

ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CRP	C-reactive protein
CVD	Cardiovascular disease
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
SAE	Serious adverse event

1 INTRODUCTION

2 Coronary artery disease (CAD) is a leading cause of death and disability worldwide.^{1,2} Patients
3 with CAD have an increased risk of cardiovascular events including death, myocardial infarction (MI),
4 stroke, and cardiac arrest; a risk that is magnified for each subsequent cardiovascular event.² Clinical
5 guideline recommended therapy for CAD and atherosclerosis reflects the complexities of the disease.² A
6 combination of lifestyle modifications and drug therapies, such as lipid lowering therapy, blood pressure
7 control, glucose control, and antithrombotic therapy, constitute the multifaceted approach to patient
8 care.² These established therapies have demonstrated efficacy in inhibiting the progression of
9 atherosclerosis and/or substantially reducing the incidence of cardiovascular events.² However, a residual
10 risk of cardiovascular events remains,^{2,3} suggesting that current treatment options could be further
11 improved.

12 In recent years, inflammation has emerged as an important therapeutic target in patients with
13 atherosclerosis.^{4,5} As first demonstrated in the Canakinumab Anti-inflammatory Thrombosis Outcomes
14 study (CANTOS), inhibition of the NLRP3 inflammasome-dependent inflammatory pathway using the
15 monoclonal antibody to interleukin-1 β canakinumab reduces major CV events. This therapeutic effect
16 was particularly marked in patients who achieved a significant reduction in biomarkers of inflammation
17 (interleukin-6 and C-reactive protein (CRP)).⁶⁻⁸ As a consequence, cardiovascular events due to plaque
18 destabilization and rupture were reduced.⁶⁻⁸

19 Colchicine, an established anti-inflammatory medication commonly used to treat gout, also
20 targets the inflammasome.^{4,9} In addition, colchicine is a relatively safe and low-cost medication which
21 has been available for centuries.¹⁰⁻¹⁶ Several randomized clinical trials have recently assessed the efficacy
22 of low-dose colchicine (0.5 mg daily) on adverse cardiovascular outcomes in patients with established
23 CAD.¹⁰⁻¹³ Our objective was to consolidate evidence from these RCTs in the form of systematic review
24 and meta-analysis to evaluate the efficacy and safety of colchicine for secondary cardiovascular
25 prevention among patients with clinically manifest CAD.

1 **METHODS**

2 ***Data sources***

3 Medline (PUBMED), EMBASE, and Cochrane central were searched to identify RCTs
4 comparing colchicine to placebo or no colchicine for secondary cardiovascular prevention (inception to
5 September 1, 2020). To maximized sensitivity, citation chasing was performed in Google Scholar,
6 Scopus, and Web of Science. Secondary prevention was defined as patients with clinically manifest or
7 established CAD. Query terms included “colchicine”, “coronary artery disease”, “acute coronary
8 syndrome”, “myocardial infarction”, “cardiovascular disease”, “atherosclerosis”, and “secondary
9 prevention”, either separately or in combination (further details provided in *Supplemental Methods*).

10 ***Study selection, data extraction, and bias assessment***

11 RCTs that met the following criteria were included in the meta-analysis: 1) compared daily use
12 of low-dose (0.5 mg) colchicine to placebo or no colchicine for secondary cardiovascular prevention; 2)
13 the study reported at least one of the following outcomes: cardiovascular death, MI, stroke, cardiac arrest,
14 or urgent coronary revascularization; 3) other than the trial medication, patients in both arms were treated
15 in accordance to guideline directed medical therapy; 4) the minimum follow-up was at least 1 year; and
16 5) trials were published in a peer-reviewed scientific journal. Review articles, editorials, meta-analyses,
17 observational studies, and published abstracts were excluded from the present meta-analysis.

18 Study selection was performed by two independent reviewers (MS and NB), using two levels of
19 screening. At the first level, titles and abstracts of searched studies were screened, followed by review of
20 full texts. The reviewers were not blinded to the title of the journals, authors, or affiliated institutions.
21 Reasons for exclusion were recorded and any discrepancies were discussed until a consensus was
22 achieved.

