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# Effect of Colchicine on Myocardial Injury in Acute Myocardial Infarction

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**BACKGROUND:** Inflammation is a key factor of myocardial damage in reperfused ST-segment–elevation myocardial infarction. We hypothesized that colchicine, a potent anti-inflammatory agent, may reduce infarct size (IS) and left ventricular (LV) remodeling at the acute phase of ST-segment–elevation myocardial infarction.

**METHODS:** In this double-blind multicenter trial, we randomly assigned patients admitted for a first episode of ST-segment–elevation myocardial infarction referred for primary percutaneous coronary intervention to receive oral colchicine (2-mg loading dose followed by 0.5 mg twice a day) or matching placebo from admission to day 5. The primary efficacy outcome was IS determined by cardiac magnetic resonance imaging at 5 days. The relative LV end-diastolic volume change at 3 months and IS at 3 months assessed by cardiac magnetic resonance imaging were among the secondary outcomes.

**RESULTS:** We enrolled 192 patients, 101 in the colchicine group and 91 in the control group. At 5 days, the gadolinium enhancement–defined IS did not differ between the colchicine and placebo groups with a mean of 26 interquartile range (IQR) [16–44] versus 28.4 IQR [14–40] g of LV mass, respectively ( $P=0.87$ ). At 3 months follow-up, there was no significant difference in LV remodeling between the colchicine and placebo groups with a +2.4% (IQR, –8.3% to 11.1%) versus –1.1% (IQR, –8.0% to 9.9%) change in LV end-diastolic volume ( $P=0.49$ ). Infarct size at 3 months was also not significantly different between the colchicine and placebo groups (17 IQR [10–28] versus 18 IQR [10–27] g of LV mass, respectively;  $P=0.92$ ). The incidence of gastrointestinal adverse events during the treatment period was greater with colchicine than with placebo (34% versus 11%, respectively;  $P=0.0002$ ).

**CONCLUSIONS:** In this randomized, placebo-controlled trial, oral administration of high-dose colchicine at the time of reperfusion and for 5 days did not reduce IS assessed by cardiac magnetic resonance imaging.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03156816

**Key Words:** clinical trial ■ colchicine ■ heart injuries ■ inflammation ■ myocardial infarction ■ thrombosis ■ ventricular remodeling

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\*A complete list of the investigators in the COVERT-MI Study is provided in the [Data Supplement](#).

This work was presented as an abstract at the European Society of Cardiology Congress, August 27 through 30, 2021.

## Clinical Perspective

### What Is New?

- Colchicine has been shown to reduce ischemic events in chronic coronary syndromes.
- This double-blinded, randomized, controlled trial tested the effect of colchicine on the injury after acute myocardial infarction assessed by cardiac magnetic resonance.
- Colchicine did not reduce infarct size and myocardial injury at 5 days and 3 months.
- An unexpected increase of left ventricular thrombus incidence in the colchicine group warrants further research.

### What Are the Clinical Implications?

- Colchicine does not reduce myocardial injury in the acute phase of myocardial infarction.
- Other studies exploring the timing, pharmacokinetics, and dose response of colchicine and other anti-inflammatory agents are needed to identify an effective method to reduce infarct size or limit remodeling.

## Nonstandard Abbreviations and Acronyms

<b>CMR</b>	cardiac magnetic resonance
<b>IS</b>	infarct size
<b>LV</b>	left ventricular
<b>PCI</b>	percutaneous coronary intervention
<b>STEMI</b>	ST segment elevation myocardial infarction

**A**fter acute myocardial infarction, an important inflammatory response starts in the minutes after reperfusion and peaks in the first days after reperfusion.<sup>1–3</sup> Inflammatory cells such as neutrophils, followed by monocytes and macrophages, rapidly infiltrate the injured myocardium with abundant proinflammatory cytokine secretions that may cause additional damage to the myocardium.<sup>4</sup> These inflammatory processes have been identified as key mediators of reperfusion injury in ST-segment-elevation myocardial infarction (STEMI).<sup>3</sup> Until now, the various anti-inflammatory approaches tested to reduce this acute inflammatory injury have yielded disappointing results.<sup>5</sup>

Colchicine is a well-known major alkaloid from *Colchicum autumnale* with potent anti-inflammatory properties. It accumulates in white blood cells and decreases their motility, mobilization (especially chemotaxis), and adhesion to the endothelium, thereby reducing the proinflammatory cytokine release and potential ensuing myocardial damage.<sup>6–8</sup>

Long-term colchicine treatment in patients with chronic coronary syndrome or the month after an acute coronary syndrome has recently been found to reduce the risk of major adverse cardiovascular events compared with placebo.<sup>9–11</sup> However, it is unclear whether short-term colchicine therapy given at the time of reperfusion reduces myocardial injury compared with placebo in patients with acute STEMI.

We designed the COVERT-MI trial (Colchicine for Left Ventricular Infarct Size Treatment in Acute Myocardial Infarction) to investigate whether colchicine reduces myocardial injury in comparison with placebo in patients who have acute STEMI referred for percutaneous coronary intervention (PCI).

## METHODS

The data that support the findings of this study are available from the corresponding author and the sponsor of this trial, the Hospices Civils de Lyon, on reasonable request.

### Trial Design and Oversight

From July 20, 2018, to July 28, 2020, we conducted this investigator-initiated, randomized, double-blinded, placebo-controlled, multicenter trial at 10 tertiary-referral sites in France.<sup>12</sup> The trial protocol (available in the [Data Supplement](#)) was approved by the Comité de Protection Personnes Sud-Est IV and by the French competent authority Agence Nationale de Sécurité du Médicament in December 2017. A data- and safety-monitoring committee provided oversight and assessed the safety profile of the trial. The Clinical Investigation Center of the Hospices Civils de Lyon (INSERM 1407) conducted and coordinated the trial and collected all trial data. Independent clinical research associates monitored the sites and verified the data.

