ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 2282–2292
doi:10.1002/ejhf.3452

RESEARCH ARTICLE

Burst steroid therapy for acute heart failure: The CORTAHF randomized, open-label, pilot trial

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Received 26 July 2024; revised 17 August 2024; accepted 22 August 2024; online publish-ahead-of-print 30 August 2024

Aims Burst steroid therapy, effective in acute respiratory diseases, may benefit patients with acute heart failure (AHF) in whom inflammatory activation is associated with adverse outcomes.

Methods and results CORTAHF assessed whether burst steroid therapy reduces inflammation and results in better quality of life and clinical outcomes in AHF. Patients with AHF, N-terminal pro-B-type natriuretic peptide >1500 pg/ml, and high-sensitivity C-reactive protein (hsCRP) >20 mg/L were randomized 1:1 to oral, once daily 40 mg prednisone for 7 days or usual care, without blinding. Patients were followed for 90 days. A total of 101 patients were randomized. At day 7 the primary endpoint, hsCRP decreased in both arms – adjusted geometric mean ratios (GMRs) were 0.30 and 0.40 in the prednisone and usual care arms (ratio of GMRs 0.75, 95% confidence interval [CI] 0.56–1.00, $p = 0.0498$). The 90-day risk of worsening heart failure (HF), HF readmission or death as reported by the unblinded investigators was significantly lower in the prednisone group (10.4%) than in usual care (30.8%) (hazard ratio 0.31, 95% CI 0.11–0.86, $p = 0.016$). The EQ-5D visual analogue scale score as reported by the unblinded patients increased more in the prednisone group on day 7 (least squares mean difference 2.57, 95% CI 0.12–5.01 points, $p = 0.040$). All effects were statistically significant in the pre-specified subgroup with centrally-measured interleukin-6 >13 pg/ml. Adverse events, particularly hyperglycaemia, occurred more in the prednisone group with no difference in infection rate.

Conclusion In this small open-label study of patients with AHF, burst steroid therapy was associated with reduced inflammation as measured by hsCRP levels at day 7 (primary endpoint). Secondary endpoints showed improved quality of life at day 7 and reduced 90-day risk of death or worsening HF. Large prospective studies are needed to evaluate these findings.

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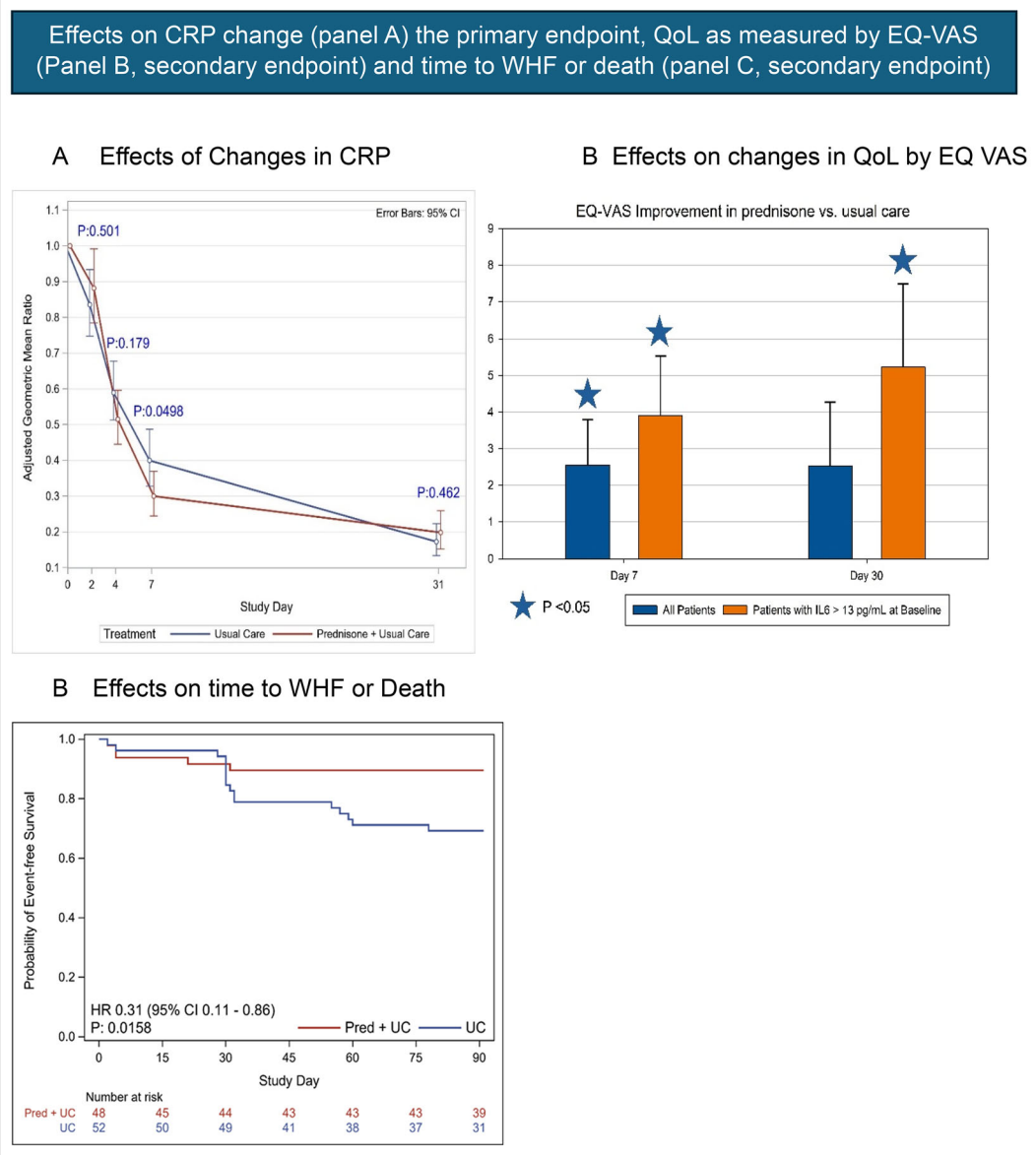
Graphical Abstract



CORTAHF: pulse prednisone (7 days 40 mg/day) therapy as compared to usual care in acute heart failure. CI, confidence interval; CRP, C-reactive protein; EQ-VAS, EuroQol visual analogue scale; IL-6, interleukin-6; QoL, quality of life; HR, hazard ratio; WHF, worsening heart failure; UC, usual care.

