexpression of several proinflammatory proteins in patients with HF and with more clinical signs/symptoms of congestion.[1] On the other hand, the evidence that anti-inflammatory therapies may either lead to improvement of congestion or prevent congestion development in HF is still lacking. In the setting of AHF, only 2 small studies of the impact of steroids on decongestion were conducted; however, they were not followed by any larger confirmatory study.[15,16] The CORTAHF (Effect of Short-Term Prednisone Therapy on C-reactive Protein Change in Emergency Department Patients With Acute Heart Failure and Elevated Inflammatory Markers) pilot trial was designed to examine the effects of a short steroid-burst therapy with prednisone on inflammation as measured by high-sensitivity CRP (hsCRP), quality of life (QoL) and 90-day clinical outcomes. The main results of the study[17,18] showed an association between prednisone administration and reduced inflammation at day 7, improved QoL at day 7 and a reduced rate of worsening of HF (WHF) and death at day 91. The current post hoc analysis was designed to examine the effects of prednisone on symptoms and signs of congestion and the potential interaction between the severity of baseline congestion and the effects of prednisone on primary and secondary outcomes in patients with AHF and pro-inflammatory activation enrolled in the CORTAHF study.

Methods

Study Design

The CORTAHF was a multicenter, prospective, randomized, open-label trial in which patients admitted to the hospital due to AHF and laboratory profiles of pro-inflammatory activation (defined as hsCRP > 20 mg/L at screening) were randomized 1:1 to receive 7-day corticosteroid (40 mg daily of oral prednisone) therapy in addition to usual care or usual care alone. The study was designed to include 120 patients but was stopped early after 100 patients were enrolled due to nonenrolment in 3 sites and financial restrictions.

The most crucial inclusion criteria were objective signs of congestion (by chest X-ray or lung ultrasound), a systolic blood pressure of ≥ 100 mmHg, and NT-proBNP levels > 1500 pg/mL. Originally, we planned to enroll patients with interleukin 6 (IL-6) > 13 pg/mL in the study. However, during the study preparation, we learned that IL-6 cannot be measured in the sites in real time due to technical constraints. Therefore, the inclusion criteria were updated to hsCRP > 20 mg/L at screening.[17] At the conclusion of the study, after all patients had reached day 31 follow-up, we have analyzed central blood samples from the patients and performed a secondary, blinded analysis restricting the patients to those who, in the central laboratory analysis, were found to have IL-6 levels > 13 pg/mL. Patients whose AHF was triggered by a correctable etiology, such as significant arrhythmia, severe anemia, acute coronary syndrome, chronic obstructive pulmonary disease exacerbation, or infection, were not eligible to participate. All patients gave written, informed consent to participate. The detailed design of the trial has been presented elsewhere.[17] The study was approved by appropriate ethics committees, and eligible patients gave written, informed consent to participate. The study is registered in ClinicalTrials.gov (NCT05916586).

Procedures

Screening occurred within 12 hours of hospital presentation. Eligible participants were randomized shortly thereafter (day 1). Randomly assigned treatments were known to investigators, participants and those assessing outcomes (aside from central laboratory staff).

Investigators provided all patients with the usual care practiced in their institutions. Patients assigned to prednisone therapy received prednisone tablets available from the hospital pharmacy. Assessments were done on days 1 (baseline), 2, 4 (or discharge if earlier), 7, and 31. At all time points, investigators assessed vital signs and HF signs and symptoms, rating their severity on ordinal scales:

- Orthopnea: the minimum number of "pillows" required to obtain/maintain comfort while supine: 0 = none; 1 = 1 pillow (10 cm); 2 = 2 pillows (20 cm); 3 = > 30°;
- Peripheral edema: 0 = complete absence of skin indentation with mild digital pressure in all dependent areas; 1 = 1+, indentation of skin that resolves over 10−15 seconds; 2 = 2+, indentation of skin is easily created with limited pressure and disappears slowly (15−30 seconds or more); 3 = 3+, large areas of indentation easily produced and slow to resolve (> 30 seconds);
- Rales: 0 = no rales, no rales after clearing with cough; 1 = rales < 1/3, moist or dry rales heard in lower 1/3 of 1 or both lung fields that persist after cough; 2 = rales 1/3−2/3, moist or dry rales heard throughout the lower half to 2/3 of 1 or both lung fields; 3 = rales > 2/3, moist or dry rales heard throughout both lung fields; and
- Jugular venous pulse (JVP): 0 ≤ 6 cm, the complete absence of discernable venous wave, even with hepatic compression; 1 = 6−10 cm, venous wave detectable during expiration or complete respiratory cycle, less than 4 cm above the clavicle (< 10 cm); 2 = > 10 cm, presence of venous wave throughout respiratory cycle sometimes ≥ 4 cm above the clavicle and increased with hepatic compressions. JVP reported as not evaluable was considered missing.

A congestion score, with possible scores ranging from 0 points (reflecting no congestion) to 9 points (reflecting the worst congestion), was computed by summing the orthopnea, edema and rales scores. Dyspnea on exertion was reported as New York Heart Association (NYHA) class I−IV. hsCRP was measured locally at investigators' hospitals on days 1, 2, 4, 7, and 31; NT-proBNP and troponin levels were measured locally on days 1 and 31, and hematology and chemistry were obtained locally on days 1, 7 and 31. Plasma samples were collected in ethylenediaminetetraacetic acid (EDTA) on days 1, 4, 7, and 31 and stored locally at -20°C or colder until shipped, frozen, to the central laboratory in Paris, France, after all patients had completed the study through day 31. IL-6 was measured using the Quantikine Human IL-6 Immunoassay ELISA (R&D Systems, Minneapolis, MN, USA).