23 Using standardized forms, data on study characteristics, patient characteristics, and outcomes
24 were extracted on the intent-to-treat population independently by two reviewers (MS and NB) from each
25 eligible study. The Cochrane Collaboration risk-of-bias tool for randomized trials was used to evaluate

1 study quality.¹⁷ The meta-analysis was conducted in accordance to the Preferred Reporting Items for
2 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (checklist in *Supplemental Material*).

3 ***Outcomes***

4 The primary efficacy endpoint was a composite of cardiovascular death, MI, ischemic stroke, and
5 urgent coronary revascularization. Secondary efficacy endpoints consisted of the components of the
6 primary endpoint, composite of cardiovascular death, MI, and ischemic stroke, as well as deep vein
7 thrombosis or pulmonary embolus, and atrial fibrillation (AF). To maximize consistency in pooling
8 efficacy endpoints among trials, the primary and secondary composite efficacy and stroke endpoints in
9 COLCOT were modified to meet the definition of primary and stroke endpoints of the LoDoCo2 trial.
10 Therefore, adjudicated events of resuscitated cardiac arrest and non-ischemic stroke in COLCOT were
11 excluded from the pooled primary endpoint. The component endpoint of stroke was also restricted to
12 include only ischemic strokes. Incidence rates and hazards ratios (HRs) were calculated for the new
13 primary composite endpoint and ischemic stroke endpoint using individual patient data from COLCOT.

14 Safety outcomes were limited to serious adverse events (SAEs) and included all-cause and non-
15 cardiovascular mortality, hospitalization for gastrointestinal event, infection, and pneumonia, as well as
16 diagnosis of cancer. Incidence of SAEs were recalculated for COLCOT using the intent-to-treat
17 population.

18 ***Data synthesis and statistical analyses***

19 The DerSimonian and Laird random-effects model was used to calculate the pooled HR and
20 corresponding 95% confidence intervals (CI) for primary and secondary endpoints in the overall trial and
21 in subgroup analyses of the primary endpoint. For safety outcomes, the DerSimonian and Laird random-
22 effects model was used to compute risk ratios (RR) and corresponding 95% CIs. Heterogeneity was
23 evaluated with the Higgins I² statistic. I² values of <25%, 25-75%, and >75% were considered to indicate
24 low, moderate, and high degrees of heterogeneity, respectively. In subgroup analyses, the Q_b statistic
25 was calculated to determine inconsistency and variability in the treatment effect between strata.¹⁸

Publication and small study bias were assessed with the Egger's regression test and visually by asymmetry in funnel plots. Sensitivity analyses were performed for the primary composite and component outcomes for 1) RCTs in patients with acute coronary syndrome (COLCOT and COPS), and 2) RCTs in patients with stable CAD (LoDoCo and LoDoCo2); and after exclusion of 3) the LoDoCo trial [open-label trial and control group was not randomized to placebo] and 4) the LoDoCo and COPS [increased dose (0.5 mg twice daily) of colchicine prescribed during first month] trials. Statistical analyses were performed using SAS software version 9.4 (*SAS Institute, Cary, North Carolina*) and Stata (Version 16, StataCorp, College Station, Texas).

RESULTS

Literature search results and risk of bias

The search strategy identified 79 studies. After the first- and second-level screening processes, four RCTs were retained in the present meta-analysis. The characteristics of included RCTs are listed in Table 1. The Low-Dose Colchicine (LoDoCo) and Low-Dose Colchicine 2 (LoDoCo2) trials assessed the efficacy of colchicine in patients with stable CAD (defined as clinically stable for ≥ 6 months).^{11,12} In comparison, the Colchicine Cardiovascular Outcomes Trial (COLCOT) was conducted in patients who had a recent MI (≤ 30 days) and the Colchicine in Patients with acute coronary Syndrome (COPS) trial enrolled patients with acute coronary syndromes (ACS).^{10,13}

The pooled sample size of enrolled patients was 11,594, of which 5774 patients were randomized to colchicine and 5820 patients were randomized to placebo (or no colchicine, in the LoDoCo trial only). Three trials were designated as "low risk" for overall bias^{10,12,13} and 1 trial was marked as being of "some concern"¹¹ in the Cochrane Collaboration risk-of-bias assessment (*Supplemental Tables S1 and S2*).

