



Low-Dose Colchicine in Coronary Artery Disease — Systematic Review and Meta-Analysis —

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Background: Recent studies have revealed the benefits of using colchicine, a drug with anti-inflammatory properties, in coronary artery disease (CAD). This study systematically reviewed the benefits and risks of low-dose colchicine in patients with CAD.

Methods and Results: We searched for randomized controlled trials (RCTs) in MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases (March 2020). Efficacy and safety outcomes were evaluated. Estimates are expressed as risk ratios (RRs) and 95% confidence intervals (95% CIs). Heterogeneity was assessed with I^2 test. Confidence in the pooled evidence was appraised using the GRADE framework. Colchicine reduced the rate of major adverse cardiovascular events (RR 0.65; 95% CI 0.49–0.86; 6 RCTs; $I^2=50%$; 11,718 patients; GRADE, moderate confidence), acute coronary syndrome (RR 0.64; 95% CI 0.46–0.90; $I^2=47%$; 7 RCTs; 11,955 patients; GRADE, very low confidence), stroke (RR 0.49; 95% CI 0.30–0.78; $I^2=0%$; 6 RCTs; 11,896 patients; GRADE, moderate confidence), and cardiovascular interventions (RR 0.61; 95% CI 0.42–0.89; $I^2=40%$; 4 RCTs; 11,284 patients; GRADE, high confidence). Colchicine did not increase the risk of adverse events, except for gastrointestinal events (RR 1.54; 95% CI 1.11–2.13; $I^2=72%$; 9 RCTs; 12,374 patients; GRADE, very low confidence).

Conclusions: Low-dose colchicine in patients with CAD is associated with beneficial effects on prognosis, although an increased risk of gastrointestinal events was confirmed.

Key Words: Atherosclerosis; Colchicine; Coronary artery disease; Inflammation

Cardiovascular diseases are a major cause of morbidity and mortality worldwide.¹ An important share of the burden of cardiovascular diseases relates to atherosclerosis, which is a process that involves inflammatory cells. Inflammation can accelerate and trigger complications of the atherosclerotic process.² Therefore, it is not unexpected that old drugs targeting inflammation, such as colchicine, could be investigated for this cardiovascular indication.

Colchicine has anti-inflammatory properties³ and is widely used in the treatment of acute gout, as well as in Behçet's disease, pericarditis, primary biliary cirrhosis, and familial Mediterranean fever.⁴ Orally administered colchicine has an estimated bioavailability of 44%, reaches peak plasma concentration in 1 h, and has a predominantly hepatic elimination.⁵ While in the circulation, colchicine concen-

trates in leukocytes, where it interferes with the kinetics of the cytoskeletal microtubules by inhibiting mitosis, and so inhibiting leukocyte motility, impairing inflammation mediated by these cells.

Results regarding the benefits of low-dose colchicine in patients with coronary artery disease (CAD) are contentious.³ Therefore, the aim of this study was to systematically review randomized controlled trials (RCTs) evaluating the prognostic effects of low-dose colchicine in patients with CAD.

Methods

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁶ and was registered in PROSPERO

Received May 24, 2021; accepted May 25, 2021; J-STAGE Advance Publication released online July 15, 2021 Time for primary review: 1 day

