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REVIEW

Effects of anti-inflammatory therapy in acute heart failure: a systematic review and meta-analysis

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Abstract

We examined current evidence regarding the effects of anti-inflammatory therapies in patients with acute heart failure (AHF) on the risk of cardiovascular outcomes, inflammatory markers, natriuretic peptides, and renal function. Despite growing evidence that inflammation plays a pivotal role in both the development and progression of heart failure, including AHF, only a few trials have been conducted to date in patients with AHF. A systematic literature search of PubMed, Medline, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was conducted in November 2024 to identify randomized controlled trials (RCTs) evaluating anti-inflammatory therapies in adult patients with AHF. Meta-analyses were conducted to estimate effects on clinical outcomes (death, HF readmission, or worsening HF) and inflammatory and other markers. Five RCTs were identified that enrolled a total of 289 patients to an anti-inflammatory intervention and 273 to a control. Prednisone was examined in two RCTs, anakinra in two, and colchicine in one. Three of the five trials required elevated C-reactive protein (CRP) level for entry. Anti-inflammatory therapy was associated with a reduced risk of the composite outcome (hazard ratio 0.55 [95% CI 0.35–0.86]) and an overall 54% greater reduction in CRP to end of therapy (ratio of geometric mean ratios 0.46 [95% CI 0.29–0.73]), which varied across studies. NT-proBNP and creatinine were not significantly affected. The analysis is limited by the small number of studies but suggests that anti-inflammatory therapy reduces inflammation and may reduce the risk of adverse clinical outcomes in patients with AHF.

Keywords Anti-inflammatory agents · Inflammation · Acute heart failure · Prognosis

Introduction

Acute heart failure (AHF) is a complex clinical syndrome characterized by the sudden onset or worsening of symptoms related to heart failure, requiring urgent medical intervention. Despite advances in the treatment of heart failure, AHF continues to have a poor prognosis, with both in-hospital and post-discharge readmission and mortality rates remaining high [1, 2].

Inflammation was first shown to be associated with heart failure (HF) 70 years ago [3] when Elster, Braunwald, and Wood demonstrated associations between c-reactive protein (CRP), congestion and increased mortality and recurrent HF in patients admitted for acute HF (AHF). Growing evidence suggests that inflammation plays a pivotal role in both the development and progression of heart failure, including AHF. Several inflammatory mediators, such as high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), soluble suppression of tumorigenesis-2 (sST2), and galectin-3, play a key role in the pathophysiology of AHF.

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These markers are closely linked to the development and progression of the disease [4].

CRP is a key inflammatory biomarker produced by the liver in response to inflammation. It is commonly measured due to its stability and ease of testing. Elevated CRP levels are associated with AHF and poor prognosis. Studies like ASCEND-HF [5] and ATTEND [6] have shown that higher CRP concentrations at hospital admission correlate with worse prognosis and increased mortality in AHF patients, highlighting its significance as a predictor of inflammation-related heart failure progression. IL-6 and IL-1 are also important inflammatory markers in heart failure. Elevated IL-6 levels are observed in most AHF patients [5, 7]. In a retrospective analysis of the PROTECT cohort, higher IL-6 levels correlated with older age, lower kidney function, and increased B-type natriuretic peptide (BNP) levels, further linking IL-6 to worse outcomes [8].

Despite the association of elevated inflammatory markers and severity and outcomes of AHF, a causal relationship between inflammatory activation and AHF has not been established partially because only a few small randomized controlled intervention studies assessing the effects of anti-inflammatory therapy in patients with AHF have been conducted. Regretfully, the use of anti-inflammatory drugs as disease-modifying therapy in AHF has not yet been fully realized, and no large studies have been conducted to assess the effects of anti-inflammatory therapy in patients with AHF. In a handful of smaller studies, specific anti-inflammatory therapies have been linked to trends — or in some cases, significant effects — on the risk of worsening HF (WHF) or death.

In the current systematic review, we examine current evidence regarding the effects of anti-inflammatory therapies in patients with AHF on the risk of cardiovascular outcomes, specifically WHF, HF readmission, and mortality. We also examine effects on inflammatory markers, natriuretic peptides, and renal function.

Methods

Eligibility criteria

Studies included were those that (1) were conducted in adult patients diagnosed with AHF; (2) compared an anti-inflammatory therapy with placebo or standard care; and (3) reported cardiovascular outcomes such as post-discharge mortality, heart failure readmission rates, and worsening heart failure events and/or reductions in inflammatory markers (4) were prospective randomized controlled trials. The included studies were those conducted in hospital settings or clinical environments where patients with acute heart failure are treated. The context focused on interventions given or initiated during hospitalization for acute heart failure.

Exclusion criteria for the meta-analysis included studies without control groups, retrospective analyses, and studies focusing on chronic heart failure or non-cardiovascular diseases. Observational studies were not included.

The review is registered in PROSPERO (CRD42024605607).

Search strategy and information sources

A systematic literature search was conducted in PubMed, Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov to identify randomized controlled trials (RCTs) evaluating anti-inflammatory therapies in patients with AHF between 1 and 4 November 2024. Filters or keywords were applied to include only clinical trials published in English. No date restrictions were applied. Animal studies were excluded. Exact searches employed for each database are given in Supplementary Table 1.

