Circulation: Heart Failure

ORIGINAL ARTICLE

Resolution of Systemic Inflammation in Patients With Recently Decompensated Heart Failure With Reduced Ejection Fraction With and Without Interleukin-1 Blockade by Anakinra

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BACKGROUND: Decompensated heart failure with reduced ejection fraction (HFrEF) is associated with systemic inflammation that predicts unfavorable outcomes. We aimed to determine whether anakinra, an IL-1 (interleukin-1) blocker, favors inflammation resolution (CRP [C-reactive protein]) and improves peak oxygen consumption (VO_2) in patients with recently decompensated HFrEF.

METHODS: We randomized 102 adult patients recently hospitalized for HFrEF and CRP ≥2 mg/L (2:1) to receive anakinra 100 mg subcutaneously daily (n=68) or placebo for 24 weeks (n=34). The primary end point was the peak VO_2 change at 24 weeks. Data are presented as median (Q1, Q3) or number (%).

RESULTS: Of the 102 patients, 84 had primary end point data available (57 treated with anakinra and 27 with placebo). Peak VO_2 increased from 13.0 (10.9, 17.0) to 14.9 (12.0, 18.0) mL·kg^{-1}·min^{-1} (P<0.001) in the entire cohort, without significant differences between anakinra and placebo (+1.5 [−0.2, +3.4] and +1.2 [+0.5, +3.9] mL·kg^{-1}·min^{-1}, respectively; P=0.40; median difference +0.30 mL·kg^{-1}·min^{-1} [95% CI from −1.70 to +0.90]). A significant reduction in CRP levels was seen, with a −76% (−87%, −36%) in anakinra-treated patients and −48% (−77%, +14%) in the placebo group (P=0.050 between groups). There were no unexpected treatment-related serious adverse events, and no differences in HFrEF events between groups. CRP<2 mg/L was achieved in 47% and 37% of the anakinra and placebo groups, respectively (P=0.48). Patients achieving CRP<2 mg/L had a significantly greater increase in peak VO_2 versus those with CRP≥2 mg/L (+2.6 [+0.7, +4.6] and +1.0 [−0.3, +1.9] mL·kg^{-1}·min^{-1}; P=0.007) and lower rates of HFrEF-related events (8% and 26%; P=0.045).

CONCLUSIONS: Patients with recently decompensated HFrEF treated with maximally tolerated medical therapy had a significant improvement in CRP and peak VO_2. The addition of anakinra had a modest effect on CRP levels and no significant effect on peak VO_2 or other clinically relevant secondary end points.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03797001.

Key Words: adult ■ heart failure ■ humans ■ inflammation ■ interleukin 1

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.125.013546.
For Sources of Funding and Disclosures, see page XXX.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- In this randomized, double-blinded clinical trial of anakinra, an IL-1 (interleukin-1) blocker, or placebo, patients with recently decompensated heart failure and reduced ejection fraction were followed for 6 months, with multiple visits and uptitration of standard medical therapy, and showed signs of systemic inflammation and impaired cardiorespiratory fitness that tended to resolve over time, independent of treatment allocation.
- Patients treated with anakinra had a marginal additive effect on systemic inflammation, measured with CRP (C-reactive protein), and no significant effect on cardiorespiratory fitness, measured with peak oxygen consumption, when compared with placebo.
- When compared with patients who could have been in the trial but chose not to, those in the trial had significantly fewer heart failure hospitalizations, and those patients who had resolution of systemic inflammation, that is, normalization of CRP, had the greatest improvement in cardiorespiratory fitness, and fewer heart failure hospitalizations.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Optimizing heart failure management is associated with resolution of systemic inflammation and improvement of cardiorespiratory fitness in approximately half of the patients.
- Patients with residual inflammation remain at high risk, indicating an opportunity for targeted therapies.
- Adding anakinra 100 mg daily to standard therapy failed to normalize CRP or significantly improve cardiorespiratory fitness.
- Additional studies of different, more powerful antiinflammatory strategies are needed.

Nonstandard Abbreviations and Acronyms

CPX	cardiopulmonary exercise testing
CRP	C-reactive protein
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
IL-1β	interleukin-1β
NT-proBNP	N-terminal pro-B-type natriuretic peptide
REDHART	Recently Decompensated Heart Failure Anakinra Response Trial
REDHART2	Recently Decompensated Heart Failure Anakinra Response Trial 2
VE/VCO_2	minute ventilation/carbon dioxide production
VO_2	oxygen consumption

IL-1β (interleukin-1β) is an apical, proinflammatory cytokine known as the fever molecule.[1] IL-1β also represents one of the mechanisms by which patients with sepsis experience cardiac dysfunction.[2–4] Increased IL-1β levels and activity are common in patients with acute decompensated heart failure with reduced ejection fraction (HFrEF).[3–5] Inhibition of IL-1 signaling has been shown to preserve and restore cardiac function in preclinical models of heart failure (HF).[3–5] Phase II clinical trials with anakinra, a recombinant human IL-1 receptor antagonist, have shown a reduction in systemic inflammation in patients with acute myocardial infarction and HF, associated with favorable changes in cardiac function, cardiorespiratory fitness, and HF symptoms.[3–12] A phase III clinical trial with canakinumab, an IL-1β antibody, given every 3 months in patients with prior myocardial infarction, significantly reduced recurrent atherothrombotic events and HF-related hospitalizations.[13,14] A substudy showed that those individuals achieving resolution of systemic inflammation, defined as a CRP (C-reactive protein) level <2 mg/L, had the most favorable outcomes.[15] Multiple different strategies are being attempted to promote prompt inflammation resolution in patients with acute decompensated HFrEF.[16]

The purpose of the current study was to determine whether improved resolution of the systemic inflammatory response with the IL-1 blocker anakinra would improve aerobic exercise capacity in patients with recent acute decompensated HFrEF.

METHODS

The protocol and the data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The rationale and design of the REDHART2 (Recently Decompensated Heart Failure Anakinra Response Trial 2) have been previously shared.[17] Prospective patients hospitalized with ADHF at Virginia Commonwealth University in Richmond or South Hill, VA, United States, were evaluated for eligibility and randomly assigned to active treatment or placebo in a 2:1 ratio.

Regulatory Aspects

Virginia Commonwealth University institutional review board approval was obtained, and all participants provided written informed consent. Anakinra (recombinant human IL-1 receptor antagonist, Kineret; Swedish Orphan Biovitrum, Waltham, MA) 100 mg daily subcutaneously or matching placebo for 24 weeks was dispensed by the Investigational Drug Services. The study met the criteria for exemption from the need for investigational new drug use according to existing US Food and Drug Administration regulations. The 2 coprincipal investigators (B.V.T. and A.A.) and a study manager (E.F.) were responsible for coordinating the study activities under the supervision of the

program officer from the National Heart, Lung & Blood Institute (Emily Tinsley, PhD), without a formal steering committee.