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ISSN-2434-0790



Table 1. Summary of the Main Characteristics of the Included Studies

Reference	Location	Condition	Main endpoint	Total no. participants (no. colchicine, control groups)	Mean age (years)	No. (%) women	Mean BMI (kg/m ²)	Smokers	Hyper-tension
O'Keefe et al ⁹	US	CAD	Angiographic restenosis	197 (colchicine 130, placebo 67)	Colchicine 59.0, placebo 62.0	Colchicine 19 (14.6), placebo 9 (13.4)	NA	NA	NA
Raju et al ¹⁰	Australia	ACS or AIS	Δhs-CRP	80 (colchicine 40 ^A , placebo 40 ^B)	Colchicine 57.2, placebo 57.2	Colchicine 6 (15.0), placebo 3 (0.8)	NA	Colchicine 31 (77.5), placebo 32 (80.0)	Colchicine 19 (47.5), placebo 15 (37.5)
Deffereos et al ⁹	NA	CAD	Angio-ISR and IVUS-ISR	222 (colchicine 112, placebo 110)	Colchicine 63.7, placebo 63.5	Colchicine 37 (37.0), placebo 31 (32.3)	Colchicine 27.4, placebo 27.5	Colchicine 36 (36.0), placebo 38 (40.0)	Colchicine 48 (48), placebo 47 (49.0)
Nidorf et al ¹¹	Australia	CAD	Composite incidence of ACS, out-of-hospital cardiac arrest, non-cardioembolic ischemic stroke	532 (colchicine 282, placebo 250)	Colchicine 66.0, placebo 67.0	Colchicine 31 (11.0), placebo 28 (11.2)	NA	Colchicine 10 (4.0), placebo 14 (6.0)	NA
Akodad et al ¹²	France	ACS	CRP peak value during hospitalization	44 (colchicine 23, placebo 21)	Colchicine 60.1, placebo 59.7	Colchicine 4 (17.4), placebo 5 (23.8)	NA	Colchicine 17 (73.9), placebo 14 (66.7)	Colchicine 9 (39.1), placebo 10 (47.6)
Hennessy ¹³	Australia	ACS	Residual hs-CRP ≥2mg/L	237 (colchicine 119, placebo 118)	Colchicine 61.0, placebo 61.0	Colchicine 30 (25.2), placebo 25 (21.2)	Colchicine 28.0, placebo 28.0	Colchicine 77 (65.0), placebo 67 (57.0)	Colchicine 64 (54.0), placebo 48 (41.0)
Tardif et al ¹⁴	Canada (multinational)	ACS	Composite of death from CV causes, resuscitated cardiac arrest, ACS, stroke, or urgent hospitalization for angina leading to coronary revascularization	4,745 (colchicine 2,366, placebo 2,379)	Colchicine 60.6, placebo 60.5	Colchicine 472 (19.9), placebo 437 (18.4)	Colchicine 28.2, placebo 28.4	Colchicine 708 (29.9), placebo 708 (29.8)	Colchicine 1,185 (50.1), placebo 1,236 (52.0)
Nidorf et al ¹⁵	Australia and Netherlands	CAD	Composite of CV death, ACS, ischemic stroke, or ischemia-driven coronary revascularization	5,522 (colchicine 2,762, placebo 2,760)	Colchicine 65.8, placebo 65.9	Colchicine 457 (16.5), placebo 389 (14.1)	NA	Colchicine 318 (11.5), placebo 330 (12.0)	Colchicine 1,421 (51.4), placebo 1,387 (50.3)
Tong et al ¹⁶	Australia	CAD	Composite of all-cause mortality, ACS, ischemia-driven urgent revascularization, and non-cardioembolic ischemic stroke	795 (colchicine 396, placebo 399)	Colchicine 59.7, placebo 60.0	Colchicine 74 (18.7), placebo 89 (22.3)	NA	Colchicine 128 (32), placebo 149 (37)	Colchicine 201 (51), placebo 199 (50)

Unless indicated otherwise, data show the number of patients with percentages in parentheses. ^A35 patients with ACS and 5 patients with AIS. ^B38 patients with ACS and 2 patients with AIS. ACS, acute coronary syndrome; AIS, acute ischemic stroke; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, C-reactive protein; CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein; ISR, in-stent restenosis; IVUS, intravascular ultrasound; NA, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

(Table 1 continued the next page.)

(Reference CRD42020178878).

Search Methods

We first searched for relevant material in March 2020 in the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Web of Science Core Collection, SciELO Citation Index, Korean Journal Database, and the Russian Science Citation Index databases. The search was updated in January 2021.

The search methods used are summarized in **Supplementary**

Data 1. In addition, we analyzed the references presented in the included studies and review articles to extract significant data.

Study Selection Criteria and Outcomes

We selected all available RCTs whose patients presented with CAD, including acute coronary syndrome (ACS) or myocardial infarction (MI) and chronic coronary syndrome or stable coronary disease, regardless of the presence of other comorbidities (including other atherosclerotic

