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Long-term colchicine therapy in acute coronary syndromes: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Anti-inflammatory therapy, particularly colchicine, has emerged as a potential secondary prevention strategy post-acute coronary syndrome (ACS). This meta-analysis assessed the impact of long-term colchicine therapy (≥12 months) compared to standard care on cardiovascular events in post-ACS patients.

A systematic search of PubMed, Cochrane, Scopus, and Web of Science was conducted on December 22, 2024, for randomized controlled trials (RCTs) comparing long-term (≥12 months) treatment with colchicine to standard care in ACS patients. Outcomes assessed included all-cause mortality, cardiovascular death, myocardial infarction (MI), ischemia-driven revascularization, and stroke.

Three RCTs (COLCOT, COPS, and CLEAR SYNERGY) with 12,602 patients were included. Colchicine did not significantly reduce all-cause mortality [hazard ratio (HR) 1.01, 95% confidence interval (CI): 0.67-1.53; I^2=54%], cardiovascular death (HR 1.01, 95% CI: 0.80-1.29; I^2=0%), or MI (HR 0.86, 95% CI: 0.71-1.05; I^2=0%). Ischemia-driven revascularization (HR 0.61, 95% CI: 0.30-1.21; I^2=81%) and stroke (HR 0.55, 95% CI: 0.18-1.64; I^2=75%) showed non-significant reductions with high heterogeneity. The composite outcome of cardiovascular death, MI, revascularization, or stroke was not significantly reduced (HR 0.80, 95% CI: 0.59-1.07; I^2=73%).

These findings suggest that long-term colchicine therapy did not confer a consistent reduction in major cardiovascular outcomes after ACS. The pooled results indicate an overall null effect; however, the substantial heterogeneity across trials limits the certainty of this conclusion. This analysis may prompt a reassessment of colchicine's preventive role in ACS. Future studies should aim to reduce heterogeneity through standardized protocols and follow-up reporting and to explore whether subgroups, such as patients with elevated inflammatory markers, may derive benefit.

Key words: colchicine, acute myocardial infarction, acute coronary syndrome, cardiovascular events, meta-analysis, secondary prevention.

Introduction

Acute coronary syndrome (ACS) is a highly prevalent manifestation of coronary artery disease (CAD), despite advances in medical treatment, remains a leading cause of morbidity and mortality [1]. Inflammation plays a central role in the initiation, progression, and rupture of atherosclerotic plaques, ultimately precipitating acute coronary events [2]. High-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation, has been shown to independently predict future cardiovascular events following ACS, underscoring the prognostic significance of baseline inflammatory burden. Elevated hsCRP levels post-ACS are associated with a higher risk of recurrent events, even in patients receiving optimal lipid-lowering and antithrombotic therapies. As such, targeting residual inflammatory risk has emerged as a complementary strategy in secondary prevention [3,4].

Recent studies have highlighted the potential benefits of targeting inflammation. The CANTOS trial demonstrated that canakinumab, an interleukin-1β inhibitor, reduced major adverse cardiovascular events (MACE) in patients with high hsCRP following ACS, enhancing the potential role of anti-inflammatory therapies in secondary prevention of cardiovascular events [5].

Colchicine, a potent anti-inflammatory drug used in various inflammatory disorders [6], has a broad action, not only targeting the NLR family pyrin domain containing 3 (NLRP3) inflammasome, whose activation leads to downstream Interleukin-1 beta (IL-1β) [6,7]. It is thought that colchicine may also be effective in treating cardiovascular disease through the reduction inflammation triggered by cholesterol crystals within atherosclerotic plaques. These crystals are known to promote local inflammation and contribute to plaque instability [8,9].

Multiple randomized clinical trials (RCTs) have investigated its role in cardiovascular disease. Current European Society of Cardiology guidelines recommend colchicine as a Class IIa treatment for patients with atherosclerotic CAD [10].

Colchicine started early after ACS targets the acute inflammatory surge from plaque rupture, but since atherosclerosis is a chronic, relapsing condition, ongoing inflammation continues to promote plaque progression. Therefore, prolonged colchicine therapy may provide lasting anti-inflammatory benefits, stabilizing plaques and reducing long-term recurrent events.

Recently, the CLEAR SYNERGY (OASIS 9) trial contributed with new evidence to this area of research, exploring the effects of prolonged use of colchicine in patients after ACS [11].

While previous meta-analyses have demonstrated that colchicine reduces the risk of recurrent acute coronary syndrome events, hospitalizations, major adverse cardiovascular events, and stroke, they did not specifically focus on the post-ACS population or the long-term effects of colchicine treatment [12,13].

Given the evolving data, we aimed to conduct an updated systematic review and meta-analysis of RCTs to assess the overall impact of prolonged colchicine therapy on MACE in patients with ACS.