The study was approved by an institutional review committee and all patients gave written informed consent.

Colchicine 0.5 mg and matching placebo capsules were provided, in the same appearance (color, size, and packaging), by the sponsor. Production, blinded labeling, packaging, and delivery of the study drugs in every site of the trial was performed by a provider following the European Union's Good Manufacturing Practice.

The study drugs and placebo were prepared by the Pharmacy of the Edouard Herriot Hospital (FRIPHARM, Hospices Civils Lyon, France) according to good preparation practices from the tablets of a commercial specialty of Colchicine (Opocalcium 1 mg, Laboratory Mayoly Spindler).

The trial was supported by a grant from the French Ministry of Health (PHRCN-16-0357). The trial was sponsored by the Hospices Civils de Lyon. The study was registered in <https://www.clinicaltrials.gov> (Unique identifier: NCT03156816) and EudraCT 2017-004090-13, before the enrollment of the first patient.

### Patients

All adult patients (>18 and <80 years of age) with a first-time STEMI referred for primary or rescue PCI admitted to the participating centers were screened against eligibility criteria. The

infarct-related artery had to be occluded at the time of initial angiography (defined as having a Thrombosis in Myocardial Infarction score  $\leq 1$ ). The additional key eligibility criterium was presentation within 12 hours of chest pain onset.

Key exclusion criteria were hemodynamic instability (ie, cardiogenic shock), any obvious contraindication to cardiac magnetic resonance (CMR) imaging (claustrophobia, pacemaker, defibrillator, history of hypersensitivity to gadoteric acid or gadolinium contrast agents or meglumine), severe liver or known renal dysfunction as defined by a glomerular filtration rate  $\leq 30$  mL/min and chronic treatment with colchicine. A full list of the inclusion and exclusion criteria is provided in the [Data Supplement](#).

## Consent and Randomization

Information and informed consent were obtained before inclusion. After consent, eligible patients were randomly assigned to receive oral colchicine or placebo. Randomization was performed in a 1:1 ratio using permuted blocks and was stratified by center and by culprit coronary artery status (to ensure equivalent proportions of left anterior descending versus non-left anterior descending coronary artery culprit artery myocardial infarctions in both groups). A centralized randomization process was performed by internet using the ClinSight software (Ennov Clinical Software, Paris, France).

## Interventions

After randomization, each patient received colchicine or matching placebo, as close as possible to PCI. Patients were given a 2-mg oral loading dose, followed by 0.5 mg twice a day by oral route for 5 days. The loading dose was recommended to be given before PCI and, if not possible, immediately after PCI.<sup>12</sup>

Dose reduction to 0.5 mg every day or early discontinuation was permitted in case of any gastrointestinal side effects (diarrhea, nausea, abdominal pain) or in case of an acute, unexpected decline in the glomerular filtration rate or red and white blood cell counts monitored throughout the first 48 hours.

Except for the study drug administration, patients received standard care in terms of revascularization procedures and medications according to international guidelines.<sup>13</sup>

Assessments during initial follow-up were made at inclusion, and on the first day, second day, and at hospital discharge. Patients remained in the hospital as long as clinically indicated.

At 5 days follow-up, patients underwent an initial CMR study with intravenous gadolinium injection for primary end point assessment. Then, a follow-up clinical visit was done at 3 months with a CMR follow-up study. The full trial design and procedures have been reported previously.<sup>12</sup>

## Trial Outcomes

The primary outcome was a comparison of infarct size (IS) in grams of left ventricular (LV) mass assessed by late gadolinium enhancement CMR at 5 days between groups. Secondary outcomes were considered in hierarchical order as follows: LV ejection fraction at 5 days by CMR, microvascular obstruction mass at 5 days by CMR; absolute adverse LV remodeling between 5 days and 3 months by CMR, relative LV remodeling between 5 days and 3 months defined as a relative increase in LV end-diastolic volume  $>12\%$  by

CMR,<sup>14</sup> IS at 3 months, LV ejection fraction at 3 months, LV end-diastolic volume at 3 months, LV end-systolic volume at 3 months, and LV thrombus frequency at the acute phase or during follow-up.

The incidence of major adverse cardiovascular events at discharge (all-cause death, nonfatal myocardial infarction, nonfatal stroke, or heart failure events) at 3 months and 1 year follow-up, quality of life measured at 12 months, and markers of inflammation during the acute phase were secondary exploratory outcomes.

## CMR Protocol and Postprocessing

All CMR studies were performed on 1.5 or 3 Tesla scanners (multivendor Siemens, Philips) at  $5\pm 2$  days and 3 months  $\pm 15$  days after admission.

All sequences were performed by using vectocardiogram monitoring and 12-element phased-array cardiac receiver coils. After localization, rest LV function was assessed with retrospective ECG-gated steady-state free precession pulse cine sequences in long- and short-axis views in the true heart axis. The short-axis scans covered the whole left ventricle.

Late gadolinium enhancement was evaluated in short-axis orientation covering the whole ventricle 10 minutes after contrast injection of gadoteric acid (0.2 mmol/kg body weight; Dotarem, Guerbet) using 3-dimensional gradient spoiled inversion recovery TurboFLASH sequence covering the left ventricle in short axis. Additional 2-chamber and 4-chamber long-axis phase-sensitive inversion recovery sequences were also performed for better spatial assessment of late gadolinium enhancement-enhanced areas.

All CMR and coronary angiogram images were transferred from the trial sites to a central image database by using a software platform as described previously.<sup>12</sup>

Centralized, off-line image analysis of the CMR images was performed by an experienced observer on a dedicated workstation for all CMR studies using the Circle imaging software (CVI42, Circle Cardiovascular Imaging Inc). This single observer was blinded to all other clinical characteristics or study status.

