

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Efficacy and Safety of Low-Dose Colchicine After Myocardial Infarction

Supplementary Materials

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Supplementary Tables

Table S1. Multivariable Cox Regression Model for Time to First Primary Endpoint.

Effect		Adjusted Hazard Ratio (95% CI)	P Value
Randomized treatment group	Colchicine vs. Placebo	0.78 (0.62-0.98)	0.03
Age at randomization (years)		1.02 (1.01-1.03)	<0.001
History of diabetes	Yes vs. No	1.86 (1.46-2.37)	<0.001
Prior coronary revascularization (PCI or CABG)	Yes vs. No	2.02 (1.58-2.58)	<0.001
Prior heart failure	Yes vs. No	1.81 (1.08-3.04)	0.03

CABG denotes coronary artery bypass graft, and PCI percutaneous coronary intervention. The model was based on 4745 observations. All baseline characteristics that showed an association ($P < 0.20$) with the occurrence of a first positively adjudicated primary endpoint were included in the stepwise multivariable Cox regression. For age at randomization, the hazard ratio is for an increase of one year of age.

Table S2. Rates and Hazard Ratios for the Primary Endpoint and its Components in the Per-Protocol Population†.

Clinical Outcome	Colchicine	Placebo	Hazard Ratio (95% CI)
<u>Per-protocol population</u>	N=2260	N=2270	
Primary endpoint - no. (%)	115 (5.1%)	162 (7.1%)	0.71 (0.56-0.90)
CV death - no. (%)	19 (0.8%)	23 (1.0%)	0.83 (0.45-1.53)
Resuscitated cardiac arrest - no. (%)	5 (0.2%)	5 (0.2%)	1.00 (0.29-3.46)
MI - no. (%)	77 (3.4%)	92 (4.1%)	0.84 (0.62-1.14)
Stroke - no. (%)	5 (0.2%)	19 (0.8%)	0.26 (0.10-0.71)
Urgent hospitalization for angina requiring revascularization - no. (%)	22 (1.0%)	47 (2.1%)	0.47 (0.28-0.78)

CV denotes cardiovascular, and MI myocardial infarction. †The per-protocol population consisted of patients without major protocol deviations.

Table S3. Primary Efficacy Composite Endpoint in Prespecified Subgroups†.

Subgroup	Colchicine	Placebo	Hazard ratio (95% CI)
<i>no. of patients with event/total no. of patients (%)</i>			
All patients	131/2366 (5.5%)	170/2379 (7.1%)	0.77 (0.61-0.96)
Smoking			
Non-smoker	47/787 (6.0%)	52/797 (6.5%)	0.90 (0.61; 1.34)
Previous smoker	46/871 (5.3%)	77/872 (8.8%)	0.59 (0.41; 0.85)
Active smoker	38/708 (5.4%)	41/708 (5.8%)	0.93 (0.60; 1.44)
History of diabetes			
Yes	40/462 (8.7%)	65/497 (13.1%)	0.65 (0.44; 0.96)
No	91/1904 (4.8%)	105/1882 (5.6%)	0.85 (0.64; 1.13)
History of hypertension			
Yes	83/1185 (7.0%)	112/1236 (9.1%)	0.76 (0.57; 1.01)
No	48/1181 (4.1%)	58/1143 (5.1%)	0.80 (0.54; 1.17)
Prior MI			
Yes	46/370 (12.4%)	47/397 (11.8%)	1.05 (0.70; 1.58)
No	85/1996 (4.3%)	123/1982 (6.2%)	0.68 (0.51; 0.89)
Prior PCI or CABG			
Yes	48/419 (11.5%)	57/447 (12.8%)	0.91 (0.62; 1.34)
No	83/1947 (4.3%)	113/1932 (5.8%)	0.72 (0.54; 0.95)
Prior stroke or TIA			
Yes	8/55 (14.5%)	9/67 (13.4%)	1.09 (0.42; 2.82)
No	123/2311 (5.3%)	161/2312 (7.0%)	0.76 (0.60; 0.96)
Sex‡			
Male	94/1894 (5.0%)	135/1942 (7.0%)	0.70 (0.54; 0.91)
Female	37/472 (7.8%)	35/437 (8.0%)	0.99 (0.63; 1.58)
White blood cell count¶			
Below median	41/660 (6.2%)	46/637 (7.2%)	0.85 (0.56; 1.29)
Above median	34/637 (5.3%)	44/664 (6.6%)	0.80 (0.51; 1.25)

