EDITORIAL

Inflammation as a Treatment Target after Acute Myocardial Infarction

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Inflammation is widely believed to play a central role in the pathogenesis of atherosclerosis and acute coronary events.[1,2] Although treatments with proven benefits for secondary prevention of coronary artery disease (e.g., statins and aspirin) appear to have salutary effects on inflammation, the identification of an effective treatment specifically targeting inflammation has been elusive.[3] The Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) provided encouragement that targeting inflammation may be an effective treatment in chronic coronary artery disease. In CANTOS, canakinumab, a monoclonal antibody inhibiting interleukin-1β, reduced the level of high-sensitivity C-reactive protein and resulted in a modestly lower risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke than did placebo.[4] Results were driven by a lower risk of nonfatal myocardial infarction, and there was a higher incidence of fatal infections among canakinumab-treated patients than among patients who received placebo, arousing concerns about risk–benefit trade-offs. Subsequently, nonspecific antiinflammatory treatment with methotrexate in the Cardiovascular Inflammation Reduction Trial (CIRT) showed no reduction in the level of high-sensitivity C-reactive protein and no benefit with regard to cardiovascular outcomes,[5] leaving open the question of whether direct intervention on inflammation can improve cardiovascular outcomes.

With this backdrop, Tardif and colleagues[6] now report in the *Journal* the results of the Colchicine Cardiovascular Outcomes Trial (COLCOT), which tested low-dose colchicine, an antiinflammatory agent clinically used to treat gout and pericarditis that works by inhibiting tubulin polymerization and microtubule formation, for secondary prevention after acute myocardial infarction. The investigators randomly assigned 4745 patients (mean age, 61 years) to receive either colchicine (0.5 mg daily) or placebo at a mean of 13.5 days after myocardial infarction; the median follow-up was 22.6 months. Participants had a high prevalence of guideline-recommended treatment: percutaneous coronary intervention for the index myocardial infarction in 93% of the patients, and the use of dual antiplatelet therapy and statins in 98% and 99%, respectively.

The risk of the primary composite end point (death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization) was lower in the colchicine group than in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02), but this result was driven predominantly by lower risks of angina and stroke. A significant effect on death from cardiovascular causes or myocardial infarction was not shown. Overall, the incidence of adverse events or serious adverse events was similar in the two groups; however, some known gastrointestinal side effects of colchicine, including nausea, were more frequent in the colchicine group, as were pneumonias. However, unlike in CANTOS, no deaths from infection were reported in COLCOT, and the incidence of septic shock in COLCOT was low and similar in the two trial groups.

Although vital status was known in 99.5% of the patients in COLCOT, 1.9% of the patients were lost to follow-up and 0.6% withdrew consent. Fur-

thermore, nearly 19% of the patients in both treatment groups stopped receiving colchicine or placebo prematurely (median treatment duration among patients discontinuing the trial regimen early, 7.1 months [interquartile range, 1.9 to 14.6] for colchicine and 6.1 months [interquartile range, 1.6 to 14.4] for placebo). This high percentage of patients discontinuing the trial regimen, combined with unknown end-point status for 2.5% of the patients, could have obscured the true cardiovascular treatment effect or adverse-event profile. Results of a secondary per-protocol efficacy analysis were only modestly more favorable (hazard ratio, 0.71; 95% CI, 0.56 to 0.90), but these findings should be interpreted with caution because numerous biases may be at play in such nonrandomized comparisons; trial interpretation should principally be informed by the primary intention-to-treat analysis. Regardless, the modest benefit driven by a soft end point of hospitalization for angina and revascularization does not support the routine use of colchicine for secondary prevention without a better understanding of the absence of effect on death or myocardial infarction.

An interesting observation in this trial was the lower risk of stroke in the colchicine group than in the placebo group. Similar findings were reported in a systematic review and meta-analysis of four other randomized trials of colchicine.[7] Whether this reflects a unique mechanistic effect of colchicine in the cerebrovasculature or is simply the play of chance is a question for further investigation.

