SUPPLEMENTARY DATA

Efficacy and safety of colchicine in post-acute myocardial infarction patients: a systematic review and meta-analysis of randomized controlled trials

Diaz-Arocutipa C et al.

Supplementary Table 1. Electronic search strategy

PubMed (colchicine[mh] OR colchicine[tiab]) AND ("myocardial infarction"[mh] OR "myocardial infarction"[tiab] OR "coronary artery disease"[mesh] OR "coronary artery disease"[tiab] OR "acute coronary syndrome"[mh] OR "acute coronary syndrome"[tiab] OR "angina pectoris"[mh] OR "angina"[tiab] OR "ischemic heart disease"[tiab] OR "coronary heart disease"[tiab] OR "heart attack"[tiab] OR "myocardial ischemia"[mh] OR "coronary disease"[mh] OR "coronary thrombosis"[mh] OR "coronary stenosis"[mh] OR "coronary occlusion"[mh]) AND (("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]))
Embase (colchicine/exp OR colchicine) AND ('myocardial infarction'/exp OR 'myocardial infarction' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'acute coronary syndrome'/exp OR 'acute coronary syndrome' OR 'angina pectoris'/exp OR 'angina pectoris' OR angina/exp OR angina OR 'ischemic heart disease'/exp OR 'ischemic heart disease' OR 'coronary heart disease'/exp OR 'coronary heart disease' OR 'heart attack'/exp OR 'heart attack' OR 'myocardial ischemia'/exp OR 'myocardial ischemia' OR 'coronary disease'/exp OR 'coronary disease' OR 'coronary thrombosis'/exp OR 'coronary thrombosis' OR 'coronary stenosis'/exp OR 'coronary stenosis' OR 'coronary occlusion'/exp OR 'coronary occlusion')
Scopus TITLE-ABS-KEY (colchicine AND ("myocardial infarction" OR "coronary artery disease" OR "acute coronary syndrome" OR angina OR "ischemic heart disease" OR "coronary heart disease" OR "heart attack" OR "myocardial ischemia" OR "coronary disease" OR "coronary thrombosis" OR "coronary stenosis" OR "coronary occlusion"))
Web of Science All=(colchicine AND ("myocardial infarction" OR "coronary artery disease" OR "acute coronary syndrome" OR angina OR "ischemic heart disease" OR "coronary heart disease" OR "heart attack" OR "myocardial ischemia" OR "coronary disease" OR "coronary thrombosis" OR "coronary stenosis" OR "coronary occlusion"))
CENTRAL (colchicine AND ("myocardial infarction" OR "coronary artery disease" OR "acute coronary syndrome" OR angina OR "ischemic heart disease" OR "coronary heart disease" OR "heart attack" OR "myocardial ischemia" OR "coronary disease" OR "coronary thrombosis" OR "coronary stenosis" OR "coronary occlusion")):ti,ab,kw

Supplementary Table 2. Ongoing randomized controlled trials (as of October 20, 2020)

Trial ID	Trial title	Experimental arm	Control arm	Country	Estimated enrollment	Estimated study completion date
NCT04218786	Effect of Colchicine in Patients With Myocardial Infarction	Colchicine 0.5 mg/day for three months	Placebo	Pakistan	800 patients	November 2020
NCT04420624	Colchicine to Prevent Sympathetic Denervation After an Acute Myocardial Infarction (COLD-MI)	Colchicine 0.5 or 1 mg/day for one month	Standard treatment	France	56 patients	September 2021
NCT03156816	Colchicine for Left Ventricular Remodeling Treatment in Acute Myocardial Infarction (COVERT-MI)	Colchicine 2mg bolus, then 1 mg/day for five days	Placebo	France	194 patients	January 2022
NCT03048825	Colchicine and Spironolactone in Patients With MI / SYNERGY Stent Registry (CLEAR SYNERGY)	Colchicine 0.5 mg/day, spironolactone 25 mg/day	Placebo	Canada	7000 patients	March, 2025

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Supplementary Table 3. Subgroup analyses according to colchicine dose

