SHORT COMMUNICATION

Effect of systemic corticosteroid therapy for acute heart failure patients with elevated C-reactive protein

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Abstract

Aims   The current study explores whether degree of inflammation, reflected by C-reactive protein (CRP) level, modifies the effect of intravenous (IV) corticosteroid administered in the emergency department (ED) on clinical outcomes in patients with acute heart failure (AHF).

Methods and results   We selected patients diagnosed with AHF in the ED, with confirmed N-terminal pro-B-type natriuretic peptide > 300 pg/mL and CRP > 5 mg/L in the ED from the Epidemiology of Acute Heart Failure in the Emergency Departments (EAHFE) registry. In these 1109 patients, 121 were treated by corticosteroid. The corticosteroid therapy hazard ratio (HR) for 30 day all-cause mortality was 1.26 [95% confidence interval (CI) 0.75–2.09, *P* = 0.38]. Although not statistically significant, HRs tended to decrease with increasing CRP level, with point estimates favouring corticosteroid at CRP levels above 20. In patients with CRP > 40 mg/L, with adjusted HRs of 0.56 (95% CI 0.20–1.55, *P* = 0.27) for 30 day all-cause mortality, 0.92 (95% CI 0.52–1.62, *P* = 0.78) for 30 day post-discharge ED revisit, hospitalization, or death, and adjusted odds ratio of 0.61 (95% CI 0.17–2.14, *P* = 0.44) for in-hospital all-cause mortality.

Conclusions   The present analysis suggests that corticosteroids might have the potential to improve outcomes in AHF patients with inflammatory activation. Larger, prospective studies of anti-inflammatory therapy should be considered to assess potential benefit in patients with the highest degree of inflammation.

Background

Abnormalities in the inflammatory cascade are well known to be associated with both the onset and progression of heart failure (HF) and related to outcome and cardiac remodelling, even though microbial infection is not involved in most cases.[1–5] Indeed, various inflammatory biomarkers have been investigated as prognostic markers in patients with acute HF (AHF).[6–10] However, only a few studies have evaluated the effect of direct anti-inflammatory therapies in AHF patients,[11,12] mostly focusing on diuresis. This is likely due to the failure of some anti-inflammatory therapies to improve clinical outcomes in patients with chronic HF.[13,14] Corticoste- roids are potent agents used to reduce inflammation and hence could be considered as potential anti-inflammatory therapy, to be administered intravenously (IV) in the emergency department (ED).

Aims

In this sub-analysis of the Epidemiology of Acute Heart Failure in the Emergency Departments (EAHFE) registry, we sought to investigate whether for AHF patients in the ED the effects of systemic IV corticosteroid therapy on mortality

and adverse events differ according to level of C-reactive protein (CRP).

Methods

The present study is a sub-analysis of the EAHFE registry,[15,16] which has prospectively enrolled 18 370 patients with exacerbation of chronic HF in 45 Spanish EDs in six 1–2 month recruitment waves between 2007 and 2018. The AHF diagnosis was initially based on the Framingham clinical criteria[17] and confirmed by natriuretic peptide measurement or echocardiography in the majority of patients. Patients with ST-segment myocardial infarction were excluded. For this sub-analysis, data from 9 EDs that had enrolled 7041 patients in the EAHFE registry were reviewed, and patients with N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 300 pg/mL and CRP > 5 mg/L in the ED with a confirmed diagnosis of HF and suggestive inflammation were included. CRP has been used as the inflammatory marker for the current analysis. CRP is performed routinely in hospital emergency rooms and was available for the majority of patients in the EAHFE registry.

Patients on chronic systemic corticosteroids, with infections triggering episodes of AHF, and whose corticosteroids use in the ED was unknown were excluded. Patients included in the analysis were divided into two groups: patients receiving corticosteroids in the ED (corticosteroid-treated group) and patients who did not receive corticosteroids (corticosteroid-untreated group). The primary outcome for this sub-analysis was 30 day all-cause mortality. Secondary outcomes were in-hospital all-cause mortality and a 30 day post-discharge composite outcome comprising ED revisit, hospitalization, or death. Subgroup analyses examining increasing CRP thresholds were carried out. The EAHFE registry protocol was approved by a central ethics committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) and conformed with the Declaration of Helsinki principles. All participating patients gave informed consent to be included in the registry and contacted for follow-up.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) and categorical data as number and percentage. Associations between corticosteroid therapy in the ED and clinical outcomes were estimated with logistic regression (for in-hospital mortality) and Cox regression models (for 30 day all-cause mortality and 30 day post-discharge combined endpoint consisting of ED revisit, hospitalization, or death). Results are expressed as odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs), respectively. Kaplan–Meier plots of cumulative event-free survival

