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ORIGINAL ARTICLE

Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention

COLCHICINE-PCI Randomized Trial

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BACKGROUND: Vascular injury and inflammation during percutaneous coronary intervention (PCI) are associated with increased risk of post-PCI adverse outcomes. Colchicine decreases neutrophil recruitment to sites of vascular injury. The anti-inflammatory effects of acute colchicine administration before PCI on subsequent myocardial injury are unknown.

METHODS: In a prospective, single-site trial, subjects referred for possible PCI (n=714) were randomized to acute preprocedural oral administration of colchicine 1.8 mg or placebo.

RESULTS: Among the 400 subjects who underwent PCI, the primary outcome of PCI-related myocardial injury did not differ between colchicine (n=206) and placebo (n=194) groups (57.3% versus 64.2%, *P*=0.19). The composite outcome of death, nonfatal myocardial infarction, and target vessel revascularization at 30 days (11.7% versus 12.9%, *P*=0.82), and the outcome of PCI-related myocardial infarction defined by the Society for Cardiovascular Angiography and Interventions (2.9% versus 4.7%, *P*=0.49) did not differ between colchicine and placebo groups. Among 280 PCI subjects in a nested inflammatory biomarker substudy, the primary biomarker end point, change in interleukin-6 concentrations did not differ between groups 1-hour post-PCI but increased less 24 hours post-PCI in the colchicine (n=141) versus placebo group (n=139; 76% [−6 to 898] versus 338% [27 to 1264], *P*=0.02). High-sensitivity C-reactive protein concentration also increased less after 24 hours in the colchicine versus placebo groups (11% [−14 to 80] versus 66% [1 to 172], *P*=0.001).

CONCLUSIONS: Acute preprocedural administration of colchicine attenuated the increase in interleukin-6 and high-sensitivity C-reactive protein concentrations after PCI when compared with placebo but did not lower the risk of PCI-related myocardial injury.

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VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: biomarker ■ colchicine ■ inflammation ■ myocardial infarction ■ percutaneous coronary intervention

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Vascular injury during percutaneous coronary intervention (PCI) induces rapid neutrophil recruitment to the site of mechanical trauma. The subsequent inflammatory cascade can be detected as early as 1 hour after PCI.[1–6] Elevated levels of inflammatory biomarkers in the setting of PCI are associated with endothelial dysfunction and microvascular obstruction and remains an independent predictor of subsequent major adverse cardiovascular events (MACE) even in the contemporary era of second-generation drug-eluting stents.[7–15]

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WHAT IS KNOWN

- Percutaneous coronary intervention can cause vascular inflammation and myocardial injury.
- Reducing inflammation after acute myocardial infarction improves outcomes, but there are no currently available drugs to rapidly reduce vascular inflammation.
- Colchicine is a potent anti-inflammatory agent that decreases the attachment of inflammatory cells to injured or inflamed vascular endothelium and platelets and also has an excellent side effect profile.

WHAT THE STUDY ADDS

- COLCHICINE-PCI (Colchicine in Percutaneous Coronary Intervention) is the first trial to demonstrate that a 1.8 mg colchicine given 1 to 2 hours preprocedure does not reduce percutaneous coronary intervention–related myocardial injury or 30-day major cardiovascular events but does reduce blood markers of vascular inflammation at 24 hours postprocedure when compared with matching placebo.
- This is the first study to show that colchicine can prevent a rise in blood markers of vascular inflammation during an acute injury.

Nonstandard Abbreviations and Acronyms

hsCRP	high-sensitivity C-reactive protein
IL	interleukin
MACE	major adverse cardiovascular events
MI	myocardial infarction
PCI	percutaneous coronary intervention
VA	Veterans Affairs

Inflammation during PCI may also increase the risk of PCI-related myocardial injury, which is associated with long-term all-cause mortality.[16]

Colchicine directly inhibits neutrophil chemotaxis and activity in response to vascular injury, indirectly reduces the production of active IL (interleukin)-1β via inhibitory effects on the inflammasome and reduces neutrophil-platelet aggregates, which may accumulate in the microvascular beds during acute myocardial infarction (MI) and contribute to myocardial injury after PCI.[17–22] A 2-dose regimen of colchicine (1.2 mg followed by 0.6 mg administered over an hour) currently used for the treatment of gout flares has rapid anti-inflammatory effects and an adverse event profile comparable to placebo.[23] The aim of this study was to determine if an acute, preprocedural oral administration of 1.8 mg of colchicine reduces PCI-related myocardial injury.

METHODS

Trial Design and Oversight

The COLCHICINE-PCI study (Colchicine in Percutaneous Coronary Intervention) is a randomized, double-blind, placebo-controlled trial to determine the effects of acute preprocedural oral administration of 1.8 mg of colchicine on PCI-related myocardial injury. A nested inflammatory biomarker substudy was performed to further delineate changes in inflammatory profiles associated with colchicine administration. The trial was funded by the Veterans Affairs (VA) Office of Research and Development and the American Heart Association. This study was approved by the local institutional review boards. All subjects provided written, informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

Adults aged ≥18 years with suspected ischemic heart disease or acute coronary syndromes referred for clinically indicated coronary angiography with possible PCI were eligible for inclusion. Subjects were excluded if they met any of the following criteria: (1) use of oral steroids or nonsteroidal anti-inflammatory agents other than aspirin within the longer of 72 hours or 3× the agent's half-life, (2) high-intensity statin treatment started within 24 hours of procedure, (3) glomerular filtration rate <30 mL/min or on dialysis, (4) use of strong cytochrome P450 3A4/*P*-glycoprotein inhibitors, (5) chronic colchicine use or history of intolerance to colchicine, (6) active malignancy or infection, (7) history of myelodysplasia, (8) participation in a competing study, (9) inability to provide informed consent, (10) any condition that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's ability to adhere with study procedures. Recruitment began May 30, 2013, at Bellevue Hospital Center and was transitioned to the VA New York Harbor Healthcare System, Manhattan Campus January 29, 2015. Study enrollment completed on August 29, 2019.