Reference	Diabetes	Hyperlipidemia	History of angina or MI	History of PCI	History of CABG	History of heart failure	History of stroke or TIA	Colchicine intervention	Control	Follow-up (months)
O'Keefe et al ⁹	Colchicine 16 (12.0), placebo 8 (12.0)	NA	Colchicine 52 (40.0), placebo 26 (39.0)	NA	Colchicine 34 (26.0), placebo 17 (25.0)	NA	NA	0.6mg, b.i.d.	Placebo	6
Raju et al ¹⁰	Colchicine 7 (17.5), placebo 6 (15.0)	Colchicine 19 (47.5), placebo 19 (47.5)	Colchicine 8 (20.0), placebo 6 (15.0)	NA	NA	Colchicine 1 (2.5), placebo 0 (0.0)	Colchicine 3 (7.5), placebo 0 (0)	1 mg/day	Placebo	1
Deftereos et al ³	Colchicine 100 (100), placebo 96 (100)	NA	NA	NA	NA	NA	NA	0.5mg, b.i.d.	Placebo	6
Nidorf et al ¹¹	Colchicine 92 (33.0), placebo 69 (28.0)	NA	Colchicine 64 (23.0), placebo 61 (24.0)	Colchicine 169 (60.0), placebo 138 (55.0)	Colchicine 62 (22.0), placebo 39 (16.0)	NA	NA	0.5mg/day	No colchicine	36
Akodad et al ¹²	Colchicine 3 (13.0), placebo 3 (14.3)	Colchicine 8 (34.8), placebo 8 (38.1)	NA	Colchicine 1 (4.3), placebo 1 (4.8)	Colchicine 0 (0.0), placebo 1 (4.8)	NA	NA	1 mg/day	No colchicine	1
Hennessy ¹³	Colchicine 27 (23.0), placebo 25 (21.0)	NA	Colchicine 18 (15.0), placebo 18 (15.0)	Colchicine 13 (11.0), placebo 14 (12.0)	NA	NA	0.5mg/day	Placebo	Placebo	1
Tardif et al ¹⁴	Colchicine 462 (19.5), placebo 497 (20.9)	NA	Colchicine 370 (15.6), placebo 397 (16.7)	Colchicine 392 (16.6), placebo 406 (17.1)	Colchicine 69 (2.9), placebo 81 (3.4)	Colchicine 48 (2.0), placebo 42 (1.8)	Colchicine 55 (2.3), placebo 67 (2.8)	0.5mg/day	Placebo	22.6
Nidorf et al ¹⁵	Colchicine 632 (22.9), placebo 662 (24.0)	NA	Colchicine 2,323 (84.1), placebo 2,335 (84.6)	Colchicine 2,100 (76.0), placebo 2,077 (75.3)	Colchicine 319 (11.5), placebo 391 (14.2)	NA	NA	0.5mg/day	Placebo	28.6
Tong et al ¹⁶	Colchicine 75 (19.0), placebo 76 (19.0)	Colchicine 180 (46.0), placebo 185 (46.0)	Colchicine 59 (15.0), placebo 59 (15.0)	Colchicine 51 (13.0), placebo 50 (13.0)	Colchicine 15 (4.0), placebo 19 (5.0)	NA	Colchicine 5 (1.0), placebo 11 (3.0)	0.5mg, b.i.d. for 1 month, then 0.5 mg/day for 11 months	Placebo	12

or ischemic events). These studies had to include a low-dose colchicine (≤ 1.5 mg/day) arm and a control group (placebo, standard treatment, or other alternative treatment). We did not exclude studies with cointerventions if they were administered to both groups of the study. In randomized cross-over trials, only the first stage was considered. We defined a minimum follow-up period of 1 month. To broadly evaluate the clinical impact of colchicine, we considered cardiovascular mortality and major adverse cardiovascular events (MACE) as the primary outcomes. Different definitions of MACE were considered. Secondary outcomes were MI, stroke, heart failure, hospitalization (all causes), cardiovascular interventions (e.g., urgent revascularization), and adverse events, namely gas-

trointestinal adverse events.

Data Extraction

The titles and abstracts yielded by the searches against the inclusion criteria were first screened by 2 independent reviewers (A.M.A., B.N.-G.). In the second stage, the reviewers read the full-text reports and determined whether the studies met the inclusion criteria. The reasons for the exclusion of articles were recorded at both screening stages. Disagreements were resolved by consensus or with the help of a third reviewer (D.C.). Regarding the same study, the most recent data were considered.