Keywords Acute heart failure • Quality of life • Worsening heart failure • Corticosteroids

Introduction

Inflammatory activation was shown to be associated with heart failure (HF) more than 70 years ago[1] when Elster, Braunwald and Wood found that C-reactive protein (CRP) was associated with more signs of congestion and increased mortality and recurrent HF in patients admitted for acute HF (AHF). This was followed by many studies confirming the association between inflammation and adverse outcomes in HF in general and AHF specifically.[2–6] Inflammation may worsen cardiac and vascular function, lead to fluid redistribution, capillary leakage and neurohormonal activation, and may ultimately favour end-organ damage, cardio-renal

syndrome and worse clinical outcomes.[7,8] However, no studies have been conducted in AHF targeting inflammation, especially after the neutral results of studies of tumour necrosis factor alpha blockers about 20 years ago.[9] In AHF only a few small studies were performed suggesting trends towards improved outcomes with anakinra[10] (an interleukin [IL]-1 blocker) and improved diuresis.[11,12] In a retrospective analysis, Miró *et al.*[13] found trends towards improved outcomes in patients with AHF and high-sensitivity CRP (hsCRP) given corticosteroids in the emergency department. These data led to the design of the CORTAHF (Effect of Short-Term Prednisone Therapy on CRP Change in Emergency Department Patients With Acute Heart Failure and Elevated Inflammatory Markers) trial. The trial was designed to examine the effects of a short steroid burst on inflammation as measured by high levels of hsCRP, quality of life and 90-day clinical outcomes. Prednisone was chosen to be tested due to its ready availability, and budget limitations did not allow for the use of more expensive anti-inflammatory agents such as anakinra or IL-6 blockers. The length of administration chosen was not based on previous studies, but rather the common length of steroid burst therapy in other disease states, as detailed in the design mansucript.[14]

Methods

Study design

The CORTAHF study is a multicentre, parallel-group, randomized, open-label, controlled pilot study for which the design has been previously published.[14] Briefly, patients aged 18–85 years and diagnosed with AHF through an unplanned presentation to one of three hospitals were enrolled. The study was approved by the Ethics Committee of Ministry of Health of the Republic of Armenia, the ethics committee of Yerevan State Medical University, and the Local Ethics Committee of 'Erebouni' Medical Center.

Patients

Patients who were hospitalized for AHF were eligible. The main inclusion criteria were objective signs of congestion (by chest-X-ray or lung ultrasound), a systolic blood pressure ≥100 mmHg and heart rate ≥60 bpm, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) >1500 pg/ml and hsCRP>20 mg/L at screening. Patients whose AHF was triggered by a correctable aetiology including significant arrhythmia, severe anaemia, acute coronary syndrome, chronic obstructive pulmonary disease exacerbation, or infection were not eligible to participate. Eligible patients gave written, informed consent to participate.

Procedures

Patients were randomized 1:1 within site to prednisone 40 mg orally once daily for 7 days plus usual care or to usual care alone. Study procedures are further detailed in the online supplementary.

Outcomes

The study primary endpoint was the change in hsCRP level from baseline to day 7. Secondary endpoints included the time to first event of worsening HF adverse event, hospital readmission for HF, or death through day 91; and change in quality of life as measured by the change in EuroQol 5-Dimension 5-Level (EQ-5D-5L) from day 1 to day 7. Worsening symptoms or signs of HF were reported as an adverse event by investigators. Primary cause of death and reason for rehospitalization were classified by the investigator according to a pre-determined list. A centralized monitoring team has confirmed all adverse events and readmission causes.

Safety was assessed at each study visit through day 31. In addition to assessment of signs and symptoms during physical examination, safety was assessed through local laboratory values obtained as standard of care and per protocol. The occurrence of any adverse events was elicited through non-directive questioning of the patient at each study visit and through recording of any event spontaneously reported by the patient or noted by the investigator. Safety was overseen by a medical monitor (GC).

The protocol was amended once, after 18 patients were enrolled, to specify that the main efficacy analysis be conducted in the per-protocol population, and to revise the first secondary endpoint to include events through day 91 rather than 31 and all adverse events of worsening HF rather than only those events meeting more restrictive criteria (occurring >24 h and ≤7 days after randomization and requiring intensification of HF therapy).

Statistical methods

Originally, we intended to evaluate steroid therapy in patients with IL-6 >13 pg/ml, which is the median level for AHF patients in our database, and similar to that seen in the ASCEND-HF study.[15] However, during feasibility it became evident that most sites cannot perform real-time IL-6 assessments; therefore we designed the study to enrol 120 patients with hsCRP >20 mg/L and measure IL-6 levels in a central lab at the study conclusion, estimating that about 100 patients out of the 120 patients enrolled would have IL-6 >13 pg/ml for a secondary blinded analysis (IL-6 measurements performed after last patient reached 30-day follow-up and all events were collected). For the primary endpoint, 60 patients per group were estimated to provide approximately 80% power to detect a 40% lower day 7 hsCRP value in the prednisone than in the usual care group at the two-sided 0.05 significance level based on results of a study of burst steroid therapy in patients with community-acquired pneumonia.[16] However, trial enrolment was terminated after 100 patients were enrolled due to funding concerns after three of the activated sites failed to enrol patients. Power for 50 patients per group was estimated at 80% for a 43% lower day 7 hsCRP value.