Methods

Search strategy and selection criteria

This study was conducted as per the PRISMA statement [14] and registered with PROSPERO (CRD42025636089).

On December 22, 2024, a systematic search using PubMed, Cochrane Central Register of Controlled Trials, Scopus and Web of Science was conducted. The search encompassed broad terms referring to "colchicine" and "myocardial infarction" or "acute coronary syndrome" (Full query in *Supplementary Table 1*). The references' lists of the included studies and relevant reviews were searched for additional publications. Eligible studies satisfied the following inclusion criteria: (1) RCTs that enrolled (2) patients with acute coronary syndrome randomized to (3) undergo standard treatment or long-term colchicine therapy (minimum 12 months) alongside standard treatment, and (4) reporting at least one outcome of interest, including all-cause mortality, cardiovascular death, myocardial infarction (MI), ischemia-driven revascularization, or stroke. No restrictions were applied for publication status or publication language.

The search records were screened by two independent reviewers at the abstract level. Following the elimination of duplicates and ineligible publications, relevant abstracts were retrieved in full text. The full text was accessed and selected independently against inclusion criteria by the same two reviewers. Any disagreements were resolved with a third researcher.

Data extraction and outcomes of interest

Data from eligible studies were independently extracted by two reviewers using a standardized extraction form. This form captured details on study design, patient characteristics, medical therapies, and clinical outcomes. Primary outcomes included all-cause mortality, cardiovascular death, MI, ischemia-driven revascularization, and stroke, reported as hazard ratios. Secondary outcomes were composite of primary outcomes and outcomes focused on the safety and tolerability of colchicine.

Quality assessment

The risk of bias in each study has been assessed using the Cochrane risk of bias tool for RCTs. The assessment of publication bias could not be performed because only 3 studies were included. Regarding certainty of evidence, the Grading of Recommendations, Assessment, Development and Evaluations framework was used.

Statistical analysis

A narrative synthesis approach was primarily used to describe and interpret findings across studies, particularly when analysis was limited by heterogeneity in outcome reporting, study populations, or outcome definitions. Where appropriate, a study-level meta-analysis was conducted based on point estimates and 95% confidence intervals (CIs) or standard deviations (SDs) reported in the individual trials, employing an intention-to-treat approach. All estimates were calculated using a random-effects model based on the DerSimonian and Laird method. Hazard ratios (HR) were analysed using the generic inverse variance method.

Heterogeneity was tested and quantified using Chi-squared test and I^2 statistics. Thresholds of I^2 statistic of 25% (low), 50% (moderate) and 75% (high) were defined.

A leave-one-out sensitivity analysis was performed for the primary outcomes. Statistical analysis was conducted using Review Manager (RevMan) software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The statistical level of significance was two-tailed p-value < 0.05.

Results

Study selection and characteristics

Literature search (Figure 1) retrieved a total of four records referring to three randomized, multicentric, clinical trials (COLCOT, COPS and CLEAR SYNERGY) [11,15-17]. Two records identified reported results from COPS trial at different follow-up periods [16,17].

The three trials were all randomized, placebo-controlled, double-blind, multicenter clinical trials, that included pooled data of a total of 12602 patients, randomly assigned to colchicine (n=6290) or placebo (n=6312). The key study features of the three trials are reported in Table 1.

The COLCOT trial enrolled patients who had experienced a MI within 30 days and underwent percutaneous coronary intervention (PCI), while CLEAR SYNERGY included patients with ACS who had received PCI within the last 72 hours prior to trial enrollment. COPS was the only trial including a percentage of ACS patients who were treated solely with medical therapy.

The median follow-up duration was 22.6 months for COLCOT, 36 months (IQR 25.7–44.5 months) for CLEAR SYNERGY, while COPS had a 12-month follow-up period.

All trials use a minimum colchicine dose regimen of 0.5mg once daily, for at least 12 months. COLCOT used 0.5 mg once daily; COPS used 0.5 mg twice daily for the first month, followed by 0.5 mg once daily; and CLEAR SYNERGY 0.5 mg once daily if <70 kg or twice daily if ≥70 kg for the first 3 months, followed by 0.5 mg once daily for all patients.

Clinical characteristics of patients

Baseline characteristics of patients included in this analysis are summarized in Table 2.

In general, most baseline characteristics appeared well-balanced between placebo and colchicine groups across all studies, indicating an adequate randomization.