Selection and data collection process and quality assessment

The studies were screened using the title and abstract, excluding duplicates and ineligible studies, followed by full-text review of the selected records. One reviewer extracted the data, and a second reviewer verified the accuracy and completeness of the extracted data. The data extracted included study design, sample size, patient demographics, intervention details (e.g., type of anti-inflammatory therapy), control group information (placebo or standard care), outcome measures (e.g., mortality, hospitalization, worsening heart failure, inflammatory markers, NT-proBNP, and creatinine), and follow-up duration. Clinical outcomes through 6 months, the "vulnerable" period following AHF hospitalization [9], and through 2 months, a follow-up period common to most studies identified, were sought. Changes in laboratory findings through end of treatment, 1 month, and 2 months were sought. Study authors were contacted regarding any missing or unclear data. Rayyan [10] was used to facilitate the review of study selection. The risk of bias in the included RCTs was assessed using the Cochrane Collaboration's Risk of Bias (RoB 2) tool [11]. The overall quality of evidence was assessed using the GRADE criteria [12].

Statistical methods

Hazard ratios (HRs) and associated standard errors (SEs) representing the effect of anti-inflammatory therapy relative to control on the primary endpoint (first event of death, HF readmission, or worsening HF) were derived directly using a Cox regression model from individual

patient data (IPD) where available, were provided by the study's authors, or were extracted from published data. Where needed, numbers of patients at risk, censored, and with an event were extracted within intervals from published Kaplan–Meier curves using PlotDigitizer™ (PORBITAL) and estimates of the HR and 95% confidence interval (CI) obtained following the methodology of Tierney et al. [13]. For one study, two intervention groups were each compared with the same placebo group; the hazard ratio for the pooled intervention arm versus placebo was computed from IPD. Meta-analyses were conducted using the "metafor" package [14] in R version 4.1.1 [15]. A random-effects model was used with individual study effect sizes expressed as log HR; standard errors (SEs) for each study were calculated from the 95% CI for the HR.

The mean difference in log-transformed changes in highly right-skewed variables including CRP, IL-6, and NT-proBNP comparing active treatment to control was computed directly from IPD or was extracted from annotations provided in published figures, with the standard deviation of the log change estimated using the confidence intervals. The combined effect was back-transformed (exponentiated) to report the effect as a ratio of geometric mean ratios (follow-up to baseline). Creatinine was first converted to common units (μmol/L) as needed, and mean differences and associated SDs comparing active and control were computed directly from IPD, were provided by study authors, or were extracted from published figures using PlotDigitizer™. Where two intervention groups were compared with the same placebo group in one study, results were calculated separately for each comparison. A random effects multivariate meta-analysis was conducted in metafor for each outcome using a methodology for multiple treatment studies [16], which accounts for the correlation between the effects of groups with a shared comparator. To adjust for this dependency, an estimated variance–covariance matrix was included in the calculations. The correlation was estimated using group sizes as weights and corresponding effect sizes.

I^2 was used as an assessment of residual heterogeneity in the combined estimates, with values > 50% considered indicative of significant heterogeneity.

For the primary composite endpoint, a funnel plot of effect sizes by their SEs was used to visually assess potential publication bias. In the absence of bias, larger studies with smaller SEs cluster near the average effect size at the top of the plot, while smaller studies with larger SEs spread more widely at the bottom, forming a symmetrical, inverted funnel shape. Although formal tests for publication bias may be underpowered with fewer than 10 studies, we assessed publication bias using Egger's regression test, specifying the SE as the predictor.

Results

Selected studies

Of 114 records identified without duplicates, 5 RCTs [17–21] met eligibility criteria with relevant endpoints (Fig. 1). A total of 562 patients (289 randomized to an intervention arm and 273 to a control arm) were enrolled in these 5 studies (Table 1). All the studies, except REDHART, enrolled patients shortly after hospital presentation for AHF, where treatment occurred or was initiated. Two studies examined 7-day prednisone therapy, two examined treatment with anakinra (a recombinant human IL-1 receptor antagonist) for 2–12 weeks, and one studied colchicine therapy over 8 weeks. Three studies required an elevated inflammatory marker for study entry, with CRP thresholds of 2, 5, and 20 mg/L. Three of the trials utilized a double-blind placebo control, while two (CORTAHF and COPE-ADHF) were open-label comparisons to standard care.

The COPE-ADHF [17] study showed some reduction in mortality and improvement in kidney function in diuretic-resistant patients given steroids. In a series of studies named Anakinra ADHF and REDHART [18, 19], the authors demonstrated that blocking interleukin-1 (IL-1) reduced inflammatory activation and showed trends towards improved outcomes in patients with AHF and high C-reactive protein (CRP). The CORTAHF and COLICA studies were published in recent months. In CORTAHF [20], 1 week of burst steroid therapy given to patients admitted due to AHF and with high levels of CRP was associated with reduced inflammation, improved quality of life, and reduced rate of WHF or death to day 90. In the COLICA study [21], administration of colchicine to patients with AHF without a CRP eligibility criterion was associated with a reduction in inflammatory markers but not with a reduction of natriuretic peptides or significant improvement in WHF or death.

Baseline characteristics of the patients enrolled in the studies are detailed in Table 2. Patients enrolled in all studies were generally aged in their 60 s and were mostly male. The baseline characteristics as well as CRP levels reflected the entry criterion for each of the studies and hence diverged to some degree. CRP levels were higher at baseline in studies requiring a high inflammatory marker concentration.