are presented. Adjustments were made for the EAHFE-3D scale, which predicts the short-term prognosis of patients with AHF.[18] The EAHFE-3D scale is derived from the following variables (maximum 165 points): age ≥ 75 years (30 points), baseline New York Heart Association III–IV (15 points), systolic blood pressure < 110 mmHg (20 points), room air oxygen saturation < 90% (30 points), hyponatraemia (20 points), inotropic or vasopressor treatment (30 points), and need for non-invasive mechanical ventilation (20 points). To account for missing data, multiple imputation by chained equations was used with 10 imputed datasets. Rubin's algorithm was used for averaging parameter estimates across the imputed datasets. A two-sided *P*-value < 0.05 was considered statistically significant. Statistical analyses were conducted using R Version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) packages: mice v3.11.0[19] and rms v6.2-0.[20]

Results

Of 7041 patients enrolled in the 9 EDs participating centres, 298 were excluded because of being on chronic corticosteroid therapy, 2374 had infection triggering the AHF episode, 22 had no record of corticosteroid use in the ED, and 3238 had CRP below 5 mg/L or unknown. Thus, 1109 patients were available for the present sub-analysis. Of them, 121 patients (10.9%) received at least one IV bolus of corticosteroids during the ED stay. Baseline characteristics by corticosteroids usage at baseline are presented in *Table 1*. Overall, patients receiving IV corticosteroids were more likely to have higher systolic blood pressure, lower room air oxygen saturation, higher rates of cerebrovascular disease, peripheral artery disease, chronic obstructive pulmonary disease (COPD), and dementia, lower rates of heart valve disease, and lower Barthel's index. The current AHF episode was more commonly triggered by hypertensive crisis. There was also a significant difference in triage level (severity). Regarding laboratory variables, patients receiving IV corticosteroids had lower urea and higher CRP. Baseline characteristics in the subgroup of 281 patients with elevated CRP (>40 mg/L) show similar differences (Supporting Information, *Table S1*). In all patients with CRP > 5 mg/L and NT-proBNP > 300 pg/mL, the cumulative risk of 30 day all-cause mortality did not differ statistically significantly between patients treated and not treated with IV corticosteroids, with mortality rates of 14.0% and 11.1%, respectively [HR 1.26 (95% CI 0.75–2.09, *P* = 0.38)]. Results followed a similar pattern for the subgroup of patients with NT-proBNP > 1500 pg/mL: HR 1.16 (95% CI 0.67–2.03, *P* = 0.60) (*Figure 1*). HRs for patients receiving IV corticosteroids relative to patients not treated with IV corticosteroids for 30 day mortality tended to decrease as the level

Table 1 Characteristics of patients in the EAHFE registry with NT-proBNP > 300 pg/mL and CRP > 5 mg/L according to whether they did or did not receive systemic corticosteroids in the emergency department