Across the included trials, the mean aged ranged from 59 to 61 years. Sex distribution was relatively balanced across trials and trial arms. In terms of comorbidities, the prevalence of diabetes and hypertension was also similar in all studies. Smoking prevalence varied between 29% and 41% in different studies, but with no significant difference between trial arms. A similar trend was observed for the history of previous MI, with the CLEAR SYNERGY trial showing a lower prevalence. Non-ST-Elevation Myocardial Infarction (NSTEMI) was more common in the COPS trial (46%) compared to the CLEAR SYNERGY trial (5%). There were no differences across the studies in terms of therapy at discharge, with dual antiplatelet therapy and statin use being consistent.

Clinical outcomes

Primary endpoints are summarized in Figure 2.

The analysis showed no statistically significant reduction in all-cause mortality among patients receiving long-term colchicine compared to those receiving placebo (HR 1.01, 95% CI: 0.67–1.53, p = 0.96; I^2 = 54%) (Figure 2A). Notably, the COPS trial was the only study that reported significantly higher mortality in the colchicine group.

Regarding cardiovascular death, the same conclusion can be made, with no statistically significant reduction observed (HR 1.01, 95% CI: 0.80–1.29, p = 0.90; I^2 = 0%) (Figure 2B).

Similarly, no significant reduction was observed for MI (HR 0.86, 95% CI: 0.71–1.05, p = 0.14; I^2 = 0%) (Figure 2C). For ischemia-driven revascularization (HR 0.61, 95% CI: 0.30–1.21, p = 0.15; I^2 = 81%) (Figure 2D) and stroke (HR 0.55, 95% CI: 0.18–1.64, p = 0.28; I^2 = 75%) (Figure 2E) pooled analysis showed a non-significant reduction, but heterogeneity was substantial in both. Ischemia-driven revascularization was significantly lower in the colchicine group in the COLCOT and COPS trials, but due to the higher impact of the CLEAR SYNERGY trial, no effect was seen in pooled analysis. For stroke, only the COLCOT trial favored colchicine.

A leave-one-out sensitivity analysis confirmed the robustness of these findings, with no changes in the primary outcomes across all iterations. However, when the CLEAR SYNERGY trial was excluded, significant benefits of colchicine emerged for stroke (HR 0.30, 95% CI: 0.13–0.68; p = 0.004; I^2 = 0%) and ischemia-driven revascularization (HR 0.46, 95% CI: 0.29–0.72; p = 0.0007; I^2 = 0%), with no evidence of heterogeneity in either outcome.

Regarding the composite outcome of cardiovascular death, MI, ischemia-driven revascularization, or stroke no significant reduction was observed (HR 0.80, 95% CI: 0.59-1.07, p=0.13; I^2 = 73%) (Figure 3), but again moderate to high heterogeneity was observed.
Overall, colchicine had no apparent risk reduction in any of the analyzed outcomes.

Safety and tolerability of colchicine

The safety profile of colchicine was generally favorable across the COLCOT, COPS, and CLEAR SYNERGY trials. Adverse events were reported in 16.0%, 23.0%, and 31.9% of colchicine-treated patients, similar to control groups (15.8%, 24.8%, and 31.7%, respectively).
Gastrointestinal (GI) events, especially diarrhea, were the most common adverse event. In COLCOT, 9.7% of colchicine-treated patients experienced diarrhea, compared to 8.9% in the control group, with no significant difference between the groups (p=0.35). In CLEAR SYNERGY, a significant difference was observed (p<0.001), with 10.2% of colchicine-treated patients reporting diarrhea, compared to 6.6% in the control group. Other GI events included nausea, flatulence, and gastrointestinal hemorrhage, although these were less frequent.
In the CLEAR SYNERGY trial, serious adverse events occurred in 6.7% of colchicine-treated patients, compared to 7.4% in the control group (p=0.22). Infection-related serious events, including pneumonia and septic shock, were also noted but were not substantially more frequent in the colchicine group in COLCOT or CLEAR SYNERGY trial.

Quality assessment

All studies demonstrated a low risk of bias, and the assessment is summarized in *Supplementary Table 2*. Based on methodological quality and consistency of results, the evidence on colchicine demonstrates high certainty for reducing MI and moderate certainty for death from any cause and cardiovascular death. However, the certainty of evidence is very low for ischemia-driven revascularization, stroke, and the composite cardiovascular outcome. (*Supplementary Table 3*).

Discussion

Over the years, multiple trials have explored colchicine's effect in chronic CAD and ACS, though the results have been inconsistent.

Clinical outcomes

This meta-analysis indicates that long-term colchicine, when compared to placebo, does not significantly reduce the risk of individual endpoints of mortality, cardiovascular death

or MI, nor the composite endpoint of cardiovascular death, MI, ischemia-driven revascularization, or stroke.