Patient Characteristics

Baseline patient characteristics for each RCT are summarized in Table 2. The mean age of patients ranged from 60 to 67 years. In all trials, <20% of enrolled patients were women and more than 90% of patients were on concomitant statin therapy. LoDoCo and LoDoCo2 trials had a higher proportion of patients who underwent prior coronary revascularization [percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery]. The distribution of all other patient characteristics was relatively similar between trials.

Clinical efficacy endpoints

Clinical efficacy results from each trial are presented in Table 3 (*Supplemental Figure S1 and Table S2*). In patients with CAD, the addition of colchicine to standard medical therapy was associated with a statistically significant reduction in the primary composite endpoint of cardiovascular mortality, MI, ischemic stroke, and urgent coronary revascularization, compared to patients on placebo or no colchicine [pooled HR 0.68 (95% CI 0.54-0.81); $I^2=37.7\%$; Figure 1]. The reduction in cardiovascular events in patients randomized to colchicine was driven by statistically significant reductions in the incidence of MIs [pooled HR 0.62 (95% CI 0.36-0.88); $I^2=68.76\%$], ischemic strokes [pooled HR 0.38 (95% CI 0.13-0.63); $I^2=0.0\%$], and urgent coronary revascularization [pooled HR 0.56 (95% CI 0.30-0.82); $I^2=65.1\%$] (Figure 1). However, there was no statistically significant difference detected for cardiovascular mortality (Figure 1). Sensitivity analyses that pooled the results of COLCOT and LoDoCo2 trials demonstrated similar effect estimates for the primary composite and component outcomes, although magnitude of effect and heterogeneity (I^2) between studies decreased (*Supplemental Figure S2 and S3*).

In sensitivity analyses of ACS trials (COLCOT and COPS; N=5540), the primary composite endpoint, MI, and urgent coronary revascularizations were statistically significantly reduced in patients randomized to colchicine compared to placebo (*Supplemental Figure S4*). Among patients with stable CAD (LoDoCo and LoDoCo 2; N=6054), the only comparable outcome between trials was MI which was statistically significantly decreased with colchicine compared to placebo (*Supplemental Figure S5*).

Although there was no statistically significant difference in the incidence of key secondary endpoints, there was a trend towards reduced AF diagnoses and AF episodes among patients randomized to colchicine [pooled HR 0.86 (95% CI 0.67-1.04); $I^2=0.0\%$] (Figure 1).

Visual inspection of funnel plots and the results of the Eggers test indicated there was no significant risk of publication bias for all outcomes ($p>0.05$ for all) except urgent coronary revascularization ($p=0.02$) (*Supplemental Figure S6*).

Subgroup analyses

The statistically significant reduction in the incidence of the primary composite cardiovascular endpoint among patients randomized to colchicine was consistent for most subgroup analyses (Figure 2). There was no significant heterogeneity of the effect of colchicine in the different subgroups studied (Figure 2). Overall, the Q_b statistic suggests that there is minimal variability and inconsistency in the treatment effect between strata in subgroup analyses ($p>0.05$ for all; *Supplemental Figure S5*).

Major adverse events

There was no statistically significant difference between treatment arms for the risk of all-cause [pooled RR 1.04 (95% CI 0.61-1.78); $I^2=62.01\%$] and non-cardiovascular mortality [pooled RR 1.38 (95% CI 0.99-1.93); $I^2=0.0\%$] (Figure 3). The rates of infections, pneumonias, hospitalizations for gastrointestinal events, and diagnoses of cancer were also not significantly different (Figure 3). For pneumonia, there was a high degree of heterogeneity between trials with opposite directions for the treatment effect ($I^2=81.5\%$; Figure 3).

DISCUSSION

In this contemporary meta-analysis of RCTs comparing colchicine to placebo (or no colchicine) for secondary cardiovascular prevention, we found that: 1) treatment with colchicine was associated with a 32% reduction in the incidence of major cardiovascular events; 2) significantly fewer MIs, ischemic strokes, and urgent coronary revascularizations were the primary drivers for the overall decrease in cardiovascular events; 3) the protective treatment effect of colchicine was relatively consistent among

most subgroups studied, and 4) colchicine had a favorable safety profile. To our knowledge, this is the first comprehensive meta-analysis of RCTs evaluating efficacy and safety of colchicine for secondary cardiovascular prevention in which the endpoints were harmonized across trials. Overall, the synthesis of current evidence in the present meta-analysis indicates that treatment with colchicine for secondary cardiovascular prevention confers beneficial clinical effects.

