ORIGINAL ARTICLE

# Colchicine in Acute Myocardial Infarction

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## ABSTRACT

### BACKGROUND

Inflammation is associated with adverse cardiovascular events. Data from recent trials suggest that colchicine reduces the risk of cardiovascular events.

### METHODS

In this multicenter trial with a 2-by-2 factorial design, we randomly assigned patients who had myocardial infarction to receive either colchicine or placebo and either spironolactone or placebo. The results of the colchicine trial are reported here. The primary efficacy outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization, evaluated in a time-to-event analysis. C-reactive protein was measured at 3 months in a subgroup of patients, and safety was also assessed.

### RESULTS

A total of 7062 patients at 104 centers in 14 countries underwent randomization; at the time of analysis, the vital status was unknown for 45 patients (0.6%), and this information was most likely missing at random. A primary-outcome event occurred in 322 of 3528 patients (9.1%) in the colchicine group and 327 of 3534 patients (9.3%) in the placebo group over a median follow-up period of 3 years (hazard ratio, 0.99; 95% confidence interval [CI], 0.85 to 1.16; P=0.93). The incidence of individual components of the primary outcome appeared to be similar in the two groups. The least-squares mean difference in C-reactive protein levels between the colchicine group and the placebo group at 3 months, adjusted according to the baseline values, was –1.28 mg per liter (95% CI, –1.81 to –0.75). Diarrhea occurred in a higher percentage of patients with colchicine than with placebo (10.2% vs. 6.6%; P<0.001), but the incidence of serious infections did not differ between groups.

### CONCLUSIONS

Among patients who had myocardial infarction, treatment with colchicine, when started soon after myocardial infarction and continued for a median of 3 years, did not reduce the incidence of the composite primary outcome (death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization). (Funded by the Canadian Institutes of Health Research and others; CLEAR ClinicalTrials.gov number, NCT03048825.)

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Inflammation is thought to be an important mechanism for atherosclerosis in both the acute and the chronic phases. Increased levels of circulating inflammatory markers are also associated with a worse prognosis in patients with acute coronary syndromes.[1] Canakinumab, an interleukin-1$\beta$ inhibitor, reduced ischemic events in patients with previous myocardial infarction but increased fatal infections.[2] Therefore, more data about the effects of antiinflammatory agents on cardiovascular events are needed.

Colchicine inhibits the actions of neutrophils and the release of inflammatory chemokines, including interleukin-1 and interleukin-6.[3] A trial involving 4745 patients in which treatment with colchicine was initiated within 30 days after myocardial infarction and a trial involving 5522 patients with stable coronary artery disease showed beneficial cardiovascular effects of colchicine; however, two recent trials involving patients with ischemic stroke showed no reductions in cardiovascular events with colchicine treatment, although in one trial the treatment duration was only 3 months.[4-7]

The European Society of Cardiology recently provided a class IIa recommendation for the use of colchicine in patients with atherosclerotic coronary artery disease.[8] However, the use of colchicine in such patients is not widespread. Given the biologic rationale for a benefit from colchicine and the encouraging evidence that colchicine may improve cardiovascular outcomes, we conducted the CLEAR trial to examine the effects of colchicine in patients after myocardial infarction.

## Methods

### Trial Design

We used a 2-by-2 factorial design in this international, investigator-initiated, multicenter, prospective, randomized, placebo-controlled trial of colchicine and spironolactone in patients with acute myocardial infarction. Information about the trial design was published previously and is provided in the protocol, available with the full text of this article at NEJM.org.[9] The results of the spironolactone trial are reported elsewhere.[10] All patients, investigators, health care providers, data collectors, and outcome adjudicators were unaware of trial-group assignments. A registry-based trial of SYNERGY stents in 733 patients with ST-segment elevation myocardial infarction (STEMI) was embedded within the larger trial of colchicine and spironolactone, and the results of the registry-based trial have been published previously.[11]

Initially, patients were eligible to participate in the trial if they had STEMI and underwent percutaneous coronary intervention. To increase recruitment numbers, the steering committee modified the protocol on April 5, 2020, to enroll patients with large non–ST-segment elevation myocardial infarction (NSTEMI) who had undergone percutaneous coronary intervention and had one or more of the following risk factors: a left ventricular ejection fraction of no more than 45%; diabetes mellitus; multivessel coronary artery disease, defined by at least 50% stenosis of a second major epicardial vessel; previous myocardial infarction; or age greater than 60 years. The detailed eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

