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Received 18 July 2024; revised 29 July 2024; accepted 8 August 2024

Abstract

Background and Aims	Acute heart failure (AHF) promotes inflammatory activation, which is associated with worse outcomes. Colchicine has proven effective in other cardiovascular conditions characterized by inflammatory activation, but has never been evaluated in the setting of AHF.
Methods	This multicenter, randomized, double-blind, and placebo-controlled trial included patients with AHF, requiring ≥ 40 mg of intravenous furosemide, regardless of their left ventricular ejection fraction (LVEF) and inpatient or outpatient setting. Patients were randomized within the first 24 h of presentation to receive either colchicine or placebo, with loading dose of 2 mg, followed by 0.5 mg every 12 h for 8 weeks.
Results	A total of 278 patients [median age 75 years, LVEF 40%, baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) 4262 pg/mL] were randomized to colchicine ($n = 141$) or placebo ($n = 137$). The primary endpoint, the time-averaged reduction in NT-proBNP levels at 8 weeks, did not differ between the colchicine group [-62.2% , 95% confidence interval (CI) -68.9% to -54.2%] and the placebo group (-62.1% , 95% CI -68.6% to -54.3%) (ratio of change 1.0). The reduction in inflammatory markers was significantly greater with colchicine: ratio of change 0.60 ($P < .001$) for C-reactive protein and 0.72 ($P = .019$) for interleukin-6. No differences were found in new worsening heart failure episodes (14.9% with colchicine vs. 16.8% with placebo, $P = .698$); however, the need for intravenous furosemide during follow-up was lower with colchicine ($P = .043$). Diarrhea was slightly more common with colchicine, but it did not result in differences in medication withdrawal (8.5% vs. 8.8%).
Conclusions	Colchicine was safe and effective in reducing inflammation in patients with AHF; however, colchicine and placebo exhibited comparable effects on reducing NT-proBNP and preventing new worsening heart failure events.

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[†] See Supplementary data online, Appendix.

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Structured Graphical Abstract

Key Question

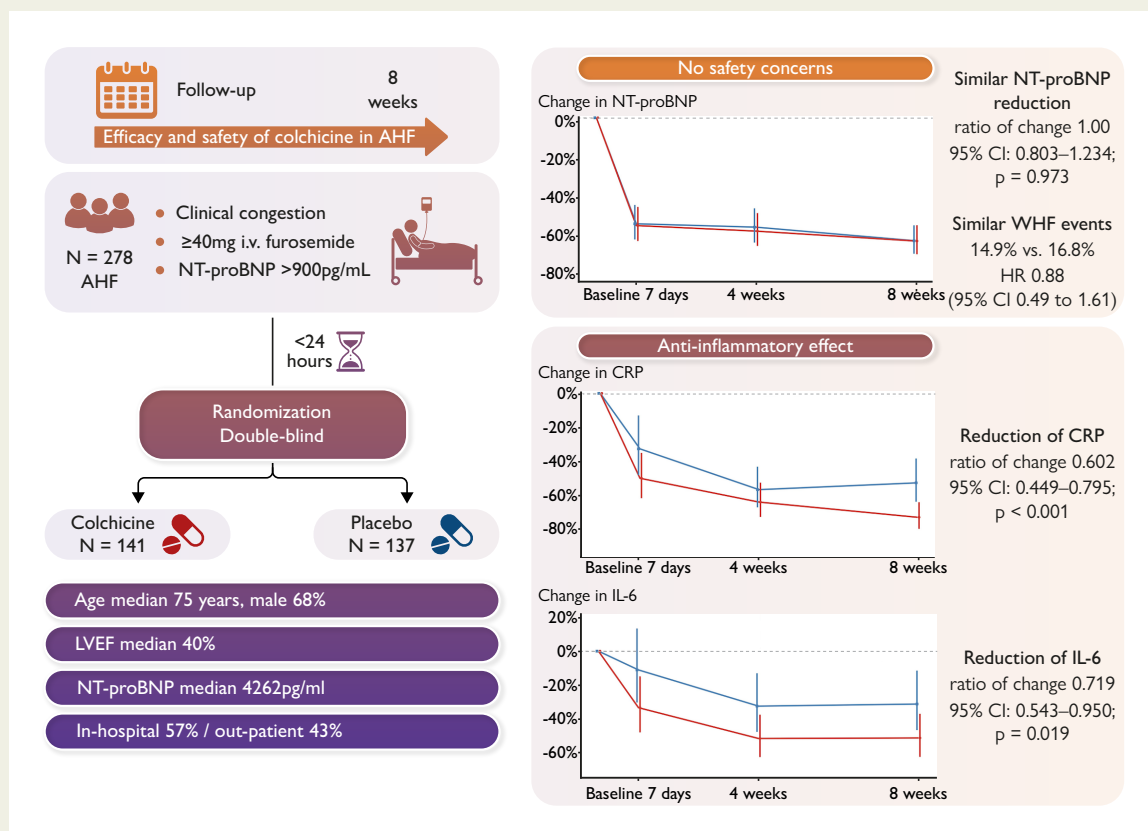
Does colchicine reduce the inflammatory outburst associated to acute heart failure (AHF)?

Key Finding

Colchicine was safe and effective and reduced C-reactive protein and Interleukin-6 levels compared to placebo, while colchicine did not affect NT-proBNP levels nor prevent new AHF episodes.

Take Home Message

Colchicine is safe and effective in reducing inflammation in patients with AHF, although these beneficial effects do not translate into an improvement of clinical endpoints. These findings justify further studies adequately powered to assess clinical endpoints.



In this randomized, double-blind, placebo-controlled trial enrolling 278 patients within 24 h of presentation with AHF, colchicine was safe and effective in reducing inflammation compared to placebo, but it had comparable effects on reducing NT-proBNP levels and preventing new WHF events. AHF, acute heart failure; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHF, worsening heart failure.