Secondary prevention of cardiovascular diseases

Although the 4 RCTs investigated the efficacy of colchicine in different segments of the CAD population, including stable CAD, recent MI, and ACS, the results of all trials consistently demonstrated that colchicine was protective against a composite endpoint of cardiovascular mortality, MI, ischemic stroke, and urgent coronary revascularization.^{10,12,13} The individual trials were not powered to detect statistically significant differences in the components of the primary endpoint. Whereas all trials showed a decrease in urgent coronary revascularizations among patients randomized to colchicine, only COLCOT detected a reduction in ischemic strokes [HR 0.25 (95% CI 0.08-0.75)] and LoDoCo2 a decrease in MIs [HR 0.70 (95% CI 0.53-0.93)].^{10,12,13} Pooling HRs from the RCTs revealed that the attenuated risk of major cardiovascular events was attributed to risk reductions of 38%, 62%, and 44% for MIs, ischemic strokes, and urgent coronary revascularization, respectively. Although the 2 largest trials, COLCOT and LoDoCo2, contributed the most weight to analyses, the inclusion of LoDoCo and COPS tended to increase the magnitude of the risk reduction by 4-5%.

Individual trials and pooled results suggest that there is no difference in the incidence of cardiovascular or all-cause mortality with colchicine. These pooled analyses provide reassurance about the safety of colchicine for the outcome of all-cause mortality. Results from both the LoDoCo2 and COPS trials showed a trend towards increased all-cause mortality with colchicine, although neither reached statistical significance [LoDoCo2 HR 1.21 (95% CI 0.86-1.71) and COPS HR 8.20 (95% 1.02-65.61)].^{12,13} The increased power from pooled analyses demonstrated that the effect of colchicine on all-

1 cause mortality was closer to null or no effect than suggested by individual trials [pooled RR 1.04 (95%
2 CI 0.61-1.78)].

3 The anti-inflammatory properties of colchicine work through various mechanisms to inhibit the
4 pathogenesis of CAD, and subsequently reduce the incidence of ischemic cardiovascular events. In
5 addition to targeting the NLRP3 inflammasome leading to the reduction of circulating levels of IL-1 β
6 and IL-6, colchicine also inhibits cholesterol crystals that promote inflammation and plaque instability
7 in atherosclerosis.^{15,16,19}

8 Real-world observational studies on the use of colchicine to prevent cardiovascular events are
9 limited to primary prevention studies in patients with gout and no baseline CAD.²⁰⁻²² Solomon et al
10 (N=501) found that colchicine was associated with a decrease in a composite outcome of MI, stroke, and
11 transient ischemic attack over 16.5 months of follow-up [adjusted HR 0.51 (95% CI 0.30-0.88)].²⁰ Shah
12 and colleagues investigated the risk of CAD and MI among gout patients prescribed colchicine compared
13 to an inverse probability weighted sample of patients not prescribed colchicine.²² CAD was defined as
14 evidence of ischemia on a stress test, stenosis of coronary arteries by angiography or coronary
15 revascularization.²² Over 96 months of follow-up, colchicine was associated with a reduction in the
16 composite outcome of CAD and MI [adjusted HR 0.37 (95% CI 0.16-0.83)].²² Although definitive
17 conclusions cannot be drawn from such observational studies, the reduced risk of cardiovascular events
18 in a low-risk population further supports the role of colchicine in inhibiting progression of atherosclerosis
19 and plaque destabilization.

20 *Treatment effects across subgroups*

21 The treatment effect of colchicine was similar with overlapping confidence intervals across age
22 categories (≤ 65 or > 65 years), presence or absence of diabetes and hypertension, and among patients
23 with or without prior coronary revascularization. Although the risk reduction appeared less marked in
24 women compared to men, less than 20% of trial populations were women (1977 women compared to

9617 men). It is, therefore, possible that the lack of a statistically significant reduction in cardiovascular events with colchicine in the subgroup analysis of women reflects limited power. There was no significant heterogeneity between the effects in subgroups and that in the overall population.