The ethics committee of each participating center and the relevant national regulatory authorities approved the trial. All patients provided written informed consent. The Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, Canada, coordinated the trial and collected and held all trial data; the third and fourth authors conducted all analyses. The steering committee developed the trial protocol, and the members of the committee (listed in the Supplementary Appendix) vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The first author wrote the manuscript with the input of the coauthors, and the steering committee made the decision to submit the manuscript for publication. The trial funders had no role in the design and conduct of the trial. An independent data and safety monitoring committee monitored the accumulating safety and efficacy data.

### Randomization

Patients were randomly assigned in a factorial 1:1:1:1 allocation to receive colchicine and spironolactone, colchicine and placebo, spironolactone and placebo, or placebo only as soon as possible after the index percutaneous coronary intervention. Randomization was performed with the use of permuted blocks within a 24-hour computerized central system at the Population Health Re-

search Institute. Randomization was stratified according to trial center and the type of myocardial infarction (STEMI or NSTEMI).

### OUTCOMES

The primary efficacy outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization, evaluated in a time-to-event analysis. Key secondary outcomes were a composite of death from cardiovascular causes, recurrent myocardial infarction, or stroke, evaluated in a time-to-event analysis; and the total number of primary-outcome events. C-reactive protein levels and safety were also assessed. Measurement of C-reactive protein was not mandated by the trial protocol, but measurements taken in the course of clinical care were recorded on case report forms. Detailed, prespecified definitions of outcomes are provided in Table S2, and a full list of outcomes is provided in Table S3.

A committee of clinicians who were unaware of trial-group assignments adjudicated all primary-outcome events, episodes of major bleeding, and stent thrombosis events. Staff at an angiographic core laboratory at the Population Health Research Institute who were unaware of trial-group assignments reviewed all ischemia-driven revascularization and stent thrombosis events.

### TRIAL INTERVENTIONS

The trial products were colchicine tablets of 0.5 mg, spironolactone tablets of 25 mg, and placebos matching the colchicine and spironolactone tablets. Tiofarma provided both trial drugs and placebos, which were manufactured with raw materials produced by Indena. At the beginning of the trial, colchicine dosage was based on weight for the first 90 days of treatment; patients weighing 70 kg or more received a dose of 0.5 mg of colchicine or matching placebo twice a day, and patients weighing less than 70 kg received a dose of 0.5 mg or matching placebo once a day. After the first 90 days of treatment, all patients received the trial product once a day. However, after blinded interim analyses showed higher-than-expected rates of discontinuation and the Colchicine Cardiovascular Outcomes Trial (COLCOT) showed efficacy with once-daily colchicine, the steering committee adopted the regimen of once-daily colchicine at a dose of 0.5 mg or matching placebo throughout the remainder of the treatment period, beginning in September 2020.[4]

### STATISTICAL ANALYSIS

The initial calculation of sample size to provide the trial with 80% power to detect a 25% relative risk reduction was based on a time-to-event analysis of the primary outcome, a composite of death from cardiovascular causes, recurrent myocardial infarction, or stroke; we anticipated a cumulative incidence of events in the placebo group of 15% at 3 years, a two-sided type I error level of 5%, a loss to follow-up of 2% of patients in both the colchicine group and the placebo group, discontinuation of the trial regimen by 12.5% of patients, and no interaction with spironolactone. On the basis of these assumptions, we estimated that 4000 patients and 512 primary-outcome events were needed to detect a 25% relative risk reduction with a log-rank test. In April 2020, a blinded interim analysis of the incidence of events found an incidence of 3% per patient-year, with an estimated cumulative incidence of 9% at 3 years, which was consistent with the data from other trials.[4,12] As a result, the sample size was increased from 4000 to 7000 patients to maintain a power of 80%, and we estimated that 546 primary-outcome events would be needed to detect a 25% relative risk reduction. The sample size was increased without knowledge of any treatment effects.