Patients reported their QoL on the EQ-5D-5L questionnaire on days 1, 7 and 31. The instrument includes a vertical visual analog scale (VAS) on which patients rate their health "today" between 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). Patients were contacted by telephone on day 91 to assess clinical outcomes.

Outcomes

The study's primary endpoint was the change in hsCRP level from baseline to day 7, and secondary endpoints included the time to first event of a worsening HF adverse event, hospital readmission for HF, or death through day 91; and change in QoL as measured by the change in EQ-5D-5L from day 1 to day 7.

For this secondary analysis, we assessed the effects of prednisone burst therapy on changes in symptoms and signs of congestion (each as a separate variable and additionally computed using a congestion score), including physician-assessed severity of signs and symptoms of congestion described above, body weight, loop diuretic dosage, and NT-proBNP, as well as changes in routine laboratory parameters and vital signs. We also examined potential interactions of the effect of prednisone burst therapy on the study's primary and secondary endpoints with baseline congestion severity. For this purpose, patients were classified based on their baseline congestion score as either < 7 or ≥ 7 points, the approximate median value.

Statistical Methods

Results are presented as means and standard deviations or medians and interquartile ranges for continuous variables and as absolute and relative frequencies for categorical variables.

Treatment groups were compared with respect to ordinal outcomes, including the congestion score, stratified by center and adjusted for baseline response by using the method described by Kawaguchi and Koch[19] and implemented using the R package sanon (Vienna, Austria), where observed values within strata at each visit were compared.[20] Treatment effects are expressed as win odds, where a value > 1 means that patients assigned prednisone had better outcomes.

Treatment effects on continuous outcomes, including change in the congestion score, were estimated using contrasts from a mixed model for repeated measures that included the effects of center, baseline value, treatment, baseline × visit and treatment × visit. hsCRP and NT-proBNP levels were natural log-transformed for analysis, and results were exponentiated to be expressed in terms of geometric mean ratios−the ratio of the follow-up to baseline. Values above the upper reporting limit of NT-proBNP levels were set to that limit (9000 pg/mL). The χ^2 tests of congestion subgroup differences were constructed from treatment effects on the continuous outcome and their associated standard errors estimated from a mixed model for repeated measures in each subgroup.

Separate linear regression models by treatment group were used to examine the association between changes in IL-6 levels and changes in congestion score, adjusted for both baseline IL-6 level and baseline congestion score.

Treatment groups were compared within baseline-congestion score groups with respect to the time to the first event of WHF adverse event, HF readmission or death from any cause from randomization through day 91 by using exact methods for a Poisson regression model, including treatment, baseline congestion score group and their interaction, with person-time as an offset. Incident rate ratios with 95% confidence intervals are presented, and an exact *P* value for the interaction between treatment and congestion group was obtained. These analyses were not stratified by site due to the low number of events.

Daily furosemide-equivalent doses were computed, considering 10 mg of torsemide equal to 20 mg intravenous furosemide or 40 mg oral furosemide. Oral doses were halved to convert to intravenous equivalents. Comparisons of concomitant medication use by class between congestion score groups at follow-up were derived by using logistic regression adjusted for baseline medication use.

SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.3[21] were used for statistical analysis. A 2-sided $P < 0.05$ was considered statistically significant.

Results

A total of 101 patients were validly randomized to the study at 3 hospitals (that enrolled 23, 26 and 52 patients) between August 11, 2023, and April 15, 2024. One ineligible patient was randomized in error, and 1 patient who was randomized in violation of protocol eligibility criteria was excluded from analyses. One patient randomly assigned prednisone died from HF on day 19, but all remaining patients were followed to day 91.

Congestion Score

The congestion score was < 7 and ≥ 7 in 49 and 51 patients, respectively. Patients with congestion scores < 7 had less severe HF that those with congestion scores ≥ 7, as determined by significantly higher EuroQol Visual Analog Scale (EQ-VAS) scores at baseline (41.8 [12.33] vs 31.4 [6.17]; $P < 0.001$, respectively) and numerically lower risk of WHF, HF readmission or death to day 90: 14.3% vs 27.5%; $P = 0.2405$. Baseline characteristics by baseline congestion score < 7 and ≥ 7 points are given in Table 1. Of note, patients who were more congested at enrolment tended to have higher weight, were more likely to have diabetes, hypertension, hypercholesterolemia, more ischemic heart disease, and higher New York Heart Association (NYHA) class and were prescribed significantly more therapy for HF, including beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors as well as diuretics and digoxin before inclusion in the study.

Effects of Prednisone Burst Therapy on Congestion Measures

In all 100 included patients, signs of congestion tended to improve more in the steroid group than in the usual-care group, as described in the main manuscript[18] and Fig. 1, A.

In patients with high proinflammatory activation (as defined by hsCRP > 20 mg/L and additionally with serum levels of IL-6 > 13 pg/mL)(n = 65), the prednisone therapy, when compared to usual care, resulted in better improvement in rales with win odds 1.62 (95% CI 1.06−2.60) at day 7, and win odds 1.52 (95% CI 1.03−2.32) at day 31, both $P < 0.05$. There was also a significant improvement in peripheral edema at day 31 in the steroid group, with win odds 1.97 (95% CI 1.21−3.54); $P = 0.006$ vs usual care (see Supplementary Table 1 and Fig. 1, B). Treatment group differences in changes in orthopnea, jugular venous pressure and NYHA class were not statistically significant (Supplementary Table 1).

At baseline, the unadjusted mean (SD) congestion score (the sum of the orthopnea, rales and peripheral edema scores) did not differ between the prednisone and usual-care groups: 6.4 (1.71) points vs 6.6 (1.52) points, respectively. The adjusted mean change (SE) from baseline to day 7 was -5.2 (0.15) and -5.0 (0.14) points in the prednisone and usual-care groups, respectively, with an adjusted mean treatment difference of -0.3 points (95% CI -0.65−0.12; $P = 0.17$). At day 31, SEs were -5.9 (0.14) and -5.4 (0.13) points, respectively, with an adjusted mean treatment difference of -0.6 points (95% CI -0.90 to -0.19; $P = 0.0028$).