Outcomes	Number of studies	Effect measures	95%CI	p-value	I^2
Cardiovascular mortality					
Colchicine 0.5 mg/day	2	RR: 0.84	0.60-1.17	0.10	0%
Colchicine 1 mg/day	2	RR: 2.28	0.01-1030.06	0.34	0%
Recurrent myocardial infarction					
Colchicine 0.5 mg/day	2	RR: 0.90	0.15-5.37	0.59	0%
Colchicine 1 mg/day	2	RR: 0.61	0.05-6.76	0.23	0%
All-cause mortality					
Colchicine 0.5 mg/day	2	RR: 0.98	0.96-1.01	0.07	0%
Colchicine 1 mg/day	3	RR: 3.05	0.12-75.12	0.27	0%
Urgent coronary revascularization					
Colchicine 0.5 mg/day	1	RR: 0.50	0.31-0.81	<0.01	-
Colchicine 1 mg/day	1	RR: 0.25	0.07-0.89	0.03	-
Stroke					
Colchicine 0.5 mg/day	1	RR: 0.26	0.10-0.71	<0.01	-
Colchicine 1 mg/day	1	RR: 0.34	0.07-1.65	0.18	-
Follow-up levels of hs-CRP					
Colchicine 0.5 mg/day	2	MD: -0.49	-5.62 to 4.65	0.44	8%
Colchicine 1 mg/day	2	MD: -8.36	-204.67 to 187.96	0.68	88%
Any adverse events					
Colchicine 0.5 mg/day	2	RR: 0.99	0.76-1.28	0.60	0%
Colchicine 1 mg/day	1	RR: 0.93	0.72-1.19	0.54	-
Gastrointestinal adverse events					
Colchicine 0.5 mg/day	2	RR: 1.19	0.02-57.37	0.67	51%
Colchicine 1 mg/day	3	RR: 5.10	0.07-365.13	0.24	82%

hs-CRP, high-sensitivity C-reactive protein; 95%CI, 95% confidence interval; RR, risk ratio; MD, mean difference.

Supplementary Table 4. Subgroup analyses according to time of follow-up

Outcomes	Number of studies	Effect measures	95%CI	p-value	I^2
Cardiovascular mortality					
Follow-up <1 year	2	RR: 1	1-1	0.21	0%
Follow-up ≥1 year	2	RR: 0.98	0-212.12	0.97	14%
Recurrent myocardial infarction					
Follow-up <1 year	2	RR: 0.25	0.01-5.42	0.11	0%
Follow-up ≥1 year	2	RR: 0.89	0.26-3.05	0.43	0%
All-cause mortality					
Follow-up <1 year	3	RR: 0.98	0.92-1.04	0.29	0%
Follow-up ≥1 year	2	RR: 2.18	0-936380.9	0.58	74%
Urgent coronary revascularization					
Follow-up <1 year	0	-	-	-	-
Follow-up ≥1 year	2	RR: 0.46	0.02-8.89	0.19	1%
Stroke					
Follow-up <1 year	0	-	-	-	-
Follow-up ≥1 year	2	RR: 0.28	0.07-1.09	0.05	0%
Follow-up levels of hs-CRP					
Follow-up <1 year	4	MD: -1.95	-12.88 to 8.98	0.61	73%
Follow-up ≥1 year	0	-	-	-	-
Any adverse events					
Follow-up <1 year	1	RR: 0.89	0.50-1.60	0.70	-
Follow-up ≥1 year	2	RR: 0.98	0.70-1.36	0.53	0%
Gastrointestinal adverse events					
Follow-up <1 year	3	RR: 6.07	0.20-180.16	0.15	62%
Follow-up ≥1 year	2	RR: 1.01	0.59-1.72	0.84	0%

hs-CRP, high-sensitivity C-reactive protein; 95%CI, 95% confidence interval; RR, risk ratio; MD, mean difference.

Supplementary Table 5. Subgroup analyses according to treatment duration

Outcomes	Number of studies	Effect measures	95%CI	p-value	I^2
Cardiovascular mortality					
≤30 days	2	RR: 1	1-1	0.21	0%
>30 days	2	RR: 0.98	0-212.12	0.97	14%
Recurrent myocardial infarction					
≤30 days	2	RR: 0.25	0.01-5.42	0.11	0%
>30 days	2	RR: 0.89	0.26-3.05	0.43	0%
All-cause mortality					
≤30 days	3	RR: 0.98	0.92-1.04	0.29	0%
>30 days	2	RR: 2.18	0-936380.9	0.58	74%
Urgent coronary revascularization					
≤30 days	0	-	-	-	-
>30 days	2	RR: 0.46	0.02-8.89	0.19	1%
Stroke					
≤30 days	0	-	-	-	-
>30 days	2	RR: 0.28	0.07-1.09	0.05	0%
Follow-up levels of hs-CRP					
≤30 days	4	MD: -1.95	-12.88 to 8.98	0.61	73%
>30 days	0	-	-	-	-
Any adverse events					
≤30 days	1	RR: 0.89	0.50-1.60	0.70	-
>30 days	2	RR: 0.98	0.70-1.36	0.53	0%
Gastrointestinal adverse events					
≤30 days	3	RR: 6.07	0.20-180.16	0.15	62%
>30 days	2	RR: 1.01	0.59-1.72	0.84	0%