For the primary analysis, patients were evaluated according to the groups to which they were randomly assigned. A two-sided log-rank test was used to compare the colchicine and placebo groups. A P value of less than 0.05 was considered to indicate statistical significance. The hazard ratios and 95% confidence intervals were estimated with the use of a Cox proportional-hazards regression model in which the trial group was the independent variable and patients were stratified according to whether they received spironolactone or spironolactone-matched placebo and whether they had STEMI or NSTEMI. At the request of the *Journal*, the Fine–Gray subdistribution hazard model was used to account for competing risks: death from noncardiovascular causes for outcomes that include death from cardiovascular causes, death from cardiovascular causes for outcomes that include death from noncardiovascular causes, and death from any cause for other, nonfatal outcomes. A total event analysis was performed with the Prentice–Williams–Peter-

**Table 1. Demographic and Clinical Characteristics at Baseline.***

| Characteristic | Colchicine (N=3528) | Placebo (N=3534) |
|---|---|---|
| **Demographic characteristics** | | |
| Mean age — yr | 60.6±10.3 | 60.7±10.3 |
| Age >75 yr — no. (%) | 301 (8.5) | 270 (7.6) |
| Female sex — no. (%) | 725 (20.5) | 713 (20.2) |
| Race or ethnic group — no. (%)† | | |
| American Indian or Alaskan Native | 7 (0.2) | 3 (0.1) |
| Asian | 95 (2.7) | 89 (2.5) |
| Black | 24 (0.7) | 23 (0.7) |
| Native Hawaiian or other Pacific Islander | 9 (0.3) | 9 (0.3) |
| White | 3233 (91.6) | 3249 (91.9) |
| Other | 153 (4.3) | 159 (4.5) |
| Geographic region — no. (%) | | |
| North America | 1010 (28.6) | 1012 (28.6) |
| Europe | 2356 (66.8) | 2359 (66.8) |
| Other | 162 (4.6) | 163 (4.6) |
| **Clinical characteristics** | | |
| Killip class ≥II — no. (%)‡ | 25 (0.7) | 24 (0.7) |
| NSTEMI at presentation — no. (%) | 165 (4.7) | 184 (5.2) |
| STEMI at presentation — no. (%) | 3363 (95.3) | 3350 (94.8) |
| Myocardial area affected by STEMI — no./total no. (%) | | |
| Anterior | 1304/3363 (38.8) | 1326/3350 (39.6) |
| Inferior | 1940/3363 (57.7) | 1892/3350 (56.5) |
| Lateral | 423/3363 (12.6) | 434/3350 (13.0) |
| Posterior | 341/3363 (10.1) | 319/3350 (9.5) |
| Multivessel coronary disease — no. (%) | 1735 (49.2) | 1742 (49.3) |
| **Medical history — no. (%)** | | |
| Current smoker | 1461 (41.4) | 1423 (40.3) |
| Hypertension | 1620 (45.9) | 1613 (45.6) |
| Diabetes mellitus | 658 (18.7) | 645 (18.3) |
| Previous myocardial infarction | 309 (8.8) | 324 (9.2) |
| Previous percutaneous coronary intervention | 345 (9.8) | 364 (10.3) |
| **Medications at discharge — no. (%)** | | |
| Aspirin | 3428 (97.2) | 3405 (96.3) |
| Clopidogrel | 1478 (41.9) | 1497 (42.4) |
| Ticagrelor | 1611 (45.7) | 1571 (44.5) |
| Prasugrel | 381 (10.8) | 413 (11.7) |
| Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker | 2750 (77.9) | 2768 (78.3) |
| Statin | 3408 (96.6) | 3416 (96.7) |
| Sodium–glucose cotransporter 2 inhibitor | 110 (3.1) | 101 (2.9) |