LV volumes and function were assessed. The infarct zone was defined semiautomatically on late gadolinium enhancement imaging by using the full-width half-maximum technique.<sup>15</sup> Microvascular obstruction was defined as areas of hypoenhancement on the late gadolinium enhancement images within the hyperenhanced myocardium.

The extent of myocardial infarcted myocardium and microvascular obstruction was expressed in grams of tissue according to the following formula:  $\Sigma$  (hypo-enhanced and hyper-enhanced area [in  $\text{cm}^2$ ])  $\times$  slice thickness (in cm)  $\times$  myocardial specific density).

The area at risk was assessed by a single expert reader from the initial angiograms, using angiographic scoring of the area at risk with the APPROACH angiographic score (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease),<sup>16</sup> with angiograms before reperfusion and immediately after. This centralized reading was also blinded to any other clinical or imaging data from the study.

## Statistical Analysis

Assuming an infarct size at 5 days in the control group equal to 34 g (SD 22 g),<sup>2,17-19</sup> we calculated that a sample size of 194 patients would provide the trial with a power of at least 80%

to detect an expected reduction of 30% in the experimental group using a Mann-Whitney rank-sum test at a 2-sided  $\alpha$  of 5%, considering an anticipated dropout rate of 15%.

All analyses were performed according to the intention-to-treat principle and were prespecified before database lock and described in the statistical analysis plan available

Analysis of the primary outcome was performed by using a linear regression model with adjustment for the randomization stratification factor (center and culprit artery), providing an estimated treatment effect with a 95% CI, and a Wald test to reject the null hypothesis of no difference between groups.

Secondary efficacy outcomes were classified in a prespecified hierarchical order and tested, in turn, using a Wilcoxon rank-sum test according to a closed-test procedure to maintain an overall  $\alpha$ -level of 5%.<sup>20</sup> We further analyzed the secondary end points by using linear or logistic regression models with adjustment for the randomization stratification factor (center and culprit artery). Nonparametric Wilcoxon rank-sum tests or Fisher exact tests were used according to the nature of the secondary outcomes.

To assess the relationship between the area at risk and IS, we performed a prespecified analysis of regression plots of IS at 5 days on angiographically estimated area at risk and compared the 2 regression plots with covariance analysis.

Planned subgroup analyses of the primary outcome were performed according to age (<70 years versus  $\geq$ 70 years), sex, diabetes, multivessel disease status, time from symptom onset to hospital admission, type of culprit coronary artery, glomerular filtration rate, and myocardial area at risk size.

A 2-sided  $P$  value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS Software version 9.4 in a Windows environment.

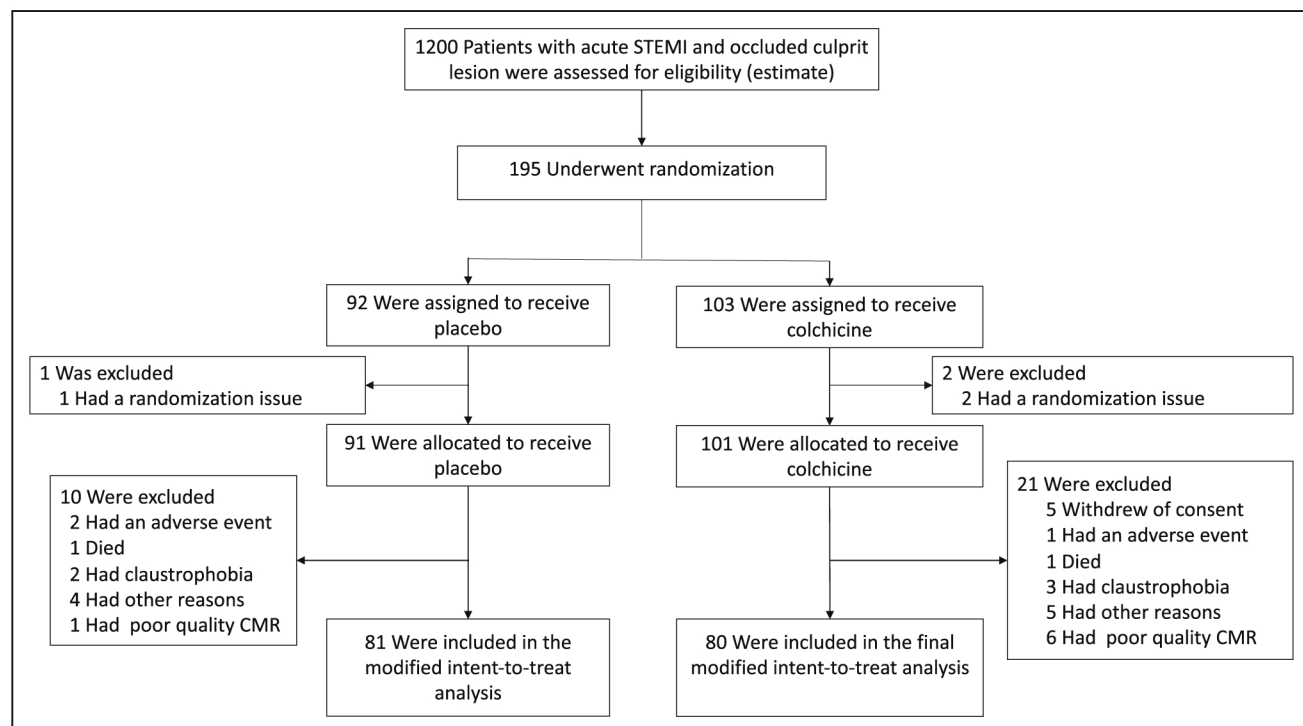
## RESULTS

### Patients

A total of 195 patients with STEMI were enrolled and underwent randomization (103 to the colchicine group and 92 to the placebo group). Screening logs were not maintained for the trial at each participating site, but an estimate of the STEMI population admitted at these centers during the inclusion period is presented in Figure 1. Three randomizations were randomization errors, 10 patients were excluded from the modified intent-to-treat analysis in the placebo group, and 23 in the colchicine group were excluded from the primary outcome analysis (Figure 1).