Effect on clinical outcomes

The occurrence of the composite of death, HF readmission, or WHF event through the last available follow-up through 6 months was obtained for all five studies except for COPE-ADHF; for this study, only all-cause

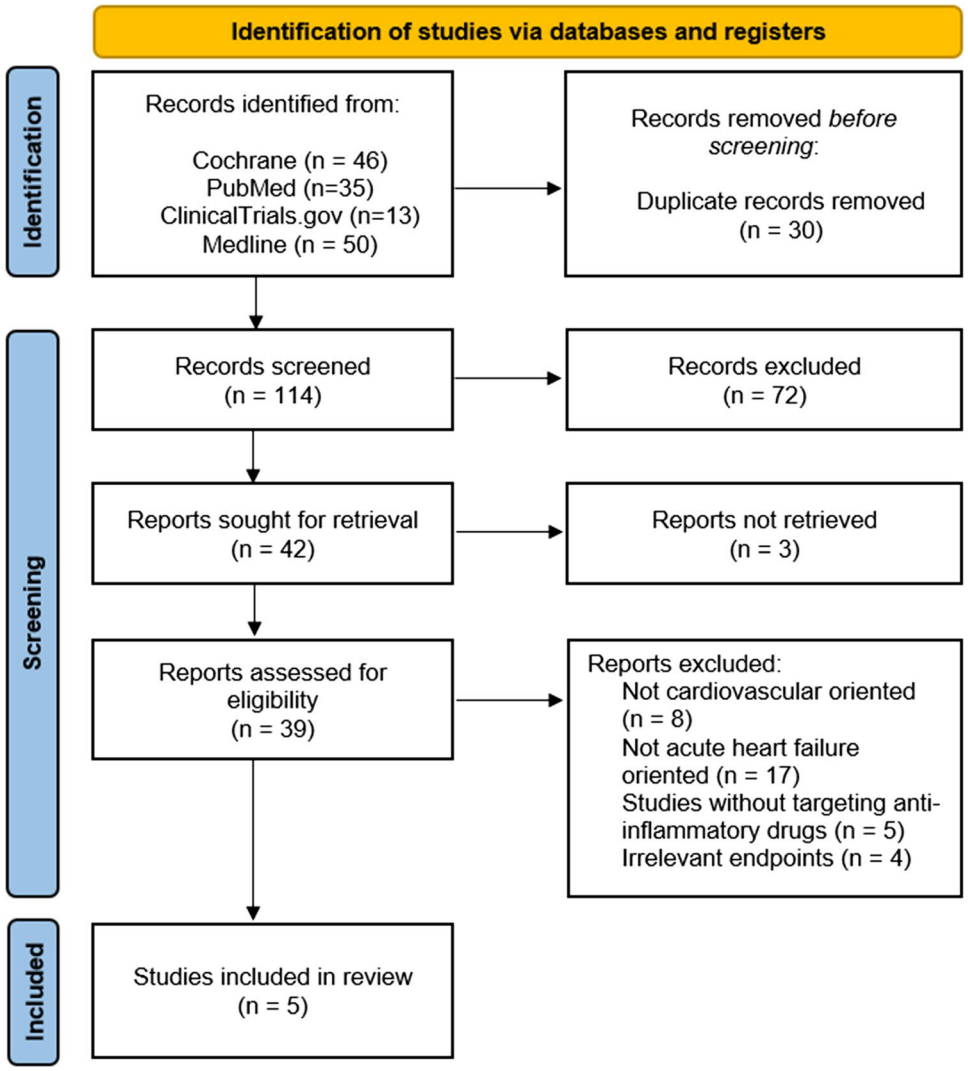

Fig. 1 PRISMA flowchart summarizing the search process

mortality through 36 months (from which earlier rates could be derived) and 30-day cardiovascular mortality were reported. All studies showed a reduction in the risk of the clinical outcome with anti-inflammatory therapy. A meta-analysis of the effect of anti-inflammatory therapy, expressed as a hazard ratio (HR), for the composite endpoint over the available follow-up period through 6 months is presented in Fig. 2. The two colchicine regimens were pooled for this analysis. The findings indicate a significant reduction in adverse clinical outcomes with anti-inflammatory therapy, yielding an overall hazard ratio of 0.55 (95% CI 0.35–0.86). Although there are very few studies to assess possible publication bias, a funnel plot of standard error versus effect size for the published studies is presented in Supplementary Fig. 1. Egger's regression test of potential publication bias was non-significant ($p = 0.37$).

To test the robustness of these results, two sensitivity analyses (Supplementary Figs. 2 and 3) were conducted: one excluding the COPE-ADHF study, which provided only mortality data, and another limited to 8-week follow-up. Both analyses demonstrated similar effect sizes (HR 0.59 [95% CI 0.35–1.01] and 0.64 [95% CI 0.39–1.04], respectively), reinforcing the primary findings.

Given the small sample sizes and limited follow-up duration in the studies, and thus the small number of events, we were unable to conduct a meta-analysis on the effects of anti-inflammatory therapy on mortality. Nonetheless, through a maximum of 6 months of follow-up, a total of 15 deaths in 273 patients treated in control (1 in REDHART, 14 in COPE-ADHF) and 10 deaths in 289 patients treated with anti-inflammatory therapy (2 in COLICA, 1 in REDHART, 1 in CORT-AHF, and 6 in COPE-ADHF) were reported.