Randomization and Study Drug Allocation

Subjects were randomly assigned to 1 of 2 treatment groups: (1) oral colchicine 1.2 mg 1 to 2 hours before coronary angiography, followed by colchicine 0.6 mg 1 hour later or immediately preprocedure if taken to the catheterization laboratory more urgently or (2) matching placebo at the same time points. A stratified randomization code was generated by an independent statistician using random block sizes and held by the research pharmacies for treatment assignment. Subjects, the investigative team, and the clinical team involved in the patient's care were blinded to treatment assignment until all subjects completed 30-day follow-up, and the study database for the primary analyses was locked. The randomization scheme was stratified according to prior hydroxymethylglutaryl coenzyme A reductase inhibitor exposure: (1) subjects who received new treatment with high-intensity statin therapy 24 hours to 7 days before the procedure (ie, increase in the patient's maintenance regimen to a high-intensity statin or newly started on a high-intensity statin), or (2) subjects on a stable statin treatment regimen (either no change in dose for at least 7 days or not

administered a statin). The decision to treat with high-intensity statin therapy before PCI was made by the treating physician. The rationale for this stratification was to decrease the potential confounding effects of acute high-intensity statin pretreatment on PCI-related myocardial injury.[24] Colchicine study drug and placebo were supplied by URL Pharma, Inc from the time of study initiation until a change in company ownership on September 30, 2016. Thereafter, study drug and placebo were supplied by the VA New York Harbor Healthcare System, Manhattan Campus Research Pharmacy.

Study Protocol

All enrolled subjects underwent assessment of Troponin I (Ultra) assay (Siemens Centaur CP Chemistry Analyzer, Siemens Healthineers, Germany) at pretreatment baseline. Subjects who underwent PCI had repeat assessment of Troponin I at 6 to 8 hours post-PCI and at 22 to 24 hours post-PCI and a clinical assessment performed at 30 days post-PCI. Subjects who met inclusion and had no exclusion criteria for the main trial were consecutively included in a nested inflammatory biomarker substudy when lab personnel was available to process biospecimens. All subjects in the nested inflammatory biomarker substudy underwent assessment of inflammatory biomarkers at pretreatment baseline. Subjects in the substudy who subsequently underwent PCI had additional assessments of IL-6 and IL-1β at 1-hour post-PCI, 6 to 8 hours post-PCI and 22 to 24 hours post-PCI. For the assessment of IL-6 and IL-1β concentrations, citrate-anticoagulated blood was centrifuged within 30 minutes of collection at 2500*g* for 10 minutes, and plasma aliquots were stored at −80°C until analysis. IL-6 and IL-1β concentrations were assessed using multiplex assays (Millipore Sigma, Burlington, MA) on the MAGPIX multiplex instrument (Luminex Corporation, Austin, TX). Additionally, hsCRP (high-sensitivity C-reactive protein) concentration was assessed at pretreatment baseline and 22 to 24 hours post-PCI with a commercial assay (Siemens ADVIA 1800 Chemistry Analyzer, Siemens Healthineers, Germany). Adverse events were monitored by a Data Safety Monitoring Committee comprised of 2 cardiologists and a rheumatologist who were also blinded to treatment allocation.

Outcomes

The primary outcome was PCI-related myocardial injury, according to the Universal Definition based on Troponin I measurements at 6 to 8 hours and 22 to 24 hours post-PCI.[25] In brief, PCI-related myocardial injury was defined as the peak postprocedure Troponin I above the upper reference limit in subjects with normal baseline cardiac biomarkers or >20% from the most recent preprocedural level in subjects with elevated but stable or falling baseline cardiac biomarkers.[25]

A key secondary outcome was the occurrence of 30-day MACE, a composite of the earliest occurrence of death from any cause, nonfatal MI, or target vessel revascularization. Nonfatal MI was defined as PCI-related (type 4a) or type 1 MI per the Third Universal Definition.[25] Another secondary outcome was PCI-related MI as defined by the Society for Cardiovascular Angiography and Interventions.[26]

The primary end point of the nested inflammatory biomarker substudy was the change in plasma IL-6 concentration between baseline and 1-hour post-PCI. Secondary end points of the nested inflammatory biomarker substudy were change in plasma IL-6 concentration between baseline and 6 to 8 hours and between baseline and 22 to 24 hours post-PCI. Other substudy secondary end points were change in plasma IL-1β concentration between baseline and 1 hour, between baseline and 6 to 8 hours, and between baseline and 22 to 24 hours post-PCI and change in hsCRP concentration between baseline and 22 to 24 hours post-PCI.

Statistical Analyses

A total of 400 subjects who undergo PCI was expected to provide 80% power at a 2-sided 0.05 significance level to detect a reduction in PCI-related myocardial injury from 30% risk in the placebo arm to 18% risk in the colchicine arm.[27] Sample size for the inflammatory biomarker substudy was calculated based on published mean plasma IL-6 concentration of 12 pg/mL and SD of 12 pg/mL 1 hour after PCI.[5] A total of 258 subjects who undergo PCI was expected to provide 78% power at a 2-sided 0.05 significance level to detect a difference in means when there is a difference of 0.35 between the null hypothesis mean difference of 0.0 between the colchicine versus placebo groups and the actual mean difference of 0.35 using a 2-sided Mann-Whitney-Wilcoxon test. These results are based on 2000 Monte Carlo samples from the normal distributions of both groups and SD of one. To account for a potential floor effect, in which low baseline inflammatory levels limit the detection of post-PCI changes, the sample size for the nested biomarker substudy was increased to 280 subjects.