Regarding all-cause mortality, no significant difference was observed with colchicine use in this meta-analysis. Notably, the COPS trial reported a higher mortality rate in the colchicine group (8 deaths vs. 1 in placebo). The cause of noncardiovascular death was related to sepsis in 4 out of the 5 events and a total of 3 out of 4 patients with sepsis-related deaths in the colchicine group discontinued study medication early in the trial (within the first 30 days) and were not taking colchicine at the time of death. The authors attributed this to a probable type I error due to the small number of events analyzed. Nonetheless, no significant differences in cardiovascular death or MI were observed between groups in any of the trials, including COPS, and overall estimates.

The COLCOT and COPS trials found a reduction in ischemia-driven revascularization, with only COLCOT reporting a reduction in stroke. In both cases, these endpoints contributed to the observed MACE risk reduction seen in each individual trial, rather than reductions in cardiovascular death or MI. In this meta-analysis, the risks of ischemia-driven revascularization or stroke were not apparently reduced and both were associated with high heterogeneity, making conclusions uncertain.

The high heterogeneity in ischemia-driven revascularization and stroke endpoints, compared to all-cause mortality, cardiovascular death, and MI, may be explained by several factors. First, the definition of ischemia-driven revascularization varies across trials and can be influenced by a wide range of factors, including clinical decision-making, which introduces variability in how and when revascularization is performed. Similarly, the definition of stroke differs among studies. The COPS trial uses a definition of non-cardioembolic ischemic stroke [16], while COLCOT does not specify stroke beyond the general term [15], and CLEAR SYNERGY defines stroke as either primary ischemic or hemorrhagic stroke event [11].

For the composite endpoint of MACE, our results align with individual endpoint findings, showing no apparent risk reduction. Although the COLCOT and COPS trials [15] had a positive result on MACE, these results did not influence the pooled result. Previous meta-analyses highlighted the COLCOT trial as the most influential due to its size [18,19], showing a significantly lower primary composite endpoint in post-MI patients. With the addition of the CLEAR SYNERGY trial [11], our findings suggest an overall null effect of colchicine, though high heterogeneity limits a definite conclusion.

The CLEAR SYNERGY trial deserves particular attention due to its large contribution to the pooled data and distinct features. With over 7000 patients, exceeding the combined total of COLCOT and COPS, it was conducted largely during the COVID-19 pandemic, likely affecting patient selection, event rates, and follow-up. Notably, while pre-COVID19 results were consistent with those of COLCOT and LoDoCo2, the overall treatment effect

was lost in the full cohort, suggesting that pandemic-related factors may have attenuated the observed benefit of colchicine.

Interpretation is further complicated by high treatment discontinuation and the inclusion of patients with NSTEMIs and left ventricular ejection fraction below 45% in CLEAR SYNERGY. Inflammation was also inadequately suppressed in the colchicine group, with a least-squares mean hsCRP of 2.98 mg/L (SE 0.19), compared to mean on-treatment hsCRP of 1.37 mg/L (IQR 0.75–2.13) in COLCOT and 0.94 mg/L (IQR 0.53–1.93) in LoDoCo2 [20]. This is relevant given that CANTOS demonstrated cardiovascular event reduction only in patients with hsCRP <2.0 mg/L—a threshold not reached in CLEAR SYNERGY. These factors likely attenuated colchicine's apparent benefit and call into question the weight of CLEAR SYNERGY in the meta-analysis.

It remains unclear whether colchicine's effect varies based on baseline inflammation levels, as elevated inflammatory markers were not consistently reported across trials. Future studies should explore if patients with higher baseline inflammation might derive greater benefit from colchicine therapy, similar to the benefits observed in the CANTOS trial with canakinumab [5].

Treatment regimens and adherence

Differences in treatment regimens among the trials included may have also contributed to the heterogeneity observed in the pooled analysis. Additionally, patient adherence and dosing regimens were not consistently reported. Variability in adherence and dosing could have influenced treatment outcomes. Future research should prioritize standardized treatment protocols and closely monitor adherence to better evaluate colchicine's role in preventing cardiovascular events.

Safety and tolerability

The risk of infectious or gastrointestinal symptoms, particularly diarrhea, appeared similar between the colchicine and placebo groups. Overall, serious adverse events did not differ significantly between patients receiving colchicine and those in the placebo group. Other meta-analyses focusing on the long-term safety of colchicine across different clinical indications have confirmed diarrhea as a well-established side effect but have not identified other significant safety concerns [21,22].

Chronic coronary syndromes

Several trials have evaluated colchicine in chronic coronary syndromes. The LoDoCo trial found that low-dose colchicine (0.5 mg daily) reduced acute coronary events over three years in patients with stable CAD [23]. The LoDoCo2 trial [24], a larger placebo-controlled study of 5522 patients, confirmed these benefits over 28.6 months, showing a

reduction in MI and ischemia-driven revascularization. However, an unexplained increase in non-cardiovascular mortality was observed in the colchicine group.