	Total (*n* = 1109)	Missing values (%)	Not treated (*n* = 988)	Treated (*n* = 121)	*P*-value
Demographic data					
Age (years)	81.2 (10.1)	0.1	81.1 (10.1)	81.6 (10.1)	0.63
Male	500 (45)	0.3	434 (44)	66 (55)	0.037
Vitals at ED during acute episode					
Systolic blood pressure (mmHg)	137.9 (29.1)	1.8	136.8 (28.3)	146.6 (33.6)	<0.001
Heart rate (b.p.m.)	91.3 (26.4)	2.8	91.0 (27.0)	93.4 (20.8)	0.36
Room air oxygen saturation (%)	92.1 (8.1)	2.8	92.6 (7.2)	87.7 (12.2)	<0.001
Comorbidities					
Hypertension	898 (83)	2.1	798 (82)	100 (86)	0.35
Diabetes mellitus	487 (44)	0.2	439 (44)	48 (40)	0.40
Dyslipidaemia	504 (46)	0.3	442 (45)	62 (52)	0.19
Ischaemic heart disease	322 (29)	0.3	286 (29)	36 (30)	0.91
Chronic kidney failure (creatinine > 2 mg/dL)	309 (28)	0.2	278 (28)	31 (26)	0.67
Cerebrovascular disease	142 (13)	0.2	119 (12)	23 (19)	0.040
Atrial fibrillation	593 (54)	0.2	539 (55)	54 (45)	0.058
Peripheral artery disease	84 (8)	0.2	68 (7)	16 (13)	0.020
Heart valve disease	269 (24)	0.2	251 (25)	18 (15)	0.016
Chronic obstructive pulmonary disease	250 (23)	0.2	206 (21)	44 (37)	<0.001
Dementia	93 (8)	0.3	70 (7)	23 (19)	<0.001
Active neoplasia	166 (15)	0.3	150 (15)	16 (13)	0.68
Hepatic cirrhosis	19 (2)	0.3	17 (2)	2 (2)	1.00
Prior episodes of AHF	690 (64)	3.1	614 (64)	76 (67)	0.54
Baseline status					
Left ventricular ejection fraction (%)	50.3 (16.7)	44.5	50.3 (16.3)	50.1 (19.6)	0.92
Triage level according to severity		10.6			<0.001
Red	47 (5)		34 (4)	13 (12)	
Orange	343 (35)		299 (34)	44 (39)	
Yellow	521 (53)		480 (55)	41 (37)	
Green	80 (8)		66 (8)	14 (12)	
NYHA class		5.7			0.80
I	244 (23)		220 (24)	24 (21)	
II	557 (53)		497 (53)	60 (53)	
III	226 (22)		199 (21)	27 (24)	
IV	19 (2)		16 (2)	3 (3)	
Barthel's index (points)	77.6 (27.6)	8.2	78.2 (27.2)	72.4 (30.1)	0.037
Triggering factor for the current AHF episode					
Rapid atrial fibrillation	216 (19)	0	197 (20)	19 (16)	0.32
Anaemia	110 (10)	0	102 (10)	8 (7)	0.26
Hypertensive emergency	63 (6)	0	48 (5)	15 (12)	0.002
Non-compliance	41 (4)	0	38 (4)	3 (2)	0.62
Acute coronary syndrome	39 (4)	0	36 (4)	3 (2)	0.69
Chronic treatments at home					
Loop diuretics	740 (67)	0.1	660 (67)	80 (66)	0.95
Thiazide diuretics	160 (14)	0.2	137 (14)	23 (19)	0.16
Mineralocorticoid-receptor antagonist	194 (18)	0.1	174 (18)	20 (17)	0.86
Renin angiotensin system inhibitors	596 (54)	0.2	529 (54)	67 (55)	0.79
Beta-blockers	517 (47)	1.2	469 (48)	48 (40)	0.098
Antibiotics in the previous week	26 (2)	0	21 (2)	5 (4)	0.29
Results of blood tests at ED					
Haemoglobin (g/dL)	11.8 (2.2)	0.4	11.8 (2.2)	12.0 (2.1)	0.50
Haematocrit (%)	36.7 (6.3)	0.5	36.7 (6.3)	37.3 (5.6)	0.29
White blood cell count (/mm^3)	9252.3 (5299.1)	0.8	9270.3 (5484.3)	9106.1 (3466.0)	0.75
Platelets (×10^9/L)	239.2 (278.9)	0.9	242.7 (294.3)	211.3 (73.5)	0.24
Glucose (mg/dL)	149.7 (76.5)	1.2	149.2 (75.0)	154.5 (87.9)	0.47
Urea (mg/dL)	76.7 (60.5)	7.6	78.2 (62.7)	63.4 (33.4)	0.016
Creatinine (mg/dL)	1.4 (0.9)	0.2	1.4 (0.9)	1.3 (0.6)	0.16
Sodium (mmol/L)	138.6 (5.7)	2.3	138.5 (5.5)	138.9 (7.2)	0.57
Potassium (mmol/L)	4.5 (0.7)	5.6	4.5 (0.7)	4.4 (0.6)	0.077
Raised troponin (>99th percentile)	503 (72)	37.2	442 (71)	61 (82)	0.052
NT-proBNP (pg/mL)	8584.1 (12 036.5)	0	8713.7 (12 278.9)	7525.8 (9815.0)	0.31
CRP (mg/L)	36.7 (49.1)	0	35.5 (47.7)	46.3 (58.5)	0.022
Severity of the AHF episode					
MEESSI-AHF risk score		48.7			0.47
Low risk	180 (32)		164 (33)	16 (24)	