Results are presented as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables and as absolute and relative frequencies for categorical variables. The treatment effect on the 7-day change in CRP, the primary endpoint, 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. CRP was natural log transformed for analysis, and results exponentiated to express in terms of geometric mean ratios (GMRs). Analyses of other continuous repeated measures, including the changes in EuroQol visual analogue scale (EQ-VAS) and index values, employed similar MMRMs, with log transformations used for highly skewed variables. Missing responses on the EQ-5D due to death were imputed as zero. Values below the detection limit were set to half the detection limit and values above the upper reporting limit were set to that limit. For variables where undetectable baseline values were reported, an indicator for whether the baseline value was detectable or not and its interaction with visit were added to the MMRM. Subgroup analyses of the

primary and secondary efficacy outcomes by age, sex, and baseline IL-6 were pre-specified. Chi-square tests of subgroup differences were constructed from treatment effects on the primary endpoint and their associated standard errors (SE) estimated from MMRMs in each subgroup. Within-group changes in biomarkers were tested using contrasts from a MMRM of baseline and follow-up values including effects of treatment, visit and treatment × visit.

Treatment groups were compared with respect to the time to the first event of worsening HF adverse event, HF readmission or death from any cause from randomization through day 91 using a log-rank test stratified by site. Kaplan–Meier estimates of the cumulative risk are presented. The hazard ratio (HR) for prednisone versus usual care was estimated from a Cox proportional hazards model. A score test of the subgroup-by-treatment interaction on the secondary composite outcome was conducted; due to fewer secondary composite events within strata among subgroups, these analyses were not stratified by site. As there were relatively few events for some of the components of the composite secondary endpoint, incidence rate ratios (IRRs) and associated 95% confidence intervals (CI) were derived using exact Poisson regression without stratification by site.

Win odds comparing treatment groups with respect to ordinal outcomes stratified by centre and adjusted for baseline response were assessed using the method described by Kanaguchi *et al.*[17] and implemented using the R package 'sanon' where observed values within strata at each visit were compared.[18] Outcomes representing counts of days were compared between treatment groups using negative binomial regression models including effects of treatment and site.

Daily loop diuretic doses were converted to furosemide equivalent doses considering 10 mg of torsemide equal to 20 mg intravenous furosemide or 40 mg for oral furosemide. After conversion to furosemide equivalent doses, oral doses were halved to convert to intravenous equivalent.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. The safety analysis population includes all patients, including the patient excluded from the per-protocol analysis set. The incidence of adverse events is presented within treatment group by System Organ Class and Preferred Term.

SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.3[19] were used for statistical analysis. A two-sided $p < 0.05$ was considered statistically significant. Pre-specified analyses were conducted by Clean Data Labs.

The study is registered on ClinicalTrials.gov (NCT05916586).

Results

Between 11 August 2023 and 15 April 2024, 101 consecutive qualified patients were validly randomized to the study at three hospitals (online supplementary *Figure S1*). One patient randomized in error was immediately identified as a screen failure and was excluded from further trial participation. One patient randomized to the prednisone group (who received one prednisone dose) and found to have been enrolled with signs of acute myocardial infarction in violation of protocol eligibility criteria was discontinued from prednisone therapy and excluded from the per-protocol analyses. Baseline characteristics are given in *Table 1*.

Primary and secondary endpoints

The unadjusted median (IQR) hsCRP value at day 7 was 8.06 (5.34–16.77) and 12.69 (8.79–23.74) mg/L in the prednisone and usual care groups, respectively. Patients in the prednisone arm had a greater decrease in hsCRP from baseline to day 7 (the primary endpoint), than in the usual care group, with adjusted GMRs (ratio of follow-up to baseline) of 0.30 (SE 1.11) versus 0.40 (SE 1.10) (adjusted ratio of GMRs 0.75, 95% CI 0.56–1.00, $p = 0.0498$) (*Figure 1A*). By day 31, hsCRP levels substantially decreased in both treatment groups, with no significant difference between the two treatment arms. Changes in IL-6 followed the same pattern (*Figure 1B*) as did changes in white blood cells (WBC) and lymphocyte percentage in the WBC differential (online supplementary *Table S1*).

Patients assigned prednisone reported a greater increase in quality of life, measured by the EQ-VAS, to day 7 (31.9 [0.95] points in the steroid arm and 29.3 [0.90] in the usual care arm [least squares mean difference 2.57, 95% CI 0.12–5.01, $p = 0.040$]; *Table 2*). Effects at day 31 and excluding imputation for death are presented in *Table 2*.

The risk of the secondary composite endpoint was lower in the prednisone (10.4%) than in the usual care group (30.8%), with a HR for worsening HF, HF readmission or death through day 91 of 0.31 (95% CI 0.11–0.86, $p = 0.016$; *Figure 2A*). The components of the endpoint included worsening HF adverse event (5 patients [10.4%] vs. 13 patients [25.0%]; IRR 0.38, 95% CI 0.11–1.14) and HF readmission (0 patients [0.0%] vs. 7 patients [13.5%]; IRR 0.11, 95% CI 0.00–0.56). One patient died in the prednisone group versus none in usual care. The combined endpoint of HF readmission or death occurred in 2.1% versus 13.5% of patients (IRR 0.15, 95% CI 0.00–1.17).