This meta-analysis, unlike other meta-analyses [18,19], excluded trials that included patients with chronic CAD, aiming to clarify the true impact of colchicine following an acute cardiovascular event.

The exact role of colchicine in atherosclerotic plaque formation and progression is not yet fully understood. Current evidence suggests that its primary benefit may lie in stabilizing plaques and slowing disease progression during the chronic phase of CAD rather than in the immediate aftermath of an acute event.

Limitations

A key limitation of this analysis is the assumption of a uniform hazard across follow-up durations, which may not reflect the time-dependent risk of recurrent major cardiovascular events, particularly during the early phase of follow-up. Future studies should aim to address this limitation by standardizing follow-up periods.

The heterogeneity observed across studies, particularly in outcomes like ischemia-driven revascularization and stroke, limits definitive conclusions about the effect of colchicine. Differences in endpoint definitions, patient populations, treatment regimens, and follow-up durations may have contributed to the heterogeneity observed.

The disproportionate weight of the CLEAR SYNERGY trial, conducted under pandemic-related constraints and with high discontinuation rates, further complicates interpretation of pooled results, as reflected in sensitivity analyses where its exclusion led to significant effects for stroke and ischemia-driven revascularization.

Another limitation arises from the study-level analysis, which relies on aggregated data from entire studies rather than individual patient data. This precludes detailed subgroup analyses based on factors such as elevated inflammatory markers, infarct extension, or specific medical therapy regimens. While these variables could significantly influence the effect of colchicine on outcomes and help identify subpopulations that may benefit most from treatment, their impact is hard to assess at the study level.

Regarding the moderate-to-high heterogeneity observed in some outcomes, sensitivity analyses, subgroup analyses, and metaregression require a larger number of studies or more granular data to yield reliable results. With only three studies included and without access to individual patient-level data, these analyses were not feasible. The small number of studies limits statistical power and increases the risk of spurious findings, while the lack of detailed data restricts the ability to explore potential effect modifiers. A patient-level analysis, where individual characteristics are considered, could overcome these limitations and provide a more nuanced understanding of which patients may derive the greatest benefit, if any, from colchicine therapy.

Conclusions

In conclusion, the addition of long-term colchicine to optimal medical care after ACS did not demonstrate a consistent benefit in cardiovascular outcomes across the overall population. Long-term colchicine therapy was not associated with a clear reduction in all-cause mortality, cardiovascular death, or MI. Outcomes for ischemia-driven revascularization and stroke remain uncertain given the high heterogeneity, with the pooled analysis suggesting no definitive effect. Importantly, the results do not exclude the possibility of benefit in selected patient groups, such as those with elevated inflammatory markers, which warrants further investigation.

This meta-analysis may prompt a reassessment of previous recommendations, as the incorporation of the CLEAR SYNERGY trial challenges prior assumptions about the preventive properties of colchicine in ACS.

Future studies should aim to reduce heterogeneity through standardized protocols and consistent follow-up, while clarifying whether subgroups defined by inflammatory status or other risk features may derive greater benefit.

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Online supplementary materials
Supplementary Table 1. Full search query.
Supplementary Table 2. Assessment of risk of bias utilizing Cochrane risk of bias tool for randomized controlled trials.
Supplementary Table 3. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) summary.

Table 1. Characteristics of the included studies.

Study, No. of Centres, Countries	Recruitment Period Follow-up Period	Key Inclusion/Exclusion Criteria	Total patients (Drug Discontinuation)	Colchicine Dose
COLCOT 2019 Tradif et al. 167 centres across 12 countries	Dec 2015 – Aug 2018 FU: Mean of 22.6 months Time from ACS to randomization (median, days): 13.5	**Inclusion criteria:** - Myocardial infarction (in the last month) with completed planned percutaneous revascularization procedures **Exclusion criteria:** - HFrEF < 35% - Stroke within the previous 3 months - Type 2 MI - CABG within the previous 3 years or planned CABG - Cancer within the previous 3 years - Severe renal, hematologic, hepatic, inflammatory bowel disease or chronic diarrhoea, neuromuscular disease, long-term systemic glucocorticoid therapy	4754 (Colchicine: 18.4% Control: 18.7%)	- 0.5 mg daily
COPS 2020 Tong et al. 17 centres across Australia	Dec 2015 – Sep 2018 FU: 12 months Time from ACS to randomization: not specified	**Inclusion criteria:** - ACS and evidence of CAD, managed with either PCI or medical therapy **Exclusion criteria:** - CAD requiring surgical revascularization - Preexisting long-term colchicine use or immunosuppressant therapy - Severe renal and hepatic disease - Pre-existing use of strong CYP3A4 or P-glycoprotein inhibitors - Known active malignancy	795 (Colchicine: 15% Control: 8%)	- 0.5 mg twice daily for the first month, followed by 0.5 mg daily
CLEAR SYNERGY (OASIS 9) 2024 Jollyr et al. 104 centres across 14 countries	Feb 2018 – Nov 2022 FU: Median of 36 months (IQR: 25.7-44.5) Time from ACS to randomization (median, hours): 26.8 hous	**Inclusion criteria:** - STEMI undergoing PCI - NSTEMI undergoing PCI plus one of the following: HFrEF<45%, DM, multivessel CAD, previous MI, age >60 years - Patients able to be enrolled/randomized within 72 hours of index PCI **Exclusion criteria:** - Systolic blood pressure < 90 mmHg - Active diarrhoea - Severe hepatic disease	7062 (Colchicine: 25.9% Control: 25.5%)	- 0.5 mg daily if <70 kg or twice daily if ≥ 70 kg for the first 3 months, followed by 0.5 mg daily