Safety

Colchicine has an established safety profile from its centuries of use to treat gout. There was a numerical imbalance in the number of non-cardiovascular deaths between study arms, which did not reach statistical significance. This trend is inconsistent with safety results from randomized clinical trials investigating colchicine use in patients with gout, familial Mediterranean fever, and pericarditis.^{23,24} Thus, it is possible that the pooled HR may be skewed by potential chance findings in the few studies included in present meta-analysis. Importantly, there was no effect of colchicine on all-cause mortality. In the COPS study, the increased dose of colchicine during the first month of follow-up might have contributed to higher non-cardiovascular deaths. In addition, 3 of 5 colchicine patients who died from non-cardiovascular causes in COPS had also discontinued colchicine prior to date of death, which may suggest that on-treatment analyses may provide further evidence to the safety of colchicine for non-cardiovascular mortality. Furthermore, the quality of follow-up in COPS was poor, with more than twice the number of patients with incomplete vital status than that of deaths due to inadequate resources (2 part-time healthcare workers following 795 patients). In contrast, the quality of follow-up and rate of vital status ascertainment of the 10,267 patients included in COLCOT and LoDoCo2 were excellent and did not reveal a significant difference in non-cardiovascular mortality between study arms. Finally, the meta-analysis showed no difference in all-cause mortality between groups.

Only the COLCOT trial detected a difference in the rate of pneumonia between patients randomized to colchicine (0.9%) or placebo (0.4%).¹⁰ Pooled analyses of COLCOT and LoDoCo2 did not show an increased risk of pneumonia with colchicine, suggesting this result in the former may have been due to chance. The lack of a difference between groups for infections, hospitalizations, and diagnoses of cancer further validates that colchicine is safe to use in patients with CAD.

1 ***Limitations***

2 Although this is the first comprehensive assessment of RCTs evaluating the efficacy and safety
3 of colchicine in secondary CVD prevention, there are several limitations to consider. First, there was
4 heterogeneity between the study populations enrolled in each trial, which may explain differences in risk
5 of cardiovascular events between studies. Nevertheless, it is conceivable that the mechanism of action of
6 colchicine in reducing cardiovascular events is similar among patients with stable CAD or a recent MI.
7 In addition, there was heterogeneity in the outcome definitions between studies. We attempted to
8 minimize this heterogeneity by conducting additional patient-level analyses for COLCOT with modified
9 outcome definitions and by excluding studies with different outcome definitions from individual pooled
10 estimates. Furthermore, statistical testing for heterogeneity may not have been optimal due to the small
11 number of studies included.

12 As we did not have access to patient-level data from 3 of 4 trials, only modified study-level data
13 was used for the present meta-analysis. Although meta-analyses based on aggregate patient data continue
14 to be the mainstay of systematic reviews that inform clinical practice, meta-analyses based on individual
15 patient data have several advantages including the ability to verify data, address new questions, and adjust
16 for the same variables across studies. Finally, the small number of eligible studies precluded meta-
17 regression analyses to determine the influence of specific variables or effect modifiers on the association
18 between colchicine and cardiovascular events. Nevertheless, the potential for effect modification was
19 addressed in part by subgroup analyses.

20

21 **CONCLUSION**

22 In patients with CAD, the addition of low-dose colchicine to standard medical therapy
23 consistently and significantly reduces the incidence of major cardiovascular events compared to standard
24 medical therapy alone. With the exception of cardiovascular mortality, significant reductions were

- 1 observed for components of the primary outcome, including MIs, ischemic strokes, and urgent coronary
- 2 revascularizations.
- 3

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FIGURE LEGEND

Figure 1. Forest plot of clinical efficacy endpoints

Figure 2. Forest plot of subgroup analyses (primary composite outcome)