**Table 1. (Continued.)**

| Characteristic | Colchicine (N=3528) | Placebo (N=3534) |
|---|---|---|
| **Initial percutaneous coronary intervention§** | | |
| Placement of bare-metal stent — no. of stents/total no. (%) | 12/4797 (0.3) | 8/4898 (0.2) |
| Placement of ≥1 drug-eluting stent — no. of stents/total no. (%) | 4619/4797 (96.3) | 4694/4898 (95.8) |
| Angioplasty only — no. of stents/total no. (%) | 146/4797 (3.0) | 165/4898 (3.4) |
| Median no. of stents per patient (IQR) | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) |
| Mean stent length — mm | 23.8±8.6 | 23.8±8.8 |
| Mean stent diameter — mm | 3.2±0.5 | 3.1±0.5 |
| Coronary artery bypass grafting — no. of stents/total no. (%) | 137/4797 (2.9) | 139/4898 (2.8) |
| Placement of intraaortic balloon pump — no. of patients (%) | 45 (1.3) | 49 (1.4) |

* Plus–minus values are means ±SD. IQR denotes interquartile range, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
† Race or ethnic group was reported by the patients.
‡ The Killip classification system is a tool to assess the risk of death based on the severity of heart failure in patients with acute myocardial infarction. The scale ranges from I to IV, with higher numbers indicating greater risk.
§ The total number of stents placed was 9695, with 4797 in the colchicine group and 4898 in the placebo group.

son model with the gap-time approach and with the Lin–Wei–Yang–Ying model. Secondary outcomes were analyzed with the same approach. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals may not be used in place of hypothesis testing. An interaction among the assigned trial regimens was not expected.

The prespecified subgroups were analyzed with the use of the Cox regression model with an interaction term for the subgroup. Patients were divided into subgroups according to the prespecified characteristics: age (<65 years vs. ≥65 years), sex (female vs. male), diabetes versus no diabetes, multivessel disease versus single-vessel disease, STEMI versus NSTEMI, estimated glomerular filtration rate (<60 ml per minute per 1.73 $m^2$ of body-surface area vs. ≥60 ml per minute per 1.73 $m^2$), initial trial dose and weight (patients weighing <70 kg who received once-daily colchicine during the first 90 days, patients weighing ≥70 kg who received twice-daily colchicine during the first 90 days, and patients weighing ≥70 kg who received once-daily colchicine during the first 90 days), and timing of trial enrollment with respect to the coronavirus disease 2019 (Covid-19) pandemic (before [February 1, 2018, to January 30, 2020], during [January 31, 2020, to January 31, 2022], or after [February 1, 2022, to the time of data analysis] the pandemic). Post hoc subgroups according to geographic region (North America vs. Europe vs. other) were added to show consistency.

We undertook on-treatment analyses with the exclusion of patients who discontinued the trial regimen on the day of randomization and censored patients 7 days after permanent discontinuation of the trial regimen.

C-reactive protein values were analyzed with the use of a linear mixed model with repeated measures and adjusted according to the baseline value; the mean difference between groups at 3 months, along with the 95% confidence interval, is reported. Additional information regarding the statistical analyses is provided in the Supplementary Appendix.

## RESULTS

### PATIENTS

Between February 1, 2018, and November 8, 2022, we enrolled 7062 patients from 104 centers in 14 countries; 3528 patients were assigned to receive colchicine and 3534 to receive placebo (Fig. S1). At the time of our analyses, the vital status was unknown for 45 of the 7062 patients (0.6%); a primary-outcome event was known to have occurred in 2 of these patients. The remaining 43 patients had no recorded outcome or final visit.

**Table 2. Primary and Secondary Outcomes.**

| Outcome | Colchicine (N=3528) | Placebo (N=3534) | Hazard Ratio (95% CI)* |
|---|---|---|---|
| | *number (percent)* | | |
| **Primary outcome** | | | |
| Death from cardiovascular causes, recurrent myocardial infarction, stroke, or ischemia-driven coronary revascularization† | 322 (9.1) | 327 (9.3) | 0.99 (0.85–1.16) |
| Components of the primary outcome | | | |
| Death from cardiovascular causes | 117 (3.3) | 113 (3.2) | 1.03 (0.80–1.34) |
| Recurrent myocardial infarction | 102 (2.9) | 111 (3.1) | 0.88 (0.66–1.17) |
| Stroke | 50 (1.4) | 43 (1.2) | 1.15 (0.72–1.84) |
| Ischemia-driven coronary revascularization | 164 (4.6) | 166 (4.7) | 1.01 (0.81–1.26) |
| **Other outcomes** | | | |
| Death from cardiovascular causes, recurrent myocardial infarction, or stroke | 241 (6.8) | 250 (7.1) | 0.98 (0.82–1.17) |
| Death from all causes | 162 (4.6) | 179 (5.1) | 0.90 (0.73–1.12) |
| Death from noncardiovascular causes | 45 (1.3) | 66 (1.9) | 0.68 (0.46–0.99) |
| Pericarditis | 33 (0.9) | 22 (0.6) | 1.53 (0.88–2.65) |
| Atrial fibrillation | 91 (2.6) | 89 (2.5) | 0.98 (0.72–1.33) |

