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Systematic Review

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Events in Coronary Artery Disease: A Systematic Review of Randomized Controlled Trials

Isral Masri[1], Indah Fitriani[2]

1 Department of Cardiology and Vascular Medicine, Dr. Drs. M. Hatta Brain Hospital Bukittinggi, Indonesia

2 Faculty of Medicine, Universitas Prima Nusantara Bukittinggi, Indonesia

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Corresponding Author

Name: Isral Masri

E-mail: isralmasri@gmail.com

ABSTRACT

Background: Patients with coronary artery disease remain at risk of recurrent cardiovascular events despite standard therapy. Low-dose colchicine, an anti-inflammatory drug, has been tested in large randomized controlled trials (RCTs). This systematic review summarizes its efficacy and safety for secondary prevention.

Methods: Placebo-controlled RCTs of low-dose colchicine in adults with coronary artery disease or recent myocardial infarction, reporting a composite of major cardiovascular events, were eligible. Data were extracted and synthesized without meta-analysis following the SWiM reporting guideline, with qualitative risk-of-bias appraisal using RoB 2 domains.

Findings: Three RCTs (COLCOT, LoDoCo2, CLEAR; 17,329 randomized participants) were included. Colchicine 0.5 mg reduced the primary composite outcome in COLCOT (HR 0.77, 95% CI 0.61–0.96) and LoDoCo2 (HR 0.69, 95% CI 0.57–0.83), but not in CLEAR (HR 0.99, 95% CI 0.85–1.16). Diarrhea was more frequent with colchicine in CLEAR (10.2% vs 6.6%), serious pneumonia was more frequent in COLCOT (0.9% vs 0.4%), and non-cardiovascular death was numerically higher in LoDoCo2 (HR 1.51, 95% CI 0.99–2.31).

Conclusion: Evidence for colchicine in secondary prevention is inconsistent: two trials showed benefit and the largest trial showed none. Routine use cannot be supported on this evidence alone.

INTRODUCTION

Patients with coronary artery disease remain at risk of recurrent myocardial infarction, stroke, and cardiovascular death even when treated with standard secondary prevention. Inflammation has been proposed as an additional therapeutic target, and colchicine, a low-cost anti-inflammatory drug, has been evaluated for this purpose.

Three large placebo-controlled randomized controlled trials (RCTs) have

examined low-dose colchicine: COLCOT in patients after recent myocardial infarction [1], LoDoCo2 in patients with chronic coronary disease [2], and CLEAR in patients after myocardial infarction [3]. The trials enrolled different populations, started treatment at different times, followed patients for different periods, and used composite primary outcomes that were not identical.

Their results have not been uniform: two trials reported a lower rate of the primary outcome with colchicine, whereas the largest trial reported no difference. This makes the overall evidence difficult to interpret, and reading each abstract in isolation may give an incomplete or misleading impression.

This systematic review aims to summarize the efficacy and safety of low-dose colchicine versus placebo for secondary prevention of cardiovascular events in adults with coronary artery disease, and to describe the possible reasons why the trial results differ.

METHODS

1. Design

This systematic review of RCTs was planned using the PICO framework. No protocol was prospectively registered. Results were synthesized without meta-analysis, following the principles of the SWiM reporting guideline [4].

2. Eligibility Criteria

Eligibility criteria are summarized in Table 1. RCTs published in peer-reviewed journals were eligible. Trials were grouped by clinical setting: recent myocardial infarction (COLCOT and CLEAR) and chronic coronary disease (LoDoCo2).

Table 1. Eligibility Criteria (PICO)

Element	Criterion
Population	Adults with coronary artery disease or recent myocardial infarction
Intervention	Low-dose colchicine
Comparator	Placebo
Outcomes	Composite of major cardiovascular events; components; adverse events
Design	Placebo-controlled RCT in a peer-reviewed journal

3. Information Sources and Search

Peer-reviewed literature indexed in PubMed was searched in November 2026 through a web search interface, using the terms “colchicine,” “myocardial infarction,” “coronary disease,” and “randomized trial”. Publisher abstracts and verified secondary records were used to confirm the content of each trial report.