The reviewers (A.M.A., B.N.-G.) then extracted data from the individual studies identified for inclusion into a

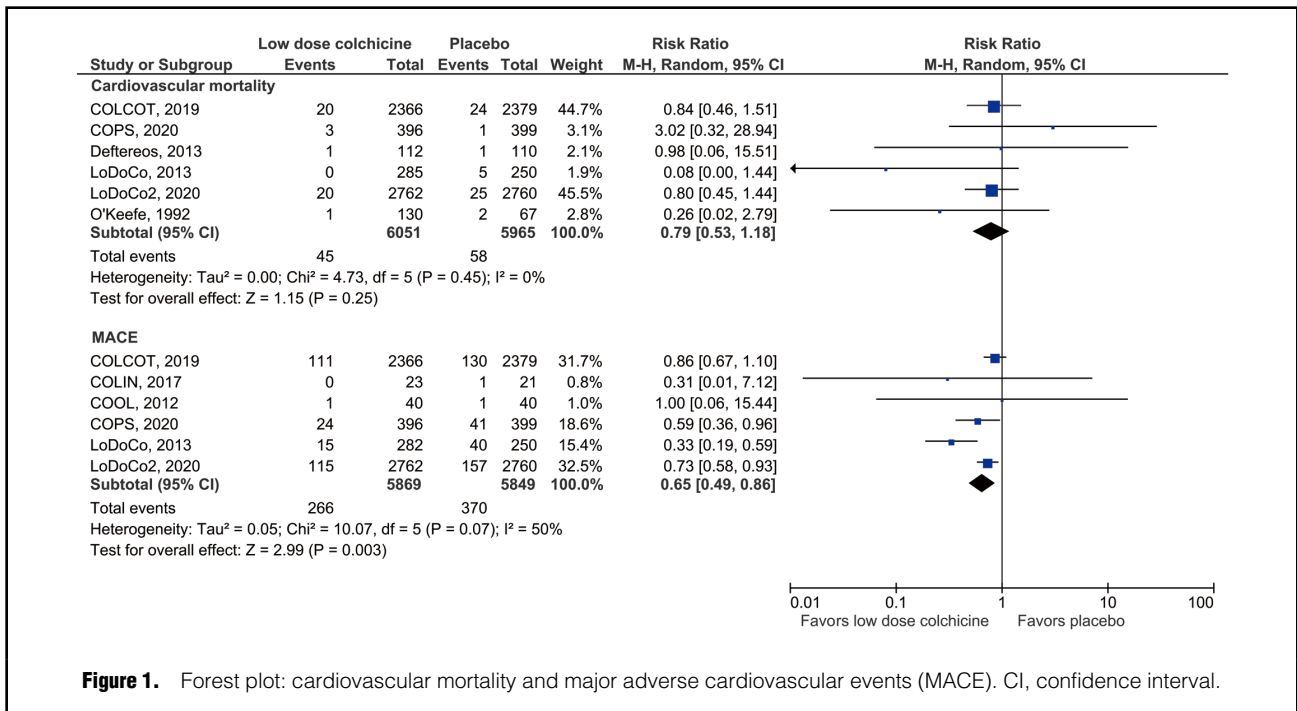


Figure 1. Forest plot: cardiovascular mortality and major adverse cardiovascular events (MACE). CI, confidence interval.

pre-piloted form that included information about the description of the intervention and controls, population characteristics, outcome measurements, statistical data, and results.

Data Evaluation, Synthesis, and Analysis

The risk of bias in the included studies was assessed using Cochrane risk of bias tool.⁷ This tool evaluates random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data. The criteria were applied by 2 independent reviewers (A.M.A., B.N.-G.) and disagreements were resolved by consensus or with the help of another 2 reviewers (M.A., D.C.).

A meta-analysis of the data retrieved from the included studies was conducted using RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2014; <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download>).

Statistical heterogeneity was used to define the method of analysis. Heterogeneity was determined through I² statistics and deemed to be substantial if greater than 50%. This index reflects the percentage of total variation among studies that is due to heterogeneity rather than random. The DerSimonian and Laird random effects model was used. Publication bias was assessed through examinations of funnel plots if more than 10 studies were included.

Assessment of Confidence in the Cumulative Evidence

The evaluation of primary outcomes was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework regarding the risk of bias, imprecision, inconsistency, indirectness, and publication bias.⁸ The pooled evidence was then classified as having very low, low, moderate, or high confidence.