Effect on inflammatory markers

Meta-analyses of the effects of anti-inflammatory therapy on changes in CRP and IL-6 from baseline to end of therapy are presented in Fig. 3a, b. Treatment effects are

Table 1 Study characteristics

Study name	Participants	Intervention	Control	Observation period	Available outcomes
COLICA	Patients with primary diagnosis of AHF (hospital or outpatient clinic) requiring at least 40 mg of i.v. furosemide; regardless of LVEF, HF type (new-onset or chronic), and inflammatory activation at baseline; NT-proBNP > 900 pg/mL; enrolled within 24 h of presentation	*N* = 141 Colchicine loading dose 2 mg (1.5 mg initially, + 0.5 mg after 1 h). Then, 0.5 mg twice daily for 8 weeks	*N* = 137 Placebo, identical regimen	8 weeks	All-cause mortality, HF hospitalization, WHF events through 8 weeks; composite through 8 weeks[a] Ratio changes in NT-proBNP, CRP, IL-6 at 7 days, 4 and 8 weeks Change in creatinine at 4 weeks[a], 8 weeks
REDHART	Patients with recently decompensated systolic HF; LVEF < 50%; CRP > 2 mg/L; enrolled within 14 days of hospital discharge	*N* = 16 Anakinra 100 mg SQ daily for 2 weeks followed by placebo daily for the remaining 10 weeks *N* = 18 Anakinra 100 mg SQ daily 12 weeks	*N* = 18 Placebo (identical regimen for 12 weeks)	24 weeks	Death or HF readmission through 24 weeks; composite clinical outcome through 24 weeks[b] Ratio changes in NT-proBNP, CRP at 2, 4, 12, and 24 weeks[b] Changes in creatinine at 2, 4, 12, and 24 weeks[b]
Anakinra ADHF	Patients hospitalized for ADHF; LVEF < 40%; CRP ≥ 5 mg/L; BNP ≥ 200 pg/mL or LVEDP > 18 mmHg; enrolled within 24 h of admission	*N* = 15 Anakinra 100 mg twice daily for 3 days, then 100 mg once daily for 11 days	*N* = 15 Placebo, identical regimen	14 days	Death, WHF, HF readmission through 2 weeks; composite through 2 weeks[b] Ratio changes in CRP, IL-6 at 2 weeks[b] Change in creatinine at 2 weeks[b]
CORTAHF	Patients hospitalized for AHF with objective signs of congestion; NT-proBNP > 1500 pg/mL; hsCRP > 20 mg/L; SBP ≥ 100 mm Hg; and HR ≥ 60 bpm	*N* = 48 Prednisone 40 mg orally once daily for 7 days along with usual care without blinding	*N* = 52 Usual care	90 days	Composite outcome through 90 days Ratio changes in CRP, IL-6 at 2, 4, 7, and 31 days; ratio change in NT-proBNP at day 31 Change in creatinine at days 7 and 31
COPE-ADHF	Patients hospitalized for ADHF with 2-pillow orthopnea, jugular venous distention, or abdominal discomfort from mesenteric congestion, included those on i.v. inotropes/vasodilators; SBP range 80–90 mm Hg	*N* = 51 Dexamethasone 20 mg i.v. followed by prednisone 1/mg/kg/day for 7 days then a 3-day taper off	*N* = 51 Standard care only	19 months (1–36 months)	CV mortality through 30 days, all-cause mortality through 36 months Change in creatinine at day 7

[a]Result provided by trialist

[b]Derived from individual patient data

Table 2 Characteristics of patients enrolled in the identified trials

Characteristic[a]	COLICA	REDHART	Anakinra ADHF	CORTAHF	COPE-ADHF
Demographics					
Age, years	75[a]	57[a]	58[a]	66.5	57.3
% Male	68	73.1	73.3	63	67.6
Weight, kg	NI	NI	NI	89.7	NI
BMI, kg/m^2	29.1	32.8[a]	37.5[a]	31.1	NI
Systolic blood pressure, mmHg	125.6	NI	NI	141.3	104.4
Oxygen saturation, %	95.8	NI	NI	82.5	NI
Medical history, %					
Diabetes	36.1	55.8	66.7	41	NI
Hypertension	72.9	92.3	96.7	86	NI
Hypercholesterolaemia	56.0	61.5	66.7	82	NI
Chronic lung disease	17.0	NI	16.7	9	6.9
Renal disease/history of dialysis	NI	NI	50.0	1	NI
Ischemic heart disease	20.9	34.6	33.3	88	27.5
Myocardial infarction	17.0	NI	NI	75	26.5
Stroke	13.7	NI	6.7	6	NI
Valvular disease	10.1	NI	NI	46	NI
Atrial fibrillation	57.2	21.2	36.7	26	17.6
ICD/CRT implant	8.3	40.4	NI	3	NI
HF history, %					
NYHA class					
I	0	0	NI	0	NI
II	41.9	32.7	NI	16	NI
III	58.1[b]	67.3	NI	73	NI
IV		0	NI	11	NI
LVEF (%)	40[a]	28–34[a]	24.6–32.5[a]	28.6	32.3
Laboratory findings					
Sodium, mmol/L	140.1	NI	NI	141.4	NI
Potassium, mmol/L	4.00–4.10[a]	NI	NI	4.3	NI
Glucose, mmol/L	NI	NI	NI	7.6	NI
AST, U/L	NI	NI	NI	24.0	NI
ALT, U/L	NI	NI	NI	27.4	NI
Total bilirubin, µmol/L	NI	NI	NI	13.5	NI
Hemoglobin, g/L	131.0–139.5[a]	NI	119–134[a]	136	NI
Urea/BUN, mmol/L	10.7	NI	NI	8.4	8.3
Creatinine, mg/dL	1.09–1.10[a]	1.3[a]	1.5[a]	1.2	1.2
eGFR, ml/min/1.73m2	57.0	NI	NI	60.6	NI
Troponin T, ng/mL	0.0345–0.0348	NI	NI	0.035[a]	NI
Troponin I, ng/mL	NI	NI	0.0335–0.0508[a]	0.021[a]	NI
WBC, 10^9/L	NI	NI	6.3–6.4[a]	9.1	NI
Lymphocytes, %	NI	NI	NI	20.8	NI
CRP, mg/L	8.20–8.30[a]	5.7[a]	23.8[a]	29.9[a]	NI
NT-proBNP, pg/mL	4262[a]	1334[a]	2921.5[a]	4335.5[a]	NI
IL-6, pg/mL	11.10–11.50[a]	NI	3.2[a]	18.5[a]	NI
IL-17, pg/mL	NI	NI	0.45–0.60[a]	0.78[a]	NI
Concomitant medications at study inclusion, prior to admission %					
ACEI, ARB, or ARNI	53.6	82.7	58.6	67.0	54.9
Beta-blocker	54.0	92.3	79.3	60.0	56.9
Diuretic	50.5	96.1	76.7	62.0	91.2
Thiazide diuretic	19.5	NI	NI	14.0	NI