With the report of COLCOT, where does this leave us with inflammation as a therapeutic target? Direct inhibition of interleukin-1β with canakinumab reduced the level of high-sensitivity C-reactive protein as expected but resulted in only a modest composite efficacy benefit driven by myocardial infarction with a worrisome infection risk; nonspecific antiinflammatory treatment with methotrexate had no effect on the high-sensitivity C-reactive protein level or cardiovascular outcomes; and colchicine, which acts through a unique mechanism, did not lower the high-sensitivity C-reactive protein level more than placebo did in the small subgroup of patients with available data but had a modest composite efficacy benefit, albeit driven predominantly by an angina end point. These observations do not lessen the overall importance of inflammation in atherosclerosis, nor should they halt efforts to find more effective antiinflammatory agents with better side-effect profiles. However, they should encourage us to revisit whether inflammation itself is the best treatment target or whether opportunities exist to identify and better understand pathophysiological processes or mediators that incite inflammation and drive atherosclerosis in order to intervene further upstream.

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

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ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

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ABSTRACT

BACKGROUND

Experimental and clinical evidence support the role of inflammation in atherosclerosis and its complications. Colchicine is an orally administered, potent antiinflammatory medication that is indicated for the treatment of gout and pericarditis.

METHODS

We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed.

RESULTS

A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months. The primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03).

CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov number, NCT02551094.)

Inflammation appears to play an important role in atherosclerosis.[1] Inhibition of interleukin-1β by the injectable monoclonal antibody canakinumab led to a 15% lower risk of cardiovascular events than was observed with placebo in the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) but also led to a slightly higher incidence of fatal infections.[2] In contrast, methotrexate did not affect cardiovascular outcomes or plasma markers of inflammation in the Cardiovascular Inflammation Reduction Trial (CIRT).[3] In light of these differing results and given that canakinumab has not been approved for cardiovascular prevention, the search for a widely used alternative antiinflammatory treatment that may reduce the risk of atherosclerotic events among patients with coronary artery disease continues.

Colchicine is an inexpensive, orally administered, potent antiinflammatory medication that was initially extracted from the autumn crocus and has been used for centuries. Its mechanism of action is through the inhibition of tubulin polymerization and microtubule generation and, possibly, effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome.[4-6] Colchicine is currently indicated for the treatment of gout, familial Mediterranean fever, and pericarditis.[7,8] In the Low-Dose Colchicine (LoDoCo) trial, patients with stable coronary disease treated with colchicine at a dose of 0.5 mg once daily had fewer cardiovascular events than those not receiving colchicine.[9] However, that trial enrolled only 532 patients and was not placebo-controlled. Because acute coronary syndromes are associated with higher risks of recurrent events and exacerbated inflammation, we conducted the Colchicine Cardiovascular Outcomes Trial (COLCOT) to evaluate the effects of colchicine on cardiovascular outcomes as well as its long-term safety profile in patients who had recently had a myocardial infarction.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this randomized, double-blind, placebo-controlled, investigator-initiated trial, we assigned patients in a 1:1 ratio to receive either colchicine (at a dose of 0.5 mg once daily) or placebo. The trial was funded by the Government of Quebec, the Canadian Institutes of Health Research, and philanthropic foundations. The trial protocol, available with the full text of this article at NEJM.org, was designed by the trial steering committee. The protocol was approved by the institutional review board at each of the 167 centers in the 12 countries that participated in the trial (see the Supplementary Appendix, available at NEJM.org). All trial support activities, including project coordination, medical review, data management, site monitoring, and statistical oversight and analyses, were performed at the Montreal Health Innovations Coordinating Center. Potential trial end-point events were adjudicated by an independent clinical end-point committee composed of experienced cardiologists and neurologists who were unaware of the trial-group assignments. The trial was overseen by a data and safety monitoring board of independent experts. The trial medication and matching placebo were provided by Pharmascience, which had no role in the design or conduct of the trial or in the preparation or review of the manuscript. The first author and the lead statistician (also an author) prepared the first draft of the manuscript, had full access to the trial database, and generated statistical analyses; they also made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Adult patients were eligible if they had had a myocardial infarction within 30 days before enrollment, had completed any planned percutaneous revascularization procedures, and were treated according to national guidelines that included the intensive use of statins. Patients were excluded if they had severe heart failure, a left ventricular ejection fraction of less than 35%, stroke within the previous 3 months, a type 2 index myocardial infarction, coronary-bypass surgery either within the previous 3 years or planned, a history of noncutaneous cancer within the previous 3 years, inflammatory bowel disease or chronic diarrhea, neuromuscular disease or a nontransient creatine kinase level that was greater than three times the upper limit of the normal range (unless due to infarction), clinically significant nontransient hematologic abnormalities, severe renal disease with a serum creatinine level that was greater than two times the upper limit of the normal range; severe hepatic disease, drug or alcohol abuse, cur-