In patients with baseline IL-6 > 13 pg/mL, the effects of prednisone therapy on symptoms and signs of congestion were generally more pronounced (Supplementary Table 1) (Fig. 1, B). The SE from baseline to day 7 was -5.3 (0.18) and -4.9 (0.19) points, respectively, with an adjusted mean treatment difference of -0.4 points (95% CI -0.90 − 0.10; $P = 0.12$). At day 31, SEs were -6.1 (0.17) and -5.3 (0.18) points, respectively, with an adjusted mean treatment difference of -0.8 points (95% CI -1.21 to -0.31; $P = 0.0012$).

Daily loop diuretic doses, expressed as intravenous furosemide equivalents, decreased more from baseline to days 7 and 31 in the prednisone group, but differences were of borderline statistical significance, either in all patients[18] or in patients with high baseline IL-6 (Supplementary Table 1).

NT-proBNP levels decreased from baseline to day 31 in all patients, but the changes were not significantly different between treatment groups, as previously reported. A similar pattern was observed in patients with baseline IL-6 > 13 pg/mL (Supplementary Table 1).

Table 1 Baseline characteristics by median of baseline congestion score

Parameter	Congestion score < 7 (n= 49)	Congestion score ≥ 7 (n= 51)	*P* Value
Demographics			
Age, years	65.5 (10.25)	67.4 (6.92)	0.2827
Male sex	32 (65.3%)	31 (60.8%)	0.6396
Vital Signs			
Weight, kg	85.6 (14.41)	93.6 (20.65)	0.0270
Systolic blood pressure, mmHg	144.3 (33.39)	138.4 (24.92)	0.3166
Oxygen saturation, %	83.0 (7.75)	81.9 (8.15)	0.4915
Medical History			
Diabetes	15 (30.6%)	26 (51.0%)	0.0384
Hypertension	39 (79.6%)	47 (92.2%)	0.0703
Chronic lung disease	0	9 (17.6%)	0.0021
Ischemic heart disease	38 (77.6%)	50 (98.0%)	0.0016
Myocardial infarction	34 (69.4%)	41 (80.4%)	0.2039
Stroke			0.1590
CVA	2 (4.1%)	1 (2.0%)	
TIA	3 (6.1%)	0	
Valvular disease	22 (44.9%)	24 (47.1%)	0.8284
Atrial fibrillation	12 (24.5%)	14 (27.5%)	0.7358
HF history			
NYHA class prior to screening			0.0087
Class I	0	0	
Class II	11 (22.4%)	5 (9.8%)	
Class III	37 (75.5%)	36 (70.6%)	
Class IV	1 (2.0%)	10 (19.6%)	
Most recent LVEF, %	30.0 (9.43)	27.2 (7.80)	0.1005
Laboratory findings			
Sodium, mmol/L	140.3 (2.74)	142.5 (3.46)	0.0004
AST, U/L	22.6 (9.20)	25.4 (17.77)	0.3308
ALT, U/L	23.8 (15.07)	30.8 (36.95)	0.2218
Total bilirubin, umol/L	12.4 (6.91)	14.6 (7.04)	0.1179
Hemoglobin, g/L	134.0 (18.59)	138.0 (21.06)	0.3231
Urea/BUN, mmol/L	8.3 (2.31)	8.6 (2.74)	0.5342
Creatinine, μmol/L	108.3 (21.73)	105.0 (19.28)	0.4250
eGFR, mL/min/1.73m2	60.6 (13.11)	60.5 (11.54)	0.9590
Troponin T*, ng/mL	0.037 (0.029, 0.048)	0.034 (0.022, 0.045)	0.8959
Troponin I*, ng/mL	0.019 (0.012, 0.030)	0.023 (0.017, 0.030)	0.7514
High-sensitivity CRP*, mg/L	29.5 (25.9, 44.0)	31.9 (25.4, 41.3)	0.3644
WBC, 10^9/L	9.5 (3.14)	8.7 (2.51)	0.1222
Lymphocytes, %	21.8 (9.00)	20.1 (9.03)	0.3409
NT-proBNP*, pg/mL	3830.0 (2175.0, 7256.0)	6254.0 (2840.0, 9322.0)	0.2642
IL6*, pg/mL	17.1 (9.2, 26.2)	19.6 (10.6, 39.7)	0.1064
Concomitant medications at pre-inclusion			
ACEI, ARB or ARNI	30 (61.2%)	37 (72.5%)	0.2584
Beta-blocker	24 (49.0%)	36 (70.6%)	0.0344
Aldosterone antagonist	12 (24.5%)	25 (49.0%)	0.0170
SGLT2 inhibitor	3 (6.1%)	12 (23.5%)	00148
Values presented are n (%), mean (SD) or *median (IQR).			

ACEI, ARB, ARNI, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor–neprilysin inhibitor; AST, aspartate transferase; ALT, alanine transaminase; BUN, blood urea nitrogen; crp, C-reactive protein; egfr, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2, sodium glucose transporter.

Patients in the prednisone group tended to lose more weight, especially by day 31 (Supplementary Fig. 1). Treatment group differences were more pronounced in patients with baseline IL-6 > 13 pg/mL (Supplementary Table 1) (Supplementary Fig. 1).

Effects of Prednisone Burst Therapy on Congestion-Related Laboratory Assessments

Treatment effects on local laboratory measures have been presented previously.[18] There were no significant differences between both study arms in terms of laboratory measures relevant to congestion and kidney function in patients with baseline IL-6 > 13 pg/mL (see Supplementary Table 2).