Keywords

Heart failure • Colchicine • Inflammation • Acute • Randomized controlled trial

Introduction

In patients with heart failure (HF), inflammation has been linked to disease development and progression and correlates with worse outcomes.¹ Unfortunately, this knowledge has not led to anti-inflammatory therapies with well-recognized benefits.^{2–5} Furthermore, most anti-inflammatory drugs, including cytokine inhibitors and steroids, have been studied in chronic HF patients who exhibit low-grade inflammation.² By contrast, numerous studies have demonstrated a greater activation of inflammatory pathways in patients with acute HF (AHF), which is associated with worse outcomes during follow-up and, in particular, during the early period (so-called 'vulnerable period').⁶

Currently, colchicine is the only anti-inflammatory drug approved in cardiovascular diseases for preventing pericarditis recurrences and reducing cardiovascular events in adults with established atherosclerotic cardiovascular disease or are at risk of developing it.^{7–9} However, only one randomized controlled trial has investigated the efficacy and safety of low-dose colchicine in patients with stable chronic HF; at 6 months, colchicine was safe and reduced inflammatory markers, but did not improve clinical endpoints.¹⁰ Colchicine has a wide spectrum of anti-inflammatory effects and, in particular, it inhibits the activation of inflammasome and the expression of various cytokines along the interleukin (IL)-1 axis, such as IL-1 β , IL-6, and IL-18.¹¹ Furthermore, elevated concentrations of related cytokines (IL-1 β and

IL-6) and acute-phase proteins (such as C-reactive protein, CRP) have been consistently associated with adverse clinical events.¹² Blocking the IL-1 receptor with anakinra has yielded conflicting results in terms of functional capacity in patients with chronic HF,^{13–15} but direct inhibition of IL-1 β with canakinumab has been found to prevent HF-related events in patients with prior myocardial infarction.¹⁶

The COLchicina en Insuficiencia Cardíaca Aguda (COLICA) trial aimed to explore whether early initiation of colchicine promotes clinical stability by lowering natriuretic peptide levels, reducing inflammation, and preventing new worsening episodes of HF in patients presenting with AHF.

Methods

Trial design

The trial design details have been previously published.¹⁷ The COLICA trial was a multicenter, randomized, double-blind, placebo-controlled trial of patients within 24 h of presenting with AHF. The COLICA trial complied with the Declaration of Helsinki and Good Clinical Practice Guidelines. The Spanish National Agency of Medications and Health Care Products (AEMPS) (MUH/CLIN/EC) and the institutional review board at each participating centre independently approved the protocol (IMIB-CO-2020-01). Written informed consent was obtained from all study participants before enrolment. The COLICA trial is registered at EudraCT (2020-000941-15), CTIS (EU CT 2023-504165-23), and ClinicalTrials.gov (NCT04705987).

Trial population

Patients aged 18 years or older presenting with a primary diagnosis of AHF were eligible for the study if they had clinical evidence of congestion requiring at least 40 mg of intravenous (i.v.) furosemide and elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>900 pg/mL). Patients were enrolled, regardless of their left ventricular ejection fraction (LVEF), HF type (new-onset or chronic), treatment setting (hospital or outpatient clinic-day hospital), and inflammatory activation at baseline.

Trial procedures

Patients were randomized within the first 24 h of presentation to receive either placebo or colchicine. Randomization was performed using a web-based system and stratified by those variables that potentially could influence NT-proBNP response (age, gender, baseline NT-proBNP, new-onset HF, LVEF, atrial fibrillation, and care setting). Both patients and investigators were blinded to the treatment group (placebo or active drug). The study drug was initiated within 24 h after presentation. Patients received a loading dose of 2 mg (1.5 mg initially, followed by an additional 0.5 mg after 1 h) and a maintenance dose of 0.5 mg twice daily for 8 weeks. For patients with reduced weight (<70 kg), elderly (>75 years old), or with a decreased renal function [estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m²], a reduced dosing regimen was employed: starting with a reduced initial dose of 1.5 mg (1 mg initially, followed by 0.5 mg after 1 h) and a daily maintenance dose of 0.5 mg per day during 8 weeks. Follow-up visits were conducted at 7 days, 4 weeks, and 8 weeks after randomization. The final visit took place at 8 weeks. Blood samples were stored and collected in a central biobank for measuring NT-proBNP concentrations and for other *post-hoc* analyses. NT-proBNP, CRP, and IL-6 concentrations were measured centrally at the end of the study.

Trial endpoints

The primary efficacy endpoint was the time-averaged proportional change in NT-proBNP concentration from baseline through Weeks 4 and 8. Secondary biomarker outcomes included time-averaged proportional changes in CRP and IL-6 as markers of inflammatory response. We also conducted analyses of secondary clinical outcomes reflecting worsening HF (WHF) episodes

defined as worsening symptoms and signs of HF after the index episode and requiring intensification of diuretics, including HF hospitalization, emergency or outpatient visit requiring i.v. furosemide, and outpatient visit requiring intensification in dose of oral diuretics. WHF episodes were centrally adjudicated. Other exploratory endpoints included symptom assessment using the New York Heart Association (NYHA) functional class, the visual analogue scale (VAS), and the 7-point Likert scale. Gastrointestinal and hematologic disorders, infections, and renal and hepatic functions were considered as safety endpoints of special interest.

Statistical analysis

A sample size of 278 patients was planned to detect a 25% greater time-averaged proportional reduction in NT-proBNP levels from baseline to Week 8 in the colchicine group than the placebo group considering a variability of 0.75 in both groups, with a statistical significance threshold of 0.05, a statistical power of 80%, and an expected loss of 25%. All studied endpoints were evaluated based on the intention-to-treat principle with the use of all available data. Baseline characteristics were described using mean \pm standard deviation and median [interquartile range (IQR)] for continuous variables (according to normality) and frequency (percentage) for categorical variables. Normality was assessed with graphical (Q–Q plots, histograms, and boxplots) and analytical methods (Kolmogorov–Smirnov tests). Continuous variables with an exponential scale were log-transformed to achieve normality. NT-proBNP, CRP, and IL-6 levels were logarithmically transformed due to the non-normal distribution of values, and changes in the transformed variable are equivalent to the geometric mean. Changes from baseline in NT-proBNP levels were compared between groups using a mixed-design model [ANOVA with a within-subjects variable (time: baseline and final) and a between-subjects variable (group: placebo and colchicine)], and considering baseline NT-proBNP levels and occurrence of acute WHF events as covariates. A similar method was used to analyse the secondary biomarker outcomes. Least-squares means were calculated to assess differences over time and between groups, and 95% confidence interval (CI) for the ratio of change was calculated using the delta method, which estimates the variance of a ratio by applying a Taylor series expansion. Clinical events were studied with survival analyses: Kaplan–Meier plots with log-rank test and Cox proportional hazards models were used. Student's *t*-test, Mann–Whitney *U* test, χ^2 test, and Wilcoxon rank-sum tests and were used to determine differences between treatment groups, as appropriate. The significance level used was 0.05, and the null hypothesis (*H*₀) was the non-existence of differences (two-tailed tests) in all cases. R v4.1.2 software was used for all analyses, with the emmeans library used to estimate marginal means from the models.