Interleukin-6 levels were measured blindly after the study enrolment was completed. In a pre-specified subgroup of patients with IL-6 levels >13 pg/ml at baseline ($n = 65$), statistically significant effects of prednisone therapy were observed on both the primary endpoint (online supplementary *Figure S2*), and the combined secondary endpoints (*Figure 2B* and *Table 2*).

Subgroup analyses of the primary and two secondary endpoints are presented in online supplementary *Figure S2*. There were no significant interactions between baseline characteristics and treatment effects.

Laboratory assessments, congestion, vital signs, length of stay, and medications

Investigators measured laboratory assessments are presented in online supplementary *Table S1*. Signs of congestion tended to improve more in the steroid group than in the usual care group (online supplementary *Table S2*). There was a significantly greater improvement in rales on day 31 (win odds 1.53, 95% CI 1.15–2.07, $p = 0.0032$) and trends towards better improvements in rales on day 7 and orthopnoea and oedema on day 31. Weight numerically decreased throughout the study period in both groups, but slightly larger decreases in the prednisone group did not reach statistical significance (online supplementary *Table S2*). The doses of diuretics prescribed to patients during the study tended to be lower in the prednisone arm at day 31 (least squares mean difference in daily intravenous furosemide equivalent dose −7.28 mg, 95%

Table 1 Baseline characteristics of patients enrolled in CORTAHF

	Prednisone + usual care ($n = 48$)	Usual care ($n = 52$)	Total ($n = 100$)
Demographics			
Age, years	66.1 (10.01)	66.8 (7.42)	66.5 (8.72)
Sex at birth, *n* (%)			
Male	31 (64.6)	32 (61.5)	63 (63.0)
Female	17 (35.4)	20 (38.5)	37 (37.0)
Vital signs			
Weight, kg	87.5 (17.50)	91.7 (18.82)	89.7 (18.23)
BMI, kg/m^2	30.6 (5.54)	31.5 (5.59)	31.1 (5.55)
Systolic blood pressure, mmHg	140.6 (34.39)	141.9 (24.18)	141.3 (29.37)
Oxygen saturation, %	81.9 (7.88)	83.0 (8.02)	82.5 (7.93)
Medical history, *n* (%)			
Diabetes	19 (39.6)	22 (42.3)	41 (41.0)
Hypertension	38 (79.2)	48 (92.3)	86 (86.0)
Hypercholesterolaemia	39 (81.3)	43 (82.7)	82 (82.0)
Malignancy	0	0	0
Chronic lung disease	6 (12.5)	3 (5.8)	9 (9.0)
Renal disease/history of dialysis	1 (2.1)	0	1 (1.0)
Ischaemic heart disease	41 (85.4)	47 (90.4)	88 (88.0)
Myocardial infarction	35 (72.9)	40 (76.9)	75 (75.0)
Stroke			
CVA	1 (2.1)	2 (3.8)	3 (3.0)
TIA	2 (4.2)	1 (1.9)	3 (3.0)
Valvular disease	20 (41.7)	26 (50.0)	46 (46.0)
Severe mitral regurgitation	0	0	0
Moderate mitral regurgitation	19 (39.6)	25 (48.1)	44 (44.0)
Severe tricuspid regurgitation	0	0	0
Moderate tricuspid regurgitation	14 (29.2)	19 (36.5)	33 (33.0)
Severe aortic stenosis	0	0	0
Moderate aortic stenosis	1 (2.1)	1 (1.9)	2 (2.0)
Moderate or severe mitral stenosis	0	0	0
Moderate or severe tricuspid stenosis	0	0	0
Atrial fibrillation	12 (25.0)	14 (26.9)	26 (26.0)
Sustained ventricular tachycardia or ventricular fibrillation	0	0	0
ICD/CRT implant	2 (4.2)	1 (1.9)	3 (3.0)
HF history			
NYHA class prior to screening			
I	0	0	0
II	9 (18.8)	7 (13.5)	16 (16.0)
III	35 (72.9)	38 (73.1)	73 (73.0)
IV	4 (8.3)	7 (13.5)	11 (11.0)
Most recent LVEF, %	28.9 (8.88)	28.3 (8.63)	28.6 (8.71)
Laboratory findings			
Sodium, mmol/L	142.0 (3.31)	140.8 (3.25)	141.4 (3.32)
Potassium, mmol/L	4.5 (0.54)	4.2 (0.57)	4.3 (0.57)
Glucose, mmol/L	7.3 (2.61)	8.0 (3.53)	7.6 (3.13)
AST, U/L	23.7 (12.17)	24.3 (16.01)	24.0 (14.23)
ALT, U/L	25.9 (19.11)	28.8 (35.15)	27.4 (28.49)
Total bilirubin, μmol/L	13.3 (7.38)	13.8 (6.75)	13.5 (7.03)
Haemoglobin, g/L	136.6 (19.95)	135.5 (20.01)	136.0 (19.89)
Urea/BUN, mmol/L	8.6 (2.55)	8.3 (2.53)	8.4 (2.53)
Creatinine, μmol/L	110.1 (20.29)	103.4 (20.31)	106.6 (20.48)
eGFR, ml/min/1.73 m^2	58.7 (13.12)	62.2 (11.30)	60.6 (12.27)
Troponin T, ng/ml	0.036 [0.026–0.042]	0.034 [0.022–0.048]	0.035 [0.023–0.047]
Troponin I, ng/ml	0.020 [0.013–0.030]	0.022 [0.014–0.032]	0.021 [0.014–0.030]
hsCRP, mg/L	28.7 [24.5–37.5]	32.3 [27.5–43.0]	29.9 [25.8–41.3]
WBC, 10^9/L	9.1 (3.15)	9.0 (2.59)	9.1 (2.86)
Lymphocytes, %	22.2 (8.13)	19.6 (9.62)	20.8 (9.00)