Baseline patients' characteristics were similar in the 2 groups, with a mean age of  $60.0 \pm 10.5$  years and 19.5% female sex (Table 1). Infarct location as determined by angiography and CMR was similar between anterior and nonanterior territories. Baseline angiographic, intervention, and pharmacological treatment at discharge were also well balanced between groups (Table 2).

The 2 study groups were similar concerning time from symptom onset to catheterization laboratory admission and the size of the angiographic area at risk. Rescue PCI after thrombolysis was performed in 27 patients (15 in the colchicine group and 12 in the placebo group). Stenting with drug-eluting stents of the culprit lesion was performed in 95.7% of patients (Table 2). Thrombosis in Myocardial Infarction 2 flow was not achieved after PCI in 1 patient from the placebo group.



**Figure 1. Enrollment and follow-up of the patients.**

CMR indicates cardiac magnetic resonance; and STEMI, ST-segment–elevation myocardial infarction.

**Table 1. Characteristics of the Patients at Baseline**

Characteristic	Colchicine (n=101)	Placebo (n=91)
Age, y	59.0±10.6	60.9±10.4
Female sex, n (%)	21/101 (20.8)	17/91 (18.7)
Body mass index*	27.3±5.0	26.9±4.4
Current smoking, n (%)	44/101 (43.6)	39/91 (42.9)
Diabetes, n (%)	12/101 (11.9)	13/91 (14.3)
Hypertension, n (%)	30/101 (29.7)	29/91 (31.9)
Dyslipidemia, n (%)†	29/101 (28.7)	34/91 (37.4)
History of coronary artery disease, n (%)	3/101 (3.0)	3/91 (3.3)
History of heart failure, n (%)	1/101 (1.0)	1/91 (1.1)
Killip class I at admission, n (%)	90/97 (92.8)	76/85 (89.4)
Systolic blood pressure at admission, mm Hg	136±25	139±24
Heart rate at admission, bpm	77±17	77±18
Estimated glomerular filtration rate, mL·min <sup>-1</sup> ·1.73m <sup>-2</sup> ‡	93.8±16.6	89.2±30.4
Blood glucose level, mmol/L	8.8±3.3	9.1±4.3
Median C-reactive protein (interquartile range), mg/L	3.0 (2.0–5.0)	3.0 (1.6–5.6)
Hemoglobin, g/L	146.2±14.5	142.8±13.4

Plus-minus values are means±SD.

\*The body-mass index is the weight in kilograms divided by the square of the height in meters.

†Dyslipidemia was defined as the receipt of treatment with cholesterol-lowering medication or an elevated level of total cholesterol (>200 mg/dL [5.2 mmol/L]).

‡Glomerular filtration rate was calculated.

## Study Treatment Delivery and Side Effects

Median delays of study treatment administration were 20 minutes (IQR, 9–26) in the colchicine group and 13 minutes (IQR, 9–27) in the placebo group. Colchicine had significantly more gastrointestinal side effects (mostly diarrhea) than placebo (33 [34.4%] versus 9 [10.1%], respectively;  $P=0.0001$ ), and 1 patient in the colchicine group presented with anemia.

## CMR Assessment

Of 192 patients, 168 (87.5%) underwent a CMR study at a median of 5 days (IQR, 4–7 days). Of these CMR studies, 161 (95.8%) were analyzable by the centralized core laboratory. For the primary end point assessment, 80 of 101 patients in the colchicine group and 81 of 91 patients in the placebo group had an accurate end point assessment at 5 days. Of 192 patients, 154 (80.2%) underwent a follow-up CMR study at a median of 95 days (IQR, 88–102 days). Of these CMR studies, 151 (98.1%) were analyzable. Reasons for noncompletion of CMR are shown in Figure 1. The delays within each group at baseline and follow-up are reported

**Table 2. Coronary Angiography, Interventions, and Medications at Discharge**

Variable	Colchicine (n=101)	Placebo (n=91)
Procedural and angiographic characteristics		
Median time from symptom onset to catheterization laboratory admission (interquartile range), h	2.9 [2.07–5.7]	3.0 [1.9–5.6]
Median time from reperfusion to study treatment administration (interquartile range), min	20 [9–26]	13 [9–27]
Culprit coronary artery, n (%)		
Left anterior descending coronary artery	50/97 (51.5)	44/91 (48.4)
Circumflex and right coronary artery	46/97 (47.4)	43/91 (47.3)
Initial thrombolysis in myocardial infarction flow<0/1, n (%)	93/97 (95.8)	86/91 (94.5)
Multivessel disease ≥2, n (%)	38/94 (40.4)	29/91 (32.3)
Area at risk size, % of left ventricle	28.8±11.7	29.4±11.5
Final thrombolysis in myocardial infarction flow ≥2, n (%)	93/95 (97.9)	90/91 (98.9)
PCI and reperfusion procedures, n (%):		
Initial thrombolysis	15/101 (14.9)	12/91 (13.2)
Thrombectomy	27/96 (28.1)	19/91 (20.9)
P2Y12 inhibitor loading dose	90/101 (89.1)	81/91 (89.0)
Glycoprotein IIb/IIIa inhibitors	25/101 (24.8)	18/91 (19.8)
Drug-eluting stenting	92/96 (95.8)	87/91 (95.6)
Medications at discharge		
Double antiplatelet therapy, n (%)	96/96 (100)	90/90 (100)
Oral anticoagulant therapy, n (%)	6/96 (6.3)	8/96 (8.9)
Vitamin K antagonists	4 (67)	3 (37.5)
Direct oral anticoagulants	2 (33)	5 (62.5)
β-Blockers, n (%)	92/96 (95.8)	86/90 (95.6)
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, n (%)	88/96 (91.7)	79/90 (87.8)
Mineralocorticoid antagonists, n (%)	3/96 (3.1)	5/90 (5.6)
Statins, n (%)	94/96 (97.9)	85/90 (94.4)
Diuretics, n (%)	14/96 (14.6)	18/90 (20)