hs-CRP, high-sensitivity C-reactive protein; 95%CI, 95% confidence interval; RR, risk ratio; MD, mean difference.

Supplementary Table 6. Sensitivity analyses without the Hartung-Knapp adjustment

Outcomes	Number of studies	Effect measures	95%CI	p-value	I^2
Cardiovascular mortality	4	RR: 0.91	0.52-1.60	0.75	0%
Recurrent myocardial infarction	4	RR: 0.87	0.67-1.14	0.31	0%
All-cause mortality	5	RR: 1.06	0.71-1.58	0.77	0%
Urgent coronary revascularization	2	RR: 0.46	0.29-0.73	<0.01	1%
Stroke	2	RR: 0.28	0.12-0.65	<0.01	0%
Follow-up levels of hs-CRP	4	MD: -1.95	-5.93 to 2.03	0.34	73%
Any adverse events	3	RR: 0.97	0.88-1.08	0.63	0%
Gastrointestinal adverse events	5	RR: 2.49	0.78-7.99	0.13	72%

hs-CRP, high-sensitivity C-reactive protein; 95%CI, 95% confidence interval; RR, risk ratio; MD, mean difference.

Supplementary Table 7. Sensitivity analyses including only trials with low risk of bias

Outcomes	Number of studies	Effect measures	95%CI	p-value	I^2
Cardiovascular mortality	2	RR: 0.98	0-212.12	0.97	14%
Recurrent myocardial infarction	2	RR: 0.89	0.26-3.05	0.43	0%
All-cause mortality	3	RR: 1.59	0.11-23.62	0.54	47%
Urgent coronary revascularization	2	RR: 0.46	0.02-8.89	0.19	1%
Stroke	2	RR: 0.28	0.07-1.09	0.05	0%
Follow-up levels of hs-CRP	1	MD: -23.80	-38.84 to -8.76	<0.01	-
Any adverse events	2	RR: 0.98	0.70-1.36	0.53	0%
Gastrointestinal adverse events	3	RR: 2.09	0.05-83.42	0.48	76%

hs-CRP, high-sensitivity C-reactive protein; 95%CI, 95% confidence interval; RR, risk ratio; MD, mean difference.

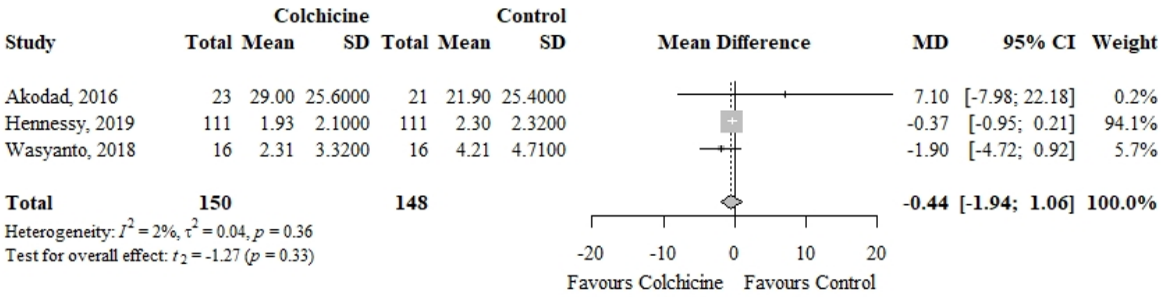
Supplementary Table 8. Comparison of published systematic reviews on the use of colchicine in patients with coronary artery disease