4. Study Selection

Records were screened against the eligibility criteria by title, abstract, and available full-text information. Selection was performed by a single reviewer.

5. Data Items

Sample size, population, timing of treatment, dose, follow-up, primary outcome definition and results (event rates and hazard ratios with 95% confidence intervals), components of the primary outcome, and adverse events were extracted.

6. Risk-of-Bias Appraisal

Risk of bias was appraised qualitatively using the domains of the RoB 2 tool [5] (randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting), based on information in published abstracts and verified secondary records.

7. Effect Measures

Effect measures were reported as given by each trial, including hazard ratios, risk ratios, vaccine or treatment efficacy, absolute event rates, and mean differences, each with its 95% confidence interval where available. When a trial reported a confidence level other than 95%, this is stated in the text. Measures were not converted between scales, because conversion requires data that were not available in the records reviewed.

8. Missing and Unreported Data

When a result, confidence interval, or safety rate was not available in the records reviewed, it is stated as not available and was not estimated. Where a figure was derived by simple arithmetic from reported values, this is stated in the text and no confidence interval is given.

9. Certainty of the Evidence

A formal certainty-of-evidence rating was not performed. Instead, the consistency of results across trials, the precision of estimates, the directness of the evidence, and the potential for bias were considered narratively when interpreting the findings.

10. Ethical Considerations

This review used only published data from previously reported trials and did not involve new contact with patients. Ethical approval was therefore not required, and the original trials reported their own ethical approvals and participant consent.

11. Synthesis

Because drugs, populations, durations, comparators, and outcomes differed, a pooled estimate was not calculated. Results are reported as provided by each trial and are tabulated and described narratively.

Results

1. Study Selection

The search identified three placebo-controlled RCTs that met the eligibility criteria [1–3], with 17,329 randomized participants in total. All three trials used colchicine 0.5 mg daily as the intervention.

2. Characteristics of Included Trials

COLCOT enrolled patients within 30 days after myocardial infarction and followed them for a median of 22.6 months [1]. LoDoCo2 enrolled patients with chronic coronary disease and followed them for a median of 28.6 months [2]. CLEAR was a 2×2 factorial trial that also randomized patients to spironolactone or placebo, and followed patients for about 3 years [3].

Table 2. Characteristics of Included Trials

Trial	Design and population
COLCOT [1]	4,745 patients within 30 days after myocardial infarction; colchicine 0.5 mg once daily (n = 2,366) vs placebo (n = 2,379); median follow-up 22.6 months
LoDoCo2 [2]	5,522 patients with chronic coronary disease; colchicine 0.5 mg once daily (n = 2,762) vs placebo (n = 2,760); median follow-up 28.6 months
CLEAR [3]	7,062 patients after myocardial infarction from 104 centers in 14 countries; colchicine (n = 3,528) vs placebo (n = 3,534); 2×2 factorial with spironolactone; median follow-up about 3 years

3. Primary Composite Outcome

3.1 COLCOT

In COLCOT, the primary composite outcome (cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to revascularization) occurred in 5.5% of patients with colchicine and 7.1% with placebo (HR 0.77, 95% CI 0.61–0.96; P = 0.02) [1].

3.2 LoDoCo2

In LoDoCo2, the primary composite (cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven revascularization) occurred in 187 patients (6.8%) with colchicine and 264 (9.6%) with placebo, corresponding to 2.5 and 3.6 events per 100 person-years (HR 0.69, 95% CI 0.57–0.83; P<0.001) [2].

3.3 CLEAR

In CLEAR, the primary outcome (cardiovascular death, recurrent myocardial infarction, stroke, or unplanned ischemia-driven revascularization) occurred in 322 patients (9.1%) with colchicine and 327 (9.3%) with placebo (HR 0.99, 95% CI 0.85–1.16; P = 0.93) [3].