rent or planned long-term systemic glucocorticoid therapy, or a history of clinically significant sensitivity to colchicine. (Details regarding eligibility criteria are provided in the Supplementary Appendix.)

Written informed consent was obtained from all the patients before enrollment. Clinical evaluations occurred at 1 month and 3 months after randomization and every 3 months thereafter.

END POINTS

The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in a time-to-event analysis. The secondary end points consisted of the components of the primary efficacy end point; a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, or stroke; and total mortality in time-to-event analyses. Coronary revascularization, hospitalization for heart failure, atrial fibrillation, and deep venous thrombosis or pulmonary embolus were prespecified as exploratory end points in the protocol. Additional prespecified exploratory end points included the change from baseline to 6 months in the high-sensitivity C-reactive protein level and the change from baseline to 12 months in the white-cell count. The C-reactive protein biomarker substudy was implemented after a protocol amendment and was optional for sites and for patients; 34 sites chose to participate in this substudy.

All serious adverse events were recorded. The only other adverse events recorded were those that were considered to be related to the gastrointestinal system, events that were judged by the investigator to be related to colchicine or placebo, or laboratory abnormalities that had been judged by the investigator to be clinically significant.

STATISTICAL ANALYSIS

In this event-driven trial, it was estimated that a sample of approximately 4500 patients undergoing randomization (with 2250 patients in each group) or, in terms of events, a total number of 301 patients with a first positively adjudicated primary end-point event would yield adequate power. The sample-size calculation was based on the primary efficacy end point and assumed a 27% lower risk with colchicine than with placebo, indicated by a hazard ratio of 0.724. With the use of a two-sided test at the 0.05 significance level, the trial would have 80% power if it continued until 301 positively adjudicated primary events occurred in the combined trial groups. The trial design assumed an event rate of 7% in the placebo group at 24 months, an 18-month recruitment period during which patients would be uniformly recruited, a 24-month minimum follow-up period, and a 1% annual rate of loss to follow-up or withdrawal of consent.

The efficacy analyses were conducted with the use of positively adjudicated data and according to the intention-to-treat principle. The primary end point was compared between the two trial groups with the use of a log-rank test, and the hazard ratio, with a 95% confidence interval, was calculated from a Cox proportional-hazards model. A Cox proportional-hazards model with adjustment for important baseline characteristics was also used as prespecified in the protocol. The analysis of the primary end point was repeated in the per-protocol population (i.e., patients without major protocol deviations). Secondary and exploratory end points expressed as time to event were analyzed similarly. The changes from baseline to follow-up were analyzed with the use of an analysis of covariance model with adjustment for baseline value, and estimates of treatment effect are presented with 95% confidence intervals.