Table 1 (Continued)

	Prednisone + usual care ($n = 48$)	Usual care ($n = 52$)	Total ($n = 100$)
NT-proBNP, pg/ml	4275.5 [2161.0–8987.0]	4528.0 [2829.5–7725.0]	4335.5 [2530.0–8343.0]
IL-6, pg/ml	20.8 [12.9–30.7]	16.5 [7.9–27.2]	18.5 [9.7–28.9]
IL-17, pg/ml	0.86 [0.40–1.86]	0.68 [0.31–1.41]	0.78 [0.35–1.59]
PRC, pg/ml	2.0 [2.0–24.2]	2.0 [2.0–12.3]	2.0 [2.0–15.8]
NEP activity, nmol/μl/min	0.30 [0.16–0.62]	0.40 [0.15–0.72]	0.32 [0.15–0.71]
Concomitant medications at study inclusion, *n* (%)			
ACEI, ARB, or ARNI	31 (63.3)	37 (71.2)	68 (67.3)
Beta-blocker	31 (63.3)	30 (57.7)	61 (60.4)
Diuretic	31 (63.3)	32 (61.5)	63 (62.4)
Thiazide diuretic	9 (18.4)	5 (9.6)	14 (13.9)
SGLT2 inhibitor	9 (18.4)	6 (11.5)	15 (14.9)
Nitrates	0	1 (1.9)	1 (1.0)
Calcium channel blocker	12 (24.5)	19 (36.5)	31 (30.7)
Digoxin	5 (10.2)	5 (9.6)	10 (9.9)
Antiplatelet	34 (69.4)	37 (71.2)	71 (70.3)

Values are given as mean (standard deviation), or median [interquartile range], unless otherwise specified.
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; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IL, interleukin; 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; SGLT2, sodium–glucose cotransporter 2; TIA, transient ischaemic attack; WBC, white blood cell.

CI −14.7 to 0.11, $p = 0.053$). Investigator-measured NT-proBNP concentrations were approximately 20% of the baseline value at day 31, without significant differences between treatment arms (online supplementary *Table S2*).

Vital sign measures are presented in online supplementary *Figure S3*.

There were no differences between the treatment groups regarding days in intensive care, days in hospital, days dead or in acute care, or days dead or in hospital through 30 days post-randomization (online supplementary *Table S3*).

All patients assigned to the prednisone group, other than the patient who violated eligibility criteria and received one 40 mg dose, received 40 mg per day for 7 days. Medications administered from prior to randomization to day 31 are presented in online supplementary *Table S4* and *Figure S4*. Administration of guideline-directed medical therapies (GDMT) increased substantially during the study in both treatment groups.

Safety and adverse events

The incidence of adverse events and serious adverse events through day 31 are presented in online supplementary *Tables S5* and *S6*. Notably, there were more adverse events in the prednisone arm driven by an increase in hyperglycaemia. No hyperglycaemia adverse events were severe, some were moderate (four and two patients in the prednisone and usual care groups, respectively), and most were mild (13 and 0 patients in the prednisone and usual care groups, respectively); glucose levels were not different at day 31 between the prednisone and usual care arms (online supplementary *Table S1*). One patient in the prednisone group and none in the usual care group died (from HF). This led to a report of one serious adverse event in the prednisone arm. A further adverse event of myocardial infarction in the prednisone arm occurred before randomization, was immediately identified as a major protocol deviation and is reported here due to the regulatory requirements to report serious adverse events in the treated population. There were no other severe adverse events in the prednisone-treated patients. Notably, there was no difference in the occurrence of infections between the two treatment arms.

Central laboratory analyses

Plasma renin concentration (PRC), measured by the central laboratory, was undetectable (<4 pg/ml) at baseline in 57.4% of patients. PRC increased significantly within the usual care group ($p = 0.026$) by day 7 but not in the prednisone-treated patients. At day 31, in prednisone-treated patients, PRC decreased below baseline levels ($p = 0.072$), but did not differ from baseline in the usual care arm. The between-group differences were not statistically significant (online supplementary *Figure S5A*).

Neutral endopeptidase (NEP), which was undetectable at baseline in three patients, followed a pattern similar to PRC with a numerically large increase in the usual care arm at day 4 and a numerically large decrease in the prednisone group at day 31 (online supplementary *Figure S5B*).

Discussion

The results of the current small study suggest that a short 'burst' course of steroid therapy in patients with AHF and elevated markers of inflammation leads to suppression of hsCRP during