* The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing.
† The P value for the primary outcome is 0.93.

Given that the missing data were rare and evenly distributed between the colchicine and placebo groups (Table S4), the data are most likely missing at random.

Baseline characteristics of the patients appeared to be well balanced between the groups; the mean age of patients was 61 years, and 20.4% of patients were women (Table 1). A total of 9.0% of patients had previous myocardial infarction, 10.0% had previous percutaneous coronary intervention, and 18.5% had diabetes mellitus; 95.1% of patients had STEMI, and 4.9% had NSTEMI. The median time from symptom onset to randomization was 26.8 hours (interquartile range, 15.9 to 42.4), and the median time from randomization to the first dose of the trial product was 1.6 hours (interquartile range, 0.6 to 7.4). The medications provided to patients at discharge from the hospital appeared to be similar in the two groups (Table 1). The median duration of follow-up was 3.00 years (interquartile range, 2.14 to 3.71); 25.9% of patients in the colchicine group and 25.5% in the placebo group discontinued the trial regimen. The least-squares mean level (±SE) of C-reactive protein at 3 months, adjusted according to the value at baseline, was 2.98±0.19 mg per liter among 1384 patients in the colchicine group and 4.27±0.19 mg per liter among 1419 patients in the placebo group (difference, –1.28 mg per liter; 95% confidence interval [CI], –1.81 to –0.75).

### EFFICACY

A primary-outcome event occurred in 322 of 3528 patients (9.1%) in the colchicine group as compared with 327 of 3534 patients (9.3%) in the placebo group (hazard ratio, 0.99; 95% CI, 0.85 to 1.16; P=0.93) (Table 2 and Fig. 1), with a median duration of follow-up of 1089 days (2.98 years) in the colchicine group and 1090 days (2.98 years) in the placebo group. The spironolactone factorial had no significant effect on the results of the comparison of colchicine with placebo for the primary outcome (P=0.96 for interaction). Death from cardiovascular causes, recurrent myocardial infarction, or stroke occurred in 241 patients (6.8%) in the colchicine group and 250 patients (7.1%) in the placebo group (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). An analysis of total events that included recurrent

primary-outcome events showed that there were 376 events (3.53% per patient-year) in the colchicine group as compared with 389 events (3.67% per patient-year) in the placebo group (hazard ratio, 0.98; 95% CI, 0.85 to 1.13), with a median duration of follow-up of 1078 days (2.95 years) in the colchicine group and 1092 days (2.99 years) in the placebo group.

Death from cardiovascular causes occurred in 117 patients (3.3%) in the colchicine group and 113 (3.2%) in the placebo group (hazard ratio, 1.03; 95% CI, 0.80 to 1.34). Other components of the primary and secondary outcomes are summarized in Table 2. Death from noncardiovascular causes occurred in 45 patients (1.3%) in the colchicine group as compared with 66 patients (1.9%) in the placebo group (hazard ratio, 0.68; 95% CI, 0.46 to 0.99).

The results of on-treatment analyses were consistent with those of the primary analysis and are shown in Table S5. The incidence of primary-outcome events appeared to be consistent across all prespecified subgroups, with the exception of patients weighing at least 70 kg who received twice-daily colchicine for the first 3 months, in whom the number of events was lower (Fig. 2). The results seemed to be similar during the different phases of the Covid-19 pandemic.