Results

Included Studies

The search yielded 314 articles. From those, 194 were excluded after screening the titles and abstracts. From the remaining 118 articles subjected to full-text assessment, 9 met the inclusion criteria.^{3,9-16} The reasons for exclusion are detailed in **Supplementary Data 2**.

From the 9 RCTs included in this study (**Table 1**), 4 involved patients with ACS or MI^{10,12-14} and 5 included patients with chronic coronary syndrome or stable coronary disease.^{3,9,11,15,16} One study enrolled patients with acute ischemic stroke in addition to patients with ACS.¹⁰

The eligible studies included 12,374 patients, 5,894 with ACS, 6,473 with chronic coronary syndrome, and 7 with acute ischemic stroke. The median age of the participants ranged between 57.2 and 67.0 years. All eligible studies enrolled a total of 1,130 (9.1%) women in the colchicine group and 1,016 (8.2%) in the placebo/no colchicine group. In all studies, patients were followed-up for a median period of 12.7 months. Seven studies compared colchicine treatment with placebo^{3,9,10,13-16} and 2 studies compared colchicine with standard treatment alone.^{11,12} A summary of the main characteristics of the studies, including cardiovascular risk factors, is presented in **Table 1**.

Risk of Bias

Regarding the risk of bias, the Colchicine Cardiovascular Outcomes Trial (COLCOT),¹⁴ Colchicine in Patients with Acute Coronary Syndrome (COPS),¹⁶ and Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease 2 (LoDoCo2)¹⁵ trials were classified as having a low risk of bias in all domains, whereas the LoDoCo-MI¹³ trial and the trial by O'Keefe et al⁹ revealed some concerns, especially due to a lack of information about the randomization and blinding process. Four trials exhibited a high