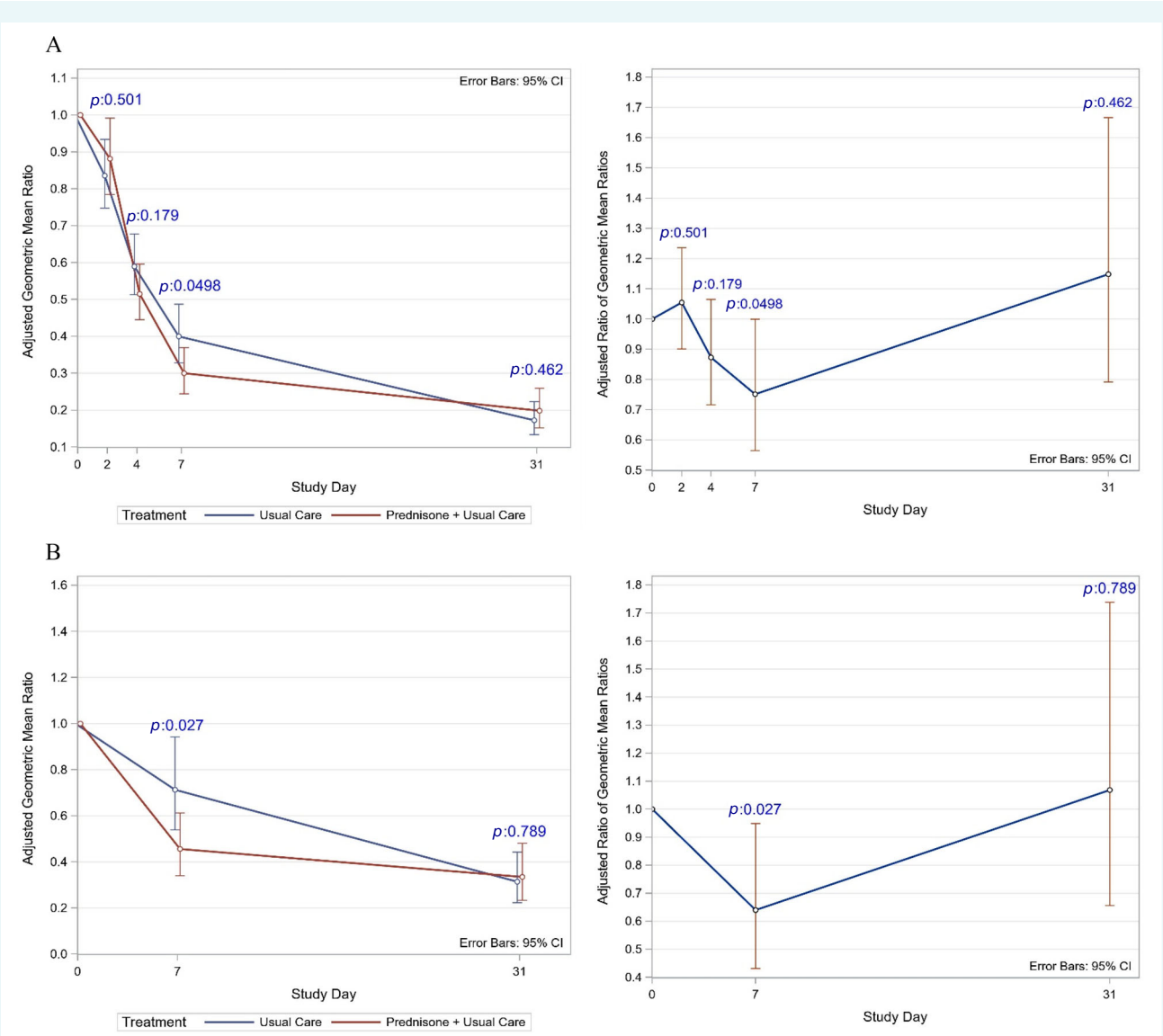


Figure 1 Primary endpoint: changes from baseline by treatment group, and treatment effect on those changes, for inflammatory markers: (*A*) high-sensitivity C-reactive protein, (*B*) interleukin-6. High-sensitivity C-reactive protein and interleukin-6 values were log-transformed for analysis. Values are geometric mean ratios (follow-up to baseline), and adjusted ratio of geometric mean ratios, with error bars representing 95% confidence intervals (CI) estimated from mixed model for repeated measures including the effects of site, baseline, treatment, visit, baseline × visit, treatment × visit.

the period of steroid administration (first 7 days of admission). In addition, in this open-label study, the short course of steroid therapy resulted in greater improvement in health-related quality of life (at day 7) and a significantly reduced risk of a worsening HF event through day 91 (*Graphical Abstract*).

Inflammation has been suggested to play a significant role in the pathogenesis of HF in general and AHF in particular by virtue of the deleterious effects that inflammatory mediators exert on the heart and circulation. Systemic inflammation is highly activated in AHF including multiple inflammatory pathways and biomarkers. This pro-inflammatory activation may have a role in the pathophysiology of the disease and may mediate some of the effects of HF on cardiac, vascular, renal, and gut dysfunction that underlie the AHF process and amplify it.[7,8,20–22]

In accordance with these previous data, in the current study we have noted changes in inflammatory markers during the steroid administration, including significant decreases of hsCRP and IL-6, an increase in leucocytes and a decrease in lymphocyte percentage. In CORTAHF, short-term administration of prednisone was associated with a significant increase in urea and a less pronounced decrease in estimated glomerular filtration rate during the first days of admission. At the same time, there were trends towards decreased loop diuretic doses, a reduction in rales, and significant improvement in quality of life as measured by the EQ-VAS. This

Table 2 Secondary endpoint: changes in EuroQol visual analogue scale over visits by treatment group in all patients in the per-protocol population and in those with baseline interleukin-6 >13 pg/ml