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CLEAR SYNERGY (OASIS-9), Colchicine and Spironolactone in Acute Myocardial Infarction Trial (part of OASIS studies); COLCOT, Colchicine Cardiovascular Outcomes Trial; COPS, Colchicine in Patients with Acute Coronary Syndrome Trial; DM, diabetes mellitus; FU, follow-up; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2. Characteristics of the patients.

	COLCOT Trial		COPS Trial		CLEAR SYNERGY (OASIS 9) Trial	
	Colchicine	**Control**	**Colchicine**	**Control**	**Colchicine**	**Control**
Age, years	60.6±10.7	60.5±10.6	59.7±10.2	60.0±10.4	60.6±10.3	60.7±10.3
Female – no. (%)	472 (19.9)	437 (18.4)	74 (19)	89 (22)	725 (20.5)	713 (20.2)
Medical and surgical history – no. (%)						
Hypertension	1185 (50.1)	1236 (52.0)	201 (51)	199 (50)	1620 (45.9)	1613 (45.6)
Diabetes	462 (19.5)	497 (20.9)	75 (19)	76 (19)	658 (18.7)	645 (18.3)
Smoking	708 (29.9)	708 (29.8)	128 (32)	149 (37)	1461 (41.4)	1423 (40.3)
Previous MI	370 (15.6)	397 (16.7)	59 (15)	59 (15)	309 (8.8)	324 (9.2)
Previous PCI	392 (16.6)	406 (17.1)	51 (13)	50 (13)	345 (9.8)	364 (10.3)
Previous CABG	69 (2.9)	81 (3.4)	15 (4)	19 (5)	-	-
Previous stroke or TIA	55 (2.3)	67 (2.8)	5 (1)	11 (3)	-	-
STEMI – no.(%)	-	-	182 (48)	208 (53)	165 (4.7)	184 (5.2)
NSTEMI – no.(%)	-	-	183 (48)	174 (44)	3363 (95.3)	3350 (94.8)
Multivessel CAD – no. (%)	-	-	-	-	1735 (49.2)	1742 (49.3)
Therapy at discharge – no. (%)						
ACEI/ARB	-	-	350 (88)	341 (86)	2750 (77.9)	2768 (78.3)
Beta-blocker	2116 (89.4)	2101 (88.3)	320 (81)	337 (85)	-	-
Aspirin	2334 (98.6)	2352 (98.9)	393 (99)	391 (98)	3428 (97.2)	3405 (96.3)
Clopidogrel	2310 (97.6)	2337 (98.2)	384 (97)	388 (97)	1478 (41.9)	1497 (42.4)
Ticagrelor					1611 (45.7)	1571 (44.5)
Prasugrel					381 (10.8)	413 (11.7)
Statin	2339 (98.9)	2357 (99.1)	389 (98)	397 (99)	3408 (96.6)	3416 (96.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; COPS, colchicine in patients with acute coronary syndrome; CLEAR SYNERGY (OASIS-9), Colchicine and Spironolactone in Acute Myocardial Infarction (part of OASIS studies); COLCOT, Colchicine Cardiovascular Outcomes Trial; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; CAD, coronary artery disease.