Table 2 (continued)

Characteristic[a]	COLICA	REDHART	Anakinra ADHF	CORTAHF	COPE-ADHF
SGLT2 inhibitor	32.5	NI	NI	15.0	NI
Nitrates	NI	25.0	27.6	1.0	NI
Calcium channel blocker	NI	NI	NI	31.0	NI
Digoxin	6.2	NI	NI	10.0	75.5
Antiplatelet	NI	NI	55.2	70.0	NI

Mean or median are presented for continuous variables

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *BMI* body mass index, *CRT* cardiac resynchronization therapy, *CRP* C-reactive protein, *DASI* Duke Activity Status Index, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *IL-6* interleukin-6, *NI* no information, *IL-17* Interleukin-17, *LVEF* left ventricular ejection fraction, *MLWHF* Minnesota Living with Heart Failure, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *NYHA* New York Heart Association, *SGLT2* sodium-glucose cotransporter-2, *WBC* White Blood Cell;

[a]Median or minimum to maximum median reported among treatment groups; the overall median lies between these values

[b]NYHA class III-IV combined is reported

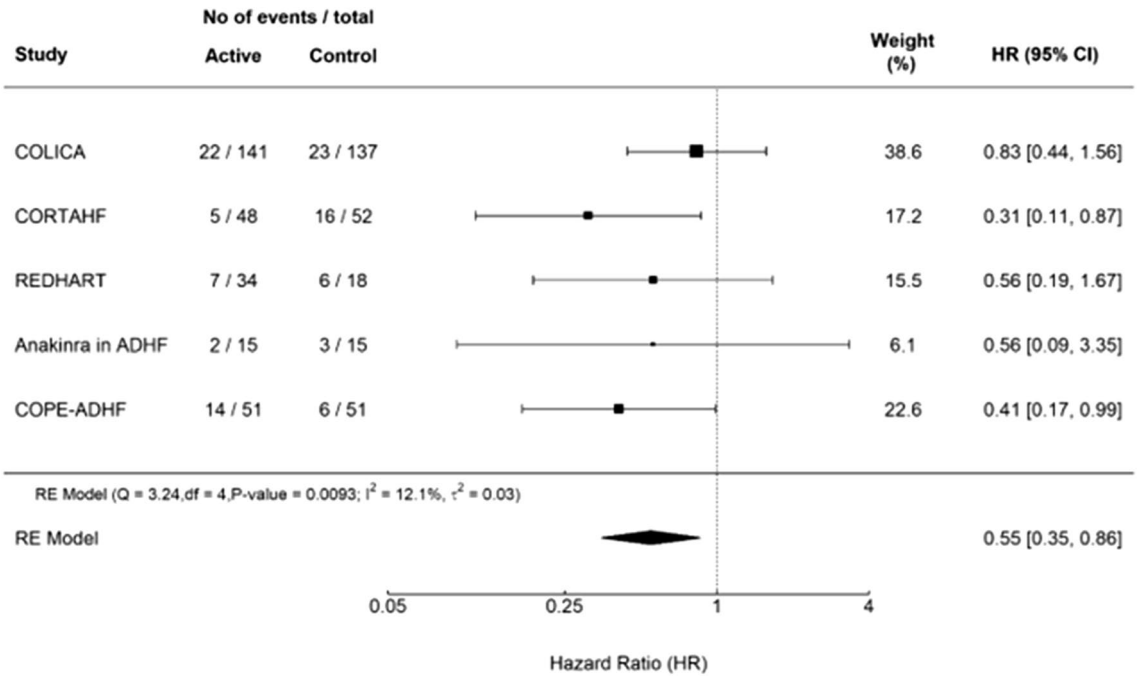

Fig. 2 Effect of anti-inflammatory therapy on the primary composite endpoint of death, HF readmission, or WHF event through the last available follow-up through 6 months

expressed as the treatment ratio of the geometric mean ratio of follow-up to baseline (i.e., the ratio of the ratios) and could be extracted for four of the five trials. Comparable changes in IL-6 were available for three of the trials. The correlation between the comparisons of each of the two anakinra regimens in REDHART to the same placebo group was accounted for in computing the overall estimate. As anticipated, results showed that anti-inflammatory therapy had significant effects on both CRP and IL-6 levels during treatment, with an overall 54% greater reduction in CRP to end of therapy (ratio of geometric mean ratios 0.46 [95% CI 0.29–0.73]), though the magnitude of CRP reduction varied ($I^2 = 68.6\%$) across studies. Anti-inflammatory therapy showed a 36% greater reduction in IL-6 to end of therapy (ratio of geometric mean ratios 0.64 [95% CI 0.50–0.82]). Smaller reductions in CRP were seen with steroid and colchicine therapy than with IL-1 blockade, while colchicine therapy also showed a comparatively modest effect on IL-6 reduction.