Treatment group	Baseline	Day 7	Day 31
EQ-VAS in all patients, points[a]			
Prednisone + usual care			
Mean (SD)	36.0 (11.86)	66.0 (10.66)	73.9 (15.07)
Mean change (SD)	N/A	29.9 (9.36)	37.9 (14.15)
Adj. mean change from baseline (SE)	N/A	31.86 (0.95)	39.78 (1.68)
Usual care			
Mean (SD)	36.9 (10.20)	64.4 (9.91)	73.6 (11.21)
Mean change (SD)	N/A	27.5 (7.11)	37.0 (8.97)
Adj. mean change from baseline (SE)	N/A	29.29 (0.90)	38.76 (1.62)
Adj. mean difference with imputation for death (95% CI)	N/A	2.57 (0.12, 5.01)	1.02 (−3.53, 5.58)
p-value	N/A	0.0398	0.6569
Adj. mean difference without imputation for death (95% CI)	N/A	2.56 (0.12, 5.01)	2.54 (−0.90, 5.99)
p-value	N/A	0.0402	0.1455
EQ-VAS in patients with IL-6 >13 pg/ml, points[a]			
Prednisone + usual care			
Mean (SD)	34.8 (8.51)	65.7 (9.57)	73.3 (15.90)
Mean change (SD)	N/A	30.9 (8.78)	38.5 (14.59)
Adj. mean change from baseline (SE)	N/A	32.90 (1.21)	40.59 (2.23)
Usual care			
Mean (SD)	36.0 (8.90)	63.3 (9.38)	71.1 (10.75)
Mean change (SD)	N/A	27.2 (7.14)	35.7 (9.00)
Adj. mean change from baseline (SE)	N/A	28.96 (1.31)	37.33 (2.50)
Adj. mean difference with imputation for death (95% CI)	N/A	3.94 (0.73−7.15)	3.26 (−3.25, 9.78)
p-value	N/A	0.0169	0.3205
Adj. mean difference without imputation for death (95% CI)	N/A	3.92 (0.70, 7.13)	5.23 (0.70, 9.76)
p-value	N/A	0.0177	0.0243

CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; IL-6, interleukin-6; MMRM, mixed model for repeated measures; N/A, not available; SD, standard deviation; SE, standard error.
[a]Presented are unadjusted mean (SD) at baseline and follow-up and the adjusted mean change from baseline to each visit within treatment group. Unadjusted and adjusted means include one death in the prednisone group whose missing EQ-VAS at day 31 was assigned a value of 0. The treatment effect is the mean difference between treatment groups estimated from a MMRM including effects for site, baseline, treatment, visit, baseline × visit, and treatment × visit.

would suggest that steroid therapy may have led to a shift in fluid from the intravascular space to other compartments, reducing congestion and making patients feel better to the point that physicians reduced their loop diuretic doses. After prednisone was discontinued, although inflammation was equally reduced in both arms at day 31, we observed progressive improvement in congestion measures (especially rales and peripheral oedema), and continuous decrease in worsening HF events in patients who were treated with prednisone. These findings suggest that the reduction in inflammatory activation during the first few days of admission, when inflammation was still highly activated, may have had longer-term effects leading to reduced congestion, reduced diuretic needs, and reduction in HF events. These results remained significant in patients with IL6 >13 pg/ml assessed in a blinded manner after enrolment was completed.

The exact mechanism by which steroid administration may improve congestion, quality of life, and longer-term outcomes during and after an AHF admission is not clear. Previous studies have suggested that steroid administration may improve lung water clearance[23] and reduce hypoxia-induced pulmonary vascular constriction.[24] Although no evidence exists for such effects to persist beyond the period of steroid administration, it is possible that some of these effects persist, and may explain the more significant effect seen on pulmonary rales.

The potential 'cross-talk' between the neurohormonal and inflammatory systems in AHF was only assessed previously in one direction – i.e. the effects of neurohormonal blockers on inflammation, showing that neurohormonal blockade reduces markers of inflammation in patients with HF.[21] This finding may have extended to this study too – given that in the current study GDMT was quickly up-titrated in both study arms with over 85% of patients receiving each of the four GDMT pillars at day 31. We have seen very substantial reductions in inflammatory activation as measured by both hsCRP and IL-6, in both arms and it is possible that the very significant drop in inflammatory markers at day 31 was partially caused by these rapid GDMT up-titration. However, the opposite direction, i.e. effects of the inflammatory blockade on neurohormonal activation in chronic and acute HF were to the best of our knowledge never assessed. Older studies have documented that steroid administration leads to a reduction in plasma renin activity,