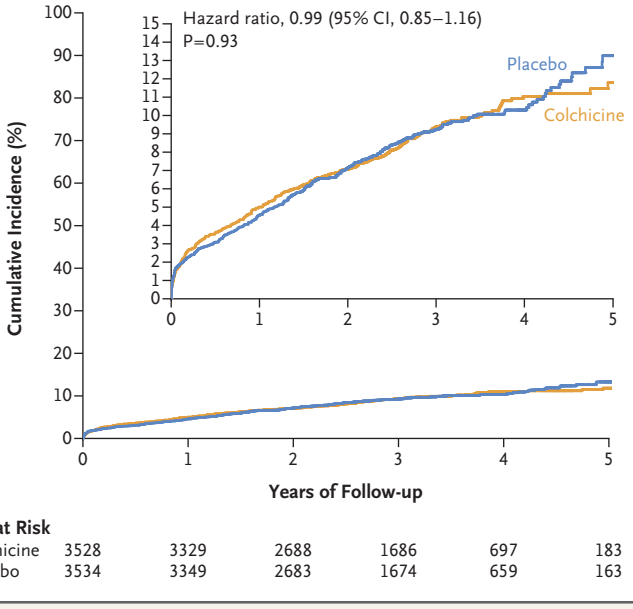


**Figure 1. Kaplan–Meier Event Curves for Death from Cardiovascular Causes, Recurrent Myocardial Infarction, Stroke, or Ischemia-Driven Revascularization.**

The inset shows a magnified version of the graph.

### SAFETY

The incidence of serious adverse events and adverse events did not differ between groups (Table 3). Diarrhea occurred in a total of 361 patients (10.2%) in the colchicine group and 233 patients (6.6%) in the placebo group (P<0.001). There was no apparent difference in the number of serious infections between the groups.

## DISCUSSION

Among patients with acute myocardial infarction, the antiinflammatory agent colchicine did not reduce the incidence of the composite primary outcome (death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization) over a median treatment duration of 3 years as compared with placebo. As expected, colchicine increased the incidence of diarrhea as compared with that among patients who received placebo.

The previous trial most comparable to CLEAR is COLCOT, which involved 4745 patients who underwent randomization within 30 days after acute myocardial infarction to receive colchicine at a dose of 0.5 mg daily or placebo; a total of 301 primary-outcome events were reported, and colchicine treatment was associated with a 23% relative reduction in death from cardiovascular causes, recurrent myocardial infarction, resuscitation after cardiac arrest, stroke, or urgent hospitalization for angina that led to revascularization.[4] The Low Dose Colchicine 2 (LODOCO 2) trial assigned patients with stable coronary artery disease to receive colchicine at a dose of 0.5 mg daily or placebo; 451 primary-outcome events were reported, and colchicine was associated with a 31% relative reduction in the composite primary outcome (death from cardiovascular causes, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization).[5] One of the largest trials of colchicine, the CHANCE-3 (Colchicine in High-Risk Patients with Acute Minor-to-Moderate Ischemic Stroke or Transient Ischemic Attack) trial, involved 8345 patients who were randomly assigned to receive colchicine at a dose of 0.5 mg twice daily on days 1 through 3 and 0.5 mg once daily on days 4 through 90 or to receive placebo. A total of 534 primary-out-