Plus-minus values are means±SD. There were no significant differences between the 2 groups for any variable. Percentages may not total 100 because of rounding. PCI indicates percutaneous coronary intervention.

## Primary Outcome

All prespecified study outcomes are summarized in Table 3. The IS after reperfusion was not significantly reduced in the colchicine group compared with the placebo group, with a mean of 26.0 g (IQR, 16.0–44.0) of LV mass in the colchicine group versus 28.4 g (IQR, 14.0–40.0) in the placebo group ( $P=0.87$  for the difference; Figure 2A). As shown in Figure 2B, there was a significant positive relationship between the IS and the angiographic area at risk (as defined by the angiographic APPROACH score on initial angiography<sup>16</sup>), larger in the

**Table 3. Prespecified Primary and Secondary Outcomes**

Outcomes	Colchicine (n=80)	Placebo (n=81)	Coefficient* and 95% CI	P value
Primary outcome				
Infarct size at 5 days, g	26.0 [16.0 to 44.0]	28.4 [14.0 to 40.0]	-0.99 (-2.55 to 4.61)	0.87
Secondary outcomes				
Microvascular obstruction at 5 days, g†	1.00 [0.0 to 5.0]	1.28 [0.0 to 7.0]	-0.13 (-1.83 to 1.56)	0.88
Microvascular obstruction incidence, n (%)‡	52 (64.2)	56 (68.3)	0.83 (0.42 to 1.65)	0.60
Relative LV remodeling, %†§	+2.4 [-8.3 to +11.1]	-1.1 [-8.0 to +9.9]	1.98 (-3.61 to 7.57)	0.48
Adverse remodeling, n (%)‡	17 (23.9)	17 (23.0)	1.11 (0.49 to 2.52)	0.79
LV thrombus incidence, n (%)‡	18 (22.2)	6 (7.4)	4.05 (1.46 to 12.67)	0.01
LV ejection fraction at 5 days, %†	46±7.9	44±7.6	2.18 (-0.06 to 4.42)	0.06
LV ejection fraction at 3 mo, %†	48±8.5	46±8.6	1.95 (-0.79 to 4.68)	0.16
Infarct size at 3 mo, g†	17.2 [10.5 to 27.8]	18.4 [10.0 to 26.5]	-0.06 (-3.48 to 3.36)	0.97

Plus-minus values are means±SD. LV indicates left ventricle.

\*β-Coefficients or odds ratio coefficients depending on the regression used.

†Secondary outcomes analyzed by linear regression with adjustment for the randomization stratification factors.

‡Secondary outcomes analyzed by logistic regression with adjustment for the randomization stratification factors

§Relative left ventricular remodeling was defined as the difference in left ventricular end-diastolic volume between the 3 mo CMR study and the 5 days CMR study, divided by the left ventricular end-diastolic volume at 5 days.

||Adverse remodeling was defined as an increase in the left ventricular end-diastolic volume of more than 12% between 5 days and 3 mo as reported by Bulluck et al.<sup>14</sup>

colchicine group than in the placebo group ( $P$  for interaction=0.03; Figure 2B).

Results according to prespecified subgroups are presented in Figure 3. There were no significant differences across prespecified subgroups except for sex ( $P$  for interaction=0.02), with a suggestion of smaller infarct size in women treated with colchicine. Caution is needed in interpreting this subgroup given the small number of women enrolled.

## Secondary Outcomes

There were no significant differences in other prespecified secondary outcomes in terms of microvascular obstruction extent, LV remodeling, and LV ejection fraction between the colchicine and placebo groups, as reported in Table 3.

There was no difference between groups in IS at 3 months (17.2 IQR [10.5–27.8] versus 18.4 IQR [10.0–26.5] g of LV mass, respectively;  $P=0.92$ ).

There was an unexpected significant increase in the rate of LV thrombus at 5 days, however, with a greater proportion of LV thrombus in the colchicine group 18 (22.2%) compared with the placebo group 6 (7.4%;  $P=0.01$ ). This difference was confirmed by the adverse event rates reporting of LV thrombi with 23 (22.8%) cases in the colchicine group and 8 (8.7%) cases in the placebo group ( $P=0.032$ ) over the whole study follow-up at 3 months. On the CMR follow-up studies at 3 months, this difference in the proportion of LV thrombus was no longer significant with 4 (5.3%) cases in the colchicine group compared with 2 (2.6%) cases in the placebo group ( $P=0.68$ ). At 3 months of follow-up, 2 (1.9%) ischemic strokes were reported in

the colchicine group and 1 (1.1%) was reported in the placebo group ( $P=1.0$ ). None of the ischemic stroke events occurred in patients in whom a LV thrombus had been identified.

In an exploratory analysis comparing patients with and without LV thrombus, the only 2 baseline variables associated with a subsequent LV thrombus were a culprit coronary artery identified as the left anterior descending or left main and the use of thrombus aspiration during PCI.