The efficacy end points expressed as time to event could be assessed in all patients because the event dates and censoring dates were complete, with the exception of one incomplete event date for atrial fibrillation; therefore, imputation for missing data was not done. In the analysis of time to event, the following censoring rules were used. For death from any cause and death from cardiovascular causes, data from event-free patients who completed the trial were censored at the date of trial completion, and data from patients who did not complete the trial, such as those who were lost to follow-up or who withdrew consent, were censored at the date of last contact or the date of the assessment of survival status, whichever was later. For the analysis of death from cardiovascular causes, patients who died from a noncardiovascular cause had their data censored at the time of death. For all other end points, including the primary end point, the same censoring rules applied, but the survival status was

Figure 1. Randomization and Follow-up of the Patients.
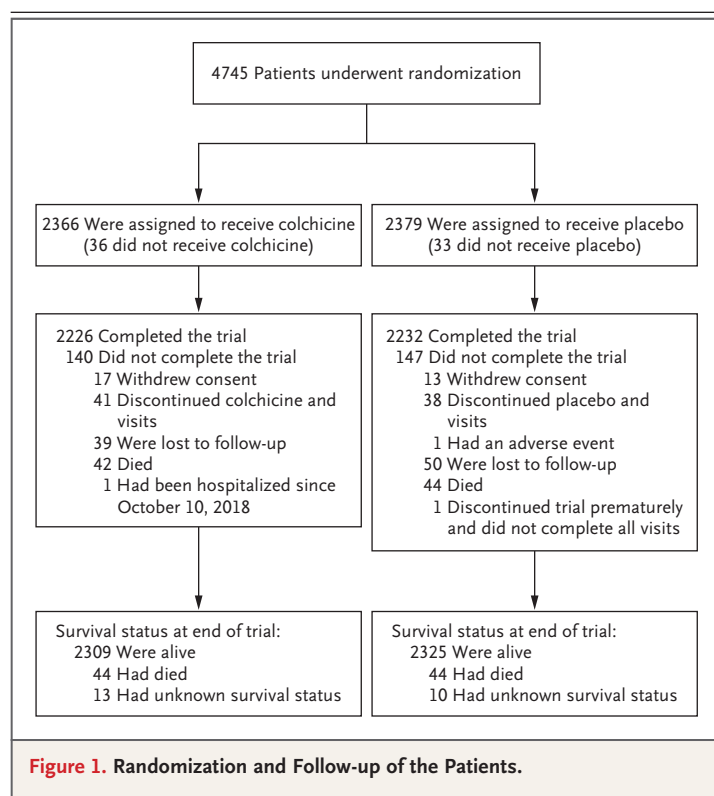
not used because no formal assessment of end points was done at the assessment of survival status. An analysis of the components of the primary end point with death from noncardiovascular causes as a competing event for death from cardiovascular causes, and with death from any cause as a competing event for the other components, was conducted with the use of the Fine and Gray subdistribution hazard model.[10] No missing data were imputed except for age in cases in which information on the day or the month and day of birth was missing. To account for the occurrence of multiple primary end-point events within patients, recurrent-event analyses were undertaken with the use of negative binomial regression, Andersen–Gill, and Wei–Lin–Weissfeld models.[11-19]

An interim analysis was performed after 50% of the primary end-point events had been positively adjudicated. The prespecified stopping rule for efficacy was based on the Lan–DeMets procedure with the O'Brien–Fleming alpha-spending function. After review of the interim results, the data and safety monitoring board recommended that the trial should continue as planned. To account for this interim analysis, the statistical significance level was set to 0.0490 for the final

analysis of the primary end point. All other statistical tests were two-sided and conducted at the 0.05 significance level. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). There was no prespecified plan to adjust for multiple comparisons across the multiple methods that were used to analyze the primary and secondary end points; results of these analyses are reported with point estimates and 95% confidence intervals, without P values. The 95% confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible. The final amendment to the statistical analysis plan was approved on August 28, 2019, before unblinding of the trial-group assignments occurred.

RESULTS

PATIENTS

Trial enrollment began in December 2015 and was completed in August 2018; the last trial visit was in July 2019. A total of 4745 patients underwent randomization (with 2366 being assigned to the colchicine group and 2379 to the placebo group) and were followed for a median of 22.6 months. At the time of the database lock on August 28, 2019, and unblinding on August 29, 2019, vital status was available for all except 23 patients (99.5%); 89 patients (1.9%) were lost to follow-up, and 30 patients (0.6%) withdrew consent. Details regarding the disposition of the patients are provided in Figure 1.