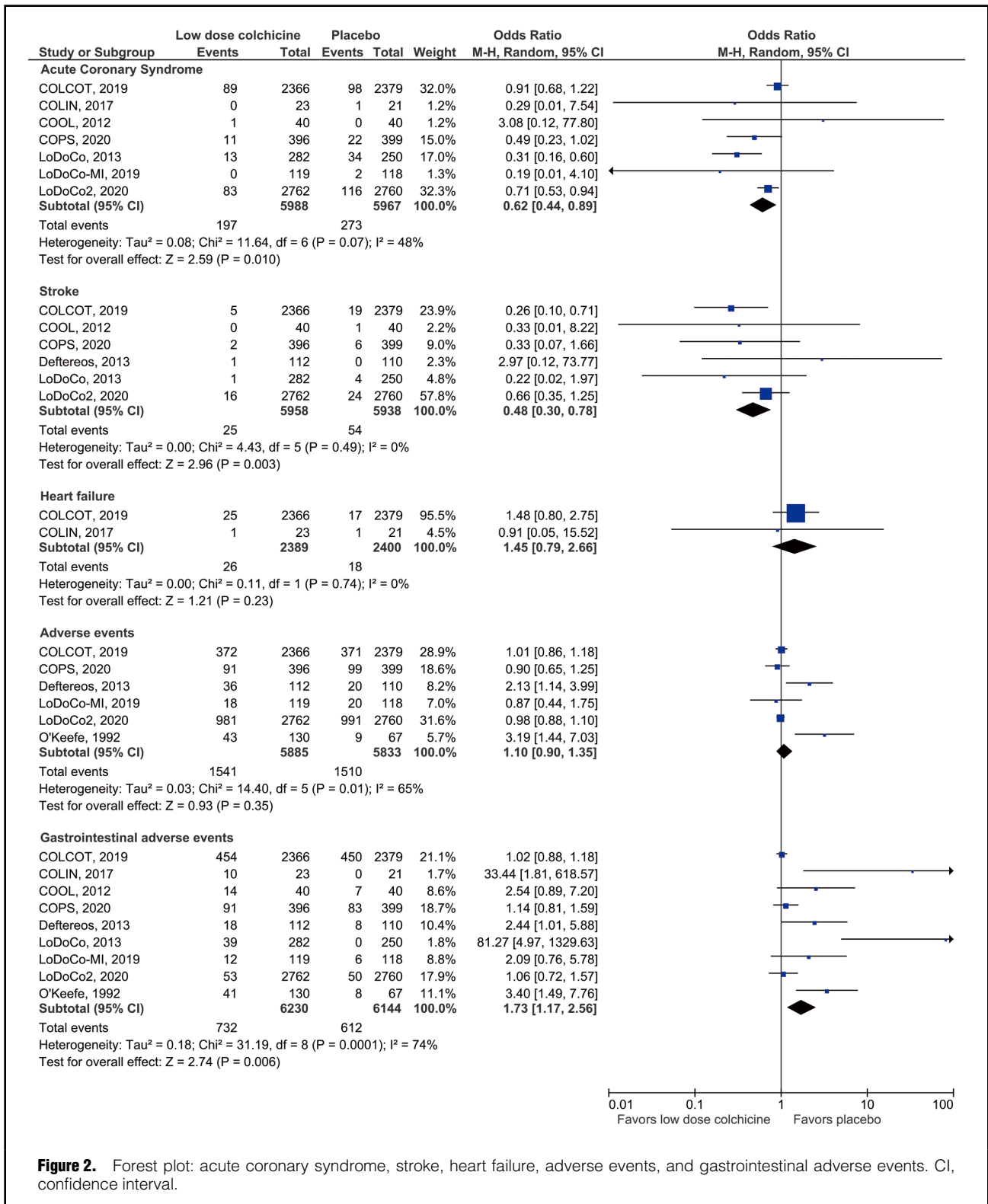


Figure 2. Forest plot: acute coronary syndrome, stroke, heart failure, adverse events, and gastrointestinal adverse events. CI, confidence interval.

overall risk of bias.^{3,10–12} Detailed information about the risk of bias is provided in **Supplementary Data 3**.

Primary Outcomes: Cardiovascular Mortality and MACE

Pooled data (**Figure 1**) showed no difference in cardiovas-

cular mortality (risk ratio [RR] 0.79; 95% confidence interval [CI] 0.53–1.18; 6 RCTs; I²=0%; 12,016 patients), but low-dose colchicine was associated with a significant risk reduction in MACE (RR 0.65; 95% CI 0.49–0.86; 6 RCTs; I²=50%; 11,718 patients).

Table 2. Summary of Findings Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach							
Outcome	No. participants (studies)	RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
			Without colchicine (%)	With colchicine (%)	Difference ^A (%)		
CV mortality	12,016 (6 RCTs)	0.79 (0.53, 1.18)	1.0	0.8 (0.5, 1.1)	-0.2 (-0.5, 0.2)	⊕⊕⊕○Moderate ^B	Colchicine likely reduces CV mortality slightly
MACE	111,718 (6 RCTs)	0.65 (0.49, 0.86)	6.3	4.1 (3.1, 5.4)	-2.2 (-3.2, -0.9)	⊕⊕⊕○Moderate ^C	Colchicine likely reduces MACE
ACS	11,955 (7 RCTs)	0.64 (0.46, 0.90)	4.6	2.9 (2.1, 4.1)	-1.6 (-2.5, -0.5)	⊕○○○Very low ^{C,D}	Colchicine may reduce ACS, but the evidence is very uncertain
Stroke	11,896 (6 RCTs)	0.49 (0.30, 0.78)	0.9	0.4 (0.3, 0.7)	-0.5 (-0.6, -0.2)	⊕⊕⊕○Moderate ^E	Colchicine likely results in a reduction in stroke
Heart failure	4,789 (2 RCTs)	1.44 (0.79, 2.63)	0.8	1.1 (0.6, 2)	0.3 (-0.2, 1.2)	⊕○○○Very low ^{B,F,G}	Colchicine may have little to no effect on heart failure, but the evidence is very uncertain
Hospitalizations	11,299 (4 RCTs)	0.76 (0.53, 1.10)	5.9	4.4 (3.1, 6.4)	-1.4 (-2.8, 0.6)	⊕○○○Very low ^{B,C}	Colchicine may reduce or have little to no effect on hospitalizations, but the evidence is very uncertain
CV interventions	11,284 (4 RCTs)	0.61 (0.42, 0.89)	4.3	2.6 (1.8, 3.8)	-1.7 (-2.5, -0.5)	⊕⊕⊕⊕High	Colchicine results in large reductions in CV interventions
AEs	11,718 (6 RCTs)	1.07 (0.92, 1.25)	25.9	27.7 (23.8, 32.4)	1.8 (-2.1, 6.5)	⊕○○○Very low ^{B,C,H}	Colchicine may increase or have little to no effect on AEs, but the evidence is very uncertain
GI events	12,374 (9 RCTs)	1.54 (1.11, 2.13)	10.0	15.3 (11.1, 21.2)	5.4 (1.1, 11.3)	⊕○○○Very low ^{C,I}	Colchicine may increase or have little to no effect on GI events, but the evidence is very uncertain