CABG denotes coronary artery bypass graft, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack. †The final amendment to the statistical analysis plan, which listed the subgroups of interest, was approved on August 28, 2019 and unblinding occurred on August 29, 2019. ‡The hazard ratio for the primary endpoint was 0.70 (0.52; 0.93) in men and 0.81 (0.47; 1.41) in women in the per-protocol population. ¶The median value for total white blood cell count was $8.64 \times 10^3/\mu\text{L}$.

Table S4. Total (First and Recurrent) Primary Endpoint Events.

Total Primary Endpoint Events		Colchicine (N=2366)	Placebo (N=2379)
Number of primary endpoint events per patient	0	2235	2209
	1	111	132
	2	18	26
	3	1	9
	4	1	3
Total number of primary endpoint events		154	223
Total follow-up months		52949	53060
Rate of primary endpoint events per 100 patient-months		0.29	0.42
		Hazard Ratio or Rate Ratio (95% CI)	
Negative binomial model†		0.66 (0.51; 0.86)	
Andersen-Gill model‡		0.69 (0.54; 0.88)	
WLW model¶	1 st Event	0.77 (0.61; 0.96)	
	2 nd Event	0.73 (0.48; 1.11)	
	3 rd Event	0.64 (0.37; 1.10)	
	Average	0.77 (0.61; 0.96)	

WLW denotes Wei-Lin-Weissfeld method.

†The negative binomial regression model was used to calculate marginal rate ratio.

‡The Andersen-Gill model was used with a robust variance estimator (sandwich estimator) to calculate hazard ratio.

¶The Wei-Lin-Weissfeld marginal model was used to calculate hazard ratios for the time to the first, second and third event as well as the weighted average of these hazard ratios. To account for the occurrence of multiple primary endpoint events within patients, recurrent event analyses were undertaken using three statistical approaches as there is no strong consensus as to which method is preferable. First, a negative binomial regression model was used with the number of events as the outcome and the length of follow-up time in months as an offset term.¹ Marginal rate ratio was provided, along with 95% confidence interval. The Andersen and Gill model² with a robust variance estimator^{3,4} was utilized to account for the dependency of within-patient events based on a gap-time approach considering the time since a previous event. The Andersen-Gill model is a simple extension of the Cox model based on all events of all patients and estimates a hazard ratio assuming that the instantaneous risk of experiencing an event is the same irrespective of whether previous events occurred. Results from these two models are often similar.^{5,6} Finally, an approach based on the Wei, Lin and Weissfeld marginal model was conducted whereby times from randomization to first, second and subsequent event were modeled with a Cox proportional hazards model that used a covariance matrix estimate for the regression coefficients that accounted for the possible intra-patient correlation.⁷⁻⁹ This approach assumes that all patients are at risk for any event since randomization. Marginal hazard ratios for a k^{th} event (i.e. based on time from randomization to k^{th} event), as well as a weighted average of these hazard ratios, were provided along with 95% confidence intervals. It has been argued that this approach preserves the randomization and permits valid treatment effect estimation.¹⁰

Table S5. Characteristics of the Trial Patients with hs-CRP data values.

Characteristic	Colchicine (N=99)	Placebo (N=108)
Age - years	62.1±9.7	61.2±10.2
Female sex - no. (%)	18 (18.2%)	14 (13.0%)
Caucasian - no. (%)	91 (93.8%)	89 (89.0%)
Body-mass index (kg/m ²)	28.8±4.5	29.1±4.2
Smoking - no. (%)	20 (20.2%)	20 (18.5%)
Hypertension - no. (%)	44 (44.4%)	62 (57.4%)
Diabetes - no. (%)	12 (12.1%)	15 (13.9%)
Prior MI - no. (%)	14 (14.1%)	16 (14.8%)
Prior PCI - no. (%)	24 (24.2%)	21 (19.4%)
Prior CABG - no. (%)	4 (4.0%)	6 (5.6%)
Prior heart failure - no. (%)	4 (4.0%)	1 (0.9%)
Prior stroke/TIA - no. (%)	1 (1.0%)	2 (1.9%)
Index MI to randomization - days	17.0±9.2	15.8±9.8
PCI for index MI - no. (%)	93 (93.9%)	104 (96.3%)
Aspirin use - no. (%)	98 (99.0%)	106 (98.1%)
Other anti-platelet agent - no. (%)	98 (99.0%)	108 (100%)
Statin use - no. (%)	99 (100%)	107 (99.1%)
Beta-blocker - no. (%)	83 (83.8%)	86 (79.6%)