The characteristics of the patients at baseline are shown in Table 1. Patients were enrolled a mean of 13.5 days after myocardial infarction. The mean age of the patients was 60.6 years, 19.2% of the patients were women, and 20.2% had diabetes. Most patients (93.0%) underwent percutaneous coronary intervention for their index myocardial infarction. Aspirin, a different antiplatelet agent, and a statin were taken by 98.8%, 97.9% and 99.0% of the patients, respectively.

At the end of the trial, the trial regimen had been discontinued in 18.4% of the patients in the colchicine group and in 18.7% of those in the placebo group. Among the patients who discontinued the trial regimen, the median duration of receipt of the trial drug was 7.1 months (interquartile range, 1.9 to 14.6) in the colchicine group, as compared with 6.1 months (interquartile range, 1.6 to 14.4) in the placebo group. Overall, the median dura-

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N = 2366)	Placebo (N = 2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

* Plus–minus values are means ±SD. Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 435 patients (215 in the colchicine group and 220 in the placebo group), body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively), and information about the index myocardial infarction for 6 (2 and 4 patients, respectively). Date of birth and race were not required fields because both were considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by July 1. CABG denotes coronary-artery bypass graft surgery, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Race was reported by the patient.

tion of receipt of the trial drug was 19.6 months in the colchicine group and 19.5 months in the placebo group.

CLINICAL EFFICACY END POINTS

A primary end-point event occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02 by the log-rank test). A multivariable Cox regression model with adjustment for baseline covariates yielded a similar result (Table S1 in the Supplementary Appendix). The event curves that were based on a Kaplan–Meier analysis of the primary efficacy end point are shown in Figure 2. In the prespecified per-protocol analysis involving patients who adhered to the protocol, the primary end point occurred in 5.1% of the patients in the colchicine group and in 7.1% of those in the pla-

cebo group (hazard ratio, 0.71; 95% CI, 0.56 to 0.90) (Table S2). Table 2 shows the percentages of patients with events and the hazard ratios for the components of the primary end point, including death from cardiovascular causes (hazard ratio, 0.84; 95% CI, 0.46 to 1.52), resuscitated cardiac arrest (hazard ratio, 0.83; 95% CI, 0.25 to 2.73), myocardial infarction (hazard ratio, 0.91; 95% CI, 0.68 to 1.21), stroke (hazard ratio, 0.26; 95% CI, 0.10 to 0.70), and urgent hospitalization for angina leading to coronary revascularization (hazard ratio, 0.50; 95% CI, 0.31 to 0.81). The hazard ratios remained unchanged in the analysis that took competing events into account.

The secondary efficacy end point consisting of a composite of death from cardiovascular causes, cardiac arrest, myocardial infarction, or stroke occurred in 4.7% of the patients in the colchicine group and in 5.5% of those in the

Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

* Only the initial event was counted in the analyses of time to first event for the primary composite end point and for the secondary composite end point. In the component analysis, the different types of events were counted separately.
† The log-rank test and the multivariable Cox proportional-hazards model including age, history of diabetes, previous coronary revascularization, and previous heart failure yielded similar P values.
‡ The secondary composite end point included death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, and stroke.
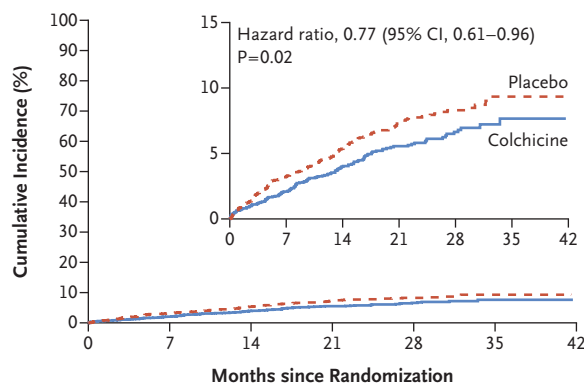
Figure 2. Cumulative Incidence of Cardiovascular Events (Intention-to-Treat Population).