^ANegative values indicate fewer events, positive values indicate more events. ^BThe relative effect has a 95% confidence interval (CI) that includes 1, which is not statistically significant. ^CThis outcome has significant heterogeneity ($I^2 \geq 50\%$) or a Chi-squared test with $P < 0.10$. ^DThe risk of bias assessment of the studies that report acute coronary syndrome (ACS) includes 3 studies with high risk and 1 with moderate risk (some concerns). ^EThe risk of bias assessment of the studies that report stroke events includes 3 studies with high risk and 3 with low risk. ^FThe risk of bias assessment of the studies that report heart failure events includes 1 study with high risk and 1 with low risk. ^GOnly 2 studies were available for this outcome. ^HThe risk of bias assessment of the studies that report adverse effects includes 2 studies with high risk, 2 with moderate risk (some concerns), and 3 with low risk. ^IThe risk of bias assessment of the studies that report gastrointestinal (GI) events includes 4 studies with high risk and 2 with moderate risk (some concerns). The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Certainty graded from very low (⊕○○○) to high (⊕⊕⊕⊕). AEs, adverse events; CV, cardiovascular; MACE, major adverse cardiac events; RCTs, randomized controlled trials; RR, risk ratio.

Secondary Outcomes

Colchicine administration was associated with a 36% risk reduction in ACS (RR 0.64; 95% CI 0.46–0.90; $I^2=47\%$; 7 RCTs; 11,955 patients) and a 51% risk reduction in stroke events (RR 0.49; 95% CI 0.30–0.78; $I^2=0\%$; 6 RCTs; 11,896 patients; **Figure 2**). The LoDoCo2¹⁵ and COLCOT¹⁴ trials were the major contributors to these outcomes.

Heart failure events (RR 1.44; 95% CI 0.79–2.63; $I^2=0\%$; 2 RCTs; 4,789 patients; **Figure 2**) and hospitalizations (RR 0.76; 95% CI 0.53–1.10; $I^2=52\%$; 4 RCTs; 11,299 patients) did not differ among the groups (**Supplementary Data 4**).

Urgent coronary revascularizations were also significantly reduced by colchicine administration (RR 0.61; 95% CI 0.42–0.89; $I^2=40\%$; 4 RCTs; 11,284 patients; **Supplementary Data 4**).

Overall adverse events (RR 1.07; 95% CI 0.92–1.25; $I^2=62\%$; 6 RCTs; 11,718 patients) did not differ between the 2 arms, but colchicine significantly increased gastrointestinal events (RR 1.54; 95% CI 1.11–2.13; $I^2=72\%$; 9 RCTs; 12,374 patients; **Figure 2**).

Subgroup Analysis

Subgroup analysis with different follow-up periods was

performed (**Supplementary Data 5**). There were no differences in the main outcomes between the 2 groups. There was a significant difference in the rate of hospitalization with a shorter follow-up period, but only 1 study was included in this subgroup analysis. The rate of gastrointestinal adverse events also differed between subgroups: studies with a longer follow-up period had a lower RR than those with a shorter follow-up period, but heterogeneity was high ($I^2=71\%$).

Assessment of Confidence in the Cumulative Evidence

Table 2 presents a summary of the findings regarding the certainty of the evidence (GRADE). Although most outcomes exhibited very low certainty, cardiovascular mortality, MACE, and stroke outcomes were of moderate certainty and cardiovascular intervention outcomes had high certainty.

Discussion

This systematic review showed that low-dose colchicine in patients with CAD is associated with a 35% risk reduction of MACE, a 36% risk reduction of ACS, a 51% risk reduc-

tion of stroke, and a 39% risk reduction of cardiovascular interventions. However, there was no significant risk reduction in cardiovascular mortality, heart failure events, or hospitalizations. As expected, the risk of gastrointestinal events was increased with colchicine, but overall adverse events were not different among the groups.