Screening and Enrollment

After an initial screening and evaluation, including high-sensitivity CRP levels ≥2 mg/L, eligible patients underwent a baseline assessment of peak oxygen consumption (VO_2) using treadmill cardiopulmonary exercise testing (CPX) within 14 days of hospital discharge and those with peak VO_2<80% predicted by age, sex, and weight using Wasserman's formula[18] were randomly assigned to anakinra 100 mg subcutaneously or matching placebo daily for 24 weeks. A complete list of the inclusion and exclusion criteria is provided in Table S1. In brief, patients needed to have been admitted with a diagnosis of acute (or acute-on-chronic) HFrEF (left ventricular ejection fraction <40%) based on symptoms, signs, cardiac biomarkers, or noninvasive or invasive measures of elevated cardiac filling pressures. Patients also needed to be considered clinically stable and ready for hospital discharge, able and willing to follow study instructions and complete study tests, but with evidence of enhanced systemic inflammation, as shown by CRP plasma levels ≥2 mg/L measured by high-sensitivity assay. Patients with systemic immune-mediated inflammatory diseases, infections, or cancer were excluded.

Study Procedures

Cardiopulmonary exercise testing was repeated at 6, 12, and 24 weeks to measure interval changes in peak VO_2 and other measures of cardiorespiratory fitness. We also collected cardiac dimensions and function using transthoracic Doppler echocardiography and cardiac biomarkers at baseline and at 6, 12, and 24 weeks. Clinical safety assessments and safety laboratory markers, including complete blood cell count with differential and comprehensive metabolic panel, were measured at 2, 6, 12, and 24 weeks. High-sensitivity CRP was repeated at 6, 12, and 24 weeks.

Randomization and Allocation Concealment

A randomization sheet was prepared by the Investigational Drug Services. Anakinra and placebo (vehicle) were purchased from Swedish Orphan Biovitrum (Waltham, MA) in 0.67-mL clear syringes identifiable by lot number but otherwise indistinguishable. The investigators were blinded to all CRP levels throughout the study, except for the screening value.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board was formed in accordance with the recommendations of the US Food and Drug Administration.[19] The Data and Safety Monitoring Board reviewed and approved the initial protocol, amendments, and enrollment and safety data every 6 months. Table S2 shows the composition and expertise of the Data and Safety Monitoring Board members.

Cardiopulmonary Exercise Testing

All patients underwent a supervised maximal aerobic exercise test administered by a trained exercise physiologist using a metabolic cart interfaced with a treadmill, utilizing a conservative ramping treadmill protocol, as previously described.[9,17,20] A peak respiratory exchange ratio value ≥1.00 was considered a minimal acceptable threshold for exercise effort.[21,22] Patients who interrupted the CPX for reasons affecting the ability to provide maximal effort (ie, ischemia, arrhythmias, claudication) were excluded and considered screen failures if occurring at the time of the baseline test. The highest 10-second average value for VO_2 during the final 30 seconds defined peak VO_2 in mL·kg^{-1}·min^{-1}.[23] The de-identified data were transferred to a Core Laboratory at the University of Illinois, Chicago, IL, for analysis by Ross Arena, PhD.

Doppler Echocardiography

All subjects underwent a transthoracic Doppler echocardiogram before initiation of treatment and at each subsequent visit to measure left ventricular dimension and function, as previously described.[24,25] Two experienced operators, blinded to treatment allocation, completed all measurements offline after the completion of the last visit. The average of the 2 measurements was used for measures differing by ≤10%, whereas those with a difference >10% were rereviewed and discussed to achieve consensus. We used noninvasive measurement of blood pressure coupled with transthoracic echocardiography to calculate arterial elastance, end-systolic elastance, and ventriculoarterial coupling, defined as the arterial elastance/end-systolic elastance ratio, as previously described.[26]

Quality of Life Assessments

Quality of life was assessed using 4 different validated questionnaires. We used the Duke Activity Status Index[27,28] to assess perceived exercise capacity, with lower scores indicating greater physical impairment, and the Kansas City Cardiomyopathy Questionnaire[29] to reflect symptom burden, with higher scores indicating a greater burden. We also used the International Physical Activity Questionnaire-Short Form,[30] and the Patient Health Questionnaire-9[31] for self-reported physical activity and depression, respectively.

Clinical Events

Clinical events for the entire cohort of 102 patients were evaluated by the investigators, reported periodically to the Data and Safety Monitoring Board and systematically reviewed by a dedicated expert committee that included cardiologists, internal medicine specialists, and infectious disease specialists not otherwise involved in the study conduct (Table S3). A list of clinical events of special interest is provided in Table S4.

Primary and Secondary End Points

The primary end point was the change in peak VO_2 (mL·kg^{-1}·min^{-1}) versus placebo at 24 weeks. Secondary end points included changes in CRP, minute ventilation/carbon dioxide production (VE/VCO_2) slope, left ventricular ejection fraction, and E/e′ ratio, as well as changes in Duke Activity Status Index and Kansas City Cardiomyopathy Questionnaire scores. A composite of HF-related events, including death, rehospitalization for HF and outpatient worsening HF, was used as the primary clinical outcome.

Statistical Analysis

Descriptive summaries of continuous measurements are reported as medians and interquartile ranges due to potential deviation from a Gaussian distribution. Descriptive summaries of categorical measurements consist of frequencies, proportions, and 95% CIs, where applicable. Interval changes are expressed as percent change from baseline. All analyses were conducted after database lock on July 22, 2024, and were based on the intention-to-treat principle. The Statistical Package for the Social Sciences (SPSS) software, version 29.0.2.0 (IBM, New York, NY) was used. The difference in interval changes in peak VO_2 at 24 weeks between the anakinra and placebo groups were compared using random-effects ANOVA for repeated measures to analyze the effects of time_×_group allocation. For cases with missing data for the primary end point at 24 weeks, the last observation at 12 or 6 weeks was carried forward, considering that excluding patients with missing data would have inevitably led to a survivorship bias.[32] Cases with no peak VO_2 data in the follow-up period were, however, omitted from the analysis. The effect size for peak VO_2 was also expressed using the median difference and 95% CI method. Unadjusted *P* values are reported throughout, with statistical significance set at a 2-tailed 0.05 level. Given an expected average peak VO_2 of 15.0 mL·kg^{-1}·min^{-1}, 68 subjects randomized to anakinra and 34 to placebo (2:1 randomization) provided >95% power to detect a difference in peak VO_2 of 1.6 mL·kg^{-1}·min^{-1}. For the secondary analyses, interval changes within the entire population and the individual groups were evaluated using the Wilcoxon test for paired data. Differences between groups were assessed using the Mann-Whitney *U* test for unpaired data. Kaplan-Meier curves with log-rank testing were used to compare event rates between groups, and Cox survival analysis was used to calculate the hazard ratios and 95% CIs.

RESULTS

Screening and Randomization

We initiated screening on January 2, 2019 and completed enrollment on December 29, 2023, with a brief interruption between March 17, 2020 and September 14, 2020, due to restrictions related to the COVID-19. We evaluated 241 patients, 96 (39.8%) of whom were excluded; 43 (17.8%) declined to participate in the trial but agreed to participate in a noninterventional registry; and 102 (42.3%) were randomly assigned to anakinra (68 [66.7%]) or placebo (34 [33.3%]; Figure 1).

Of the 102 patients, 4 (3.9%) were withdrawn by the investigators before the first follow-up visit due to pandemic restrictions under local IRB guidance due to concerns about the conduct of the trial and access to care, and 14 (13.7%) withdrew from the trial before the first follow-up visit, leaving 84 patients with data available for the primary end point, 57 (67.9%) treated with anakinra and 27 (32.1%) with placebo (Figure 1).