Results

Study population

A total of 279 patients were enrolled at 12 participating centers from February 2021 to March 2024. One patient was randomized inappropriately and did not receive any doses of the trial drug. The efficacy analyses included 278 patients, of whom 141 were randomly assigned to receive colchicine and 137 to receive placebo (Figure 1). The trial database was locked on 17 May 2024. The baseline characteristics of the patients are shown in Table 1. There were no clinical or demographic differences between the colchicine and placebo groups. At randomization, the median age was 75 years (IQR: 64–81), and 68% of the participants were male. The median LVEF was 40%, with 57% having reduced LVEF \leq 40% and 31% having LVEF \geq 50%. Almost half of patients had a prior history of HF (54%) or were in-hospital (57%). Baseline NT-proBNP concentrations had a median of 4262 pg/mL (IQR: 2349–7778), and were similar between groups: 4253 pg/mL (IQR: 2490–8068) in the colchicine group and 4366 pg/mL (IQR: 2349–7517) in the placebo group.

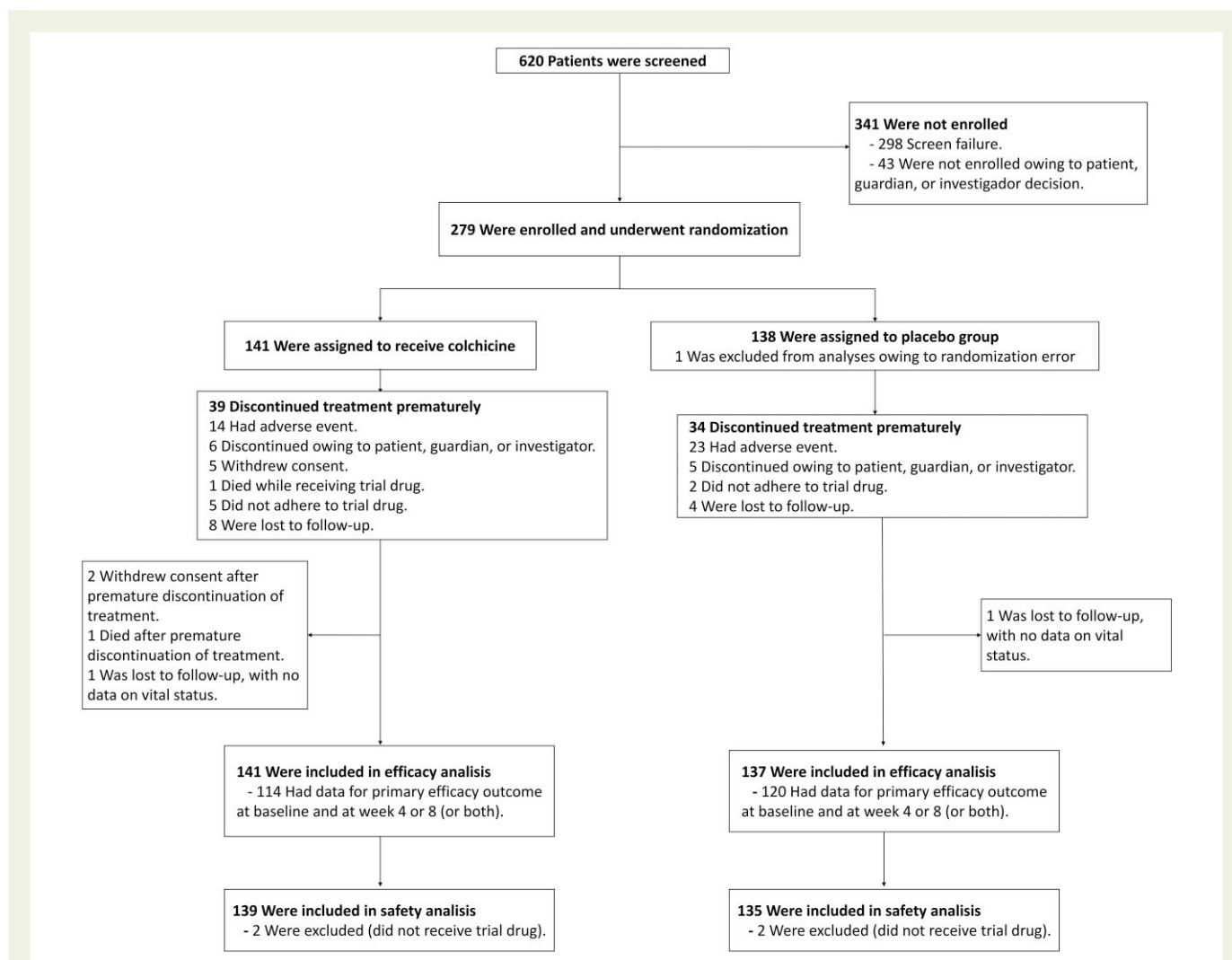


Figure 1 Consort diagram of the COLICA trial: screening, randomization, and follow-up

Trial treatment

Patients received the trial drug at a median of 15 h (IQR: 4–20) after initial administration of i.v. furosemide, with a median dose of 80 mg at randomization (IQR: 60–120). At least one dose of a trial drug was administered to 274 patients (139 with colchicine and 135 with placebo); these patients were included in the safety analyses (i.e. analyses of adverse events). Excluding discontinuation due to death, the trial drug was discontinued prematurely in 38 patients (26.9%) in the colchicine group and in 34 patients (24.8%) in the placebo group (see [Supplementary data online, Table S1](#) in the [Supplementary data online, Appendix](#)). No safety concerns were observed. Diarrhea was slightly more prevalent in the colchicine group (13.7% vs. 11.9%, $P = .727$), but it did not result in differences in permanent medication withdrawal (8.5% vs. 8.8%) (see [Supplementary data online, Table S1](#)). Other safety events were below 1%, with only one episode of pneumonia reported in each group, which was not related with medication.