	Our study	Xia et al.	Xiang et al.	Al-Abdouh et al.	McKnight et al.	Samuel et al.	Tien et al.	Ullah et al.
Year of publication	2021	2021	2021	2020	2020	2020	2020	2020
Aim	To evaluate the efficacy and safety of colchicine in patients post-acute MI	To determine the clinical utility of colchicine treatment in patients with CAD	To evaluate the efficacy and safety of colchicine in the secondary prevention of CAD	To evaluate the benefits of colchicine in patients with CAD including stable and after ACS	To evaluate the efficacy and safety of colchicine for secondary prevention after ACS	To evaluate the efficacy and safety of colchicine for secondary CV prevention among patients with clinically manifest CAD	To evaluate the CV protective effects of colchicine on patients with CAD	To bring consensus on the clinical use of colchicine in patients with stable and non-stable CAD
Search databases	PubMed, Embase, Scopus, Web of Science, CENTRAL	PubMed, Cochrane, Scopus	PubMed, Embase, CENTRAL, Web of Science, Google Scholar	PubMed, Embase, Cochrane	Medline, Embase	PubMed, Embase, CENTRAL	PubMed, Embase	Medline, Embase, Cochrane
Search cut-off date	January 18, 2021	August, 2020	August 31, 2020	February 28, 2020	June, 2020	September 1, 2020	April 28, 2020	December 2, 2019
Population	Patients post-acute MI	Patients with CCS and ACS	Patients with CCS and ACS	Patients with CCS and ACS	Patients with ACS	Patients with CCS and ACS	Patients with CCS and ACS	Patients with CCS and ACS
Included studies	6 RCTs	5 RCTs	8 RCTs	6 RCTs	9 RCTs	4 RCTs	10 RCTs	6 RCTs
Total	6005 patients	11790 patients	11463 patients	6154 patients	5756 patients	11594 patients	6699 patients	5820 patients

number of patients								
Risk of bias assessment	RoB 2.0 tool	RoB 1.0 tool	RoB 2.0 tool	RoB 1.0 tool	Jadad Scale	RoB 2.0 tool	RoB 1.0 tool	RoB 1.0 tool
Outcomes	CV mortality, recurrent MI, all-cause mortality, stroke, urgent coronary revascularization, hs-CRP, any adverse events, and GI adverse events	MACE, CV mortality, MI, urgent revascularization, stroke, non-CV mortality, GI events	MACE, all-cause mortality, urgent coronary revascularization, stroke, acute MI, diarrhea	MACE, myocardial infarction (MI), all-cause mortality, CV mortality, stroke	CRP, cytokines, infarct size, CV events	MACE, CV mortality, MI, stroke, urgent coronary revascularization, deep vein thrombosis or pulmonary embolus, atrial fibrillation, non-CV mortality, infection, pneumonia, hospitalization for GI event, diagnosis of cancer	MI, restenosis after PCI, all-cause mortality, GI events	MACE, mortality, ACS, cardiac arrest, stent restenosis, revascularization, stroke, GI adverse events
Conclusion	In patients with MI, colchicine does not reduce CV or all-cause mortality, recurrent MI, or other CV outcomes. Also,	Colchicine treatment may reduce the risk of future CV events in CAD patients	Colchicine is an accessible, safe, and effective drug that could be successfully utilized for the secondary prevention of CAD	Colchicine was not associated with a significant decrease in CV endpoints and mortality in patients with CAD	Adjunctive colchicine 0.5 mg daily for greater than 30 days is reasonable for an ACS population on guideline-directed medical therapy treated with PCI	The addition of low-dose colchicine to standard medical therapy reduces the incidence of major CV events, except CV mortality, when compared to standard medical	There is a decreased composite risk of MI and restenosis after PCI with the use of colchicine in patients with CAD. However,	In patients with CAD presenting with an ACS or stable angina, colchicine might offer no significant reduction in MACE and could potentially be

	colchicine not increase drug-related adverse events					therapy alone	colchicine did not appear beneficial for all-cause mortality, and it led to a higher risk of GI events	harmful due to a significantly higher risk of GI-related adverse events

MI, myocardial infarction; CAD, coronary artery disease; CCS, chronic coronary syndrome; ACS, acute coronary syndrome; CV, cardiovascular; CENTRAL, Cochrane Controlled Register of Trials; RCTs, randomized controlled trials; hs-CRP, high-sensitivity C-reactive protein; RoB, risk of bias; MACE, major adverse cardiovascular events; GI, gastrointestinal; PCI, percutaneous coronary intervention.



Supplementary Figure 1. Sensitivity analysis by excluding Deftereos et al. trial of the effect of colchicine on follow-up levels of high-sensitivity C-reactive protein (mg/L). SD indicates standard deviation; MD, mean difference; CI; confidence interval.