Characteristics of the Patients

Table 1 summarizes the clinical and demographic characteristics of the 84 patients. Of these, 56 (67%) were male; 59 (70%) were Black; 23 (27%) were White; 1 (1%) was Asian; and 1 (1%) reported other. Median age was 57.5 (46.2, 65.0) years. Baseline CRP was 6.1 (3.6, 13.2) mg/L and peak VO_2 was 13.0 (10.9, 17.0) mL·kg^{-1}·min^{-1}. Guideline-directed medical therapies for HFrEF at baseline and at the end of the study are shown in Table 1 and Table S5, respectively. At baseline, the patients in the anakinra group had a slightly higher body mass index and a lower peak respiratory exchange ratio and VE/VCO_2 slope, while statin use was more common in the placebo group.

Treatment and Follow-Up

The median duration of treatment and follow-up was 167 (157, 169) days, with 84 (100%) completing at least the 6-week, 64 (76%) the 12-week, and 57 (68%) the 24-week follow-up. The primary end point was available in 84 patients, 57 treated with anakinra and 27 with placebo. The 24-week treatment was completed in 37 and 20 in the anakinra and placebo groups, respectively.

Effects on Peak Aerobic Capacity (Peak VO_2) – Primary End Point

Peak VO_2 significantly increased from 13.0 (10.9, 17.0) to 14.9 (12.0, 18.0) mL·kg^{-1}·min^{-1} (*P*<0.001) in the entire cohort, without any significant differences between anakinra and placebo (+1.5 [−0.2, +3.4] and +1.2 [+0.5, +3.9] mL·kg^{-1}·min^{-1}, respectively, *P*=0.40 for treatment × group allocation and *P*=0.60 for between-group differences; Table 2 and Figure 2). The median difference between groups was +0.30 mL·kg^{-1}·min^{-1}, favoring anakinra; however, the 95% CI was wide, ranging from −1.70 to +0.90.

A sensitivity analysis of only those who completed the 24-week treatment showed similar results (+1.8 [+0.5, +3.9] versus +1.2 [+0.5, +6.3] mL·kg^{-1}·min^{-1} in anakinra and placebo, respectively, *P*=0.87). We also found no significant differences between anakinra or placebo at 6 and 12 weeks in those who completed treatment (all *P*>0.05). Similar results were also obtained stratifying patients according to sex and to race (all *P*>0.05).

Effects on Systemic Inflammation Measured as CRP Levels

A significant reduction in CRP levels was seen in the entire cohort at 24 weeks, from 6.1 (3.6, 13.2) to 2.2 (0.8, 5.0) mg/L, with a −76% (−87%, −36%) in anakinra-treated patients and −48% (−77%, +14%) in the placebo group (*P*=0.050 for interval percent changes between groups; Table 2; Figure 2).

Additional End Points

The VE/VCO_2 slope improved from 33.5 (29.0, 38.1) to 30.4 (27.5,35.5; *P*<0.001) in the entire cohort. The VE/

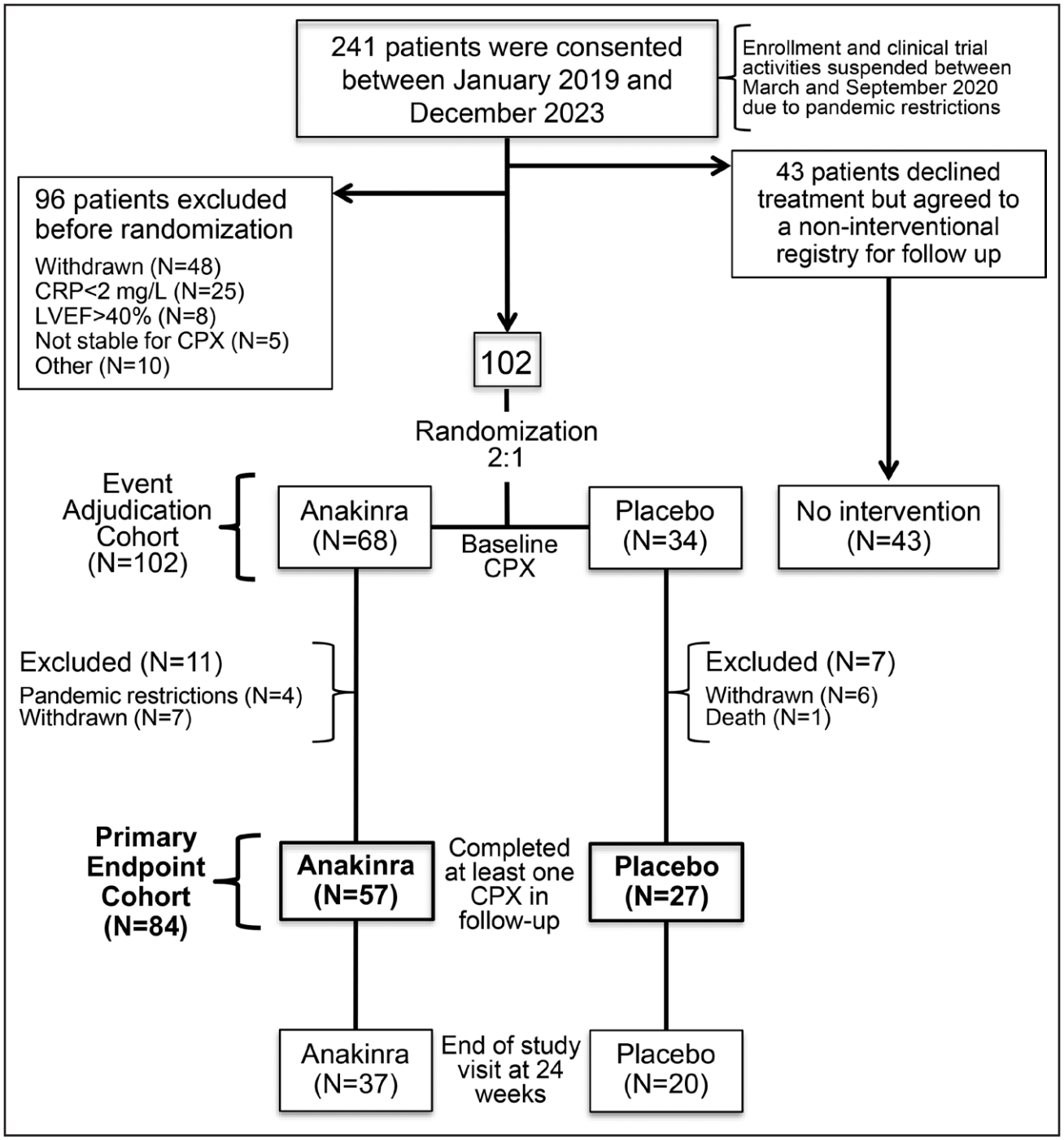

Figure 1. Screening and enrollment of patients.
The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown reflecting screening and randomization activities. All study activities were interrupted between March and September 2020 due to pandemic restrictions. Individuals who were eligible but not interested in the clinical trial were offered to be part of a noninterventional registry. Of the 241 patients, 96 were excluded before randomization, 43 patients declined treatment but agreed to be part of the noninterventional registry for follow-up, and 102 patients were randomly assigned to anakinra or placebo, 2:1, in a double-blinded fashion. Of the 102 patients, 84 had completed at least 1 cardiopulmonary exercise test (CPX) in the follow-up allowing for the calculation of the primary end point (primary end point cohort), whereas 18 patients were excluded beforehand. Of the 84 patients, 57 completed the 24-week treatment and CPX, 37 in the anakinra group and 20 in the placebo group, representing 56% of the randomized population. Clinical events were calculated on all 102 patients in the trial and the 43 patients who received no intervention (event adjudication cohort).