## Major Adverse Cardiovascular Outcomes at 3 Months and Serious Adverse Events

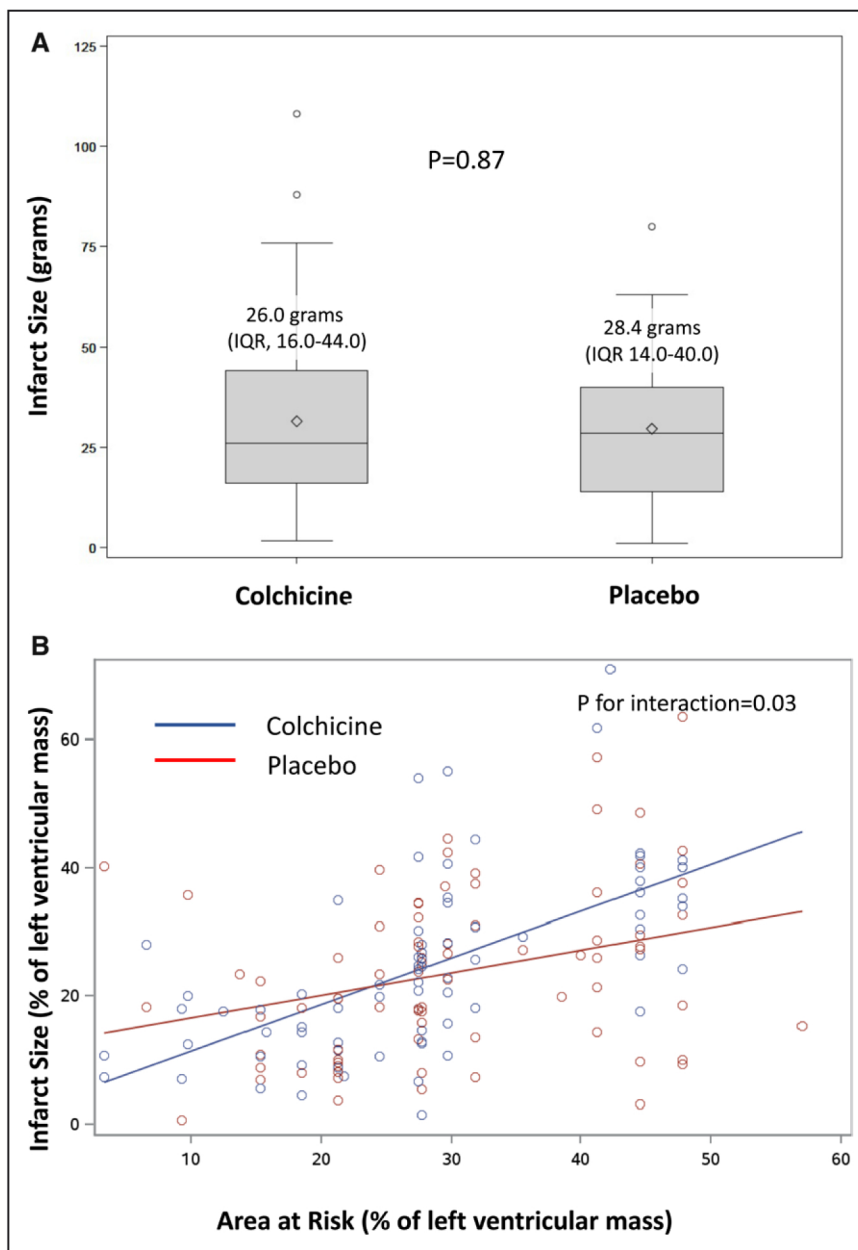
There were no significant differences in major cardiovascular events reported at 3 months between groups

The number of serious adverse events was 40 (38.8%) in the colchicine group and 32 (34.8%) in the placebo group at 3 months, with no significant difference ( $P=0.66$ ;

## Biomarkers

There were no differences in total creatine kinase release at admission, 6 hours, 24 hours, and 48 hours between groups.

We observed no significant differences between groups regarding inflammatory biomarkers such as white blood cell count, neutrophil count, and fibrinogen at admission, 24 hours, and 48 hours. C-reactive protein levels were not significantly lower in the colchicine group than in the placebo group at 48 hours (15.7 mg/L [IQR, 6.3–37.5] versus 23.6 mg/L [IQR, 10.9–46.0];  $P=0.06$ ).



**Figure 2. Assessment of infarct size by late gadolinium enhancement cardiac magnetic resonance and as a function of the area at risk (A).**

Infarct size (IS) was measured in a centralized core laboratory by quantification of the area of late gadolinium enhancement (LGE) by cardiac magnetic resonance at 5 days. IS Colchicine administration did not result in a significant reduction in IS in comparison with placebo (estimate: 0.99 [95% CI, -2.64 to 4.61];  $P=0.59$ ). The IS measured by LGE was expressed as a function of the APPROACH angiographic score,<sup>16</sup> an estimate of the area at risk, as shown in **B**. To assess the relationship between the area at risk and IS, we performed a prespecified analysis of regression plots of IS by LGE at 5 days on angiographically estimated area at risk. There was a significant association between the 2 variables in the colchicine group ( $\beta=0.73$ ;  $P<0.001$ ) and the placebo group ( $\beta=0.35$ ;  $P=0.003$ ). There was a significant positive relationship between the 2 variables in both groups, and significantly larger in the colchicine group ( $P$  interaction=0.03). These data suggest that, for the largest areas at risk, colchicine administration was associated with an increase in the resulting infarct size as measured by LGE. This difference was confirmed to be significant by analysis of covariance ( $P$  for interaction= 0.03). APPROACH indicates Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; and IQR, interquartile range.