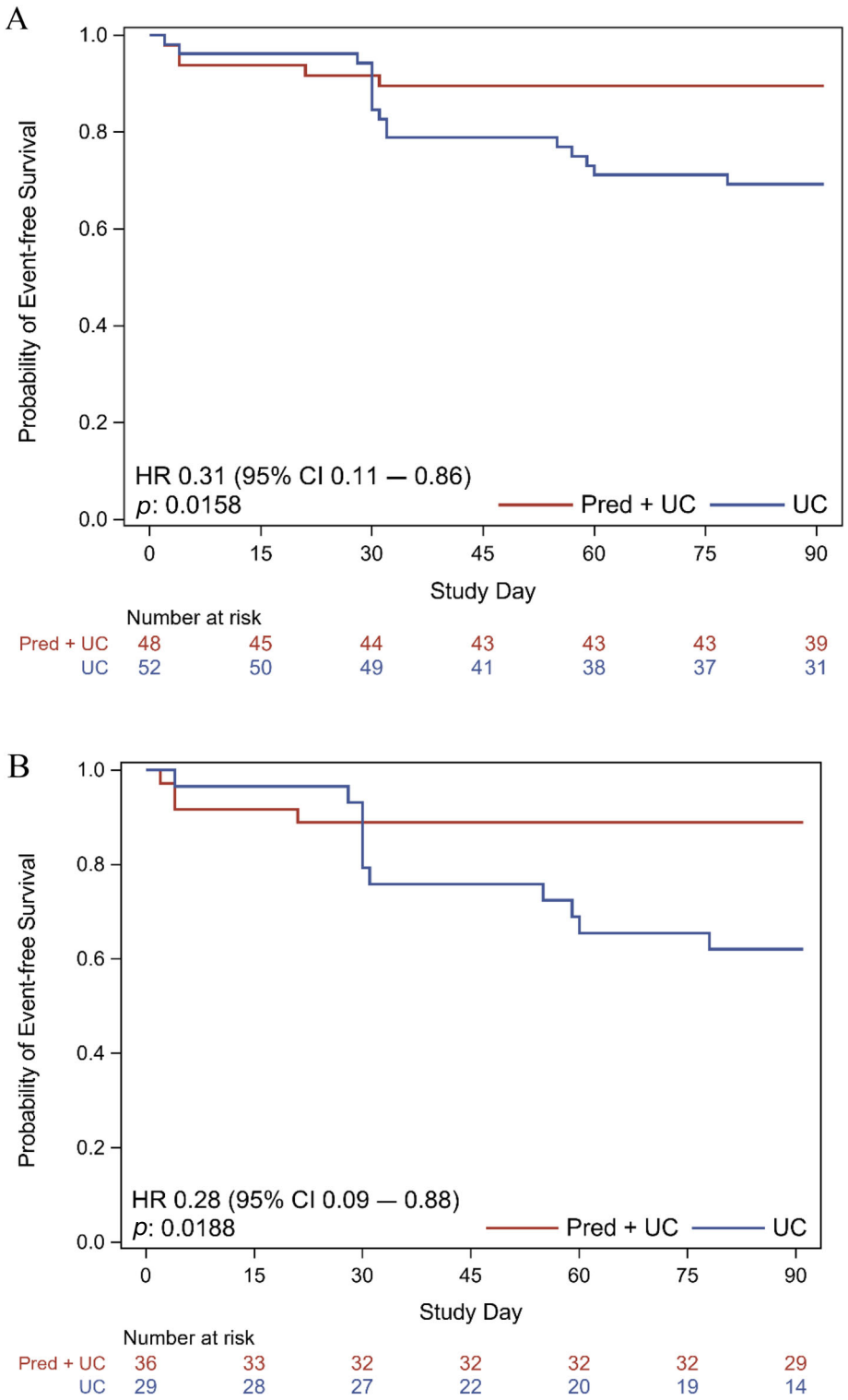


Figure 2 Secondary endpoint: Kaplan–Meier estimates of cumulative risk of worsening heart failure adverse event, or readmission for heart failure or death through 90 days post randomization. Curves presented are unadjusted. Hazard ratios (HR) and 95% confidence intervals (CI) from a Cox proportional hazards model stratified by site. *P*-values from log-rank test stratified by site. (*A*) All patients ($n = 100$); (*B*) patients with interleukin-6 >13 pg/ml at baseline ($n = 65$). UC, usual care.

aldosterone, and norepinephrine levels,[25–27] however, those studies were not conducted in patients with HF. In the present study, after the conclusion of enrolment, we measured in a central laboratory, blindly, levels of PRC, and NEP. We observed during the first days of the study a strong trend towards increases in both PRC and NEP in the usual care arm, but no significant increases in the prednisone treatment arm, while at day 31 return to randomization levels in the usual care arm, but a trend towards a 20–30% reduction in these biomarkers in the prednisone arm. Of note, the numeric reductions in PRC and NEP at day 30 in the prednisone arm are similar to those induced by beta-blockers[28] (PRC) and angiotensin receptor–neprilysin inhibitor[29] (NEP) in previous studies.

In recent years, studies have been published suggesting that burst steroid therapy may have a beneficial effect in improving recovery and outcomes in a plethora of acute diseases, such as chronic obstructive pulmonary disease,[30] septic shock[31] and pneumonia,[32] to name a few. The results of the current study add to this body of literature suggesting that anti-inflammatory therapy may be beneficial also in AHF.

Finally, it should be noted that the safety assessments in the study have detected no excess of either fluid accumulation events or infections during and shortly after the prednisone burst course. There was an increase in milder adverse events, notably hyperglycaemia, but those were transitory and controlled by therapy. This mild increase in adverse events is reassuring and in line with data from other studies where burst steroid therapy was administered in acute patients.[30–32]

Limitations

This was a small pilot study with 100 randomized patients, and the overall number of events was also relatively small. As such, the results of the present study should be regarded as provisional. One cannot conclude that steroid therapy is clearly effective in AHF, nor should steroids be administered to patients with AHF until larger prospective randomized studies are conducted. The assessments were reported by the investigators who were not blinded to therapy and this could be an important source of bias. The results are further limited by the lack of power to detect effects on clinical events, and the non-centralized measurement of the primary endpoint, hsCRP, and classification of clinical events.

Conclusions

In this small open-label randomized study of patients with AHF and high hsCRP levels, a 7-day burst steroid administration was associated with reduced inflammatory activation during the steroid administration, improved quality of life, and reduced 90-day risk of worsening HF or HF readmission. Further studies are needed to evaluate these potential effects.

Acknowledgements

We thank Dr. Gary Koch for his advice regarding statistical analysis.

Supplementary Information

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

Funding

Sponsored by Heart Initiative (Durham, NC, USA). Biomarker assays provided by the Heart Initiative; Université Paris Cité, INSERM UMR-S 942 (MASCOT), France; and University of Groningen, Department of Cardiology, University Medical Centre Groningen, The Netherlands.

Conflict of interest: 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 Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. 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, SalubrisBio. HH has nothing to declare. D.M. is on the scientific advisory board of Tenaya therapeutics, HAYA Therapeutics, 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. M.P. has received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. 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. 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 coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. All other authors have nothing to dosclose.

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