Table 1. Baseline Demographic and Clinical Characteristics

	All (n=84)	Placebo (n=27)	Anakinra (n=57)	*P* value
Age, y	58 (46–65)	61 (47–67)	57 (45–64)	0.50
Sex, male	56 (67%)	21 (78%)	35 (61%)	0.14
Race, Black	59 (70%)	21 (78%)	38 (67%)	0.43
Body mass index, kg/m^2	32 (28–39)	30 (26–34)	34 (30–40)	0.015
Arterial hypertension	67 (80%)	25 (93%)	42 (74%)	0.04
Diabetes	32 (38%)	12 (44%)	20 (35%)	0.41
Hyperlipidemia	47 (56%)	18 (67%)	29 (51%)	0.17
Tobacco use	49 (58%)	12 (44%)	37 (65%)	0.08
Coronary artery disease	26 (31%)	11 (41%)	15 (26%)	0.18
Atrial fibrillation	21 (25%)	7 (26%)	14 (25%)	0.89
Peripheral vascular disease	3 (4%)	1 (4%)	2 (4%)	1.00
Chronic kidney disease	23 (27%)	5 (19%)	18 (32%)	0.21
Chronic obstructive lung disease	18 (21%)	8 (30%)	10 (18%)	0.21
Obstructive sleep apnea	16 (19%)	4 (15%)	12 (21%)	0.50
DVT/PE	11 (13%)	6 (22%)	5 (9%)	0.16
Biomarkers				
CRP, mg/L	6.1 (3.6–13.2)	6.0 (2.6–29.4)	6.3 (4.0–11.4)	0.89
NT-proBNP, pg/mL	1036 (503–2653)	2195 (595–3963)	836 (403–1890)	0.06
Hb, g/dL	13.7 (12.6–15.1)	13.5 (12.9–14.7)	14.0 (12.4–15.2)	0.63
PLT, ×10^3/μL	258 (218–288)	266 (233–312)	253 (215–274)	0.10
Creatinine, mg/dL	1.21 (0.98–1.58)	1.28 (1.01–1.54)	1.20 (0.96–1.67)	0.47
WBC, ×10^3/μL	6.8 (5.5–8.0)	6.3 (5.3–8.0)	6.8 (5.6–8.0)	0.32
Neu, %	60.6 (48.0–68.5)	61.2 (47.2–69.4)	60.6 (48.2–68.2)	0.84
Lymph, %	26.3 (19.9–35.7)	24.8 (18.8–38.5)	26.6 (20.3–34.7)	0.99
Mono, %	9.6 (7.5–11.2)	9.4 (7.2–11.0)	9.6 (7.6–11.3)	0.39
Eos, %	2.5 (1.7–4.1)	2.1 (1.4–3.7)	2.7 (1.8–4.2)	0.13
Baso, %	0.7 (0.4–1.0)	0.7 (0.5–1.0)	0.7 (0.4–1.1)	1.00
NYHA				0.71
NYHA class II	46 (55%)	14 (52%)	32 (56%)	
NYHA class III	38 (45%)	13 (48%)	25 (44%)	
Quality of life assessments				
DASI score	26.5 (16.6–38.2)	24.7 (19.0–37.5)	26.7 (14.7–38.2)	0.93
KCCQ Summary Score	54.5 (32.6–66.8)	47.4 (24.0–64.6)	55.7 (36.7–69.8)	0.24
IPAQ-SF score, MET·min/wk	325 (41–2027)	594 (0–2076)	304 (81–2079)	0.98
PHQ-9 score	6 (3–12)	6 (4–14)	6 (3–11)	0.61
Doppler echocardiography				
LVEDV, mL	198 (151–240)	184 (149–212)	205 (160–268)	0.15
LVESV, mL	141 (107–184)	132 (105–147)	149 (108–197)	0.18
LVEF, %	28 (21–34)	28 (25–34)	28 (21–35)	0.52
SV, mL	51 (43–67)	51.0 (44.3–66.7)	54.2 (43–67.2)	0.78
LAV, mL	90 (73–115)	87 (69–98)	99 (74–119)	0.10
E′, cm/s	5.5 (4.7–6.5)	5.1 (4.5–6.1)	5.6 (4.8–6.6)	0.29
E/E′ ratio	16.1 (11.9–19.6)	17.8 (11.8–20.0)	15.3 (11.9–19.6)	0.48
TAPSE, cm	2.0 (1.7–2.2)	1.9 (1.4–2.1)	2.0 (1.7–2.2)	0.16
Ea, mm Hg/mL	1.93 (1.66–2.60)	1.93 (1.76–2.62)	1.89 (1.62–2.59)	0.53
Ees, mm Hg/mL	0.81 (0.56–1.04)	0.84 (0.62–1.10)	0.76 (0.52–1.01)	0.17
Ea/Ees	2.56 (1.93–3.75)	2.57 (1.95–3.17)	2.56 (1.88–3.76)	0.55

(*Continued*)

Table 1. Continued

	All (n=84)	Placebo (n=27)	Anakinra (n=57)	*P* value
Cardiopulmonary exercise test				
Exercise time, s	437 (328–599)	440 (314–546)	434 (331–610)	0.50
Peak RER	1.16 (1.07–1.25)	1.19 (1.11–1.28)	1.13 (1.07–1.21)	0.043
Peak VO_2, mL·kg^{-1}·min^{-1}	13.0 (10.9–17.0)	13.2 (10.6–16.2)	12.9 (11.0–17.4)	0.87
VE/VCO_2 slope	33.5 (29.0–38.1)	36.6 (31.8–42.6)	31.6 (28.6–37.5)	0.013
OUES, mL/min	1.5 (1.2–2.0)	1.4 (1.2–1.8)	1.6 (1.2–2.1)	0.18
Therapy, n (%)				
ACE inhibitor/ARBs	42 (50%)	13 (48%)	29 (51%)	0.82
ARNI	27 (32%)	9 (33%)	18 (32%)	0.87
SGLT2i	12 (14%)	2 (7%)	10 (18%)	0.32
β-adrenergic receptor blockers	76 (90%)	23 (85%)	53 (93%)	0.26
Aldosterone blockers	32 (38%)	7 (26%)	25 (44%)	0.11
Hydralazine/isosorbide	20 (24%)	5 (19%)	15 (26%)	0.43
Loop diuretics	77 (92%)	25 (93%)	52 (91%)	1.00
Furosemide equivalent dose, mg	80 (40–80)	40 (40–120)	80 (40–80)	0.91
Statins	47 (56%)	21 (78%)	26 (46%)	0.006
Colchicine	4 (5%)	1 (4%)	3 (5%)	1.00
Cardiac resynchronization therapy	4 (5%)	0	4 (7%)	0.30
Implantable cardiac defibrillator	22 (26%)	7 (26%)	15 (26%)	0.97

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; Baso, basophils; CRP, C-reactive protein; DASI, Duke Activity Status Index; DVT/PE, deep vein thrombosis/pulmonary embolism; E/E′, ratio of early mitral inflow velocity to average early diastolic mitral annular velocity (septal and lateral); E′, average early diastolic mitral annular velocity (septal and lateral) by tissue Doppler imaging; Ea, effective arterial elastance; Ea/Ees, ventriculoarterial coupling ratio; Ees, end-systolic elastance; Eos, eosinophils; Hb, aemoglobin; IPAQ-SF, International Physical Activity Questionnaire-Short Form; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; Lymph, lymphocytes; Mono, monocytes; Neu, neutrophils; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; PHQ-9, Patient Health Questionnaire-9; PLT, platelets; RER, respiratory exchange ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2 slope, minute ventilation-carbon dioxide production slope; VO_2, volume of oxygen production; and WBC, white blood cell count.