CABG denotes coronary artery bypass graft surgery, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

Table S6. Biomarkers of Inflammation.

Biomarker	Colchicine	Placebo
Hs-C reactive protein (mg/L)	N=99	N=108
Randomization, geometric mean (IQR) [†]	4.27 (2.12, 7.22)	5.09 (2.45, 11.96)
6 months, geometric mean (IQR)	1.37 (0.75, 2.13)	1.60 (0.90, 2.65)
Adjusted GM percent change (95% CI) [‡]	-70.0 (-74.6, -64.5)	-66.6 (-71.5, -60.8)
Placebo-adjusted GM percent change (95% CI) [¶]	-10.1 (-28.6, 13.4)	- -
Total white blood cell count (10 ³ /μL)	N=992	N=980
Randomization, geometric mean (IQR) [†]	8.54 (7.10, 10.40)	8.63 (7.20, 10.70)
12 months, geometric mean (IQR)	6.95 (5.99, 8.30)	7.03 (5.96, 8.48)
Adjusted GM percent change (95% CI) [‡]	-18.81 (-20.12, -17.47)	-19.02 (-20.46, -17.55)
Placebo-adjusted GM percent change (95% CI) [¶]	0.26 (-2.15, 2.72)	- -
Circulating lymphocytes (10 ³ /μL)		
Randomization, geometric mean (IQR) [†]	1.79 (1.40, 2.40)	1.79 (1.42, 2.46)
12 months, geometric mean (IQR)	1.83 (1.50, 2.44)	1.82 (1.50, 2.44)
Adjusted GM percent change (95% CI) [‡]	1.80 (-0.46, 4.11)	0.69 (-1.54, 2.98)
Placebo-adjusted GM percent change (95% CI) [¶]	1.10 (-2.06, 4.36)	- -
Circulating neutrophils (10 ³ /μL)		
Randomization, geometric mean (IQR) [†]	5.45 (4.36, 7.15)	5.47 (4.30, 7.46)
12 months, geometric mean (IQR)	3.95 (3.27, 5.08)	3.99 (3.34, 5.20)
Adjusted GM percent change (95% CI) [‡]	-27.63 (-29.48, -25.73)	-27.95 (-29.91, -25.93)
Placebo-adjusted GM percent change (95% CI) [¶]	0.45 (-3.28, 4.32)	- -

GM denotes geometric mean, HS high-sensitivity, and IQR inter-quartile range.

[†]The geometric mean was obtained by exponentiating the mean of log-transformed data.

[‡] The adjusted geometric mean percent change was obtained by exponentiating the adjusted mean from the analysis of covariance model (based on log-transformed data), then subtracting 1 and multiplying by 100. The bounds of the 95% confidence intervals were obtained similarly.

¶The placebo-adjusted geometric mean percent change was obtained by exponentiating the adjusted mean difference between groups from the analysis of covariance model (based on log-transformed data), then subtracting 1 and multiplying by 100.

The C-reactive protein biomarker sub-study was implemented following a protocol amendment and was optional for sites and for patients; 34 sites accepted to participate in this substudy. There were 213 and 208 patients who provided blood samples at baseline and 6 months, respectively. Paired baseline and 6-month hs-CRP values were available in 207 patients. Clinically available white blood cell counts were obtained from 2598 patients at baseline and 1998 patients at 12 months, and paired baseline and 12-month values were available in 1972 patients. Statistical analysis was conducted on the patients who provided both baseline and follow-up data and as these were exploratory analyses, no missing data was imputed.

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