Figure 3. Forest plot of serious adverse events

Table 1. Study characteristics

	LoDoCo¹¹	COLCOT¹⁰	COPS¹³	LoDoCo2¹²
Year	2013	2019	2020	2020
Study design	Single-blind RCT	Double-blind, placebo controlled RCT	Double-blind, placebo controlled RCT	Double-blind, placebo controlled RCT
Study population	Stable CAD	Recent MI (<30 days)	ACS	Stable CAD
N	532	4,745	795	5,522
Key inclusion criteria	Angiographically proven CAD; clinically stable for ≤6 months	MI within 30 days prior; completed planned percutaneous revascularization procedures; treated according to national guidelines that included intensive use of statins	ACS (STEMI/NSTEMI/UA); Evidenced CAD on coronary angiography, managed with either PCI or medical therapy	Evidence of CAD on invasive angiography or computed tomography angiography or a coronary calcium score of ≥400 Agaston units on a coronary-artery calcium scan; clinically stable condition for ≥6 months
Key exclusion criteria	Bypass surgery within 10 years prior	Severe heart failure; left ventricular ejection fraction <35%; stroke within the previous 3 months; type 2 index MI; coronary-bypass surgery either within previous 3 years or planned; severe renal or hepatic disease; known cancer	CAD requiring surgical revascularization pre-existing long-term colchicine use or immunosuppressant therapy; severe hepatic or renal insufficiency; known active malignancy	Moderate-to-severe renal impairment; severe heart failure; severe valvular disease
Median follow-up	24 months	22.6 months	12 months	28.6 months
Primary endpoint	Composite: ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke	Composite: CV mortality, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization	Composite: All-cause mortality, ACS (STEMI/NSTEMI/UA), ischemia-driven revascularization, or non-cardioembolic ischemic stroke	Composite: CV death, MI, ischemic stroke, or ischemia-driven coronary revascularization

*ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; RCT, randomized controlled trial; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina

Table 2. Patient characteristics at baseline

	LoDoCo¹¹		COLCOT¹⁰		COPS¹³		LoDoCo2¹²	
	Colchicine N=250	Control N=282	Colchicine N=2366	Placebo N=2379	Colchicine N=396	Placebo N=399	Colchicine N=2762	Placebo N=2760
Age, years (mean ± SD)	67 ± 9.2	66 ± 9.6	60.6 ± 10.7	60.5 ± 10.6	59.7 ± 10.2	60.0 ± 10.4	65.8 ± 8.4	65.9 ± 8.7
Women (%)	11.2%	11.0%	19.9%	18.4%	18.7%	22.3%	16.5%	14.1%
Hypertension (%)	Not reported	Not reported	50.1%	52.0%	50.8%	49.9%	51.4%	50.3%
Diabetes (%)	27.6%	32.6%	19.5%	20.9%	18.9%	19.0%	17.8%	18.7%
History of PCI (%)	55.2%	59.9%	16.6%	17.1%	12.9%	12.5%	76.0%	75.3%
History of CABG (%)	15.6%	22.0%	2.9%	3.4%	3.8%	4.8%	11.5%	14.2%
Statin use (%)	94.0%*	96.1%*	98.9%	99.1%	98.2%	99.5%	93.9%	94.0%

*The LoDoCo trial only reported use of high dose statins, not any statin use.

Table 3. Study efficacy outcomes

	LoDoCo ¹¹		COLCOT ¹⁰		COPS ¹³		LoDoCo2 ¹²	
	Colchicine N=250	Control N=282	Colchicine N=2366	Placebo N=2379	Colchicine N=396	Placebo N=399	Colchicine N=2762	Placebo N=2760
Primary composite outcome: Cardiovascular mortality, myocardial infarction, ischemic stroke, urgent revascularization								
Events, N (%)	NA	NA	130 (5.5%)	168 (7.1%)	19 (4.8%)	41 (10.3%)	187 (6.8%)	264 (9.6%)
HR (95% CI)	NA		0.77 (0.61-0.97)		0.47 (0.27-0.82)		0.69 (0.57-0.83)	
Cardiovascular mortality								
Events, N (%)	NA	NA	20 (0.8%)	24 (1.0%)	3 (0.8%)	1 (0.3%)	20 (0.7%)	25 (0.9%)
HR (95% CI)	NA		0.84 (0.46-1.52)		3.09 (0.32-29.71)		0.80 (0.44-1.44)	
Myocardial infarction								
Events, N (%)	4 (1.6%)	14 (5.6%)	89 (3.8%)	98 (4.1%)	11 (3.7%)	22 (5.5%)	83 (3.0%)	116 (4.2%)
HR (95% CI)	0.25 (0.08-0.76)		0.91 (0.68-1.21)		0.52 (0.25-1.07)		0.70 (0.53-0.93)	
Ischemic stroke								
Events, N (%)	1 (0.4%)	4 (1.6%)	4 (0.2%)	16 (0.7%)	2 (0.5%)	6 (1.5%)	16 (0.6%)	24 (0.9%)
HR (95% CI)	0.23 (0.03-2.03)		0.25 (0.08-0.75)		0.34 (0.07-1.70)		0.66 (0.35-1.25)	
Urgent coronary revascularization								
Events, N (%)	NA	NA	25 (1.1%)	50 (2.1%)	3 (0.8%)	12 (3.0%)	135 (4.9%)	177 (6.4%)
HR (95% CI)	NA		0.50 (0.31-0.81)		0.26 (0.07-0.92)		0.75 (0.60-0.94)	

*NA= not applicable. A study result was designed NA when the outcome in the study did not closely match the outcome in the present meta-analysis.