VCO_2 slope was significantly higher (worse) in the placebo group at baseline but not at follow-up, resulting in a significantly greater reduction in VE/VCO_2 slope with placebo (−3.9 [−5.4, −0.8] versus −1.2 [−3.5, +1.7], *P*=0.014; Table 2). Left ventricular ejection fraction and E/e′ improved from 28 (21, 34) to 35 (27, 47) % (*P*<0.001) and from 16.1 (11.9, 19.6) to 11.4 (9.1, 17.2; *P*<0.001), respectively, in the entire cohort, without significant differences between the anakinra and placebo groups (+8.7 [+0.3, +16.0]% versus +7.0 [−1.9, +15.0]%; *P*=0.55, and −2.1 [−6.9, +1.2] versus −3.0 [−7.0, −0.6]; *P*=0.48, respectively). Ventriculararterial coupling (arterial elastance/end-systolic elastance) significantly improved from 2.56 (1.93, 3.75) to 1.85 (1.13, 2.71; *P*<0.001) in the entire cohort, without significant differences between the anakinra and placebo groups (−0.68 [−1.28, −0.11] versus −0.63 [−1.32, +0.18]; *P*=0.63). The NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels improved from 1036 (503, 2653) to 482 (174, 1532) pg/mL (*P*<0.001) in the entire cohort, without significant differences between the anakinra and placebo groups (−47 [−79, −12]% versus −53 [−86, +3]%; *P*=0.43). The Duke Activity Status Index, Kansas City Cardiomyopathy Questionnaire overall summary score, and clinical summary score improved significantly from 26.5 (16.6, 38.2) to 37.5 (22.5, 50.6; *P*<0.001), from 54.5 (32.6, 66.8) to 84.4 (64.6, 91.7) and from 59.2 (42.2, 78.0) to 89.2 (73.0, 95.2; *P*<0.001), respectively, in the entire cohort, without significant differences between the anakinra and placebo groups (+7.5 versus +3.5, *P*=0.50; +24.7 versus +23.7, *P*=0.55; and +16.7 versus +29.2; *P*=0.17, respectively). Similarly, the International Physical Activity Questionnaire-Short Form and Patient Health Questionnaire-9 scores improved significantly from 325 (41, 2027) to 1659 (464, 4852) metabolic equivalent •min/wk (*P*<0.001) and from 6 (3, 12) to 2 (0, 9; *P*<0.001), respectively, in the entire cohort, without significant differences between the anakinra and placebo groups (+737 versus +480 metabolic equivalent min/wk, *P*=0.34, and −3 versus −4; *P*=0.51, respectively; Table 2).

Clinical Events

Kaplan-Meier curves were created to assess for time-dependent events in the cohort of 102 patients. There were 18 patients who died, had re-admission for HF,

Table 2. Data at the 24-Week Visit (Longest Available Follow-Up/End of Study)

	Placebo (n=27)	Anakinra (n=57)	Δ% Placebo	Δ% Anakinra	*P* value for Δ%
Biomarkers					
CRP, mg/L	4.1 (0.9–7.3)	2.1 (0.8–4.0)	−48 (−77 to +14) %	−76 (−87 to −36) %	**0.050**
NT-proBNP, pg/mL	664 (222–1663)	448 (167–1290)	−53 (−86 to +3) %	−47 (−79 to −12) %	0.43
Hb, g/dL	13.8 (12.4–15.0)	14.3 (12.9–15.3)	0 (−6 to +4) %	0 (−5 to +11) %	0.57
PLT, ×10³/μL	239 (193–274)	206 (175–241)	−7 (−22 to −1) %	−15 (−26 to −2) %	0.27
Creatinine, mg/dL	1.14 (0.97–1.74)	1.15 (0.93–1.65)	−6 (−14 to +12) %	−2 (−12 to +13) %	0.42
WBC, ×10³/μL	7.2 (5.4–7.8)	5.8 (4.6–7.5)	3 (−11 to 21) %	−13 (−25 to +6) %	**0.004**
Neu, %	64.3 (52.9–69.4)	53.5 (42.2–61.7)	+7 (−3 to +16) %	−9 (−21 to +5) %	**0.001**
Lymph, %	26.5 (18.9–33.2)	31.6 (23.8–38.4)	−6 (−19 to +11) %	+12 (−5 to +35) %	**0.021**
Mono, %	8.5 (7.0–9.9)	9.1 (7.7–12.2)	−12 (−22 to +12) %	−3 (−17 to +19) %	0.40
Eos, %	2.1 (1.5–3.1)	4.2 (2.2–6.8)	−8 (−31 to +33) %	+31 (0 to +107) %	**0.016**
Baso, %	0.6 (0.4–0.8)	0.7 (0.5–1.0)	−8 (−29 to +3) %	0 (−33 to +33) %	0.20
Quality of life assessments					
DASI score	37.5 (19.5–50.7)	37.5 (23.2–50.2)	18 (0–45) %	22 (0–79) %	0.54
KCCQ summary score	82.0 (63.8–93.5)	84.5 (72.6–91.1)	45 (22–183) %	51 (19–78) %	0.59
IPAQ-SF score, MET·min/wk	1096 (495–3192)	2151 (351–4988)	21 (−34 to 569) %	100 (−38 to 781) %	0.53
PHQ-9 score	3 (1–8)	2 (0–9)	−75 (−93 to 0) %	−53 (−91 to −21) %	0.64
Doppler echocardiography					
LVEDV, mL	150 (129–190)	160 (115–239)	−4 (−27 to +8) %	−13 (−26 to +3) %	0.37
LVESV, mL	108 (65–150)	113 (63–172)	−13 (−42 to +5) %	−20 (−44 to −3) %	0.30
LVEF, %	35 (27–49)	35 (26–47)	+24 (−6 to +50) %	+27 (+1 to +63) %	0.65
SV, mL	58 (52–67)	58 (45–75)	+5 (−12 to +41) %	+5 (−13 to +34) %	0.56
LAV, mL	68 (56–104)	85 (65–112)	−13 (−28 to +15) %	−12 (−25 to +7) %	0.95
E′, cm/s	5.8 (4.4–7.5)	5.9 (4.4–7.7)	+11 (−7 to +33) %	−5 (−20 to +36) %	0.41
E/E′ ratio	11.0 (9.4–16.9)	12.6 (9.0–18.0)	−26 (−37 to −3) %	−14 (−44 to +11) %	0.44
TAPSE, cm	2.0 (1.6–2.3)	2.1 (1.8–2.3)	+12 (−4 to +30) %	+5 (−9 to +21) %	0.32
Ea, mm Hg/mL	1.96 (1.71–2.33)	1.87 (1.53–2.32)	−10 (−29 to +20) %	−5 (−26 to +14) %	0.94
Ees, mm Hg/mL	0.98 (0.81–1.88)	0.95 (0.59–1.81)	+20 (−1 to +80) %	+26 (−2 to +77) %	0.76
Ea/Ees	1.85 (1.04–2.69)	1.79 (1.14–3.00)	−31 (−48 to +9) %	−33 (−51 to −5) %	0.51
CPET parameters					
Exercise time, s	562 (380–643)	546 (432–666)	+17 (+10 to +43) %	+22 (+7 to +39) %	0.70
Peak RER	1.21 (1.08–1.28)	1.18 (1.10–1.27)	+2 (−5 to +10) %	+4 (−4 to +13) %	0.38
Peak VO_2, mL·kg^{-1}·min^{-1}	15.4 (11.9–18.0)	14.2 (12.0–18.1)	+11 (3–36) %	+9 (−1 to +25) %	0.37
VE/VCO_2 slope	31.5 (28.2–38.3)	30.1 (27.4–34.3)	−9 (−17 to −2) %	−4 (−10 to +5) %	**0.022**
OUES, mL/min	1.6 (1.4–2.1)	1.75 (1.34–2.21)	+7 (−1 to +32) %	+6 (−6 to +20) %	0.21