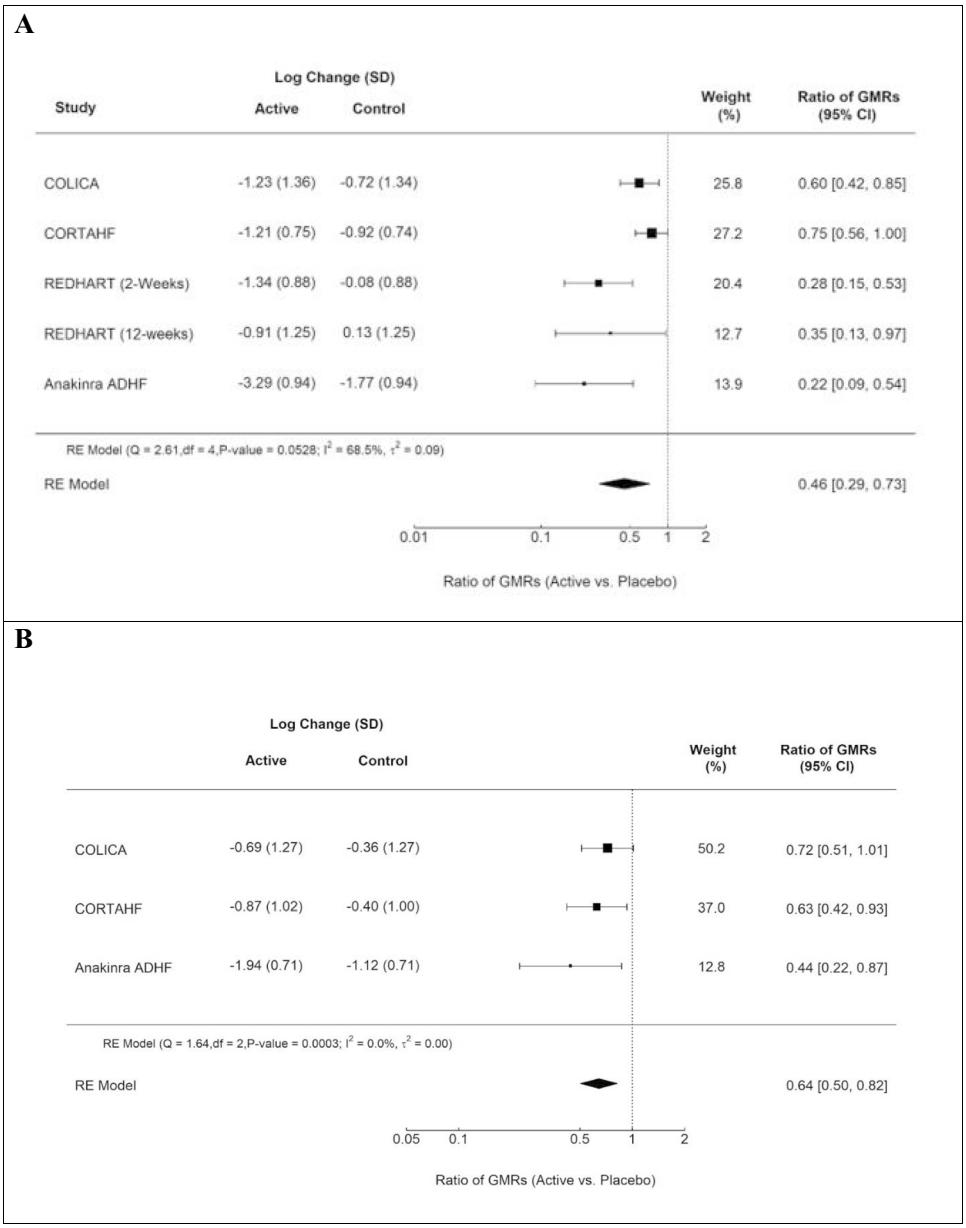

Fig. 3 Effects of anti-inflammatory therapy through end of treatment on inflammatory markers: **a** CRP, **b** IL-6

Effects on other biomarkers

Finally, relative changes in NT-proBNP could be extracted for four studies, and absolute changes in creatinine from baseline to 4 weeks could be extracted for all five trials. Meta-analyses suggest no effect of anti-inflammatory therapy on natriuretic peptides or creatinine (Fig. 4a, b). However, a minor overall numerical reduction in creatinine was observed, primarily driven by findings from the COPE-ADHF study, which enrolled patients with diuretic resistance.

Effects on safety

No serious infections or any unexpected untoward serious side effects were reported in any of the analyzed studies. Studies utilizing steroids reported increases in hyperglycemia [17, 20]; however, none were reported to be severe. There were no reports of worsening of HF, neurological side effects, sodium retention, or increased occurrence of worsening renal function, hypertension, or fractures.