An intention-to-treat approach in randomized subjects undergoing PCI was utilized for the primary analytic approach. The entire randomized study cohort with or without PCI was utilized for the safety assessment. Categorical variables are presented as frequency (proportion), normally distributed continuous variables as mean±SD, and skewed continuous variables as median [interquartile range]. Categorical variables and outcomes were compared between colchicine and placebo groups using χ^2 test, or Fisher exact test if the cell number was <5, and continuous variables were compared between colchicine and placebo groups using 2-sample *t* test or Mann-Whitney *U* test when appropriate. Inflammatory markers were examined in subjects from baseline to post-PCI using Wilcoxon signed-rank test. Percent changes in IL-6 and IL-1β concentrations from baseline to 1 hour, from baseline to 6 to 8 hours, and from baseline to 22 to 24 hours and percent change in hsCRP concentration from baseline to 22 to 24 hours were compared between the colchicine and placebo groups using the Mann-Whitney *U* test. A sensitivity analysis was performed of the repeated inflammatory marker measures over time by treatment group using a linear mixed model analysis. Statistical significance was set at a 2-sided α level of 0.05.

RESULTS

Baseline Characteristics

Of the 904 patients eligible to participate in the trial, 714 (79%) were included in the study cohort, 146 from Bellevue Hospital Center, and 568 from the VA New York Harbor Healthcare System, Manhattan Campus

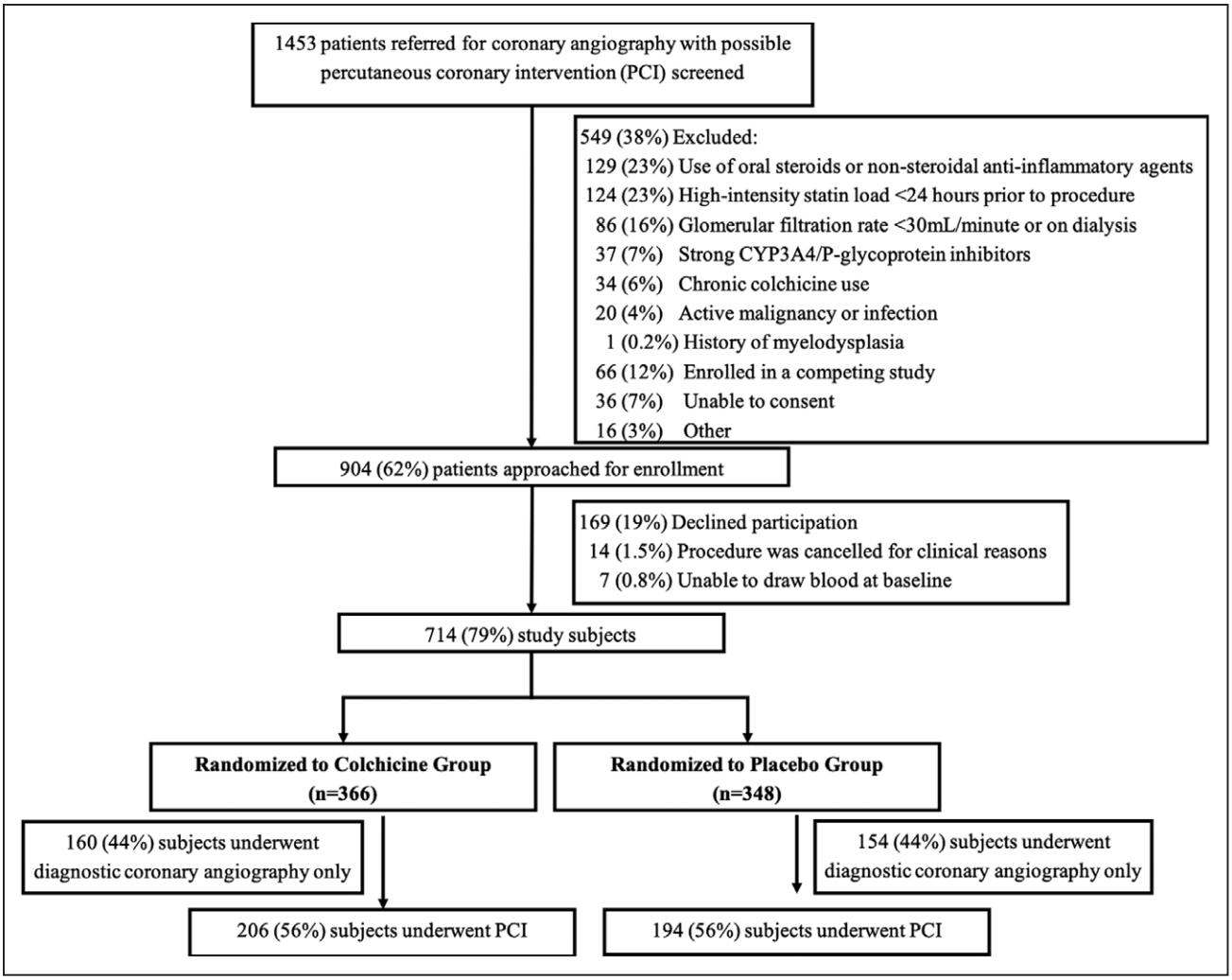


Figure 1. Screening, enrollment, and randomization of study population.
PCI indicates percutaneous coronary intervention.

(Figure 1). Baseline characteristics of the entire study cohort are presented in Table I in the Data Supplement. Of the 366 subjects randomized to acute preprocedural oral administration of colchicine 1.8 mg, 206 (56%) underwent PCI, and of the 348 subjects randomized to matching placebo, 194 (56%) underwent PCI (Figure 1).