Colchicine has a well-documented therapeutic use in inflammatory conditions, and so a potential benefit of colchicine in patients with coronary and cerebrovascular disease has been previously hypothesized. Colchicine is a classical antimitotic drug, the primary mechanism of action of which is tubulin disruption. This leads to down-regulation of multiple inflammatory pathways and modulates innate immunity. Newly described mechanisms of action of colchicine include blocking the activity of the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome, with suppression of interleukin (IL)-1 β and IL-18 release.^{17,18} NLR3 inflammasomes are activated by cholesterol crystals that form early in disease, leading to the secretion of active proinflammatory Type 1 cytokines IL-1 β and IL-18. Both IL-1 β and IL-18 have been associated with plaque formation, progression, and rupture.¹⁸ In fact, blockade of the IL-1 β pathway was recently shown in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) study to effectively reduce cardiovascular events.¹⁹ That randomized double blind placebo-controlled trial included more than 10,000 patients with a history of MI and a persistent proinflammatory response, defined as a high-sensitivity C-reactive protein concentration of ≥ 2 mg/L, and showed that treatment with canakinumab, a monoclonal antibody targeting IL-1 β , led to a 15% lower risk of cardiovascular events, independent of decreases in lipid levels.¹⁹

One of the major findings of the present study was an important reduction in the risk of stroke with colchicine use. One possible reason for this is related to the possible prevention of atrial fibrillation and the consequent reduction in cardioembolic stroke, as observed in studies using colchicine in patients undergoing cardiac surgery.²⁰ Despite the fact that we could not discriminate between stroke subtypes using the available data, it seems reasonable to assume that the reduction in stroke risk may include not only cardioembolic stroke, but also atherosclerotic stroke.

The putative benefits of colchicine have been not only in RCTs, but also in earlier observational studies enrolling patients with gout, which indicated that colchicine use was associated with a reduced risk of cardiovascular events.²¹

Together, both RCTs (pooled in our systematic review) and observational data support a beneficial effect of colchicine use in patients with CAD. Furthermore this seems to be a cost-effective intervention in patients who experience an ACS.²²

In clinical practice, gastrointestinal adverse events are expected to occur with the use of colchicine, mainly diarrhea, nausea, and vomiting, all of which are generally mild in severity.

Study Limitations

There are some study limitations to consider regarding the results and conclusions of the analysis. All trials have their own limitations, and pooling them together using their meta-data limits the robustness of data interpretation. Across studies, because of the allowed broad spectrum of cardiovascular diseases, the baseline conditions could differ. In addition, a study was included in which there was a

negligible proportion of patients with acute ischemic stroke,¹⁰ although we are confident that this did not interfere with the main results. Most studies enrolled a modest number of participants, and some of the outcomes were only reported by few studies, making it difficult to identify clinical differences for each outcome. In addition, women constituted a minor proportion of the population included, probably due to a higher percentage of CAD in men. However, this unequal sex representation limits data extrapolation to women.

Another study limitation concerns the different definitions used for MACE, heart failure, and hospitalizations, which could limit the interpretation of the results and possible assumptions (**Supplementary Data 6**).

Conclusions

The use of low-dose colchicine in patients with CAD seems to be associated with a significant risk reduction in MACE, ACS, stroke, and cardiovascular interventions. However, there is an increased risk of gastrointestinal events, which should be expected in treated patients.

Authors Contributions

A.M.A. and D.C. created the concept and wrote the first draft of the manuscript. A.M.A., B.N.-G. and D.C. were responsible for data acquisition and extraction. All the authors contributed to data analysis, interpretation, draft revision and approved the final version of the submitted manuscript. D.C. is the guarantor.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

M.A. has participated in conferences with Boehringer-Ingelheim, AstraZeneca, Bayer, Bristol Myers Squibb Grünenthal, Tecmede, and Merck Sharp & Dohme. D.B. reports personal fees from lectures or participation in advisory boards from Amgen, AstraZeneca, Boehringer-Ingelheim, Novartis, Pfizer, Roche Diagnostics, Servier and Vifor Pharma, all outside the submitted work. F.J.P. has received consultant and speaker fees from AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, and Daiichi Sankyo. D.C. has participated in educational meetings and/or attended conferences or symposia (including travel, accommodation) with Daiichi Sankyo, Menarini, Merck Serono and Roche in the past 3 years.

IRB Information

This study was granted an exemption from requiring ethics approval from an ethics committee because the study was a systematic review with meta-analysis.

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circrep.CR-21-0065>