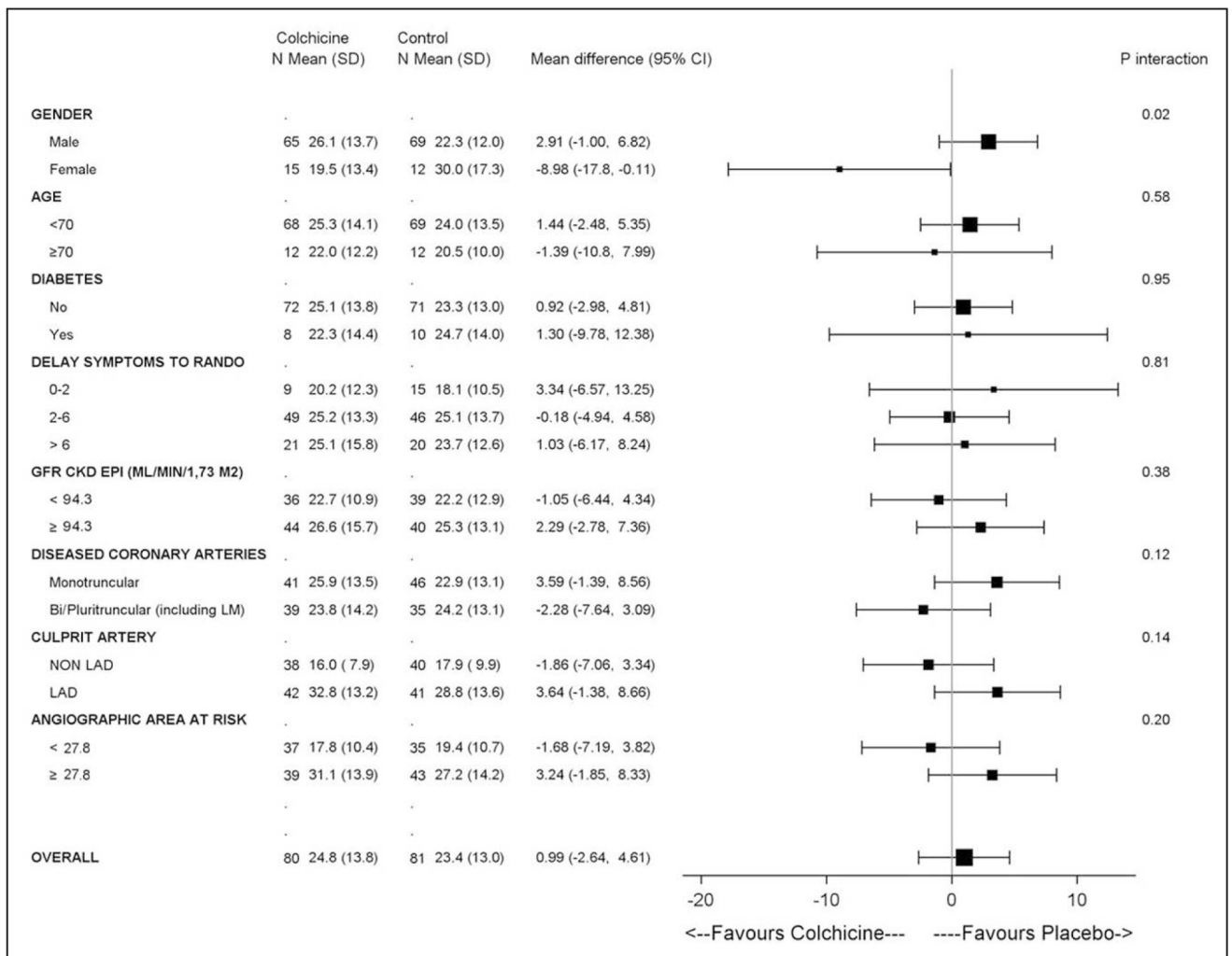
## DISCUSSION

Our findings show that short-term oral colchicine treatment at high doses given at the time of reperfusion in patients who have acute STEMI did not reduce infarct size as determined by CMR in comparison with placebo. There was also no significant change in other indices of myocardial damage such as microvascular obstruction and LV remodeling. However, there was an unexpected 3-fold increase in the incidence of LV thrombus in patients receiving colchicine compared with those receiving placebo, without evidence of subsequent adverse clinical outcomes.

There has been recent interest in treating the chronic inflammation associated with atherosclerotic disease with low-dose colchicine. The Colcot (Colchicine Car-

diovascular Outcome Trial) and LoDoCo2 (Low-Dose Colchicine 2) trials<sup>10,11</sup> showed benefit of low-dose colchicine (0.5 mg every day) started within a month after myocardial infarction or in patients with chronic coronary disease after at least 6 months of a clinically stable condition. In another recent trial, colchicine given earlier and at a higher dose of 0.5 mg twice a day for 1 month followed by 0.5 mg every day for 11 months after an acute coronary syndrome failed to demonstrate any benefit, and there was increased mortality in the colchicine group.<sup>21</sup> This discrepancy has generated debate.<sup>22</sup> The present phase II randomized trial was designed to explore a different hypothesis. We specifically targeted the inflammatory response that occurs in the acutely injured myocardium immediately after reperfusion.<sup>3</sup> There was no reduction of myocardial infarct size in patients receiv-





**Figure 3. Subgroup analyses for the primary outcome at 5 days.**

CKD indicates chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; GFR, glomerular filtration rate; LAD, left anterior descending coronary artery; LM, left main coronary artery; and RANDO, randomization.

ing colchicine. This finding is in keeping with previous reports assessing the effects of colchicine on myocardial injury and inflammation,<sup>23–26</sup> but it does not confirm previous results suggesting up to a 50% reduction of IS with a similar regimen.<sup>27</sup> In this latter study, IS reduction was assessed by using myocardial biomarker release, and IS reduction on CMR imaging was only reported in a subgroup of patients. Another explanation for this difference may be related to a difference between study populations. In this former study, patients' Thrombosis in Myocardial Infarction flow was not reported, suggesting potential confounding factors.<sup>27</sup> The present trial used an accepted primary end point with core laboratory measurement of CMR infarct size.