Primary efficacy outcome

The time-averaged reduction in NT-proBNP did not show a significant difference between the colchicine and placebo groups ([Table 2, Figure 2](#)). NT-proBNP concentrations decreased significantly in both treatment groups from Day 7: percent change of -54.4% (-62.2 , -45.0) with

colchicine and -53.5% (-61.4 , -44.0) with placebo. By Week 8, the percent change with colchicine vs. placebo group was -62.2% (95% CI: -68.9 to -54.2) vs. -62.1% (95% CI: -68.6 to -54.3), respectively [ratio of change 1.00 (95% CI: 0.803 to 1.234; 0 = 0.973)]. No interaction was observed in the subgroup analysis by age ($P = .578$), LVEF ($P = .104$), and baseline concentrations of NT-proBNP ($P = .205$), CRP ($P = .624$), and IL-6 ($P = .936$) above or below the median.

Secondary efficacy outcomes

Regarding secondary endpoints ([Table 2](#)), the time-averaged reduction in inflammatory markers was significantly greater in the colchicine group from Day 7 through Week 8 ([Figure 3](#)). The mean change of CRP was -48.5% with colchicine and -31.7% with placebo at 7 days (ratio of change 0.756; 95% CI: 0.571 to 0.994; $P = .044$) and -70.8% with colchicine and -51.1% with placebo at 8 weeks (ratio of change 0.602; 95% CI: 0.449 to 0.795; $P < .001$). The mean change of IL-6 was -32.5% with colchicine and 10.8% with placebo at 7 days (ratio of change of 0.756; 95% CI: 0.577 to 0.990; $P = .040$) and -49.9% with colchicine and -30.4% with placebo at 8 weeks (ratio of change of 0.719; 95% CI: 0.543 to 0.951; $P = .019$). New WHF episodes (any i.v. diuretic intensification leading to hospitalization or not) did not differ between groups: 14.9% in the colchicine group vs.

Table 1 Characteristics of the study population

Variables	Colchicine n = 141	Placebo n = 137	P
Age, years	75.31 [63.61, 82.26]	74.42 [65.41, 81.08]	.755
Male sex	96 (68.1)	94 (68.6)	1.000
BMI, kg/m ²	29.28 ± 5.84	29.01 ± 4.83	.678
Characteristics at randomization			
SBP, mmHg	126.31 ± 22.97	124.88 ± 22.50	.599
DBP, mmHg	75.80 ± 14.96	75.49 ± 15.47	.865
HR, bpm	82.09 ± 21.46	81.71 ± 22.80	.887
Oxygen saturation, %	95.79 ± 2.83	95.84 ± 2.40	.865
NYHA class			.648
II	61 (43.6)	55 (40.1)	
III-IV	79 (56.4)	82 (59.9)	
LVEF, %	39.45 ± 16.43	40.02 ± 16.63	.773
LVEF category			.733
≤40%	83 (58.9)	75 (54.7)	
41%–49%	16 (11.3)	17 (12.4)	
≥50%	42 (29.8)	45 (32.8)	
Patient location			.690
Out-patient clinic	59 (41.8)	62 (44.9)	
Hospital	82 (58.2)	75 (55.1)	
IV furosemide, mg	80 [60, 120]	80 [60, 125]	.304
Time from first dose, hours	14.75 [3.75, 20.00]	16.00 [4.00, 20.55]	.540
IV inotropics	1 (0.7)	0 (0.0)	1.000
IV vasodilators	5 (3.6)	8 (5.8)	.543
Respiratory support	17 (12.1)	25 (18.2)	.212
Symptoms scales			
VAS scale	5.63 ± 1.92	5.49 ± 1.77	.527
Likert scale	4.21 ± 1.06	4.18 ± 1.12	.809
Laboratory at randomization			
Creatinine, mg/dL	1.10 [0.88, 1.40]	1.09 [0.90, 1.36]	.925
Urea, mg/dL	63.54 ± 20.43	65.15 ± 23.70	.555
eGFR, mL/min/1.73 m ²	56.20 ± 28.90	57.76 ± 28.43	.662
eGFR category			.387
30–60 mL/min/1.73 m ²	66 (49.3)	57 (43.2)	
>60 mL/min/1.73 m ²	68 (50.7)	74 (56.1)	
Sodium, mmol/L	140.49 ± 3.58	139.65 ± 4.30	.078
Potassium, mmol/L	4.00 [3.63, 4.30]	4.10 [3.70, 4.50]	.196
Uric acid, mg/dL	7.51 ± 2.20	7.69 ± 2.07	.534
NT-proBNP, pg/mL	4253 [2490, 8068]	4366 [2349, 7517]	.285
CRP, mg/L	8.20 [3.72, 19.25]	8.30 [3.80, 23.60]	.859