Baso indicates basophils; CPET, cardiopulmonary exercise test; CRP, C-reactive protein; DASI, Duke Activity Status Index; E/E′, ratio of early mitral inflow velocity to average early diastolic mitral annular velocity (septal and lateral); E′, average early diastolic mitral annular velocity (septal and lateral) by tissue Doppler imaging; Ea, effective arterial elastance; Ea/Ees, ventriculoarterial coupling ratio; Ees, end-systolic elastance; Eos, eosinophils; Hb, hemoglobin; IPAQ-SF, International Physical Activity Questionnaire-Short Form; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; Lymph, lymphocytes; Mono, monocytes; Neu, neutrophils; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OUES, oxygen uptake efficiency slope; PHQ-9, Patient Health Questionnaire-9; PLT, platelets; RER, respiratory exchange ratio; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2 slope, minute ventilation-carbon dioxide production slope; and WBC, white blood cell count.

or experienced an outpatient worsening of HF, with a 24-week rate of 20.2% with no significant differences between placebo and anakinra groups (21.0% and 19.9%, respectively, log-rank *P*=0.99; Cox HR, 0.99 [95% CI, 0.37–2.65]; Figure 3 and Table S6). The results were similar if the analysis had been restricted to the 84 patients included in the analysis of the primary end point (log-rank *P*=0.61; Cox HR, 1.35 [95% CI, 0.43–4.24]). In contrast, the incidence of the combined end point of death, HF rehospitalization, and outpatient worsening HF in the registry was 43.7% (log-rank *P*=0.049 when comparing 3 groups and *P*=0.014 when comparing with the anakinra and placebo arms combined; Cox HR, 1.54 [95% CI, 1.08–2.19]; Figure 3). A complete list of serious adverse events is presented in Table S6. Regarding serious infections, 7 patients in the placebo group and 12

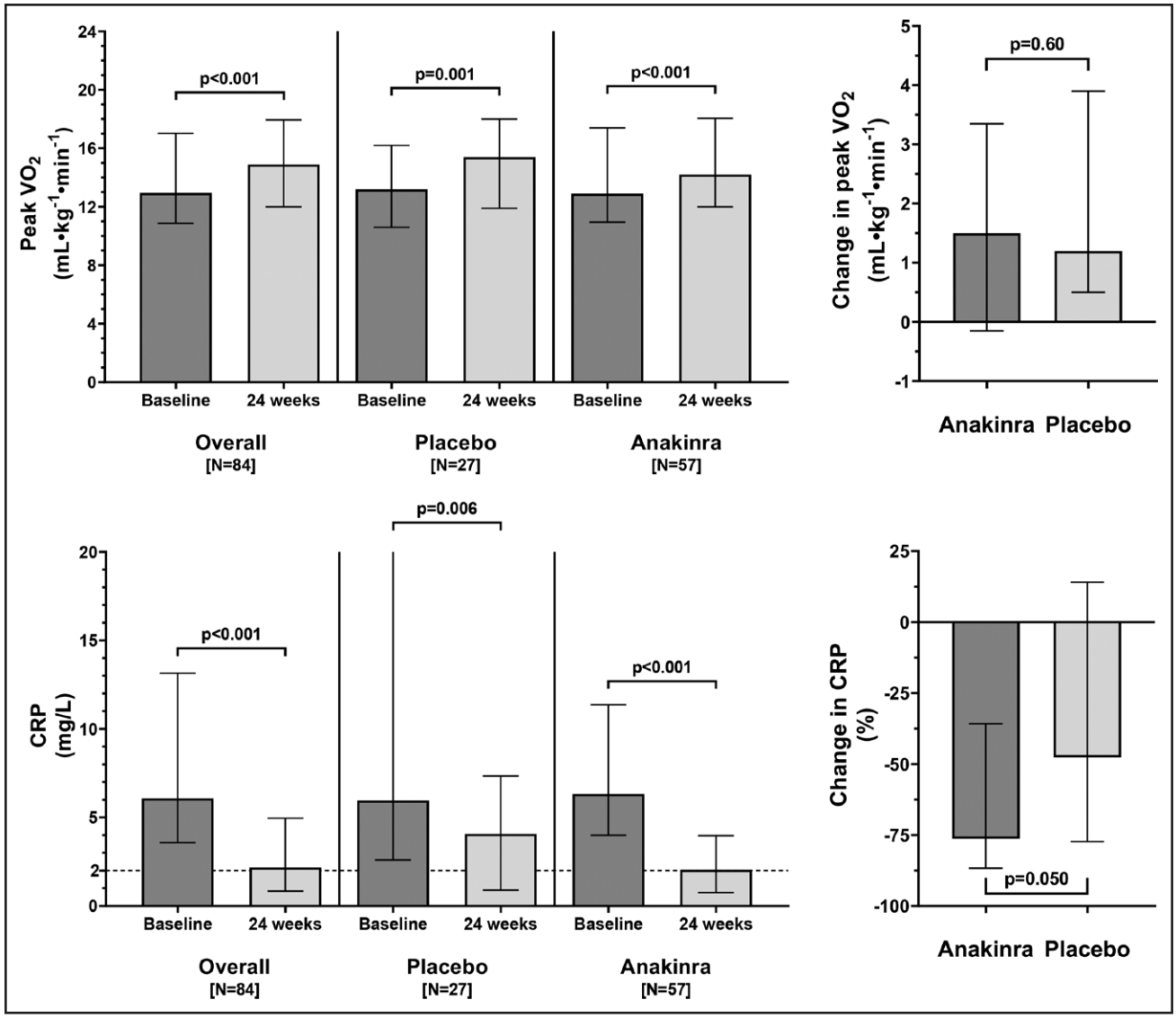

Figure 2. Changes in CRP (C-reactive protein) and peak oxygen consumption (VO_2) without and with anakinra treatment. Median and quartiles of the changes in CRP and peak VO_2 after a follow-up of 167 [157–169] days are shown in the top and bottom panels, respectively. Overall indicates all patients in the primary end point cohort (n=84), whereas Placebo and Anakinra indicate the 2 groups. A significant improvement in peak VO_2 was seen in the overall cohort as well as in the placebo and anakinra groups, without any significant difference in the changes between the 2 groups. A significant reduction in CRP values was seen in the overall cohort as well as in the placebo and anakinra groups, with a significantly greater reduction in the anakinra group.

patients in the anakinra group experienced an infection requiring prescription of an antimicrobial drug (log-rank *P*=0.61; Cox HR, 0.78 [95% CI, 0.31–2.00]). Injection site reactions were more common in the anakinra versus placebo groups (22 versus 2, respectively, log-rank *P*=0.003, Cox HR, 6.45 [95% CI, 1.52–27.46]).