Baseline demographic and clinical characteristics of subjects who underwent PCI did not differ between the colchicine and placebo groups (Table 1). A majority of the subjects were male, 76% were white, and 21% were of Hispanic ethnicity. Cardiovascular risk factors were common, with hypertension, hyperlipidemia, and diabetes mellitus in 92%, 89%, and 58% of subjects, respectively. Prior MI was reported in 26% of subjects, prior coronary revascularization in more than a third, and renal insufficiency in 21%. A majority of subjects were treated with aspirin and statin therapy before the procedure, and approximately two-thirds had been loaded with a P2Y12 inhibitor. Among subjects not prescribed aspirin or a P2Y12 inhibitor at the baseline assessment, an acute loading dose of aspirin 325 mg or clopidogrel 600 mg were administered immediately preprocedure based on clinician discretion. Ninety-one percent of the subjects were on statin therapy preprocedure, 66% on chronic high-intensity statin therapy, and 21% on a new treatment with high-intensity statin therapy 24 hours to 7 days preprocedure. The proportion of subjects with a preprocedural hsCRP concentration ≥2 mg/L was 62%. Severe multivessel coronary artery disease was present in 55% of subjects.

Of the 50% (n=198) of subjects with acute coronary syndrome as the indication for coronary angiography, 30% (n=59) presented with unstable angina, and 70% (n=139) with MI. Troponin I concentration was abnormal at baseline in 29% (n=117) with no difference between the colchicine and placebo groups (31% versus 27%, *P*=0.48). A down-trending troponin pattern was observed in 24% (n=95), whereas 5.5% (n=22) had elevated troponins pattern that had not yet declined from the peak measurement before PCI. The troponin pattern at baseline did not differ between the colchicine and placebo groups (*P*=0.64).

Table 1. Baseline Demographic and Clinical Characteristics of Subjects Undergoing Percutaneous Coronary Intervention Randomized to an Acute Preprocedural Oral Load of Colchicine or Placebo

	Colchicine (n=206)	Placebo (n=194)
Age, y	65.9±9.9	66.6±10.2
Male sex, %	193 (93.7)	181 (93.3)
Race, %		
White	159 (77.2)	144 (74.2)
Black	41 (19.9)	37 (19.1)
Asian	5 (2.4)	12 (6.2)
Other	1 (0.5)	1 (0.5)
Hispanic ethnicity, %	42 (20.4)	43 (22.2)
Body mass index, kg/m^2	29.9±5.8	29.3±5.4
Waist circumference, cm	98.9±14.3	98.1±13.0
Hypertension, %	192 (93.2)	175 (90.2)
Dyslipidemia, %	182 (88.3)	173 (89.2)
Diabetes mellitus, %	114 (55.3)	117 (60.3)
Insulin-treated diabetes mellitus, %	54 (26.3)	49 (25.3)
Prior myocardial infarction, %	51 (24.8)	52 (26.8)
Prior coronary revascularization, %	75 (36.4)	75 (38.7)
Congestive heart failure, %	44 (21.4)	28 (14.4)
Stroke or transient ischemic attack, %	19 (9.2)	17 (8.8)
Carotid artery disease, %	9 (4.4)	10 (5.2)
Peripheral artery disease, %	16 (7.8)	18 (9.3)
Renal insufficiency, %	45 (21.8)	38 (19.6)
Chronic obstructive pulmonary disease, %	29 (14.1)	32 (16.5)
Tobacco use, %	148 (71.8)	134 (69.1)
Current tobacco use, %	43 (20.9)	46 (23.7)
Aspirin, %	196 (95.1)	187 (96.4)
P2Y12 inhibitor, %	126 (61.2)	118 (60.8)
Statin, %	185 (89.8)	177 (91.2)
High-intensity statin, %	131 (63.6)	134 (69.4)
New treatment with high-intensity statin therapy 24 h to 7 days preprocedure, %	42 (20.4)	42 (21.6)
β-blocker, %	180 (87.4)	159 (82.0)
Calcium channel blocker, %	48 (23.3)	38 (19.6)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, %	130 (63.1)	132 (68.0)
LDL-cholesterol, mg/dL	77 [57–105]	81 [62–97]
HDL-cholesterol, mg/dL	39 [33–45]	38 [34–46]
Non–HDL-cholesterol, mg/dL	109 [81–140]	109 [87–131]
Hemoglobin A1c, %	6.3 [5.8–7.7]	6.4 [5.7–7.8]
Glucose, mg/dL	113 [97–145]	110 [95–145]
Glomerular filtration rate, mL/(min·1.73 m^2)	78 [62–95]	79 [64–95]
White blood cell count, ×10^9/L	7.2 [6.1–8.4]	7.3 [5.9–8.6]
Neutrophil/lymphocyte ratio	2.55 [1.79–3.52]	2.50 [1.83–3.77]
Hemoglobin, g/dL	13.9 [12.4–14.7]	13.8 [12.5–14.6]
Platelet count, ×10^9/L	211 [183–251]	211 [175–248]
High-sensitivity C-reactive protein, mg/L	3.3 [1.1–9.1]	3.1 [0.1–9.0]
High-sensitivity C-reactive protein ≥2 mg/L, %	127 (62.6)	113 (60.1)
Left ventricular ejection fraction, %		
Normal or borderline	145 (72.1)	132 (69.8)
Mildly/moderately reduced	40 (19.9)	44 (23.3)
Severely reduced	16 (8.0)	13 (6.9)
Indication for coronary angiography, %		
Acute coronary syndrome	103 (50.0)	95 (49.0)
Number of coronary arteries severely diseased, %		
1	91 (44.2)	91 (46.9)
2	76 (36.9)	56 (28.9)
3	39 (18.9)	47 (24.2)
Left main disease, %	5 (2.4)	6 (3.1)
LAD artery, %	150 (72.8)	136 (70.1)
Proximal LAD artery disease, %	61 (29.6)	46 (23.7)
Circumflex artery disease, %	104 (50.5)	98 (50.5)
Right coronary artery disease, %	101 (49.0)	106 (54.6)
Multivessel coronary artery disease, %	115 (55.8)	103 (53.1)

HDL indicates high-density lipoprotein; LAD, left anterior descending artery disease; and LDL, low-density lipoprotein.