There was no association between IL-6 change and congestion score change from baseline to day 7 in the usual-care arm ($P = 0.58$), but in the prednisone arm, the change in IL-6 was inversely associated with the change in congestion score, with a mean change of -0.273 (SE 0.12) points per log increase in IL-6 change($P = 0.026$). At day 31, a

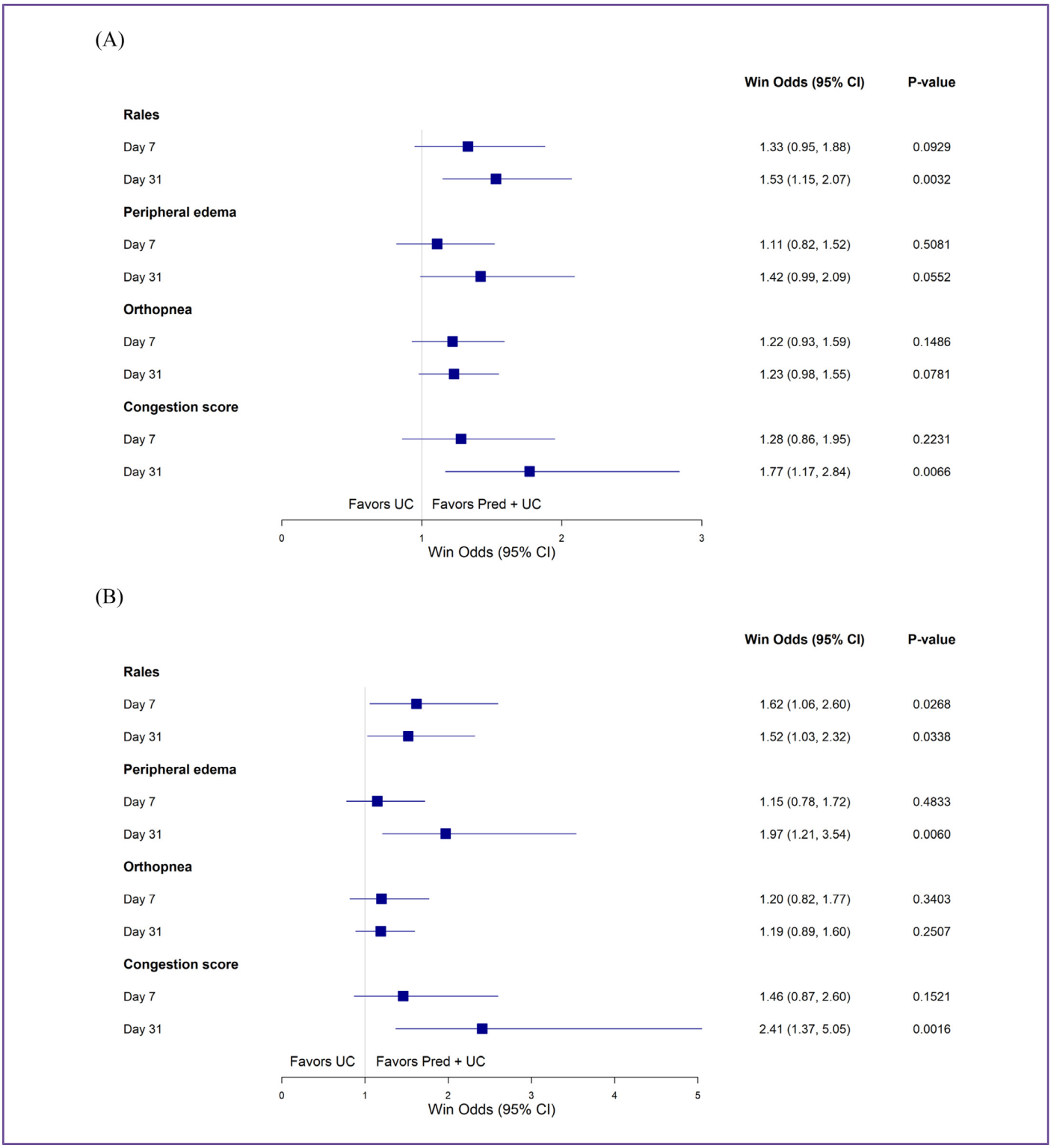

Fig. 1. A, Effects of prednisone therapy on measures of congestion as assessed by the win odds in all patients and patients with IL6 > 13 pg/mL at baseline. B, win odds > 1.0 favors prednisone therapy.

greater decrease in IL-6 was associated with a greater decrease in congestion score in the usual-care arm, with a mean increment of 0.540 (SE 0.19) points per log change in IL-6 ($P = 0.0059$), but there was no association between IL-6 change and change in congestion score in the prednisone arm ($P = 0.68$).

Treatment Effects on Primary and Secondary Endpoints by Baseline Congestion Severity

The adjusted ratio of geometric mean ratios in hsCRP from baseline to day 7 (the primary endpoint) was 0.75 (95% CI 0.48−1.17) in patients with baseline congestion scores

< 7 points and 0.78 (95% CI 0.52−1.16) in patients with baseline congestion score ≥ 7 points (Fig. 2, A). The effects of prednisone therapy on time to WHF adverse event, HF readmission, or death to day 91 by congestion score < 7 points and ≥ 7 are presented in Fig. 3. The effects of prednisone therapy on changes in EQ-VAS from baseline to day 7 and 31 are presented in Fig. 4.