(*Continues*)

Table 1 (continued)

	Total (*n* = 1109)	Missing values (%)	Not treated (*n* = 988)	Treated (*n* = 121)	*P*-value
Intermediate risk	254 (45)		219 (44)	35 (53)	
High risk	78 (14)		69 (14)	9 (14)	
Very high risk	57 (10)		51 (10)	6 (9)	
Prognostic scale					
EAHFE-3D scale	41.6 (23.6)	11.6	40.7 (23.3)	48.4 (25.0)	0.001

AHF, acute heart failure; CRP, C-reactive protein; EAHFE, Epidemiology of Acute Heart Failure in the Emergency Departments; ED, emergency department; MEESSI-AHF, Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
Values are mean (standard deviation), *n* (%).

Figure 1 Kaplan–Meier plots showing cumulative risk of 30 day all-cause mortality in acute heart failure patients treated with corticosteroids in the emergency department vs. without corticosteroids in the emergency department. AHF, acute heart failure; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
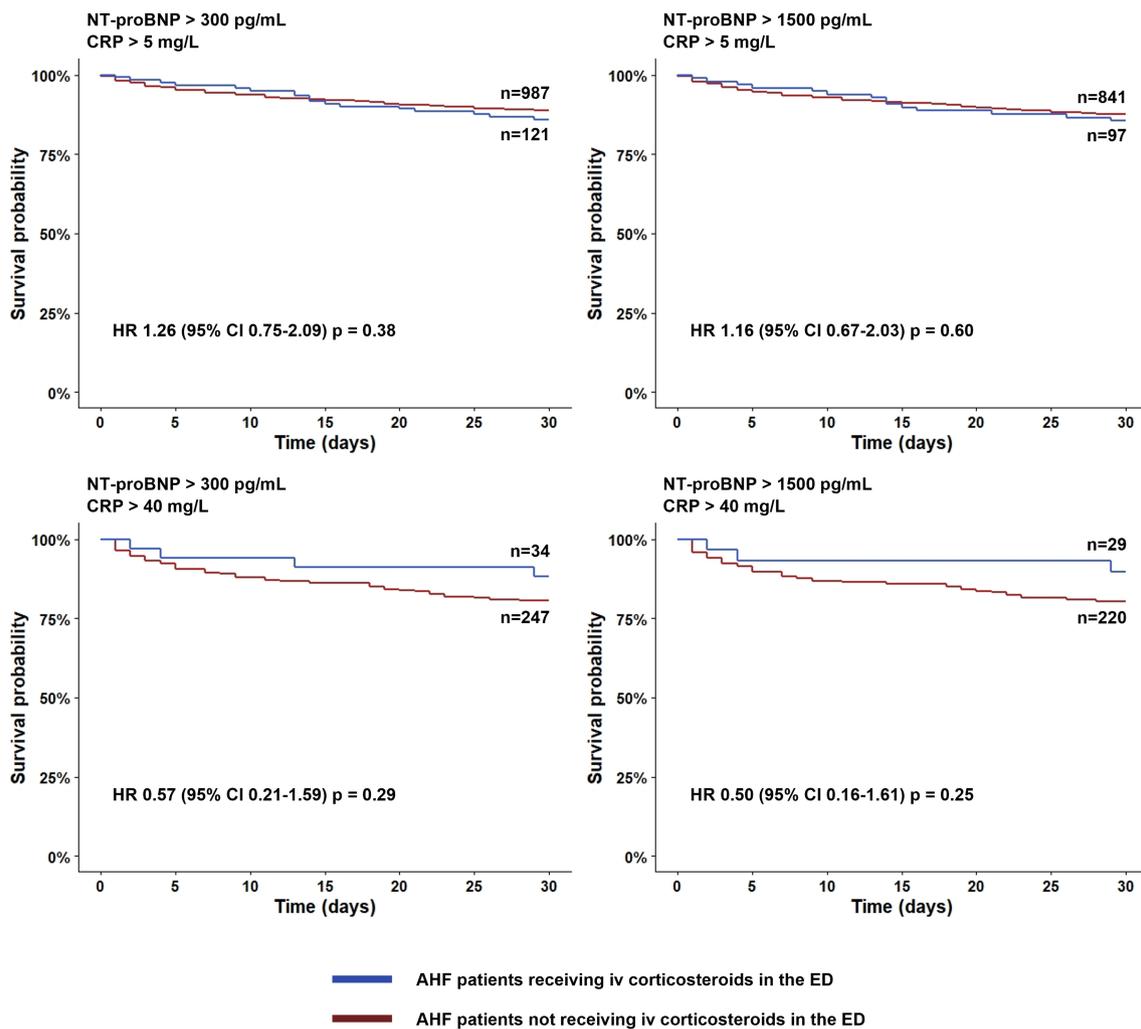
of CRP increased in populations with NT-proBNP both >300 and >1500 pg/mL (*Figure 2* and Supporting Information, *Figure S1*), with point estimates for HRs suggesting a possible protective effect of corticosteroids in subgroups of patients defined by a CRP threshold > 20 mg/L. In patients with very highly elevated inflammatory markers (i.e. CRP > 40 mg/L), the hazards of 30 day mortality were 7.7% and 9.2% lower in