One may hypothesize that the discrepancy between our study results and recent phase III colchicine trials could be related to a dose effect. Colchicine has dose-related effects with a narrow therapeutic margin.<sup>7</sup> Gastrointestinal effects are the most common adverse effect and the first signs of toxicity, as well.<sup>28</sup> Our dose regimen was established on a previous report by Defftereos et al,<sup>27</sup>

and we found a similar frequency of gastrointestinal side effects, mostly diarrhea. These side effects were significantly increased compared with placebo, and their frequency was also significantly greater than that reported in trials with low-dose colchicine of 0.5 mg every day.<sup>10,11</sup>

Other factors influencing IS may contribute to the absence of the efficacy of colchicine in reducing final IS. Total ischemic time, area at risk size, thrombolysis, or factors associated with reperfusion could have interfered with the effect of colchicine. Although our protocol strictly followed the protocol of the initial report by Defftereos et al,<sup>27</sup> the timing, dose, and duration of colchicine administration remain poorly explored. Regarding the oral administration used in our study, it was also reported and used in the study by Defftereos et al.<sup>27</sup> In addition, previous pharmacokinetic reports indicate that, after an oral ingestion of colchicine, the plasma levels peak at ≈1 hour with a mean half-life of 26 hours. The bioavailability of colchicine ranges from 24% to 88% (mean 45%).<sup>29</sup> There are no data regarding the impact of myocardial infarction on colchicine gastrointestinal absorption. It

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may be delayed, as previously seen for instance, with ticagrelor with a 34% reduction of ticagrelor bioavailability in patients with STEMI versus patients with non-ST-segment-elevation myocardial infarction.<sup>30</sup> This could affect its efficacy, although it was not the case in the report by Deffereos et al.<sup>27</sup>

The present knowledge regarding the inflammatory response after myocardial ischemia reperfusion shows a proinflammatory phase that lasts for 3 to 7 days with marked immune cell recruitment, tissue digestion, and reactive oxygen species production. The peak of this inflammatory phase is between 24 and 72 hours, and its duration is  $\approx$ 5 to 7 days. The proinflammatory phase switches toward a reparative and proliferative phase with inflammation resolution, scar formation, and wound healing.<sup>31</sup> Thus, the timing of an early administration of colchicine seemed appropriate.

Regarding the increased incidence of early LV thrombus in the colchicine group, there is no evidence in the literature of any prothrombotic effect associated with colchicine,<sup>28</sup> but the effect of colchicine on platelet function appears to be complex.<sup>26,32</sup> Several hypotheses can be raised to explain this finding. The first is a chance finding attributable to the small sample size. Nonetheless, the magnitude of the difference and the consistency between the core laboratory assessment and the investigators' adverse event notifications suggest otherwise. Our exploratory analysis plotting IS against angiographic area at risk showed significantly larger IS in the colchicine group. This may be related to the short duration of high-dose colchicine therapy in our study. Colchicine's antithrombotic effect is mostly related to its anti-inflammatory properties through inhibition of neutrophil degranulation<sup>33</sup>; it is conceivable that a proinflammatory rebound at the early discontinuation of therapy (as described with other anti-inflammatory drugs<sup>34</sup>) may have fostered increased LV damage and subsequent thrombus formation.<sup>35–37</sup> Of note, an *in vitro* study on human umbilical vein endothelial cell line investigating colchicine anti-inflammatory mechanisms suggested that, in addition to its interaction with microtubules, colchicine also impacts cell response at the transcriptional level. The effects of colchicine are complex and activate different pathways at different doses and duration regimens.<sup>38</sup> These observations regarding early thrombus formation and IS in patients with a larger area at risk are purely exploratory and should be interpreted with caution. We suggest that thrombosis should be prospectively examined in future trials investigating anti-inflammatory interventions in acute myocardial infarction.

A recent study<sup>39</sup> found a promising effect of interleukin 6 selective inhibition with tocilizumab in patients with acute myocardial infarction. Colchicine features an original anti-inflammatory mechanism of action combining tubulin disruption, inhibition of NLRP3 inflammasome, and stimulation of dendritic cell maturation and antigen

presentation.<sup>7</sup> We hypothesized that these mechanisms were more likely to induce a more favorable modulation of the immunoinflammatory response than a targeted cytokine inhibition. Together with the unexpected results of our study, this demonstrates the complex nature of this inflammatory response and the numerous remaining unexplored areas that need to be tackled in further studies to better understand and treat it to limit the final myocardial damage.

The present trial has several limitations. First, it is a phase II trial with a limited sample size. However, adherence to the protocol and the overall good quality in data acquisition and processing with centralized reading make the findings robust. Second, there was a higher-than-expected number of missing CMR studies. We had anticipated 15% of missing data but the actual proportion was eventually 20%. However, the absence of difference between groups regarding the primary outcome makes it unlikely that 5 more CMR studies in each group would have changed the conclusion. Third, the primary end point assessment by CMR at 5 days may have led to overestimation of final IS as suggested by previous reports.<sup>40</sup> However, IS was also assessed at 3 months follow-up, with consistent results.

In patients with a first episode of STEMI and occluded culprit coronary artery, high-dose colchicine given orally at the time of reperfusion for a short period did not reduce myocardial damage induced by ischemia-reperfusion and the resulting inflammation compared with placebo. Further studies exploring the timing, pharmacokinetics, and dose response of colchicine and other anti-inflammatory agents are needed to identify an effective therapy to reduce infarct size or limit remodeling.

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## Disclosures

None.

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