Post Hoc Analysis Based on Treatment CRP Levels

CRP<2 mg/L was achieved in 44% of patients, 47% in the anakinra and 37% in the placebo groups (*P*=0.37). Patients achieving CRP<2 mg/L had a significantly greater increase in peak VO_2 than those with CRP≥2 mg/L (+2.6 [+0.7, +4.6] versus +1.0 [−0.3, +1.9] mL·kg^{-1}·min^{-1}; *P*=0.007), greater reductions in E/e′ (−26 [−46, +14]% versus −8 [−32, +19]%; *P*=0.006), LVEDV (−15 [−28, −3]% versus 0 [−26, +9]%; *P*=0.042), and NT-proBNP levels (−73 [−84, −27] % versus −38 [−68, +3]%; *P*=0.014), and significantly lower rates of HFrEF-related events (8% versus 26%; log-rank *P*=0.045; Cox HR, 0.30 [95% CI, 0.08–1.05]; Figure 4 and Table S7).

DISCUSSION

Patients with decompensated HFrEF are characterized by a large burden of symptoms, functional impairment, and frequent rehospitalizations. Acute decompensated

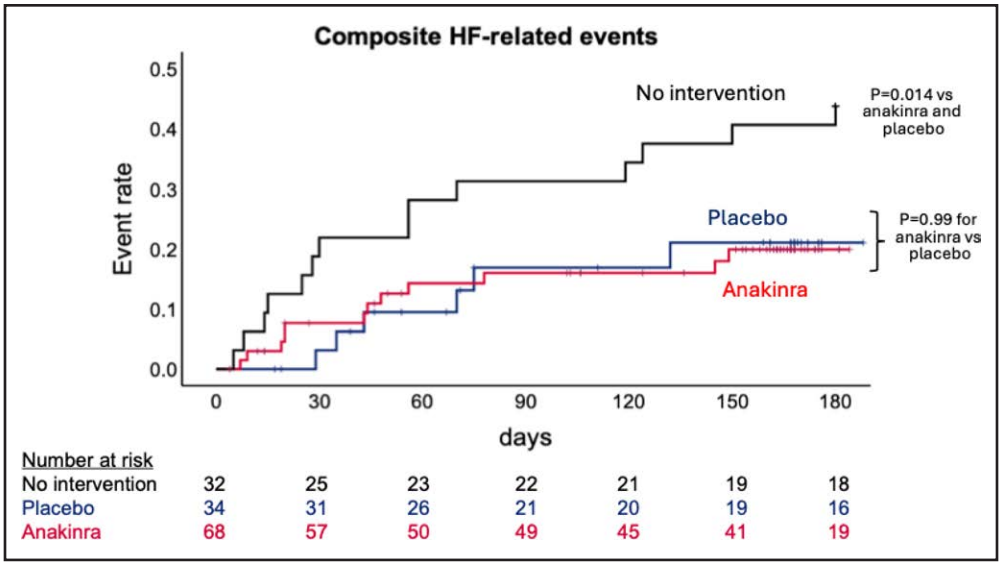

Figure 3. Clinical outcomes.
Kaplan-Meier curves are shown for patients in the placebo and anakinra arms of the clinical trial and in the noninterventional registry. There was no significant difference between anakinra and placebo groups, whereas the patients in the nonintervention registry had significantly more events than those in the clinical trial at a follow-up of 167 (157–169) days. Log-rank *P* value is shown.

HFrEF is also associated with systemic inflammation, measured by elevated CRP levels. We report herein that patients with recently decompensated HFrEF treated with modern, maximally tolerated guideline-directed medical therapy exhibit a significant improvement in CRP and peak VO_2, indicating that resolution of systemic inflammation is associated with clinical improvement. Several clinical trials have tested whether broad or targeted antiinflammatory therapies can help expedite the resolution of systemic inflammation and improve outcomes in HFrEF.[16] We herein show that the addition of anakinra, an IL-1 blocker used to treat rheumatologic diseases, had only a modest additional effect on CRP, and other inflammatory biomarkers (ie, neutrophil count), and no significant effects on the primary end point (ie, peak VO_2). Anakinra also failed to show any significant improvement over placebo in the secondary end points, including other measures of cardiorespiratory fitness, HF cardiac biomarkers, or clinical events.

Earlier, smaller phase II studies with anakinra had shown a significant reduction of CRP levels and improvement in peak VO_2 in stable ambulatory patients with HF and reduced or preserved ejection fraction.[5,10–12] A secondary analysis of the canakinumab trial also showed improved peak VO_2 in stable patients with prior MI and HFrEF.[33] A small clinical trial of patients hospitalized with HFrEF showed that twice-daily dosing of anakinra

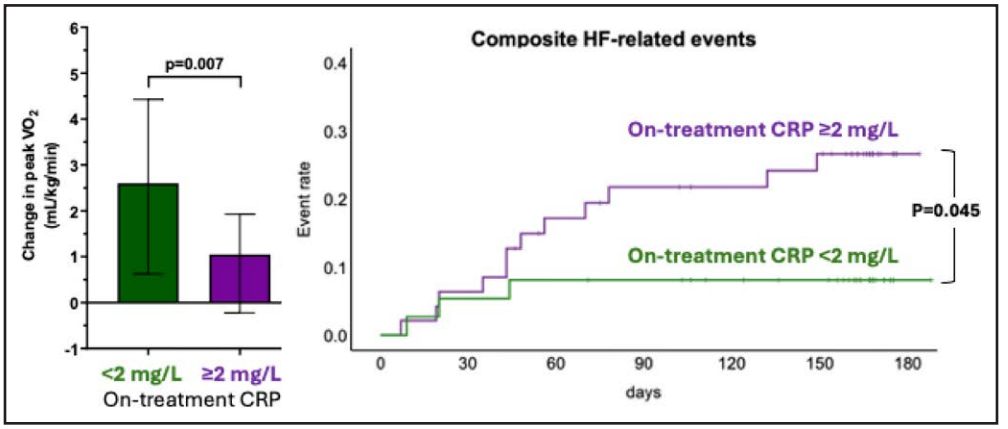

Figure 4. Changes in peak oxygen consumption (VO_2) and clinical outcomes in patients without and with on-treatment CRP (C-reactive protein) values.
A post hoc analysis of on-treatment CRP values shows that those patients with CRP <2 mg/L had significantly greater increase in peak VO_2 (median and quartiles) and significantly fewer heart failure (HF)-related events than those with CRP≥2 mg/L at a follow-up of 167 (157–169) days. *P* value was obtained with Mann-Whitney *U* test comparing changes between the 2 groups. Log-rank *P* value is shown for the survival curve.