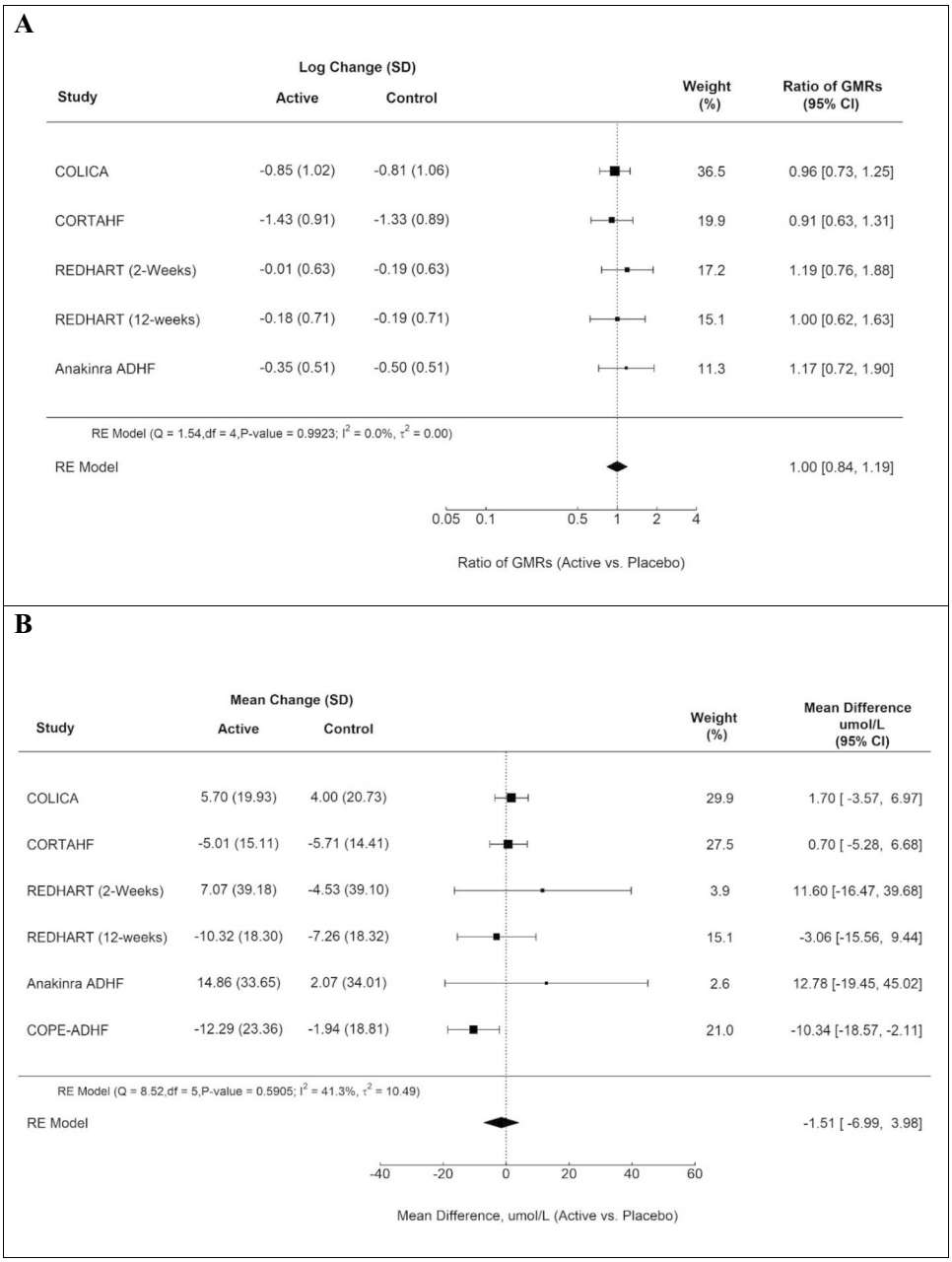

Fig. 4 Effects of anti-inflammatory therapy on last available measure through 4 weeks on **a** NT-proBNP and **b** creatinine

Quality of the evidence

The risk of bias for our primary outcome assessed through the RoB 2 tool was low for all five studies, but some concern arises for two studies (Supplementary Fig. 4). CORTAHF and COPE-ADHF were both open-label studies, which, theoretically, could have affected the investigators' ascertainment of clinical outcomes. Additionally, only mortality data were available for COPE-ADHF, which we included in the analysis of the composite outcome. None of the studies were funded by industry.

The overall quality of the evidence may be judged as high for each of our five outcomes according to GRADE criteria (Supplementary Fig. 5) and suggests confidence in the estimated effects. However, only five small RCTs examining various anti-inflammatory therapies in AHF have been conducted. Larger, confirmatory studies are required before providing firm recommendations regarding treatment of patients with AHF.

Discussion

Despite consistent evidence linking inflammation with worse outcomes in patients with AHF [4, 5, 22–26], no large prospective randomized trial has yet been conducted to assess

the potential effects of anti-inflammatory therapy in AHF. The current analysis summarizes the data from five randomized controlled trials assessing the effects of steroids, IL-1 blockade, and colchicine in a total of 562 patients with AHF. Results of the current meta-analysis suggest that anti-inflammatory therapy reduces inflammation in patients with AHF as measured by reductions in the levels of CRP and IL-6 and may potentially reduce the rate of a composite endpoint comprising WHF, HF readmission, or death during the first months after an AHF event. That the results of the studies included concur on this potential benefit, despite slight differences in study eligibility criteria and the use of different interventions, strengthens the suggestion that anti-inflammatory therapy is of potential benefit in AHF.

As previously suggested [27], inflammation may play a critical role in AHF and therefore represents an important therapeutic target. The current data imply that the role of inflammation in AHF is significant, potentially linked to the core pathophysiological mechanisms of AHF, and that its inhibition could mitigate adverse outcomes. It is plausible that neurohormonal and inflammatory activation are interconnected in AHF, amplifying each other; consequently, dampening one pathway may reduce the other. On the other hand, they must also be independent to some degree as both pathways play different biological roles in physiology. Therefore, the therapies targeting these two axes may provide synergistic effects in the AHF population. This may also explain why the "pure" anti-inflammatory therapy did not significantly reduce the natriuretic peptide levels. This "counter-vicious" cycle may underlie the significant improvements in outcomes observed in our analysis.