Shown are the Kaplan–Meier event curves for the primary efficacy composite end point of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in the colchicine group and the placebo group in a time-to-event analysis. The inset shows the same data on an enlarged y axis.

placebo group (hazard ratio, 0.85; 95% CI, 0.66 to 1.10). Data on the primary, secondary, and exploratory efficacy end points are provided in Table 2. Two patients had a first positively adjudicated event of urgent hospitalization for angina leading to coronary revascularization within 14 days after randomization. The median time to this clinical end point was 258 days. Efficacy results in prespecified subgroups are shown in Table S3. The total number of primary end-point events (first and recurrent) was 154 in the colchicine group and 223 in the placebo group, over periods of 52,949 and 53,060 patient-months of follow-up, respectively. Thus, the primary end-point event rates per 100 patient-months were 0.29 in the colchicine group and 0.42 in the placebo group (rate ratio, 0.66; 95% CI, 0.51 to 0.86) (Table S4).

BIOMARKERS OF INFLAMMATION

High-sensitivity C-reactive protein was measured in a subgroup of only 207 patients at the time of randomization and 6 months later, and the median concentration at trial entry was 4.28 mg per

liter. The baseline characteristics of these patients were similar to those of the overall population (Table S5), but the small and selected subgroup with these data limits the interpretation of these analyses. The adjusted geometric mean percent changes in the high-sensitivity C-reactive protein level at 6 months after myocardial infarction were −70.0% in the colchicine group and −66.6% in the placebo group, and the placebo-adjusted geometric mean percent change was −10.1 percentage points in the colchicine group (95% CI, −28.6 to 13.4) (Table S6).

Information about white-cell counts at baseline and at the 12-month follow-up were also available for a relatively small subgroup of 1972 patients. The adjusted geometric mean percent changes from baseline to 1 year in the total white-cell count were −18.8% in the colchicine group and −19.0% in the placebo group, with no significant difference between groups (0.3 percentage points; 95% CI, −2.2 to 2.7).

SAFETY AND ADVERSE EVENTS

The incidence of adverse events that were considered to be related to the active drug or placebo was 16.0% in the colchicine group and 15.8% in the placebo group, and the overall incidence of serious adverse events was 16.4% and 17.2%, respectively (Table 3). At least one gastrointestinal adverse event during the double-blind period occurred in 17.5% of the patients in the colchicine group, as compared with 17.6% of those in the placebo group. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35), and nausea was more common in the colchicine group than in the placebo group (1.8% vs. 1.0%, P=0.02). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group, as compared with 0.4% of those in the placebo group (P=0.03).

DISCUSSION

In COLCOT, the risk of the primary composite efficacy end point of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization, as assessed in a time-to-event analysis, was significantly lower among the patients who were randomly assigned to receive 0.5 mg of colchicine

Table 3. Adverse Events (Safety Population).*			
Event	Colchicine (N=2330)	Placebo (N=2346)	P Value
	number of patients (percent)		
Any related adverse event†	372 (16.0)	371 (15.8)	0.89
Adverse events			
Gastrointestinal event	408 (17.5)	414 (17.6)	0.90
Diarrhea	225 (9.7)	208 (8.9)	0.35
Nausea	43 (1.8)	24 (1.0)	0.02
Flatulence	15 (0.6)	5 (0.2)	0.02
Gastrointestinal hemorrhage	7 (0.3)	5 (0.2)	0.56
Anemia	14 (0.6)	10 (0.4)	0.40
Leukopenia	2 (0.1)	3 (0.1)	0.66
Thrombocytopenia	3 (0.1)	7 (0.3)	0.21
Serious adverse events			
Any serious adverse event‡	383 (16.4)	404 (17.2)	0.47
Gastrointestinal event	46 (2.0)	36 (1.5)	0.25
Infection	51 (2.2)	38 (1.6)	0.15
Pneumonia	21 (0.9)	9 (0.4)	0.03
Septic shock	2 (0.1)	2 (0.1)	0.99
Hospitalization for heart failure	25 (1.1)	17 (0.7)	0.21
Cancer§	43 (1.8)	46 (2.0)	0.77