SUPPLEMENTAL MATERIAL

Search strategies	2
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Supplementary Methods:

Search Strategy

Search terms included:

“colchicine” [all fields] OR “colchicine” [MeSH terms]
“coronary artery disease” [all fields] OR “coronary artery disease” [MeSH terms] OR “CAD” [all fields] or “Percutaneous coronary intervention” [all fields] OR “Percutaneous coronary intervention” [MeSH] or “PCI” [all fields] OR “acute coronary syndrome” [MeSH terms] OR “acute coronary syndrome” [all fields] or “ACS” [all fields] or “myocardial infarction” [MeSH terms] or “MI” [all fields]
“clinical trial” [MeSH] or “randomized controlled trial” [MeSH] or “randomized controlled trial” [all fields]
“human” [MeSH] NOT “animal” [MeSH]



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	ND
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 & supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



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METHODS			
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplemental Table S2. Cochrane Collaboration Risk-of-Bias Tool

Study details

Reference

Ref 10 – Tardif JC et al. *N Engl J Med* 2019
 Ref 12 – Nidorf SM et al. *N Engl J Med* 2020
 Ref 11 – Nidorf SM et al. *J Am Coll Cardiol* 2013
 Ref 13 – Tong DC et al. *Circulation*. 2020

Study design

- ☒ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias

Composite: Cardiovascular mortality, myocardial infarction, ischemic stroke, urgent coronary revascularization

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

HR, 0.68; 95% CI, 0.54-0.81; $I^2=37.70\%$

Is the review team's aim for this result...?

- ☒ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ☒ Journal article(s) with results of the trial
- ☒ Trial protocol
- ☒ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

- ☐ “Grey literature” (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCo2
1.1 Was the allocation sequence random?	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	Y	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N
Risk-of-bias judgement	Low	Low	Low	Low
Optional: What is the predicted direction of bias arising from the randomization process?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCo2
2.1. Were participants aware of their assigned intervention during the trial?	Y	N	N	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	N	N	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Y	Y	Y	Y
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	PN	PN	PN	PN
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	PN	PN	PN	PN
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?				
Risk-of-bias judgement	Some concern	Low	Low	Low

Optional: What is the predicted direction of bias due to deviations from intended interventions?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable
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Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCo2
2.1. Were participants aware of their assigned intervention during the trial?	Y	N	N	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	N	N	N
2.3. <u>If Y/PY/NI to 2.1 or 2.2:</u> Were important co-interventions balanced across intervention groups?	Y			
2.4. Could failures in implementing the intervention have affected the outcome?	Y	Y	Y	Y
2.5. Did study participants adhere to the assigned intervention regimen?	Y	Y	Y	Y
2.6. <u>If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4:</u> Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	Y	Y	Y
Risk-of-bias judgement	Some concern	Low	Low	Low

Optional: What is the predicted direction of bias due to deviations from intended interventions?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable
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Domain 3: Missing outcome data

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCO2
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?				
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?				
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?				
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?				
Risk-of-bias judgement	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to missing outcome data?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCo2
4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	N	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	N	N	N	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?				
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?				
Risk-of-bias judgement	Low	Low	Low	Low
Optional: What is the predicted direction of bias in measurement of the outcome?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signaling questions	LoDoCo	COLCOT	COPS	LoDoCo2
5.1 Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ?	Y	Y	Y	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...				
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	N
5.3 ... multiple analyses of the data?	N	PN	N	N
Risk-of-bias judgement	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to selection of the reported result?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable

Overall risk of bias

	LoDoCo	COLCOT	COPS	LoDoCo2
Risk-of-bias judgement	Some concern	Low	Low	Low
Optional: What is the predicted direction of bias due to selection of the reported result?	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable	Favors experimental / Favors comparator / Toward null /Away from null / Unpredictable