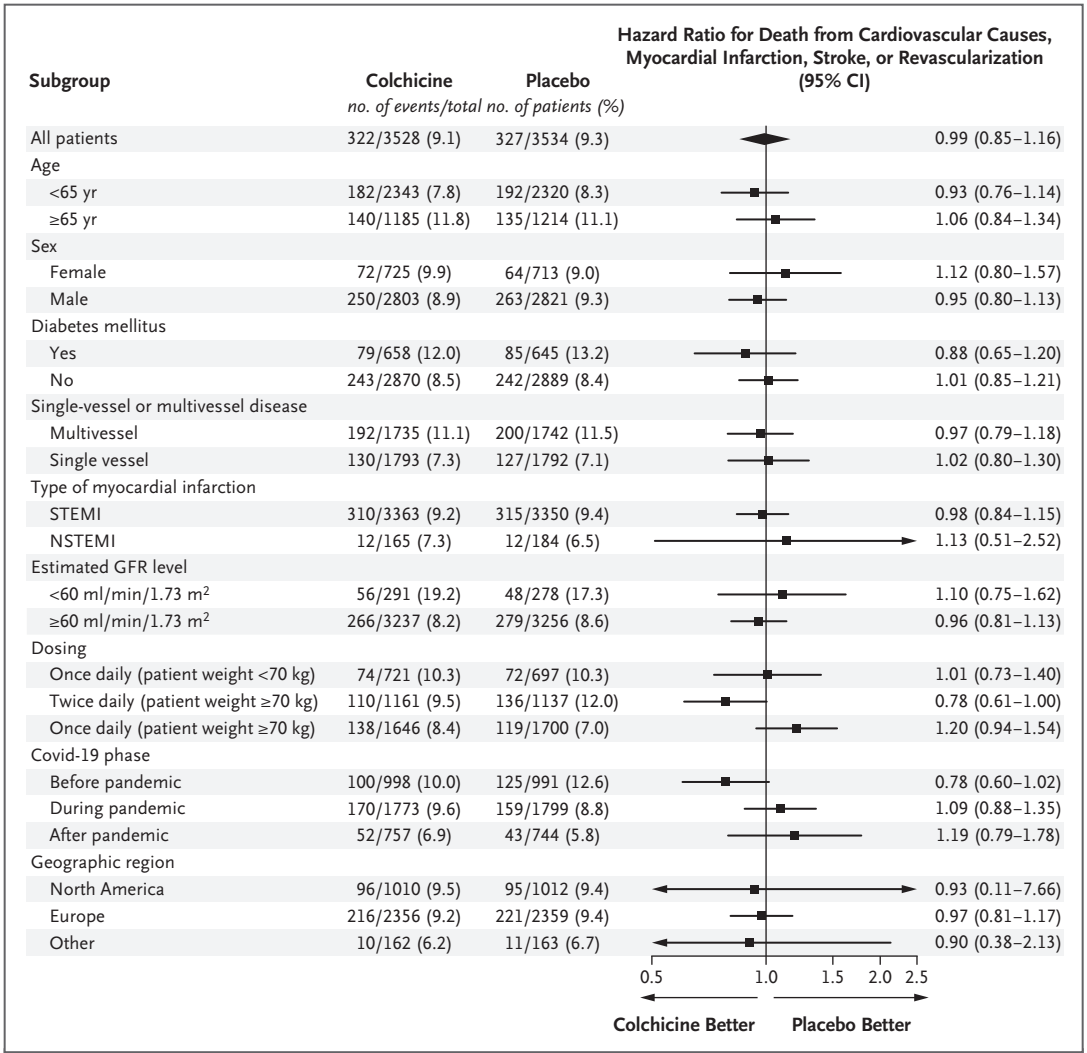


**Figure 2. Forest Plot of the Primary Outcome According to Prespecified Subgroups.**

The hazard ratio for the North American subgroup at 1 year of follow-up was calculated with the use of the Cox model with a time-dependent covariate to account for the violation of the proportional-hazards assumption. GFR denotes glomerular filtration rate (expressed as milliliters per minute per 1.73 $m^2$ of body-surface area), NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

come events occurred, and colchicine was found to have no effect on the incidence of stroke (hazard ratio, 0.98; 95% CI, 0.83 to 1.16) or on the secondary outcome, a composite of death from cardiovascular causes, myocardial infarction, transient ischemic attack, or stroke (a total of 607 events; hazard ratio, 0.96; 95% CI, 0.82 to 1.13).[7] However, the CHANCE-3 trial was a short-term treatment trial, and the duration of treatment may not have been long enough to show a treatment effect. In the CONVINCE (Colchicine for Prevention of Vascular Inflammation in Noncardioembolic Stroke) trial, 3154 patients with ischemic stroke were randomly assigned to receive colchicine at a dose of 0.5 mg daily or usual care for a median of 34 months; with 338 primary-outcome events reported, no effect of colchicine on the primary outcome — a composite of ischemic stroke, myocardial infarction, cardiac arrest, hospitalization for unstable angina, or death from vascular causes — was found (hazard ratio, 0.84; 95% CI, 0.68 to 1.05).[6]

In our trial, 649 first primary-outcome events occurred; an analysis of previous trials showed that those with more than 600 outcome events rarely produced spurious results disproven by

subsequent trials.[13] The results of our on-treatment analysis were consistent with those of our intention-to-treat analysis. Furthermore, our subgroup analyses did not suggest that our results were affected by the Covid-19 pandemic. The effects estimates appeared to be consistent throughout all the individual components of the primary and secondary outcomes and on-treatment analysis. The increase in the incidence of diarrhea and the reduction in C-reactive protein were as expected and provide support for the biologic effects of colchicine in this trial.