Procedural Characteristics

Procedural characteristics of subjects who underwent PCI are presented in Table 2. PCI was successfully performed in 98% of subjects, and intraprocedural complications occurred in 4.5% of subjects with no differences between the colchicine and placebo groups. Radial arterial access was used for PCI in 88%. A median of one coronary stent was deployed per subject, and only about 10% underwent multivessel intervention during the index procedure. The 400 subjects underwent PCI of 500 lesions. Fewer than 10% of treated lesions had Thrombolysis in Myocardial Infarction 0/1 flow before PCI, and 99% of subjects had Thrombolysis in Myocardial Infarction 3 flow post-PCI. Fewer than 1 in 5 treated lesions were bifurcation or calcified lesion, and 1 in 5 treated lesions was ≥33 mm in length. The majority of treated lesions treated were de novo and not within a prior stent.

Outcomes

Less than 1% of subjects were missing cardiac biomarker data post-PCI, and no subjects were lost to follow-up. The primary outcome of PCI-related myocardial injury defined by the Universal Definition did not differ between the colchicine and placebo groups (Table 3). There remained no difference between the colchicine

Table 2. Procedural Characteristics of Subjects Undergoing PCI Randomized to an Acute Preprocedural Oral Load of Colchicine or Placebo

	Colchicine (n=206)	Placebo (n=194)	*P* Value
Access site, %			0.96
Radial artery	179 (86.9)	167 (86.1)	
Femoral artery	24 (11.7)	24 (12.4)	
Radial and femoral arteries	3 (1.5)	3 (1.5)	
No. of stents deployed	1 [1–2]	1 [1–2]	0.56
Total stent length, mm	28 [18–38]	28 [18–38]	0.79
Number of inflations	6 [4–8]	6 [4–8]	0.68
Multivessel intervention, %	25 (12.1)	21 (10.8)	0.80
Lesion level characteristics	(n=258)	(n=242)	
Preprocedural TIMI 0/1 flow, %	13 (5.0)	19 (7.9)	0.95
Stent diameter, mm^2	3.00 [2.50–3.00]	2.75 [2.50–3.00]	0.59
Maximum pressure on last device, atm	20±4	20±5	0.65
Bifurcation, %	40 (15.5)	36 (14.9)	0.89
Heavily calcified, %	35 (13.6)	45 (18.6)	0.63
Tortuous, %	17 (6.6)	25 (10.3)	0.74
Chronic total occlusion, %	14 (5.4)	11 (4.5)	0.86
Lesion length >33 mm, %	57 (22.1)	52 (21.5)	0.77
Thrombus, %	12 (4.7)	9 (3.7)	0.91
Restenosis, %	16 (6.2)	11 (4.5)	0.82
	(n=206)	(n=194)	
Postprocedural TIMI 3 flow, %	202 (98.1%)	193 (99.5%)	0.37
Successful PCI, %	203 (98.5)	190 (97.9)	0.94
Intraprocedural complication, %			
Abrupt closure	0	1 (0.5)	0.49
Side branch occlusion	4 (1.9)	2 (1.0)	0.69
Persistent flow reduction	1 (0.5)	3 (1.5)	0.36
Distal embolus	0	1 (0.5)	0.49
Major dissection	3 (1.5)	3 (1.5)	0.99
Coronary perforation	0	1 (0.5)	0.49
Any complication	8 (3.9)	10 (5.2)	0.71

Continuous data are presented as mean±SD and compared using 2-sample *t* test. Skewed continuous data are presented as median [interquartile range] and compared using Mann-Whitney *U* test. Categorical data are presented as frequency (proportion) and compared using χ^2 test or Fisher exact test if the cell number is <5. For lesion level characteristics, a linear mixed effect model and a logistic mixed effect model were used to account for the effect of individual subjects on continuous and categorical variables, respectively. PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

and placebo groups when evaluated by different thresholds of troponin (>1 to 5 upper reference limit: 27.2% versus 29.5%; ≥5 upper reference limit: 30.1% versus 34.7%). Key secondary outcomes of 30-day MACE and PCI-related MI, as defined by the Society for Cardiovascular Angiography and Interventions (also did not differ between the colchicine and placebo groups (Table 3).

The effect of colchicine versus placebo on PCI-related myocardial injury did not differ in prespecified subgroups based on acute coronary syndrome indication for PCI, presence of intraprocedural complication, baseline hsCRP ≥2 mg/L, or new treatment with high-intensity statin therapy 24 hours to 7 days preprocedure (Figure I in the Data Supplement). All outcomes are presented by acute coronary syndrome presentation status in Table II in the Data Supplement.

Inflammatory Biomarker Substudy

Characteristics of randomized subjects who underwent PCI and were enrolled in the nested inflammatory biomarker substudy versus those not enrolled in the substudy are presented in Table III in the Data Supplement. There were no differences in the demographic, clinical, and procedural characteristics between subjects in the nested inflammatory biomarker substudy who underwent PCI and were randomized to colchicine (n=141) versus placebo (n=139; data not shown).

For all subjects in the substudy, median IL-6 concentration did not significantly increase from baseline (3.71 pg/mL [0.99–9.60]) to 1 hour after PCI (4.49 pg/mL [1.21–11.15], *P*=0.10) but did increase from baseline to 6 to 8 hours after PCI (8.58 pg/mL [2.71–18.55], *P*<0.0001) and from baseline to 22 to 24 hours after PCI (7.48 pg/mL [2.52–14.20], *P*<0.0001). Although colchicine did not attenuate the percent increase in IL-6 concentrations at 6 to 8 hours post-PCI, it did attenuate the median percent increase in IL-6 concentrations at 22 to 24 hours post-PCI when compared with placebo (Figure 2A). Median IL-6 concentrations over time in the colchicine versus placebo groups are shown in Figure IIA in the Data Supplement.

For all subjects in the substudy, median IL-1β concentration did not significantly increase from baseline (0.63 pg/mL [0.38–1.26]) to 1-hour post-PCI (0.63 pg/mL [0.33–1.26], *P*=0.68), to 6 to 8 hours post-PCI (0.67 pg/mL [0.31–1.26], *P*=0.85), and to 22 to 24 hours post-PCI (0.63 pg/mL [0.29–1.26]), *P*=0.46). There were no differences in the median percent change in IL-1β concentration from baseline to post-PCI between the colchicine and placebo groups (Figure 2B). Median IL-β concentrations over time in the colchicine versus placebo groups are shown in Figure IIB in the Data Supplement.