Figure 2 Unadjusted and adjusted 30 day all-cause mortality according to the CRP levels in patients with N-terminal pro-B-type natriuretic peptide > 300 pg/mL. CRP, C-reactive protein; EAHFE, Epidemiology of Acute Heart Failure in the Emergency Departments.

Hazard ratio for patients receiving corticosteroids relative to patients not treated with corticosteroids
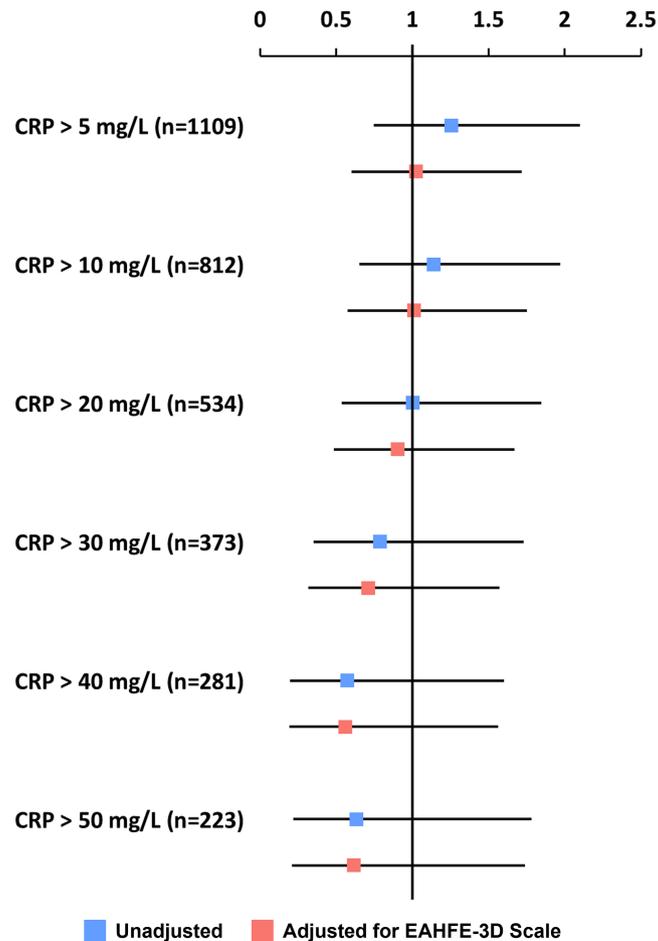
Table 2 Unadjusted and adjusted outcomes in patients receiving corticosteroids (N-terminal pro-B-type natriuretic peptide > 300 pg/mL and C-reactive protein > 40 mg/L)

	Event number (%)		Unadjusted model				Adjusted model			
	Not treated	Treated	OR or HR	Lower CI	Upper CI	P-value	OR or HR	Lower CI	Upper CI	P-value
30 day all-cause mortality (HR)	48 (19.4%)	4 (11.8%)	0.57	0.21	1.59	0.29	0.56	0.20	1.55	0.27
30 day post-discharge combined endpoint[a] (HR)	74 (43.8%)	11 (42.3%)	0.92	0.49	1.73	0.79	0.92	0.52	1.62	0.78
In-hospital all-cause mortality (OR)	33 (13.4%)	3 (8.8%)	0.63	0.18	2.17	0.46	0.61	0.17	2.14	0.44