Treatment Effects on Vital Signs by Baseline Congestion Severity

Vital-signs changes throughout the study by congestion score at baseline are presented in Supplementary Fig. 2. Trends toward greater decreases in heart rate and respiratory rate and improvement in oxygen saturation in prednisone-treated patients were observed. In patients with baseline congestion scores ≥ 7, the mean treatment differences in heart rate were -3.74 bpm (95% CI: -7.86−0.37; $P = 0.074$) and -3.73 bpm (95% CI: -6.86 to -0.61; $P = 0.020$) for prednisone-treated patients compared to usual care at days 7 and 31, respectively. For changes in respiratory rate, the treatment differences were -0.26 breaths/min (95% CI -1.17 to 0.64; $P = 0.558$) and -0.83 breaths/minute (95% CI: -1.67 to 0.02; $P = 0.055$) at days 7 and 31, respectively. The treatment differences in oxygen saturation were 0.66% (95% CI: -0.32 to 1.64; $P = 0.182$) and 1.02% (95% CI -0.03 to 2.07; $P = 0.057$) at days 7 and 31, respectively.

Medication Administration by Baseline Congestion Severity

Medications prescribed by baseline congestion score are presented in Supplementary Table 3. In general, guideline directed medical therapy (GDMT) was significantly uptitrated in patients with congestion score <7 or ≥7 at baseline, although patients with congestion score ≥7 at baseline were more uptitrated on SGLT-2 inhibitors.

Adverse Events by Treatment Group and Baseline Congestion Severity

The incidence of adverse events and serious adverse events through day 31 are presented in Supplementary Tables 4 and 5 by congestion score < 7 and ≥ 7 at baseline and treatment group. Adverse events were reported through day 31 in 8 (34.8%) patients with baseline congestion score < 7 in the prednisone group vs 6 (23.1%) in the usual-care group. In patients with baseline congestion scores ≥ 7, 16 (64.0%) in the prednisone group reported adverse events vs 11 (42.3%) in the usual-care group (interaction $P = 0.79$). The most common adverse events were cardiac failure and hyperglycemia. Hyperglycemia occurred more commonly in patients treated with prednisone than with usual care, but the difference was similar by baseline congestion status. One serious adverse event of cardiac failure was reported in a prednisone-treated patient, who had a baseline congestion score ≥ 7 points.

Discussion

The results of this post hoc analysis suggest that 7-day oral steroid therapy added to usual care in patients with AHF and pro-inflammatory activation leads to further improvement in signs of congestion, most notably rales, orthopnea and peripheral edema, when compared to usual care alone. We calculated congestion scores (based on assessment of rales, peripheral edema and orthopnea). In the overall patient population, the congestion score was ~ 6.5 points in both study groups at randomization (that corresponds to severity 2−3 in each for each component of the score), but by day 31, it was reduced to to 0.6

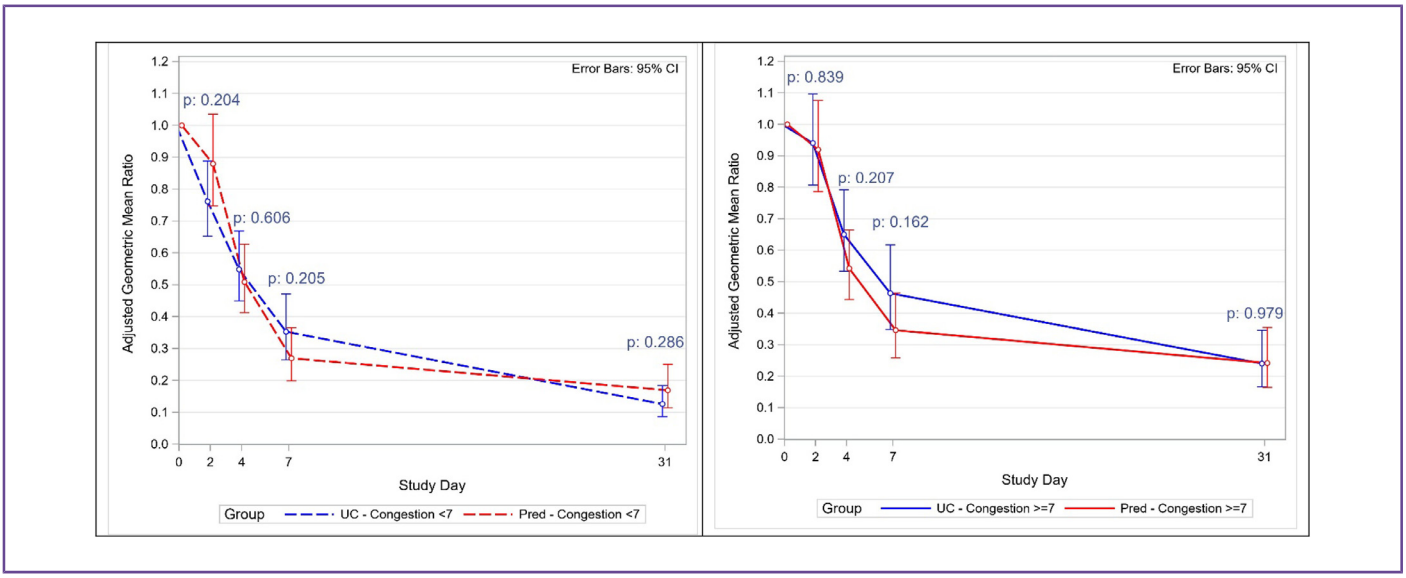

Fig. 2. Changes from baseline by treatment group and baseline congestion score for high-sensitivity CRP (hsCRP).