For all subjects in the substudy, hsCRP concentration increased from baseline (3.0 mg/L [0.9–9.2]) to 22 to 24 hours post-PCI (4.9 mg/L [1.7–11.9], *P*<0.0001). Colchicine attenuated the median percent increase in hsCRP concentration from baseline to 22 to 24 hours post-PCI when compared to placebo (Figure 2C). Median hsCRP concentrations over time in the colchicine versus placebo groups are shown in Figure IIC in the Data Supplement.

Subjects in the substudy were further evaluated by the presence (n=74) or absence (n=206) of an abnormal Troponin at baseline as shown in Figure III in the Data Supplement.

Table 3. Outcomes in Patients Undergoing PCI Randomized to an Acute Preprocedural Oral Load of Colchicine or Placebo

	Colchicine (n=206)	Placebo (n=194)	*P* Value
Primary outcome			
PCI-related myocardial injury	118 (57.3)	122 (64.2)	0.19
Secondary outcomes			
30-day major adverse cardiovascular events	24 (11.7)	25 (12.9)	0.82
Type 4a myocardial infarction (universal definition)	23 (11.2)	23 (12.1)	0.89
Type 1 myocardial infarction (universal definition)	0	1 (0.5)	0.49
Target vessel revascularization	0	0	…
All-cause mortality	1 (0.5)	1 (0.5)	0.99
PCI-related myocardial infarction (SCAI definition)	6 (2.9)	9 (4.7)	0.49

Data are presented as frequency (proportion) and compared using χ^2 test or Fisher exact test if the cell number is <5. PCI indicates percutaneous coronary intervention; and SCAI, Society of Coronary Angiography and Interventions.

Adverse Events

Periprocedural adverse events from baseline assessment through hospital discharge in the entire study cohort are shown in Table 4. The most common adverse events were chest pain (8.1%), which did not differ between groups, and gastrointestinal symptoms (6.3%), which occurred more frequently in the colchicine (9.3%) versus placebo (3.2%) group. Other adverse events occurred at a low frequency. Although 5 serious adverse events occurred in the colchicine group (compared with 12 in the placebo group), only one was deemed by the Data Safety Monitoring Committee to be possibly or probably due to study participation. This event was abdominal discomfort postprocedure that resulted in additional testing with an abdominal ultrasound and prolongation of hospital stay by one day.