One also needs to remember that AHF is a wide spectrum of different phenotypes and profiles, which implies some differences in underlying pathophysiology that go far beyond ejection fraction phenotyping in CHF. Thus, we need to acknowledge that, at the moment, we lack precise and clinically available biomarker profiles of AHF patients that might identify the group of patients with the highest chances to benefit from anti-inflammatory therapy.

Notably, there appears to be a potential association between IL-6 reduction and improved outcomes across studies, consistent with prior research [8] linking IL-6 closely with adverse outcomes in AHF. This raises the possibility that the degree of IL-6 blockade achieved by different anti-inflammatory therapies in this meta-analysis may drive the observed improvements in outcomes. This hypothesis is supported by previous studies showing only modest reduction in IL-6 in patients treated by colchicine, in the vicinity of 30%, consistent with the results seen in the COLICA study, suggesting that the lower treatment effects on the primary outcome observed in COLICA may have been the result of partial blockage of IL-6. However, to confirm this hypothesis, a direct study specifically investigating IL-6 blockade in AHF would be necessary. Ongoing studies, such as the HERMES trial, are investigating the effects of ziltivekimab—a monoclonal antibody targeting interleukin-6 (IL-6)—in patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation. The HERMES [28] trial aims to assess whether ziltivekimab can reduce morbidity and mortality in this patient population. Results from this trial are anticipated in the next 2–3 years and may provide valuable insights into the role of IL-6 inhibition in heart failure treatment.

Finally, one has to remember that guideline-directed medical therapy including blockers or the renin angiotensin, aldosterone, and adrenergic systems as well as glucose co-transporters have effects on the inflammatory system that may also contribute to their beneficial effects [29, 30] in HF and AHF. Although it is not possible to separate those effects from their effects of neurohormonal-adrenergic blockade, it was noted that in CORTAHF [20], when rapid uptitration of those medication was implemented, the reduction of inflammation in the control arm was more pronounced than in previous studies.

When it comes to safety, the only significant adverse event that was reported more commonly in patients treated with anti-inflammatory therapy was hyperglycemia in the studies where steroids were administered [17, 20]. When it comes to fluid accumulation, the analysis of CORTAHF has demonstrated an improvement in congestion and trend to reduction in weight [31]. In CORTAHF, measures of quality of life have improved more in the steroids arm [20] while in COPE-ADHF, there was improvement in dyspnea [17] which are known to be driven in AHF by congestion. The current analysis did not find an increase in creatinine in the patients treated by anti-inflammatory agents. There were no reports of any fractures, neurological disorders, or any other adverse events in the anti-inflammatory arms of any of the studies.

Importantly, the results of the current analysis suggest that it may be key to establishing thresholds for inflammation in patients with AHF who would identify those who are most likely to benefit from anti-inflammatory therapy [32].

Limitations

The current analysis is based on five small studies. With so few studies, the risk of publication bias cannot be reliably assessed. The primary analysis assumes that the effect of anti-inflammatory on clinical outcomes is constant through 6 months, and only about a third of patients enrolled in the studies were women. Thus, conclusions should be regarded as hypothesis-generating and anti-inflammatory therapy should not be administered to patients with AHF until

further research confirms or refutes the hypothesis generated here and further delineates which patients may benefit.

Conclusions

In patients with AHF, anti-inflammatory therapy reduced inflammation. The results suggest that anti-inflammatory therapy may reduce the risk of WHF, HF readmission, or deaths. No effects of anti-inflammatory therapy on changes in natriuretic peptides or creatinine were observed in these patients. These results need to be confirmed in further large prospective randomized trials.

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Data availability The data that support the findings of this study are not openly available due to reasons of data privacy and are available from the authors of the individual studies upon reasonable request.

Declarations

Competing interests BAD, GC, LA, CE, MN, and KT are employees of Momentum Research, which has received grants for research from the Heart Initiative, Corteria, Windtree, Echosens, and 4teen4. AA has served as a consultant to Kiniksa, MonterosaRx, and Novo Nordisk. DPF has received consultancy and speaker fees and lectures from AstraZeneca, Novartis, Roche Diagnostics, Pfizer, Vifor, Rovi, Bayer. JNV has received consultancy and speaker fees and lectures from AstraZeneca, Alleviant, Amgen, Bayer, Boehringer Ingelheim, CSL Vifor, Daiichi Sankyo, GSK, Lilly, Pfizer, Novartis, NovoNordisk, and Rovi. JB has received honoraria from Bayer, Boehringer Ingelheim, and AstraZeneca, Alleviant Medical and WhiteSwell. OC has received grants from Servier. ACS has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. GF has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier, and Amgen. JMTM 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. MM received consulting honoraria from Abbott Structural, Astra-Zeneca, Bayer, Boehringer Ingelheim, Edwards LifeSciences, NovoNordisk, Richie Diagnostics in the last three years. MP has received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. The employer of AAV 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. AM 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. DLM is on the scientific advisory board for Tenaya Therapeutics, HAYA Therapeutics, Cardurion Therapeutics and is a consultant from Novo holdings and Tourmaline Therapeutics. ABG has participated in advisory boards and/or lectured for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche Diagnostics, Vifor. All other authors have nothing to disclose. CL has nothing to disclose.

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