Adjustments were performed for Epidemiology of Acute Heart Failure in the Emergency Departments (EAHFE)-3D scale, which predicts the short-term prognosis of patients with acute heart failure. EAHFE-3D scale contains the following variables (maximum 165 points): age ≥ 75 years (30 points), baseline New York Heart Association III–IV (15 points), systolic blood pressure < 110 mmHg (20 points), room air oxygen saturation < 90% (30 points), hyponatraemia (20 points), inotropic or vasopressor treatment (30 points), and need for non-invasive mechanical ventilation (20 points).
CI, confidence interval; HR, hazard ratio; OR, odds ratio.
[a]Thirty-day post-discharge combined endpoint indicates emergency department revisit, hospitalization, or death.

corticosteroid-treated patients, in patients with NT-proBNP > 300 and >1500 pg/mL, respectively, although these findings were not statistically significant (*Figure 1*). *Table 2* shows the unadjusted and adjusted effects of the association between corticosteroid use and the outcomes in patients with elevated CRP (>40 mg/L). Adjusted HRs for patients receiving corticosteroids relative to patients not treated with corticosteroids were all <1 for all 3 outcomes, though not statistically significant [30 day all-cause mortality: adjusted HR 0.56 (95% CI 0.20–1.55), *P* = 0.27; 30 day post-discharge combined endpoint: adjusted HR 0.92 (95% CI 0.52–1.62), *P* = 0.78; in-hospital all-cause mortality: adjusted OR 0.61 (95% CI 0.17–2.14), *P* = 0.44].

Discussion

Acute heart failure patients with elevated inflammatory markers have a poor prognosis.[6–10] In the current analysis, we explored the effects of anti-inflammatory therapy (IV corticosteroids) administered in the ED to AHF patients according to levels of CRP. We have found numerical trends suggesting that some short-term outcomes in AHF may be affected by corticosteroid therapy in unadjusted and adjusted analyses in patients with highly elevated signs of inflammation such as CRP > 40 mg/L. Although corticosteroids have been classically viewed as anti-inflammatory agents, corticosteroids can cause sodium and water retention, potentially leading to worsening of HF. However, it has been reported that the administration of corticosteroids to patients with severe AHF produced a potent diuretic effect and improved fluid overload and renal function.[21,22] In addition, a recent publication from our group showed that there is no evidence of harm related to the new onset of systemic corticosteroid therapy during an episode of AHF in the ED.[23] Several limitations of this sub-analysis should be noted. Firstly, this was a retrospective analysis, corticosteroid therapy was not randomized, and the distribution of some variables differed between the corticosteroid-treated and corticosteroid-untreated groups. Even the best regression model cannot fully resolve this issue, and some confoundings may still exist. In addition, it is also unclear why the physician used corticosteroids, potentially due to diagnostic uncertainty. Secondly, given the non-prospective design of the study, details regarding the IV corticosteroid administration including the dose and duration were not available. Thirdly, CRP levels were not followed after baseline. Therefore, it is unclear whether corticosteroids lowered CRP levels in this sub-analysis and whether prognosis was dependent on changes in CRP. Fourthly, the corticosteroid-treated group was quite limited in size. In fact, some of the CIs estimated in this study were rather wide, reflecting insufficient statistical power to detect significant trends. Fifthly, in this study, CRP was used as an inflammatory marker in patients with AHF, although not necessarily a well-established marker in these patients. Future studies using other novel inflammatory markers might be required. Sixthly, patients treated with corticosteroids more often had COPD and had a lower mean oxygen saturation. Despite adjustment for the EAHF-3D scale, which takes oxygen saturation into account, the potential benefits of corticosteroids at high CRP levels could be due to effects on COPD rather than HF. Finally, this is a post hoc cohort analysis limited to hypothesis generation that requires confirmation in future trials.

Conclusions

Although not statistically significant, the current analysis suggests that corticosteroids might have the potential to improve outcomes in AHF patients with inflammatory activation. Taken together with previous studies of potentially improved diuresis,[21,22] the results suggest that future randomized trials on anti-inflammatory therapy are needed to assess potential benefit in patients with the highest degree of inflammation.

Acknowledgements

Conflict of interest

Funding

Supporting information

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

Table S1. Baseline characteristics of patients in the EAHFE registry with NT-proBNP > 300 pg/mL and CRP > 40 mg/L according to whether they did or did not receive systemic corticosteroids in the emergency department.
Figure S1. Unadjusted and adjusted 30-day all-cause mortality according to the CRP levels in patients with elevated NT-proBNP (> 1500 pg/mL).

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