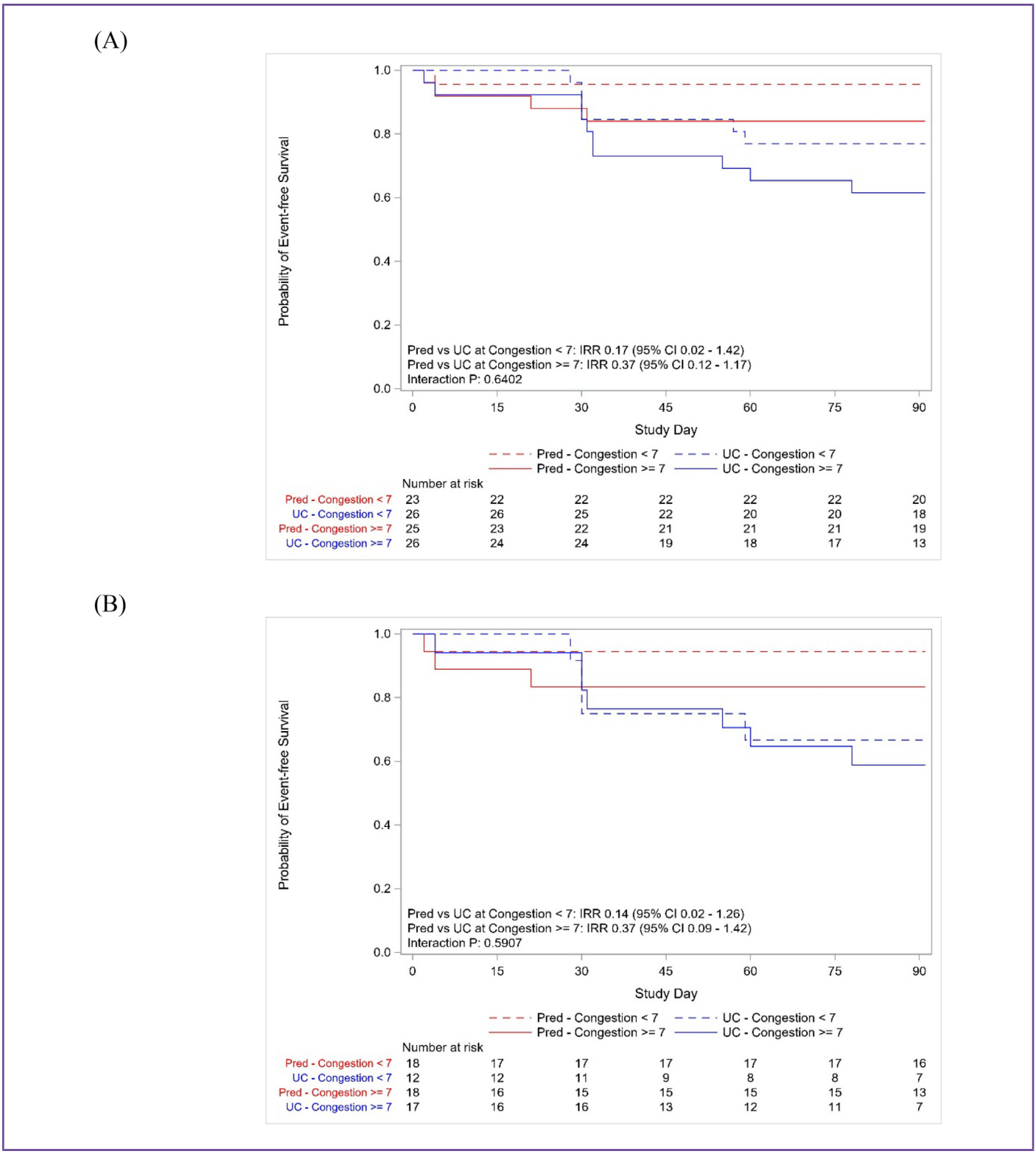

Fig. 3. Kaplan-Meier estimates of cumulative risk of worsening HF adverse event, readmission for HF or death through 90 days post randomization by treatment and baseline congestion score. A, all patients (n = 100); B, patients with IL-6 > 13 pg/mL at baseline (n = 65).

points in the prednisone arm (corresponding to severity 0−1 in 1 of the components of the score and 0 in the 2 others). In patients with significant congestion at baseline (congestion score ≥ 7 points), at day 31 there was also a reduction in heart rate and strong trends toward a reduction in respiratory rate and improvement in oxygen saturation in the prednisone-treated patients as compared to those who received usual care. The impact of the steroids on QoL was more pronounced in patients with more congestion at baseline. In agreement with our previous