Continued

Table 1 *Continued*

Variables	Colchicine n = 141	Placebo n = 137	P
IL-6, pg/mL	11.10 [5.52, 20.05]	11.50 [5.85, 21.92]	.691
Hs-TnT, pg/mL	34.50 [22.82, 49.65]	34.80 [23.40, 65.10]	.212
Cholesterol, mg/dL	142.68 ± 39.07	148.23 ± 42.06	.288
GGT, U/L	58.00 [29.75, 96.25]	56.50 [35.00, 114.50]	.647
Haemoglobin, gr/dL	13.10 [11.85, 14.85]	13.95 [12.00, 15.30]	.130
Medical history			
Hypertension	96 (68.6)	106 (77.4)	.130
Diabetes	52 (37.1)	48 (35.0)	.810
Dyslipidaemia	73 (52.1)	82 (59.9)	.241
Smoking	34 (24.3)	28 (20.4)	.533
Alcoholism	13 (9.3)	12 (8.8)	1.000
Prior HF	81 (57.9)	69 (50.4)	.258
AF or flutter	83 (58.9)	76 (55.5)	.653
CAD	34 (24.3)	24 (17.5)	.230
AMI	26 (18.6)	21 (15.3)	.576
Pacemaker	18 (12.9)	18 (13.1)	1.000
ICD	12 (8.6)	11 (8.0)	1.000
Valve prosthesis	13 (9.2)	15 (10.9)	.780
TIA or stroke	16 (11.4)	22 (16.1)	.345
PVD	9 (6.4)	10 (7.3)	.961
COPD	20 (14.3)	27 (19.7)	.297
Hypothyroidism	7 (5.0)	6 (4.4)	1.000
Cancer	19 (13.6)	23 (16.8)	.755
Previous medication			
ACEIs or ARBs	56 (39.7)	50 (36.5)	.668
ARNI	24 (17.0)	19 (13.9)	.575
Betablockers	78 (55.3)	72 (52.6)	.732
MRA	44 (31.2)	38 (27.7)	.615
SGLT2i	49 (35.0)	41 (29.9)	.440
Oral furosemide	69 (49.3)	71 (51.8)	.762
Thiazides	29 (20.7)	25 (18.2)	.714
Statins	78 (55.7)	74 (54.0)	.870
Digoxin	8 (5.7)	9 (6.6)	.963

Mean ± SD, median [IQR], and n (%) are represented as appropriated.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; VAS, visual analogue scale; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; AF, atrial fibrillation; AMI, acute myocardial infarction; ICD, Implantable cardioverter-defibrillator; HF, heart failure; NT-proBNP, N-terminal pro-B type natriuretic peptide; Hs-TnT, High-sensitivity troponin T; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; IV, intravenous; IL-6, Interleukin-6; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonist; ARNI, angiotensin receptor-neprilysin inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitors; eGFR, estimated glomerular filtration rate (MDRD equation).

Table 2 Secondary efficacy outcomes at 8 weeks

Outcome	Colchicine n = 141	Placebo n = 137	Colchicine vs. placebo	
Clinical outcomes — no. (%) or median [IQR]			HR (95% CI)	P
Index AHF episode				
Length hospitalization, days ^a	7.0 [5.0, 8.0]	6.0 [5.0, 8.0]		.987
Length IV furosemide, days ^a	3.00 [1.00, 4.00]	2.00 [1.00, 4.00]		.722
Dose IV furosemide, mg ^a	160 [80, 320]	190 [100, 312]		.404
Follow-up				
Death	2 (1.4)	0 (0.0)	4.88 (0.40 to 35.80)	1.000
WHF events				
HF hospitalization	9 (6.4)	7 (5.1)	1.25 (0.47 to 3.36)	.654
Out-patient i.v. furosemide	11 (7.8)	18 (13.1)	0.59 (0.28 to 1.27)	.178
Dose, mg ^a	120 [100, 125]	170 [120, 247]		.043
Length, days ^a	1.00 [1.00, 2.75]	3.00 [1.00, 7.00]		.066
Oral diuretics intensification	4 (2.8)	3 (2.2)	1.93 (0.35 to 10.57)	.445
Any WHF event	21 (14.9)	23 (16.8)	0.88 (0.49 to 1.61)	.698
HF hospitalization or i.v. furosemide	17 (12.1)	21 (15.3)	0.78 (0.41 to 1.48)	.451
No-HF-related hospitalization	9 (6.4)	10 (7.3)	0.87 (0.35 to 2.14)	.762
Biomarker outcomes — % (95% CI)			Ratio of change (95% CI)	P
Change in CRP, mg/L	−70.8 (−77.4 to −62.2)	−51.1 (−61.9 to −37.2)	0.60 (0.45 to 0.80)	<.001
Change in IL-6, pg/mL	−49.9 (−60.8 to −36.0)	−30.4 (−45.4 to −11.2)	0.72 (0.54 to 0.95)	.019
Change in hs-TnT, pg/mL	−21.1 (−33.5 to −6.4)	−28.8 (−39.7 to −15.9)	1.11 (0.91 to 1.34)	.294
Change in creatinine, mg/dL	3.6 (−1.0 to 8.5)	3.1 (−1.3 to 7.8)	1.00 (0.95 to 1.06)	.850
Symptoms scales — mean (SD)			Difference (95% CI)	P
Change in VAS scale	1.36 ± 0.36	1.28 ± 0.41	0.08 (−0.43 to 0.60)	.749
Change in Likert scale	0.79 ± 0.28	0.81 ± 0.32	−0.02 (−0.31 to 0.28)	.914
Change in NYHA scale	−0.64 ± 0.15	−0.61 ± 0.14	−0.03 (−0.20 to 0.15)	.759

Events are expressed as number (%), median [interquartile range], mean ((95% CI), and mean ± standard deviation (SD).

HF, heart failure; WHF, worsening heart failure; IV, intravenous; NT-proBNP, N-terminal pro-B type natriuretic peptide; hs-TnT, High-sensitivity troponin T; CRP, C-reactive protein; VAS, visual analogue scale; NYHA, New York Heart Association; IL-6, interleukin-6.

^aMann–Whitney U test was used.

16.8% in the placebo group (HR 0.88, 95% CI 0.49 to 1.61). However, patients in the colchicine group had lower rates of i.v. furosemide intensification, with reduced total dose and duration. No differences were observed in terms of death ($n = 2$) or HF hospitalizations (6.4% vs. 5.1%).