for 3 days significantly reduced CRP as compared with placebo.[8] A follow-up pilot trial in patients with HFrEF who were being discharged from the hospital (REDHART [Recently Decompensated Heart Failure Anakinra Response Trial]), however, showed that 2 weeks of anakinra had no significant effects on peak VO_2, despite a reduction in CRP, whereas a numerically greater increase in peak VO_2 was seen in the group that received anakinra for 12 weeks.[9] The goal of the current study (REDHART2) was therefore to confirm and expand prior findings by treating patients with HFrEF for 24 weeks with anakinra. While patients treated with anakinra for 12 weeks in the REDHART trial and those treated for 24 weeks in the REDHART2 trial experienced a significant improvement in peak VO_2 (+2.1 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) in REDHART and (+1.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) in REDHART2, a difference is apparent between the placebo groups in the 2 trials (+0.3 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ in REDHART and +1.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ in REDHART2). Along the same lines, there was no significant change in CRP levels in the placebo group at 3 or 6 months in REDHART, whereas a significant 47.7% reduction in CRP was observed at 6 months in REDHART2. These data suggest that the improvement in the management of patients with HFrEF over the past decade may have led to a better treatment of the HF, and a reduction, and in some cases, resolution of systemic inflammation. Novel treatments include the more aggressive use of statins and renin-angiotensin-aldosterone and neprilysin inhibitors, and the introduction of sodium-glucose cotransporter 2 inhibitors.[34]

We also observed significantly lower rates of adverse HF outcomes among patients participating in the randomized clinical trial in either the anakinra or placebo arms (20.5%) when compared with those in the observational registry (43.6%). Notwithstanding the biases derived from nonrandom allocation, these data suggest a potential benefit of trial participation with multiple visits, CPX, Doppler echocardiography, and compliance with guideline-directed medical therapy, which may be associated with a significant reduction in HF rehospitalization rates, independent of treatment allocation. These data validate other studies of rapid uptitration of medications.[35] The favorable effects of this intensive strategy may, however, have jeopardized the ability to detect additional effects of anakinra. This may have implications for future HFrEF trials, which may benefit from a more selective inclusion of patients with residual inflammatory risk after optimization of standard HF therapy, the use of more powerful and long-acting antiinflammatory drugs, and possibly the inclusion of additional mechanistic biomarkers.

Given the improvement in HFrEF management, one may wonder whether there is a role for antiinflammatory therapies. A recent meta-analysis of different broad and targeted antiinflammatory therapies, including anakinra, showed a reduction in CRP and a trend toward more favorable clinical outcomes,[16] suggesting that add-on therapy may still have a role in this population. It is essential to note that, despite improvements in peak VO_2 and other measures of cardiorespiratory fitness, the median peak VO_2 remains low, consistent with significant limitations in daily activities.[36] Similarly, despite the improvements, the quality-of-life questionnaires show a persistent burden of symptoms. These symptoms are also associated with a non-negligible number of patients requiring rehospitalization during the 24-week follow-up. Finally, the median CRP levels at follow-up remain elevated in most patients in the placebo group (4.1 mg/L, with only 37% showing levels <2 mg/L), thus suggesting that systemic inflammation may still be relevant.

The lack of significant improvement with anakinra requires further discussion. Anakinra is a powerful and clinically effective disease-modifying drug in rheumatologic diseases.[37] In prior trials of patients at risk for or with HFrEF, anakinra 100 mg once daily significantly reduced CRP levels to <2 mg/L.[6,7] In a clinical trial of patients with ST-segment–elevation myocardial infarction, twice-daily anakinra was not better than once-daily anakinra in reducing CRP levels or preventing new-onset HF.[6] It is unclear why anakinra failed to normalize CRP levels in >50% of patients in the current trial. One possibility is treatment noncompliance. The moderately greater reduction in CRP for anakinra versus placebo, and the higher rates of injection-site reactions with anakinra, are somewhat reassuring regarding allocation and compliance. However, the challenges and disruptions to clinical care, including research-related procedures during the COVID-19 pandemic, may have hindered treatment compliance. The COVID-19 pandemic may also have impacted the detection and classification of HF-related events. Finally, it is possible that during the COVID-19 pandemic, the systemic inflammation in patients with HFrEF was enhanced and less responsive to IL-1 blockade with anakinra. Of note, severe COVID-19 in children and vaccine-related myocarditis were associated with neutralizing autoantibodies directed against the naturally occurring IL-1 receptor antagonist.[38,39]

The post hoc on-treatment analysis for CRP provides some confidence that the resolution of systemic inflammation may be favorable in patients with HFrEF. While only a minority of patients reached CRP<2 mg/L in this study, they did significantly better in terms of improvement in peak VO_2 and clinical events. This is consistent with what seen with canakinumab in patients with prior myocardial infarction,[13,14] where those patients with on-treatment CRP<2 mg/L derived the greatest benefit in terms of HF hospitalization. These data raise the question of whether a different antiinflammatory strategy could result in further improvement in outcomes in patients with HFrEF. It is possible that a higher dose of anakinra or a different strategy to block IL-1 may be needed. More potent IL-1 blockers are available, allowing for near-complete IL-1 neutralization with less frequent

dosing.[3,4,40] IL-6 blockers, such as ziltivekimab, are being studied in clinical trials of patients with stable cardiovascular disease, HF, and MI.[41] In a phase II trial, Ziltivekimab reduced CRP levels by >90%.[42]

It is important to note that the study has many significant limitations. First, it includes a small number of patients, thus limiting the power of the analysis. Given the smaller-than-expected difference between the 2 groups, a larger sample size would be necessary. An imbalance in baseline characteristics may have impacted the analysis. The missing data, which are also partially a result of the COVID-19 pandemic, provide additional uncertainty. The limited number of patients receiving 24 weeks of treatment further limits the power of the analysis.

In conclusion, patients with recently decompensated HFrEF treated with maximally tolerated guideline-directed medical therapy, followed by a strict protocol of frequent clinical assessments including echocardiography and CPX, have a significant improvement in CRP and peak VO_2. The addition of anakinra had a modest added effect on CRP, with borderline statistical significance, and no significant effects on peak VO_2 or other clinically relevant measures. Patients who show resolution of systemic inflammation (CRP <2 mg/L) exhibit, however, a greater increase in peak VO_2 and a reduction in HFrEF-related clinical events. Additional studies are warranted to determine whether a different strategy of antiinflammatory therapies could provide a greater resolution of systemic inflammation and improve outcomes in patients with HFrEF on optimal guideline-directed medical therapy.

ARTICLE INFORMATION

Received July 21, 2025; accepted November 7, 2025.

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Acknowledgments

The authors like to thank all patients who have participated in the trial, the members of the Data and Safety Monitoring Board and the Event Adjudication Committee (listed in Tables S2 and S3), as well as all the clinical providers at Virginia Commonwealth University Health, Virginia Commonwealth University, Richmond, VA, who assisted the research team in the completion of the study.

Sources of Funding

This study was been funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH; R33 HL139943) to Drs Abbate and Van Tassell, and a Clinical and Translational Science Award to Virginia Commonwealth University (UM1 TR004360 from the National Center for Research Resources) to support the clinical research unit at VCU Health. Drs Canada and Trankle were supported by the NHLBI or the NIH (K23 HL159270 and K23 HL166956, respectively).

Disclosures

Dr Abbate has served as a consultant for Kiniksa, Monte Rosa Therapeutics, and Novo Nordisk. The other authors report no conflicts.

Supplemental Material

Tables S1–S8

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