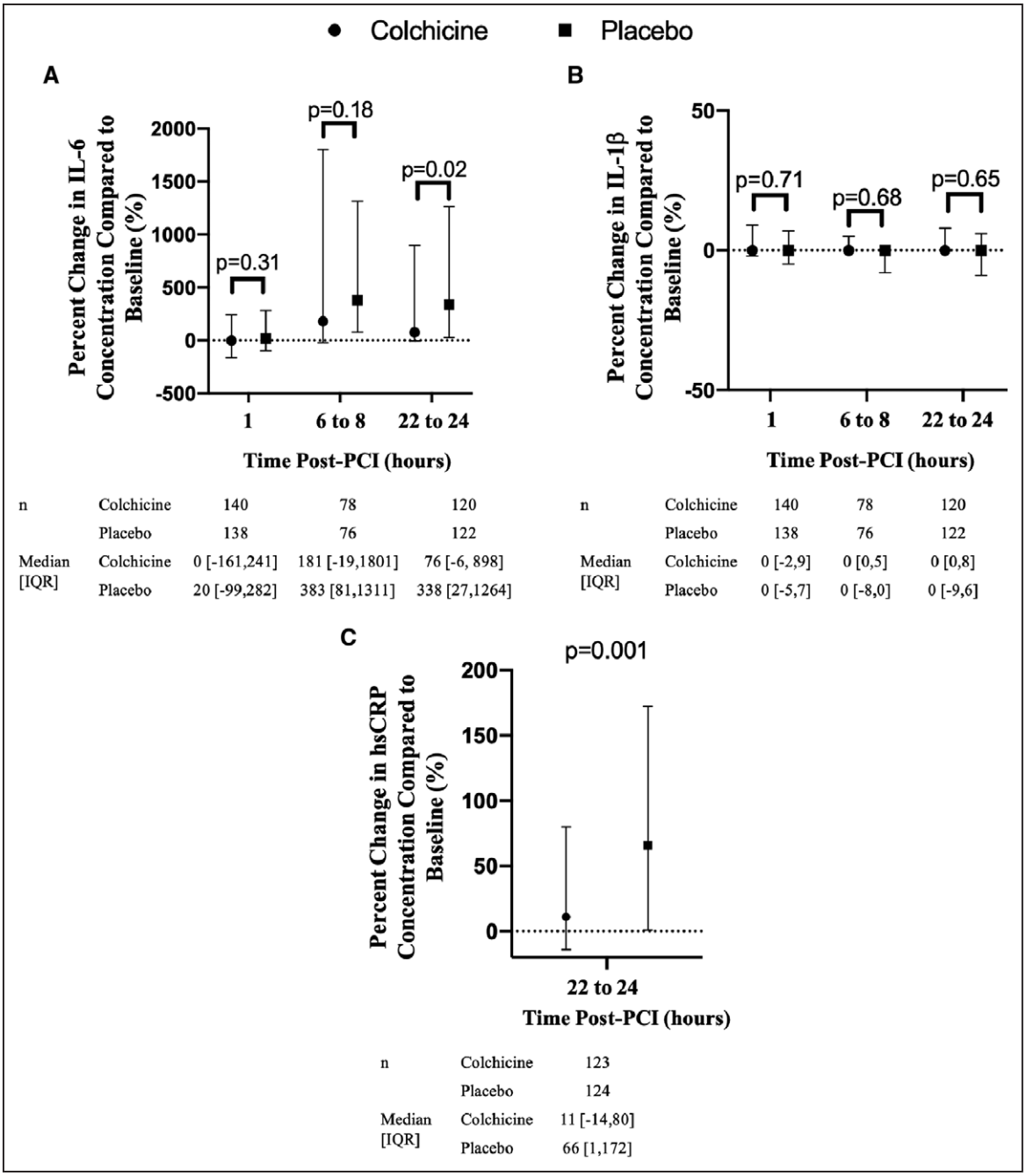
DISCUSSION

This single-site prospective randomized double-blind study is the first to evaluate the effects of an acute preprocedural administration of colchicine versus placebo on markers of myocardial injury and inflammation in patients undergoing PCI. The most salient findings are that preprocedural administration of 1.8 mg colchicine did not lower the risk of PCI-related myocardial injury, PCI-related MI, or MACE at 30 days when compared with placebo but did significantly attenuate the increase in IL-6 and hsCRP concentrations 22 to 24 hours post-PCI when compared with placebo. Finally, PCI was not associated with increase in IL-1β in either treatment group, suggesting that IL-1β is not an appropriate marker for vascular injury and inflammation in this setting.

PCI-related myocardial injury may be partly due to wire injury, microdissections at the site of balloon inflations, and vascular trauma due to high-pressure balloon inflations. Leukocytes are rapidly recruited to sites of endothelial injury with subsequent increases in IL-6 concentrations.[2,3,5,6] PCI-related myocardial injury may also result from mechanical events, such as distal microemboli and side branch occlusion from plaque shift. A proinflammatory state during PCI may lead to endothelial dysfunction and leukocyte-platelet aggregates in distal beds, which, in turn, can limit the ability of the coronary microvasculature to accommodate atherothrombotic debris.[28–31] Despite the use of contemporary techniques, devices, and pharmacology, systemic inflammation at the time of PCI is associated with adverse events, including cardiac death, stent thrombosis, and target lesion revascularization, as early as 30 days post-PCI.[7,9,15]

Colchicine, an anti-inflammatory agent traditionally used to treat gout, suppresses neutrophil homotypic adhesion, modulates neutrophil deformability, decreases neutrophil extravasation, and suppresses an enzymatic component of the inflammasome, leading to reductions in IL-1β and IL-6.[18,19] Colchicine has also been shown to decrease levels of neutrophil-platelet aggregates, and incrementally decrease hsCRP concentrations on a background of aspirin and statin therapy.[32] The lack of benefit of colchicine on PCI-related myocardial injury in the current study may be attributable to the pharmacodynamics of colchicine—including too short of a time period for colchicine administration pre-PCI or an insufficiently potent dosage, particularly in the setting of acute coronary syndrome and mechanical intraprocedural complications, plaque shift, distal emboli. The 1.8 mg dose of colchicine used in the current trial was chosen based on pharmacodynamic data demonstrating maximum plasma concentration within 1 to 2 hours of administration and safety and efficacy data in acute gout flares.[23] However, these efficacy data are confounded by the daily administration of colchicine thereafter, which was not done in our trial. Alternatively, the presence of redundant pathways of vascular injury and inflammation in a high-risk cohort with multiple vascular risk factors may play a role in negating any possible colchicine effect.

Anti-inflammatory therapy remains a promising therapeutic option to reduce cardiovascular risk in patients undergoing PCI. Acute preprocedural administration of high-intensity statin therapy has been shown to reduce



n	Colchicine	140	78	120
	Placebo	138	76	122
Median [IQR]	Colchicine	0 [-161,241]	181 [-19,1801]	76 [-6, 898]
	Placebo	20 [-99,282]	383 [81,1311]	338 [27,1264]

n	Colchicine	140	78	120
	Placebo	138	76	122
Median [IQR]	Colchicine	0 [-2,9]	0 [0,5]	0 [0,8]
	Placebo	0 [-5,7]	0 [-8,0]	0 [-9,6]

n	Colchicine	123
	Placebo	124
Median [IQR]	Colchicine	11 [-14,80]
	Placebo	66 [1,172]

Figure 2. Percent change in inflammatory marker concentrations from baseline to 1 h, baseline to 6 to 8 h, and baseline to 22 to 24 h post-percutaneous coronary intervention (PCI) in the colchicine vs placebo.
Data are shown as median (interquartile range [IQR]) of the percent changes, and percent changes in interleukin (IL)-6 concentration (**A**), IL-1β concentration (**B**), and high sensitivity C-reactive protein (hsCRP) concentration (**C**) from baseline to 1 h, from baseline to 6 to 8 h, and from baseline to 22 to 24 h were compared between the colchicine and placebo groups using Mann-Whitney *U* test.

PCI-related myocardial injury and MI before elective PCI and in patients undergoing PCI for acute coronary syndrome, though the supportive studies are few, leaving some debate on their effects on the extent of PCI-related myocardial injury.[27,33,34] Decreases in PCI-related myocardial injury associated with acute high-intensity statin pretreatment parallel attenuations in post-PCI elevation of inflammatory cellular adhesion molecules.[35,36] However, since statins exert their actions via post-translational modification of small G proteins, they were administered at least 12 hours in advance of PCI in prior trials. CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) demonstrated the anti-IL-β antibody, canakinumab, to reduce MACE in the setting of lowering IL-6 and hsCRP concentrations in patients with prior MI but is not available for a cardiovascular indication due to its side effect profile.[37] Therefore, there remains a