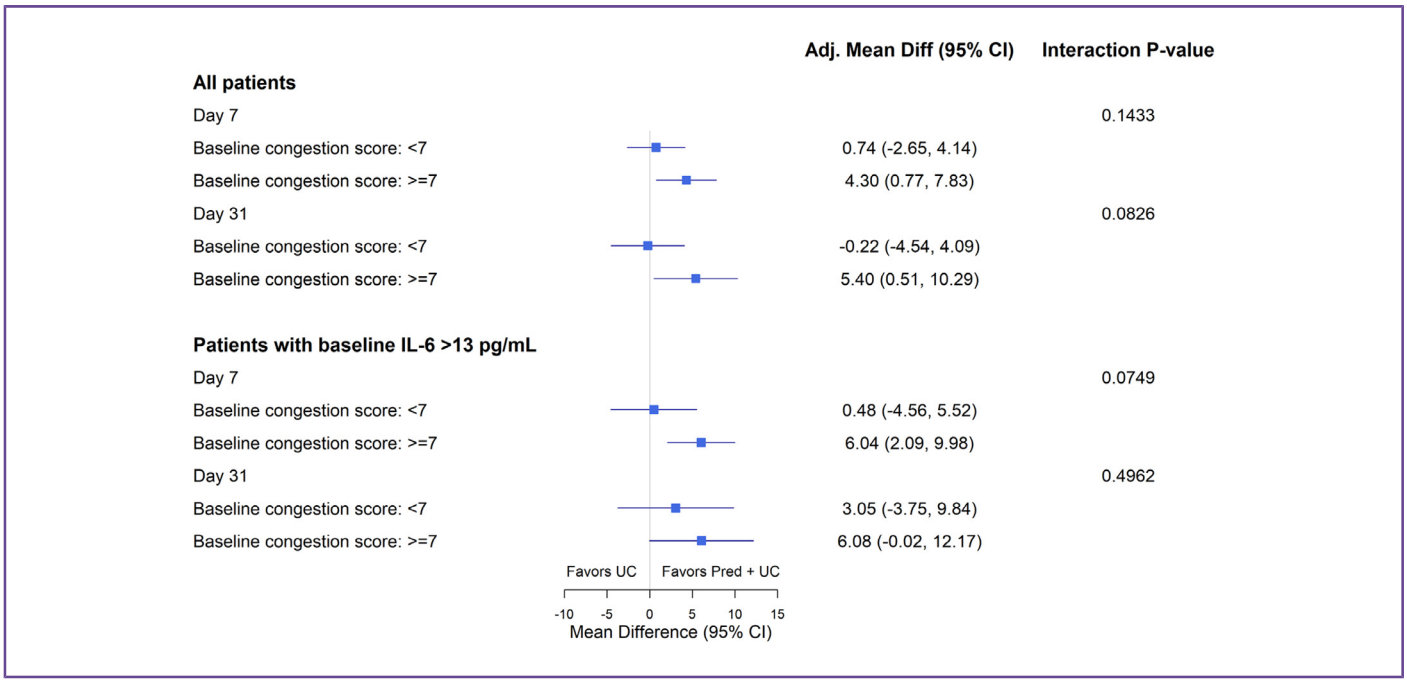

Fig. 4. Effects of prednisone therapy on changes in EQ-VAS from baseline to days 7 and 31 in patients with baseline congestion scores < 7 and ≥ 7, including all patients and those with baseline IL-6 > 13 pg/mL.

report, patients in both study arms, who were treated with high dosages of GDMT on top of diuretics, had substantial reductions in congestion by day 31.[22] Importantly, however, these effects were greater in patients receiving prednisone, and especially in those who were more congested at baseline, with almost a lack of symptoms and signs of congestion at day 31. Of note, in patients who presented with higher pro-inflammatory activation (as evidenced by both hsCRP > 20 mg/L and IL-6 > 13 pg/mL at screening), an improvement in markers of congestion was more pronounced, which may support the hypothesis of inflammation as an important mechanism underlying the development of congestion in HF (with subsequent clinical consequences), and they represent a potential target for anti-inflammatory therapies.

Multiple congestion scores have been used in clinical studies, many of which have used, interchangeably, edema (and adding to it, sometimes, pleural effusion and ascites), orthopnea, rales, and JVP.[23-25] We believe, based on previous publications, that the use of JVP is not advisable, because the reliability of assessing JVP in clinical practice is low.[26] Therefore, in the current analysis, we have opted to use a 3- rather than a 4-component congestion score, excluding JVP. This congestion score was associated with worst QoL at baseline and numerically more events of WHF, HF readmission or death during follow-up.

Low-grade systemic inflammation, including multiple inflammatory pathways and biomarkers, characterizes HF and has been postulated as a relevant pathophysiological mechanism involved in the development and progression of this clinical syndrome.[1,4,12,27-33] Pro-inflammatory drive is particularly activated in the setting of AHF, but no large prospective studies with anti-inflammatory therapies have been conducted in these patients, which explains why the causal relationship remains unknown.[14] A few small studies have, however, suggested potential benefits. Van Tassel et al. demonstrated that patients with AHF treated with anakinra, an IL-1 receptor antagonist, showed reduced hsCRP, improvement in peak VO_2 at 12 weeks and a trend toward reduced death or rehospitalization due to HF at 24 weeks.[34] Additionally, steroid therapy was found to improve diuresis and weight loss and to improve glomerular filtration rate in another small, single-arm observational study in patients with decompensated HF and with diuretic resistance.[16] In a separate randomized study of 102 patients with AHF, the glucocorticoid group showed improvement in creatinine levels at day 7 and a reduction in 30-day cardiovascular death rates (3 patients in the steroid arm vs 10 in control).[15] Finally, the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) demonstrated that in patients with previous myocardial infarction, elevated hsCRP, with or without established HF therapy with canakinumab (an interleukin-1β inhibitor) reduced the risk of HF hospitalization (most of which are clinically driven by congestion).[35] Interestingly, on examining the association between changes in IL-6 and congestion scores, one observed that a greater IL-6 drop at day 7 in the prednisone arm was associated with less decongestion, suggesting that to some degree during prednisone treatment, effects on decongestion are limited. However, at day 31, larger reductions in IL-6 levels were associated with more decongestion in the

usual-care arm but not in the prednisone arm, suggesting that prednisone therapy has prevented the longer-term effects of inflammation on congestion beyond the administration period.

The current study's results are interesting from several perspectives. Apart from diuretics, the usual care in the study followed the rapid up-titration of GDMT proposed in the STRONG-HF (Safety, Tolerability and Efficacy of Up-titration of Guideline-Directed Medical Therapies for Acute Heart Failure) protocol and, in addition, the initiation of SGLT2 inhibitors. Thus, both arms experienced significant improvement in congestion, which is in line with previous reports.[22,36,37] However, congestion was significantly improved further by steroids therapy. There are 3 potential mechanisms that may explain the distinctive pattern of changes in the markers of congestion observed in the study.