Concomitant guideline-directed medical therapy

Figure 4 illustrates the medication management of patients based on LVEF phenotype ($\leq 40\%$ or $>40\%$). Guideline-directed medical therapy (GDMT) was optimized early from the time of randomization. At randomization, the rates of GDMT were 84% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) or angiotensin receptor–neprilysin inhibitor (ARNI), 77% for beta-blockers, 68% for mineralocorticoid receptor antagonist (MRA), 52% for sodium–glucose cotransporter 2 inhibitors (SGLT2i) in patients with LVEF $\leq 40\%$,

and 32% with quadruple GDMT. By 7 days, these rates improved to 85%, 89%, 75%, 70%, and 47%, respectively, indicating an optimized GDMT. The rates of SGLT2i in patients with LVEF $>40\%$ were 50% at randomization and 60% at 7 days. The median daily dose of oral furosemide was 60 mg/day (IQR: 40, 80) at 7 days, decreasing to 40 mg/day (IQR: 20, 80) at 8 weeks. No differences were observed between colchicine and placebo groups (see [Supplementary material](#)).

Discussion

The COLICA trial is the first randomized, placebo-controlled trial specifically designed to assess the benefit of targeting inflammatory response with colchicine in patients with acutely decompensated HF. While confirming the anti-inflammatory effects in AHF and the favorable safety profile, the trial did not find significant reductions in

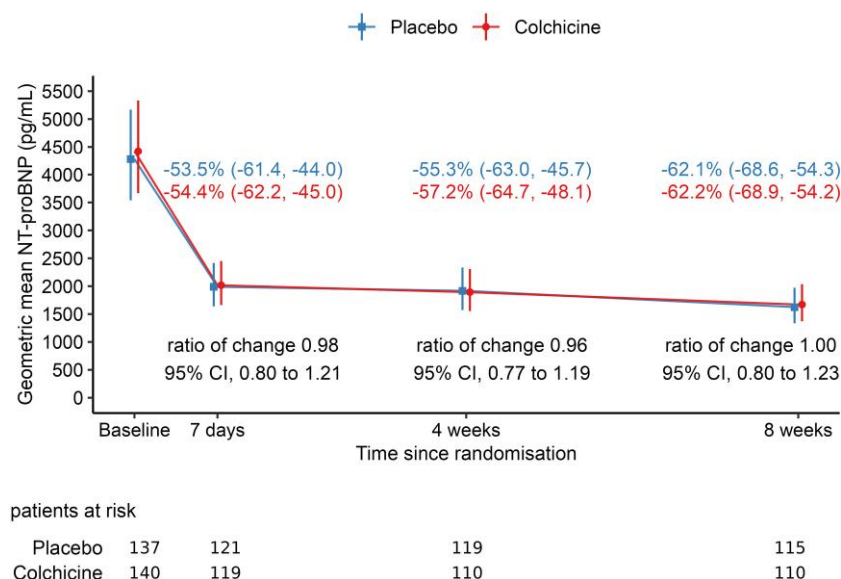


Figure 2 Change in NT-proBNP concentration

NT-proBNP levels or significant clinical benefits ([Structured Graphical Abstract](#)).

This study covers an unmet need. Despite ample evidence linking inflammation to HF progression, specific therapies are lacking. Colchicine has emerged as a relevant anti-inflammatory therapy in cardiovascular disease. Besides its role in treating acute pericarditis, the use of low-dose colchicine has proved effective in chronic coronary artery disease and has led to be approved as the first anti-inflammatory drug for patients who have established atherosclerotic cardiovascular disease or are at risk of developing it.^{8,18} To date, there was only one randomized clinical trial studying colchicine in HF patients. Deftereos *et al.* studied 279 patients with stable chronic HF and LVEF $\leq 40\%$, excluding patients with a recent (3 months) hospitalization. In this trial, treatment with colchicine for 6 months was effective in reducing inflammatory biomarkers (CRP and IL-6), but it was not effective in improving NYHA class or reducing risk of death and/or HF hospitalization.¹⁰

The COLICA trial expands the knowledge about the role of colchicine in HF to those patients with AHF across the spectrum of LVEF. The early initiation of colchicine in this setting, at a median of 15 h after the first administration of i.v. furosemide, demonstrated superiority over placebo in controlling the inflammatory response, as evidenced by reductions in CRP and IL-6 levels. This effect was observed early at 7 weeks and maintained throughout the study period of 8 weeks. It is well established that inflammatory parameters, including CRP, tumor necrosis factor- α , IL-6, IL-1 β , and ST2, are notably upregulated during AHF episodes.^{2,6} This heightened inflammatory response is associated with worse prognosis, increased risk of death, and higher rates of hospitalization.^{1,2,6} In this context, the COLICA trial provides evidence supporting the effectiveness of colchicine in mitigating this detrimental inflammatory response in HF.

The COLICA trial focused on changes in NT-proBNP concentrations as its primary endpoint, given its widespread adoption as a surrogate marker for HF status. We observed a substantial reduction in NT-proBNP levels early on, with a mean reduction exceeding 50% at 7 days, consistent across both the colchicine and placebo groups. This reduction is notably greater than anticipated based on prior trials. For instance, in the PIONEER-HF¹⁹ trial [HF with reduced ejection fraction (HFrEF)] and the PARAGLIDE-

HF²⁰ trial [HF with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF)], control groups (without ARNI nor SGLT2i) showed mean reductions of -25.3% and -16.3% at 4/8 weeks, respectively. In contrast, in the COLICA trial, the control group exhibited a reduction of 62% at 8 weeks, including both ARNI and SGLT2i as contemporary therapies. This significant reduction can be attributed to the early adoption of GDMT within the first 24 h of patient randomization, where rates of all pillars of therapy increased significantly among HFpEF patients, including SGLT2i among HFpEF patients ([Figure 4](#)). The benefits of this optimized approach and close follow-up were also reflected in a low rate of adverse clinical events, with only two deaths and 5.8% of patients experiencing HF hospitalizations.

The COLICA trial also assessed the need for diuretics as a relevant secondary endpoint and included an expanded definition of WHF events in the follow-up, considered need for i.v. furosemide or an increase in oral dose of diuretics. During the index AHF episode, no differences were found between colchicine and placebo groups in terms of total need or i.v. furosemide; however, during the follow-up, rates of i.v. furosemide use and total dose required were lower in the colchicine group. This finding is relevant given that these patients were managed into specific post-discharge programs and ambulatory HF clinics of participating sites. In this context, while speculative, it is plausible that the anti-inflammatory effects of colchicine may contribute to a tendency towards reduced congestion and need for i.v. diuretics after the index episode.