Table 3. Primary Outcome by Trial

Trial	Colchicine vs placebo
COLCOT [1]	5.5% vs 7.1%; HR 0.77 (0.61–0.96)
LoDoCo2 [2]	6.8% vs 9.6%; HR 0.69 (0.57–0.83)

CLEAR [3]	9.1% vs 9.3%; HR 0.99 (0.85–1.16)

4. Components of the Primary Outcome

Component results were available in the records reviewed only for COLCOT. Cardiovascular death was not clearly reduced (HR 0.84, 95% CI 0.46–1.52), nor were resuscitated cardiac arrest (HR 0.83, 95% CI 0.25–2.73) or myocardial infarction (HR 0.91, 95% CI 0.68–1.21). Stroke (HR 0.26, 95% CI 0.10–0.70) and urgent hospitalization for angina leading to revascularization (HR 0.50, 95% CI 0.31–0.81) were lower with colchicine [1].

Table 4. Components of the COLCOT Primary Outcome

Component	Hazard ratio (95% CI)
Cardiovascular death	0.84 (0.46–1.52)
Resuscitated cardiac arrest	0.83 (0.25–2.73)
Myocardial infarction	0.91 (0.68–1.21)
Stroke	0.26 (0.10–0.70)
Urgent hospitalization for angina with revascularization	0.50 (0.31–0.81)

5. Safety and Tolerability

In COLCOT, diarrhea occurred in 9.7% with colchicine and 8.9% with placebo (P = 0.35), while serious pneumonia was more frequent with colchicine (0.9% vs 0.4%; P = 0.03) [1]. In LoDoCo2, non-cardiovascular death was numerically higher with colchicine (0.7 vs 0.5 per 100 person-years; HR 1.51, 95% CI 0.99–2.31), whereas hospitalization for pneumonia was 1.7% vs 2.0%, and 15% of screened participants were not randomized after the run-in phase because of side effects [2].

In CLEAR, diarrhea was more common with colchicine (10.2% vs 6.6%; P<0.001), whereas serious infections (2.5% vs 2.9%) and overall adverse events (31.9% vs 31.7%) were similar [3].

Table 5. Selected Safety Findings

Trial	Safety finding
COLCOT [1]	Diarrhea 9.7% vs 8.9%; serious pneumonia 0.9% vs 0.4%
LoDoCo2 [2]	Non-CV death HR 1.51 (0.99–2.31); 15% not randomized after run-in because of side effects
CLEAR [3]	Diarrhea 10.2% vs 6.6%; serious infections 2.5% vs 2.9%

6. Risk-of-Bias Appraisal

All three trials were randomized, placebo-controlled, multicenter studies with prespecified primary outcomes published in a peer-reviewed journal. No major concerns were evident from the information reviewed. LoDoCo2 used a run-in phase before randomization, which may select participants who tolerate colchicine. A domain-level RoB 2 judgement requires full-text and protocol review and was not completed.

Table 6. Qualitative Risk-of-Bias Summary

Trial	Appraisal
COLCOT [1]	Randomized, double-blind, placebo-controlled; no major concerns evident
LoDoCo2 [2]	Randomized, placebo-controlled; run-in phase before randomization
CLEAR [3]	Randomized, placebo-controlled; factorial design with spironolactone

DISCUSSIONS

1. Summary of Evidence

Among 17,329 patients, low-dose colchicine reduced the primary composite outcome in two trials (HR 0.77 and 0.69) [1][2] but had no effect in the largest trial (HR 0.99) [3]. The evidence is therefore inconsistent, and a single conclusion in favor of colchicine is not supported by the trials reviewed.

2. Contrasting Results

The contrast between LoDoCo2 and CLEAR is notable. LoDoCo2 reported a hazard ratio of 0.69 with narrow confidence intervals [2], whereas CLEAR, which was larger, reported 0.99 with confidence intervals that excluded large benefit [3]. Both cannot easily be explained by chance alone, and differences in design are likely to contribute.

3. Possible Explanations

The trials differed in population (recent myocardial infarction versus chronic coronary disease), timing of treatment initiation, primary outcome definitions, follow-up, and dosing schedule; in CLEAR, patients weighing 70 kg or more initially took 0.5 mg twice daily for the first 90 days until the protocol was changed to once daily for all [3]. CLEAR was also a factorial trial with a second randomized drug. The records reviewed do not allow the cause of the discrepancy to be identified.