First, as suggested by previous studies,[15,16,38] steroid therapy may lead to improved diuresis. However, the reduction in weight observed in the current study (0.5 kg in the overall population and 1 kg in those with IL-6 > 13 pg/mL, both not statistically significant) cannot, by itself, explain the significant effects seen in the current study on QoL and worsening HF events, because similar reductions in weight have been seen in previous studies assessing enhanced diuretic therapy in AHF, where no improvements in either QoL or outcomes were observed.[24,39,40] Second, the effects of steroids may be related to their effects on interstitial fluid drainage and vascular function/permeability. Previous studies have suggested that steroid administration may improve lung-water clearance (thus decreasing extravascular lung water), reduce hypoxia-induced pulmonary vascular constriction as well as modulate pulmonary vasculature reaction to various vasoconstrictive mediators, which is crucial for pulmonary decongestion.[41-43] Third, anti-inflammatory therapy may further reduce noeurhormonal activation. The results of the current study are similar to those of the STRONG-HF study, where rapid up-titration of neurohormonal blockers in patients immediately after an AHF admission was associated with both better decongestion and improved QoL and outcomes.[22] Equally, the initiation of the SGLT-2 inhibitor empagliflozin in the EMPULSE trial (EMPagliflozin in patients hospitalised with acUte heart failure) resulted in both decongestion and improvements in patient-reported well-being.[44-46] Targeting additionally inflammatory pathways (in unspecific ways) may have augmented these effects due to potential cross-talk between inflammation and neuroendocrine activation. On 1 hand, neurohormonal blockers may improve inflammation.[47] But the inverse has not been shown to affect patients with HF. Although data exist showing that steroids reduce plasma renin activity, aldosterone and norepinephrine levels, none of these studies were conducted in patients with HF.[48-50] In the current study, trends were observed toward greater decreases in measures of neurohormonal activation at day 31, especially plasma renin concentrations and neutral endopeptidase levels, extending the data from non-HF studies to patients with HF.[18,31] These data suggest that potentially anti-inflammatory therapy may augment reductions in neurohormonal activation, leading to further reductions in congestion.

It is important to note that the decongestive effects seen in this study at day 31 are of the same level of magnitude and even greater than those seen in previous studies, such as STRONG-HF, diuretic studies and studies implementing SGLT2 inhibitors in AHF[22,36,37,40,44-46] (despite the use of slightly different congestion scores in each study). Indeed, at day 31 in the current study, in patients treated with GDMT and prednisone, the average congestion score was 0.6, meaning that the majority of patients had either no signs or 1 sign or symptom of congestion and even at a level of 0−1 on a scale of 3. This finding was observed despite the fact that at baseline, most patients had severity levels of 2−3 out of 3 for all symptoms and signs of congestion. This very significant extinction of congestion is the largest observed in recent clinical studies. Of note, the severity of congestion observed in the present study in the usual-care arm, who were fully treated with SGLT2 inhibitors, is similar to that observed in the active arm in the EMPULSE study, suggesting that the decongestion induced by prednisone was, indeed, additive to that induced by GDMT plus SGLT2 inhibitors. Given all these results, we may speculate that treatment with prednisone on top of high levels of GDMT opens the door to a new era of AHF treatment. In this approach, patients with significant pro-inflammatory activation during an AHF event would be treated with both high dosages of GDMT and anti-inflammatory therapy to experience substantial drops in both inflammation and neurohormonal activation, leading to fast, almost complete decongestion and dramatic improvements in QoL and reduction in worsening HF events.

Limitations

This was a small, open-label study of 100 patients, and statistical comparisons were not adjusted for multiple comparisons. Thus, the results may represent chance findings. Some patients may have been misclassified due to interobserver variability in investigator-assessed signs and symptoms of congestion. Although in the study, oral 40 mg prednisone was used as an anti-inflammatory agent, it is very likely that it is not the best drug, with the optimal dosage to dampen the inflammation in AHF. Moreover, in the manuscript, we generalize in the context of the anti-inflammatory activity of steroids, but it is very probable that differing classes of agents may provide slightly different biological effects. However, despite positive signals of benefit, steroids should not be administered to patients with AHF until these results are confirmed in larger prospective randomized studies.

Conclusions

In this small open-label randomized study of patients with AHF and high hsCRP levels, a 7-day burst of steroid administration was associated with improved symptoms and signs of congestion up to day 31 and improved measures of QoL and 90-day WHF event rates. The mechanism of this effect may relate to enhanced diuresis, direct effects of steroids on fluid clearance in the lungs and vascular function, or cross-talk between the inflammatory and neurohormonal systems in AHF. These data are based on a small pilot study, so patients should not be treated with steroids during AHF admissions. Those potential mechanisms should be explored in larger prospective studies.

Lay summary

In the CORTAHF study, we assessed the effects of a short course of steroids (prednisone) in 100 patients with acute heart failure and inflammatory activation as measured by CRP > 20 mg/L. Patients had significant congestion at baseline (congestion score of 6.5 out of 9). Patients randomized to prednisone 40 mg a day for 7 days had more reduction of congestion at day 30, led by reduction in rales and edema, which led to improved measures of quality of life.

JAN BIEGUS

CRediT authorship contribution statement

JAN BIEGUS: Project administration. **GAD COTTER:** Writing – review & editing, Project administration. **BETH A. DAVISON:** Writing – review & editing, Project administration. **YONATHAN FREUND:** Project administration. **ADRIAAN A. VOORS:** Project administration. **CHRISTOPHER EDWARDS:** Formal analysis, Data curation. **MARIA NOVOSADOVA:** Project administration. **KOJI TAKAGI:** Data curation. **Hamlet HAYRAPETYAN:** Project administration. **ANDRANIK MSHETSYAN:** Project administration. **DRAMBYAN MAYRANUSH:** Project administration. **ALAIN COHEN-SOLAL:** Project administration. **JOZINE M. TER MAATEN:** Project administration. **GERASIMOS FILIPPATOS:** Project administration. **OVIDIU CHIONCEL:** Project administration. **MALHA SADOUNE:** Data curation. **MATTEO PAGNESI:** Project administration. **TABASSOME SIMON:** Project administration. **MARCO METRA:** Project administration. **DOUGLAS L. MANN:** Project administration. **ALEXANDRE MEBAZAA:** Project administration. **PIOTR PONIKOWSKI:** Project administration.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2024.09.002.

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