In hindsight, one might question whether the COLICA trial should have enrolled patients with elevated baseline inflammatory biomarkers. Other therapies targeting IL-1, like anakinra and canakinumab, have demonstrated that baseline CRP levels and their response can influence clinical outcomes. In HF patients recently discharged (<14 days) with reduced ejection fraction (LVEF $<50\%$) and CRP >2 mg/dL, those treated with anakinra for 12 weeks showed significantly reduced CRP levels, improved functional capacity, and exhibited a trend towards lower rates of death or HF hospitalization after 24 weeks.¹³ In another small trial ($n = 30$) involving patients admitted within 24 h for AHF (LVEF $<40\%$), anakinra was associated with a greater reduction of

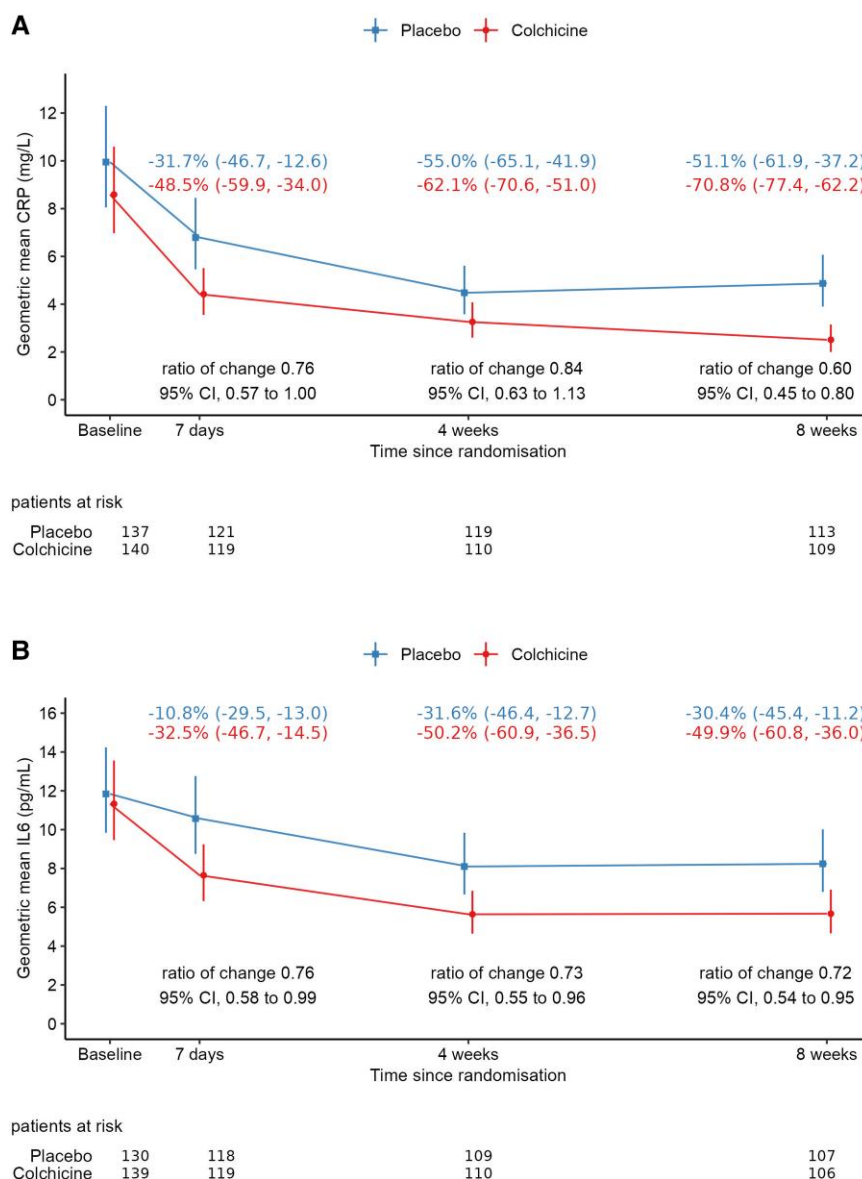


Figure 3 Change in inflammatory markers: C-reactive protein (CRP) and interleukin-6 (IL6)

CRP at 14 days without differences in the length of hospital stay.¹⁵ The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial found that in participants who responded to canakinumab (as evidenced by a reduction in CRP to <2 mg/dL), IL-1 β blockade was associated with a significant 38% reduction in HF hospitalizations and a 32% reduction in the composite of HF hospitalizations and all-cause death compared with placebo.¹⁶

Another critical consideration regarding anti-inflammatory therapies is their safety profile. Indeed, treatment with anti-cytokine therapies is often constrained by an unfavourable cost-benefit balance and a higher rate of fatal infections.^{5,12} In the COLICA trial, colchicine regimen included a loading dose, followed by 0.5 mg twice a day. This higher dose, compared with that used in coronary artery disease studies, was intended to address the greater inflammation associated with the acute episode of HF and the associated short period of vulnerability. As anticipated, the rate of diarrhoea was slightly elevated in colchicine

than placebo group, but this did not result in a higher rate of permanent discontinuations. Overall, high discontinuation rates in both colchicine and placebo groups might be primarily attributed to the advanced age of the study population (median 75 years), which exceeded that of other studies. Besides diarrhoea, no other significant adverse effects were reported, including infections, underscoring the acceptable safety profile of colchicine in the short-term and long-term uses.