* The safety population was defined as patients who took at least one dose of colchicine or placebo. All serious adverse events were recorded, and the only other adverse events recorded were those that were related to the gastrointestinal system, events that were judged by the investigator to be related to colchicine or placebo, or laboratory abnormalities that were judged by the investigator to be clinically significant. This table lists serious adverse events that were present in more than 2% of the patients in either trial group, adverse events that were considered to be related to colchicine or placebo in more than 5% of the patients in either trial group, and any other safety events of special interest. Chi-square tests were conducted to compare the incidence of adverse events between the trial groups.
† These adverse events were considered to be related to colchicine or placebo by the physician in charge of the participant.
‡ There was one serious adverse event of myopathy, which was attributed to high-dose statin therapy (rosuvastatin at a dose of 40 mg daily) by the local investigator and academic sponsor, in a man of short stature (165 cm, 68 kg) with normal renal function in the colchicine group who had received colchicine for 8 days 3 months before the adverse event.
§ Cancers, excluding nonmelanoma skin cancers, occurred in 42 patients (1.8%) in the colchicine group and in 44 patients (1.9%) in the placebo group.

once daily than among those who received placebo. This result was due predominantly to a lower incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization.

These results were observed against a background of appropriate medications, which included aspirin, a different antiplatelet agent, and a

statin in 98 to 99% of the patients. In addition, percutaneous coronary intervention was performed in 93% of the patients for their index myocardial infarction. The benefits of colchicine with regard to cardiovascular end points in COLCOT were at least as large as those of canakinumab in CANTOS.[2] In the small subgroup of patients with available data, as expected, a large (>65%) reduction in the C-reactive protein level occurred over the first 6 months after myocardial infarction in both trial groups in COLCOT, but the difference between the changes in the groups was not significant. These findings must be interpreted cautiously given that this was a small subgroup that was not randomly selected from the full trial sample. A similar observation was made with white-cell counts. The different patient populations involved in the two trials — early after myocardial infarction in COLCOT and stable coronary disease in CANTOS — may also have affected the relationship between biomarkers of inflammation and the effects of treatments on ischemic end points.

The known benefits of colchicine in the treatment of pericarditis were not at play in COLCOT. Postinfarction pericarditis typically occurs within the first few days after the injury, whereas the mean time from the index myocardial infarction to randomization was 13.5 days. There were only two patients with a first positively adjudicated event of urgent hospitalization for angina leading to coronary revascularization within 14 days after randomization, and the median time to this clinical end point was 258 days.

The most common adverse events observed were gastrointestinal. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group, and nausea occurred in 1.8% and 1.0%, respectively. Infection as a serious adverse event was more frequent in the colchicine group than in the placebo group (in 2.2% vs. 1.6% of the patients), and pneumonia as a serious adverse event was also more frequent in the colchicine group (0.9% vs. 0.4%).

These differences in the incidence of infections could be due to the play of chance or could reflect altered immunologic responses. In contrast to canakinumab,[2] colchicine did not increase the incidence of septic shock in our trial. Infections have previously been described in patients who have attempted suicide by taking an overdose of colchicine.[20] There was no serious adverse event of myopathy linked to colchicine despite the use of statins in 99% of the patients in the trial.

Our trial has certain limitations. The duration of follow-up was relatively short at approximately 23 months. The risks and benefits of longer-term treatment with colchicine were not evaluated. Although the inclusion of 4745 patients was sufficient for the trial to show a significant benefit with regard to the primary composite efficacy end point, a larger trial could have allowed a better assessment of individual end points and subgroups and the risks associated with colchicine. Finally, our results apply only to patients who have recently had a myocardial infarction.

In conclusion, among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower percentage of patients with ischemic cardiovascular events than placebo.

APPENDIX

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