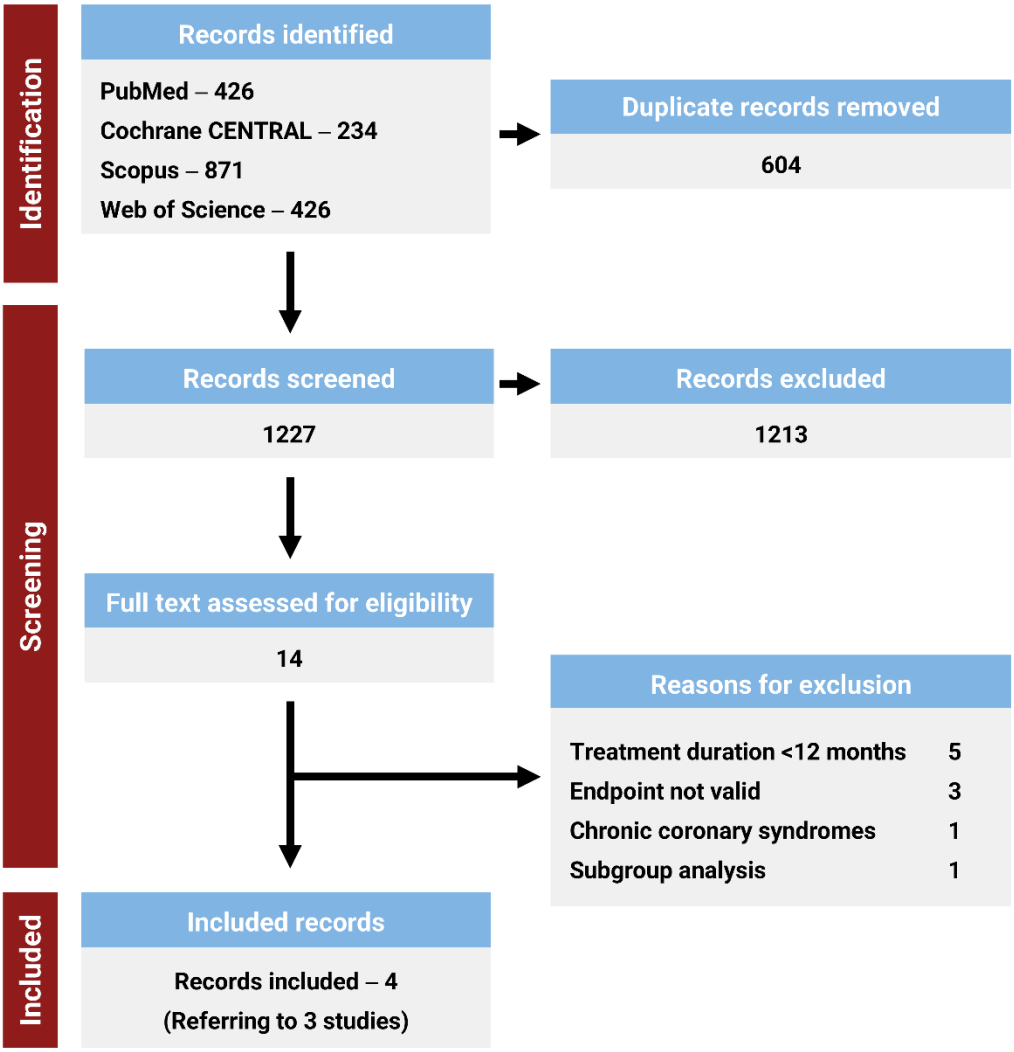

Figure 1. PRISMA Flowchart. Study identification and selection process through the different stages of the systematic review. Cochrane CENTRAL: Cochrane Central Register of Controlled Trials.