The reasons for the divergence between the results of our trial and those of previous trials of colchicine in patients with cardiovascular diseases are not immediately evident; however, three of the latest trials, CLEAR, CHANCE, and CONVINCE, provide what is likely to be the most recent evidence to date of the effects of colchicine in patients with vascular disease. Recent meta-analyses have shown a nominal excess in death from noncardiovascular causes with colchicine.[14] We found the opposite: a lower rate of death from noncardiovascular causes in the colchicine group than in the placebo group. COLCOT showed an excess of pneumonia among patients who received colchicine, whereas the LODOCO 2 trial did not show any increase in serious infection.[4,5] We also found no excess in serious infection with colchicine as compared with placebo.

In 2024, the European Society of Cardiology upgraded its recommendation for colchicine from class IIb to class IIa for patients with atherosclerotic coronary artery disease; however, this change was made before the current data were available.[8] Similarly, the U.S. Food and Drug Administration had approved colchicine to treat coronary artery disease before the current data were available.

Canakinumab, an interleukin-1$\beta$ inhibitor, was associated with a 15% reduction in ischemic events in patients after myocardial infarction in CANTOS (the Canakinumab Antiinflammatory Thrombosis Outcome Study).[2] Another trial involving 4786 patients who had myocardial infarction or multivessel coronary artery disease showed no benefit of methotrexate with respect to the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, stroke, and hospitalization for unstable angina that led to urgent revascularization (hazard ratio, 0.96; 95% CI, 0.79 to 1.16); however, methotrexate did not reduce inflammatory markers. The ongoing ARTEMIS (Effects of Ziltivekimab vs. Placebo on Cardiovascular Outcomes in Patients with Acute Myocardial Infarction) trial involving 10,000 patients is evaluating the effects of ziltivekimab on the primary outcome, a composite of death from cardiovascular causes, myocardial infarction, or stroke. The divergent results of the trials of canakinumab, methotrexate, and colchicine highlight the need for large trials that target different parts of the inflammatory pathways.

**Table 3. Adverse Events.**

| Event | Colchicine (N=3528) | Placebo (N=3534) | P Value |
|---|---|---|---|
| | *number (percent)* | | |
| Any serious adverse event | 235 (6.7) | 261 (7.4) | 0.22 |
| Serious adverse gastrointestinal event | 35 (1.0) | 33 (0.9) | 0.81 |
| Serious adverse hematologic event* | 0 (0) | 8 (0.2) | 0.005 |
| Serious infection | 87 (2.5) | 101 (2.9) | 0.85 |
| Any adverse event | 1124 (31.9) | 1119 (31.7) | 0.86 |
| Diarrhea | 361 (10.2) | 233 (6.6) | <0.001 |

* Anemia occurred in 3 patients, febrile neutropenia in 2 patients, pancytopenia in 3 patients, and thrombocytopenia in 2 patients.

Our trial has limitations. Women and members of diverse racial and ethnic groups were underrepresented in the trial relative to the incidence of cardiovascular disease in these groups worldwide (Table S6). The percentage of patients who discontinued the trial regimen, 25%, was higher than anticipated; however, our on-treatment sensitivity analyses produced results consistent with those of our primary analyses. Our trial was not designed to evaluate the effect of twice-daily colchicine, and this dosing will need to be tested in future clinical trials. Adherence to the trial regimen was assessed only through patient reports, because pill counts were not possible during the pandemic. The incidence of gout was not assessed as an outcome in the trial.

Among patients with acute myocardial infarction, treatment with colchicine that began soon after myocardial infarction and continued for a median of 3 years did not reduce the incidence of the composite primary outcome (death from cardiovascular causes, recurrent myocardial infarc-

tion, stroke, or unplanned ischemia-driven revascularization) but was associated with an increase in the incidence of diarrhea.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

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