The main limitation of this trial is the sample size, which prevents definitive conclusions regarding the benefit of colchicine in patients with AHF. The trial was underpowered due to a greater than expected reduction in NT-proBNP levels in patients on placebo, likely influenced by the high prescription rate of GDMT, which may have also blunted the effects of colchicine. Additionally, the study medication was discontinued in nearly a quarter of patients in both the colchicine and placebo arms during the short 8-week follow-up period, potentially limiting the ability to detect an effect of colchicine over placebo and differences

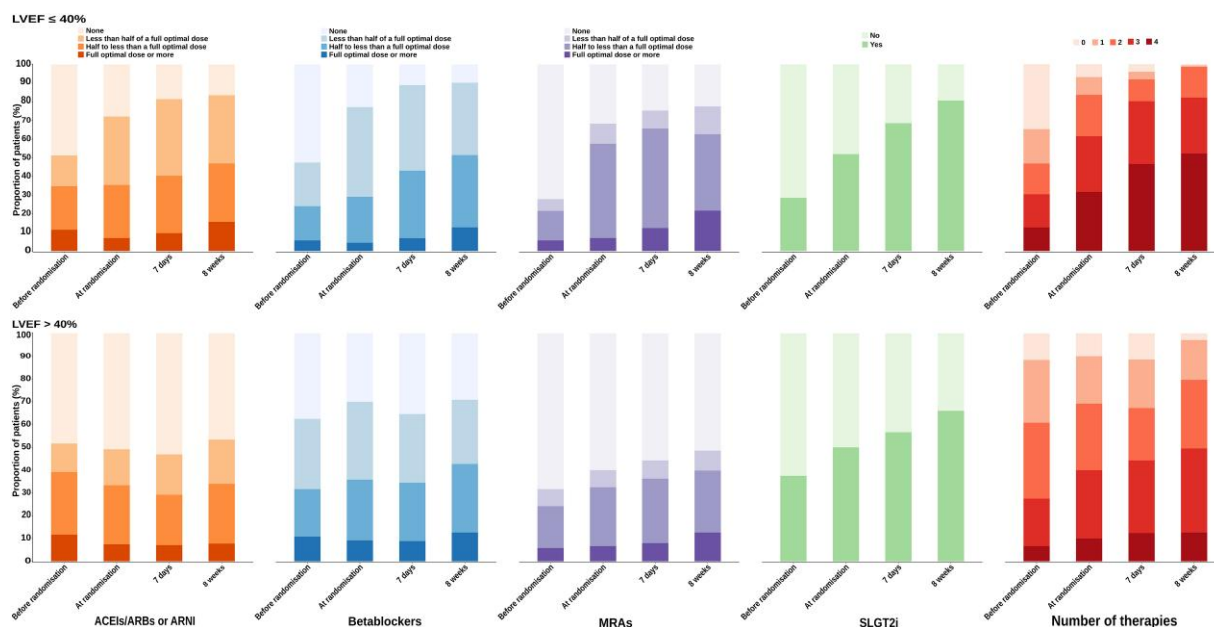


Figure 4 Change in guideline-directed medications according to left ventricular ejection fraction phenotype

in clinical events. Furthermore, the design aimed to include a broad range of patients with AHF, which reflects clinical practice, but may have limited the ability to identify specific subgroups that could benefit from the treatment. Nonetheless, the randomized controlled trial design does demonstrate an early and sustained anti-inflammatory effect of colchicine in this population, superior to placebo on contemporary GDMT. The COLICA trial indicates that in an optimal setting with high rates of GDMT initiated promptly after an AHF episode, colchicine does not provide additional benefits in terms of NT-proBNP levels, a surrogate biomarker of HF status, but it provides an additional anti-inflammatory effect on both CRP and IL-6. These findings support the need for further studies adequately powered to determine if the observed anti-inflammatory effects translate into reductions in clinical endpoints, particularly in achieving better congestion stability in both short- and long-term contexts. This necessity is underscored by the favourable safety profile of colchicine observed in our study, as well as in other clinical scenarios.

In conclusion, while colchicine demonstrates robust anti-inflammatory effects by reducing CRP and IL-6 levels over 8 weeks in patients with AHF, it does not achieve a substantial reduction in NT-proBNP levels compared to placebo. Further well-designed studies with sufficient power are needed to evaluate colchicine impact on clinical stability and patient outcomes. These studies should take into account the favourable safety profile observed in patients receiving contemporary guideline-directed therapy.

Acknowledgements

We are grateful for the contribution and collaboration of the Clinical Trials Platform of IMIB-Pascual Parrilla and the National Clinical Trials Network (SCReN (Spanish Clinical Research Network) founded by the Carlos III Institute (PT20/00115 y PT23/00029) and co-founded by the European Union (FEDER), and the collaboration of Biobank Network of the Region of Murcia, BIOBANC-MUR, registered on the Registro Nacional de Biobancos (B.0000859).

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

DPF has received consultancy and speaker and lecture fees from Astra Zeneca, Novartis, Roche Diagnostics, Pfizer, Vifor, and Rovi. ABG has participated in advisory boards and/or lectured for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Roche Diagnostics, and Vifor. JN has received consultancy and speaker and lecture fees from Astra Zeneca, Alleviant, Amgen, Bayer, Boehringer Ingelheim, CSL VIFOR, Daiichi Sankyo, GSK, Lilly, Pfizer, Novartis, Novonordisk, and Rovi. Rest of authors: none declared.

Data Availability

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

Funding

The COLICA trial has been funded by Instituto de Salud Carlos III (ISCIII) through the project ICI19/00055 and co-funded by the European Regional Development Fund (ERDF). The CNIC is supported by the ISCIII, the Ministerio de Ciencia, Innovación y Universidades (MICIU), and the Pro CNIC Foundation, and is a Severo Ochoa Centre for Excellence (Grant CEX2020-001041-S funded by MICIU/AEI/10.13039/501100011033).

Ethical Approval

The COLICA trial complied with the Declaration of Helsinki and Good Clinical Practice Guidelines. The Spanish National Agency of Medications and Health Care Products (AEMPS) (MUH/CLIN/EC) and the

institutional review board at each participating centre independently approved the protocol (IMIB-CO-2020-01). Written informed consent was obtained from all study participants before enrolment.

Pre-registered Clinical Trial Number

The COLICA trial is registered at EudraCT (2020-000941-15), CTIS (EU CT 2023-504165-23), and ClinicalTrials.gov (NCT04705987).

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