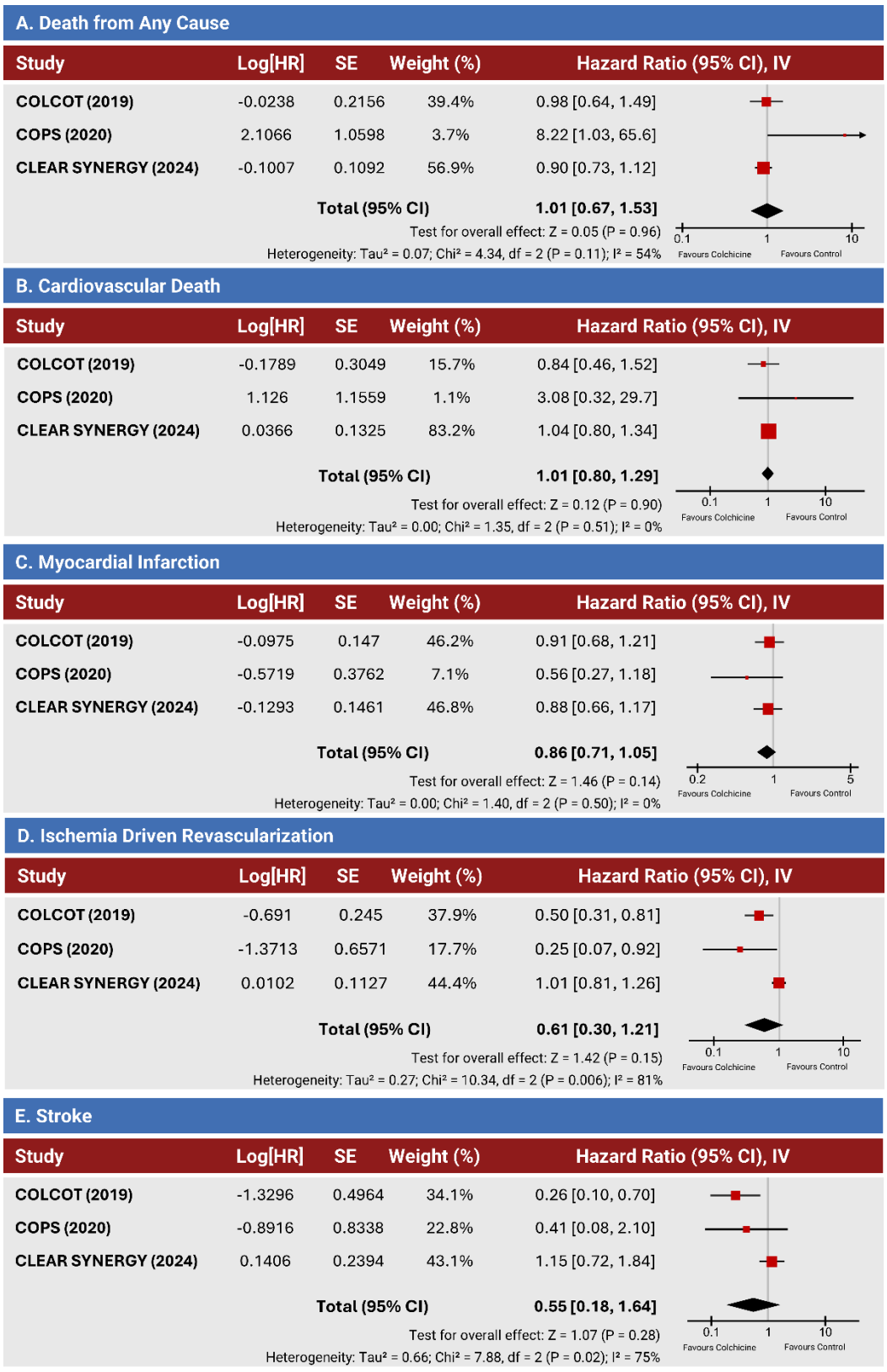

Figure 2 Meta-analysis of the impact of long-term colchicine treatment on clinical outcomes in acute coronary syndromes. (A) All-cause mortality, (B) cardiovascular death, (C) myocardial infarction, (D) ischemia-driven revascularization, and (E) stroke. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) for individual studies and pooled estimates. The size of the squares represents the weight of each study in the analysis, and the diamonds represent the overall effect size. Heterogeneity is assessed using I^2 and p-values for each outcome.

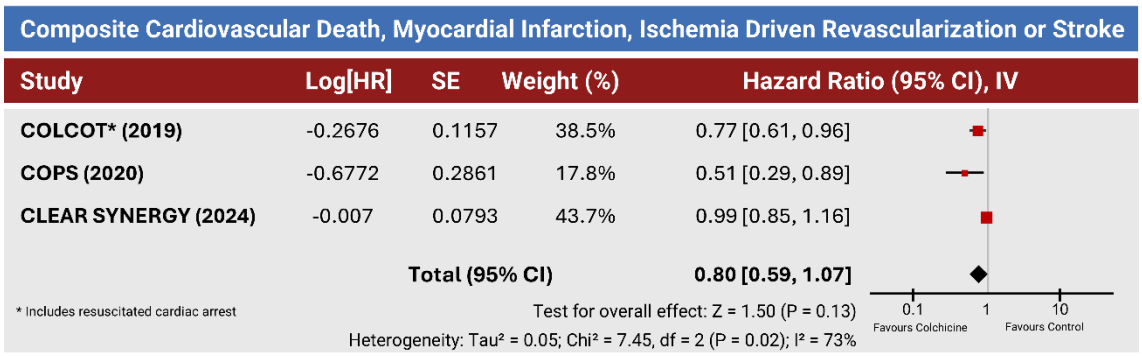

Figure 3 Meta-analysis of the of the impact of long-term colchicine treatment on the composite outcome of cardiovascular death, myocardial infarction, ischemia-driven revascularization, or stroke. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) for individual studies and pooled estimates. The analysis showed no significant overall benefit of long-term colchicine treatment. While two studies reported a meaningful reduction in the composite outcome, one study found no significant difference. Moderate heterogeneity was observed across the studies.