Table 4. Adverse Events

	Colchicine (n=366)	Placebo (n=348)	*P* Value
Chest pain, %	33 (9.0)	25 (7.2)	0.45
Gastrointestinal symptoms, %	34 (9.3)	11 (3.2)	0.001
Hypersensitivity reaction, %	4 (1.1)	4 (1.1)	0.99
Access site discomfort, %	4 (1.1)	4 (1.1)	0.99
Hemodynamic instability, %	0	5 (1.4)	0.03
Fever, %	0	2 (0.6)	0.24
Elevated creatinine, %	1 (0.3)	2 (0.6)	0.62
Ischemic stroke, %	1 (0.3)	0	0.99
Fluid overload, %	1 (0.3)	1 (0.3)	0.99
Urinary retention, %	2 (0.5)	0	0.50
Bleeding, %	1 (0.3)	2 (0.6)	0.62
Palpitations, %	0	1 (0.3)	0.49
Headache, %	1 (0.3)	0	0.99
Serious adverse events total, %	5 (1.4)	12 (3.4)	0.11

Categorical data are presented as frequency (proportion) and compared using χ^2 test, or Fisher exact test if the cell number is <5.

need for a well-tolerated, oral, rapid-acting anti-inflammatory agent, especially in the settings of urgent PCI and patients who are referred for PCI but have not received statin therapy before the procedure.[38,39]

The observed primary event rate in the current trial was higher than expected at 64% in the placebo arm when compared with reported rates in the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty; stable angina) and ARMYDA-Recapture (stable angina and non–ST-segment–elevation acute coronary syndrome) trials.[24,32] The higher event rate in our trial might be attributable to higher rates of diabetes mellitus, severe multivessel coronary artery disease, and acute coronary syndromes in our study cohort. Although the primary event rate of PCI-related myocardial injury was more easily captured in the subgroup that did not present with acute coronary syndrome, the rate of 30-day MACE, driven predominately by type 4A MI defined by the Universal Definition, was higher in the subgroup that presented with acute coronary syndrome.

To our knowledge, this is the first study to demonstrate that colchicine can prevent an acute rise of inflammatory biomarkers in an acute setting. Our observations that colchicine suppressed post-PCI increase in IL-6 and hsCRP concentrations without inhibiting myocardial damage suggest that increases in these markers may be secondary, rather than contributory to myocardial injury, or any effect of colchicine via these markers may require a longer time frame to appreciate. Although one report randomized 40 acute coronary syndromes patients to an acute colchicine loading dose versus no colchicine before cardiac catheterization and demonstrated a lower concentration of coronary sinus concentrations of both IL-6 and IL-1β with colchicine, they did not have baseline concentrations to compare to, and the single time-point measurements were taken pre-PCI.[40] In the current trial, colchicine attenuated the increase in both IL-6 and hsCRP concentrations at 22 to 24 post-PCI but did not affect the increase in these markers observed at 6 to 8 hours post-PCI, and, therefore, it is possible that earlier preprocedural administration of colchicine may have a benefit. Prior reports have also demonstrated a difference in the concentration and rise in concentrations of inflammatory markers by sampling source.[5,40] However, another report of 25 patients predominantly with acute coronary syndromes demonstrated only a 1.5-fold increase in median IL-6 concentration from baseline to one hour post-PCI, whereas at 24 hours post-PCI, there was a 3.2-fold increase in median IL-6 concentration, paralleling the trend in relative change in median IL-6 concentrations post-PCI in the current trial.[6]

Limitations

The current findings are supported by several strengths of the study design and execution, including the double-blind, placebo-controlled randomized study design, and high adherence to study procedures. There are several caveats that limit interpretation of the findings. First, the high proportion of multiple cardiac risk factors of the study population due to referral bias at an academic medical center limits generalizability of the findings. Furthermore, the majority male population enrolled within the VA system limits interpretation for women undergoing PCI. Second, our observations are limited to the selected acute preprocedural dosing regimen and the short-term timepoints for biomarkers of myocardial injury and inflammation in study participants with heterogeneous presentations for PCI. Prior clinical studies of colchicine in the stable coronary artery disease population evaluated at least 30 days of colchicine at 0.5 mg daily, and prior studies in other clinical settings have shown colchicine's anti-inflammatory effects to continue to increase over days.[31,41,42] The large, randomized, multicenter COLCOT (Colchicine Cardiovascular Outcomes Trial; https://www.clinicaltrials.gov; NCT02551094) and CLEAR SYNERGY OASIS 9 (Colchicine and Spironolactone in Patients With ST-Elevation Myocardial Infarction; https://www.clinicaltrials.gov; NCT03048825) trials will provide insight into the effects of low-dose daily colchicine within 3 months of MI and twice-daily dose of colchicine within 48 hours of ST-segment–elevation MI, respectively, on long-term MACE. Third, the primary outcome of the current trial was limited to short-term follow-up at 24 hours. Elevated post-PCI inflammatory biomarkers are associated with an increased rate of restenosis, and one prior study demonstrated a reduction in restenosis with colchicine at 6 months follow-up.[1,10,11,13,43] Finally, genetic data were not collected in the current trial. Resistance to colchicine has been described in 5% to 18% of the familial Mediterranean fever population due to polymorphisms of

codon 3435 in the multiple drug resistance gene that encodes the P-glycoprotein membrane efflux pump.[43–45]

In conclusion, short-term preprocedure colchicine administration attenuated the increase in IL-6 and hsCRP concentration after PCI but did not reduce PCI-related myocardial injury or MACE when compared with placebo.

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Dr Shah serves on the advisory board for Philips Volcano and Radux Devices and serves as a consultant for Terumo Medical. Dr Pillinger serves as a consultant for Horizon, Sobi and Ampel Biosciences, and is the recipient of investigator-initiated grant support from Hikma and Horizon. Dr Cronstein has research grant funding from Astra Zeneca and Arcus and is a founder of Regenosine, Inc. Dr Feit is a shareholder of Boston Scientific, Medtronic, and Johnson and Johnson. Dr Zhong, Dr Lorin, Dr Smilowitz, Y. Xia, N. Ratnapala, and Dr Keller report no relationships with industry. Dr Katz has research grant funding from Astra Zeneca, Pfizer, Amgen, Luitpold, AMAG Pharmaceuticals, Eidos Therapeutics, and Array BioPharma and serves as a consultant for Merck.

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