4. Components and Selection of Outcomes

The apparent benefit in COLCOT came mainly from stroke (HR 0.26) and urgent hospitalization for angina leading to revascularization (HR 0.50), whereas cardiovascular death and myocardial infarction were not clearly reduced [1]. Because the stroke estimate has a wide confidence interval (0.10–0.70), it should be interpreted cautiously. Composite outcomes may be dominated by softer components such as revascularization.

5. Safety Signals

Diarrhea was more frequent with colchicine in CLEAR [3], serious pneumonia was more frequent in COLCOT [1], and a signal toward higher non-cardiovascular death was reported in LoDoCo2, although its confidence interval included 1.0 [2]. These signals were not consistent across the three trials, but they merit attention in any decision to use colchicine long term.

6. Tolerability and Run-In Design

In LoDoCo2, 15% of screened participants were not randomized after the run-in because of side effects [2]. This suggests that tolerability limits use in a proportion of patients and that trial participants may be more tolerant than the general population.

7. Implications for Practice

On this evidence, colchicine cannot be recommended for routine secondary prevention. The records reviewed did not include data from Indonesian patients, nor information on cost or access. Any use should follow local guidance and involve careful patient selection and monitoring.

8. Implications for Research

Future research should explore differences by population, timing, and dose, include independent patient-level pooling of the three trials, and examine long-term safety, including infection and non-cardiovascular mortality.

9. Strengths of the Review

This review focused on randomized controlled trials published in major peer-reviewed journals, which are the strongest design for estimating intervention effects. Each trial result was cross-checked against the published abstract or a verified secondary record, and the numbers reported here are those given by the trial authors. The reporting of synthesis without meta-analysis followed a published guideline, and limitations in the methods are described openly.

10. Certainty and Consistency of the Evidence

Considered narratively, the certainty of the evidence depends on three features: the number and size of the trials, the consistency of the direction and size of effects between trials, and the precision of the estimates. Where trials agree in direction and have narrow confidence intervals, the evidence is stronger; where trials disagree or have wide confidence intervals, the evidence is weaker and conclusions should be more cautious. A formal grading of certainty was not undertaken and would be needed before the findings are used to support a guideline recommendation.

11. Generalizability

Trial participants are selected by eligibility criteria and often receive closer monitoring than patients in routine care, so effects seen in trials may differ in practice. The populations in the included trials may differ from

patients in Indonesia in baseline risk, access to care, and background treatment, and the findings should be applied with attention to local circumstances.

12. Recommendations for an Updated Review

An updated review suitable for journal submission should register a protocol in a public registry before the search, search several databases such as PubMed, Embase, and the Cochrane Library with an exportable strategy, and screen records independently in duplicate. Data should be extracted from full-text reports and trial registries, risk of bias should be assessed domain by domain with RoB 2, and, where trials are sufficiently similar, a random-effects meta-analysis with an assessment of heterogeneity should be performed. The certainty of evidence for each outcome should then be graded using the GRADE approach.

13. Limitations

Several limitations should be acknowledged. Searching was performed through a web interface rather than an exportable multi-database search and no protocol was registered, so relevant trials may have been missed. Selection and extraction were performed by one reviewer, using published abstracts and verified secondary records. A formal RoB 2 assessment was not completed and no pooled estimate was computed. Only three trials were included, no pooled estimate was computed, and component and safety data were incomplete in some records. The review should be repeated with a documented multi-database search and independent duplicate review before the findings are used for clinical recommendations.

CONCLUSIONS

Evidence from three large RCTs on low-dose colchicine for secondary prevention in coronary artery disease is inconsistent: two trials showed a lower risk of major cardiovascular events, whereas the largest showed no benefit and more diarrhea. Colchicine cannot be recommended for routine secondary prevention on this evidence alone.

Future work should include a pre-registered, multi-database systematic review with meta-analysis, formal risk-of-bias and certainty-of-evidence assessment, and exploration of differences by population, timing, and dose.

Author Contribution Statement

The author performed all aspects of this study.

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