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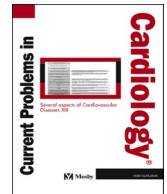
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# The effect of colchicine on myocardial infarction: An updated systematic review and meta-analysis of randomized controlled trials

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## ABSTRACT

**Introduction:** Myocardial infarction (MI) is associated with a significant post-event inflammatory response which further contributes to post-MI prognosis. Colchicine, an anti-inflammatory agent, exhibits potential benefits in various cardiovascular conditions such as coronary artery disease, pericarditis and atrial fibrillation. This meta-analysis predominantly aimed to provide an up-to-date evaluation of the efficacy and safety of colchicine in reducing adverse cardiovascular events in patients following acute MI.

**Methods:** A Comprehensive search was conducted on PubMed, Cochrane Library, Scopus, Google Scholar and clinicaltrials.gov for randomized controlled trials (RCTs) investigating the effect of colchicine on patients with MI from inception till May 2024. Our primary outcome was a composite of adverse cardiovascular events, while secondary outcomes included all-cause mortality, incidence of stroke, incidence of cardiac arrest, hospitalization urgency, incidence of recurrent MI, adverse gastrointestinal events and levels of high-sensitivity C - reactive protein (Hs-CRP). Risk ratios (RR) and mean differences (MD) were pooled under the random-effects model.

**Results:** Eleven trials with 7161 patients were included in our analysis out of which 3546 (49.51 %) were allocated to colchicine and 3591 (50.14 %) received placebo. Colchicine demonstrated

**Abbreviations:** ACS, Acute coronary syndrome; AMI, Acute Myocardial infarction; CAD, Coronary artery disease; cTn, Cardiac troponin level; hs-CRP, high sensitivity C-reactive protein; IL-6, Interleukin-6; IL-18, Interleukin-18; MI, Myocardial infarction; MMP-9, Matrix metalloproteinase-9; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin-domain-containing-3; NOX-2, NADPH oxidase 2; NSTEMI, Non-ST-Elevation MI; STEMI, ST-segment Elevation Myocardial infarction; TGF- $\beta$ , Transforming growth factor beta.

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statistically significant reduction in the composite of adverse cardiovascular events (RR = 0.75, 95 % CI: 0.60-0.94,  $P = 0.01$ ,  $I^2 = 47\%$ ), and hospitalization urgency (RR = 0.46, 95 % CI: 0.31-0.68,  $P = 0.0001$ ,  $I^2 = 0\%$ ) but statistically significant increment in adverse gastrointestinal events (RR = 1.86, 95 % CI: 1.14-3.02,  $P = 0.01$ ,  $I^2 = 79\%$ ). However, all-cause mortality (RR = 1.00, 95 % CI: 0.72-1.39,  $P = 0.98$ ,  $I^2 = 0\%$ ), incidence of cardiac arrest (RR = 0.81, 95 % CI: 0.33-1.95,  $P = 0.63$ ,  $I^2 = 0\%$ ), incidence of stroke (RR = 0.45, 95 % CI: 0.17-1.19,  $P = 0.11$ ,  $I^2 = 36\%$ ), incidence of recurrent MI (RR = 0.78, 95 % CI: 0.57-1.06,  $P = 0.11$ ,  $I^2 = 11\%$ ) and the levels of hs-CRP (MD = -0.87, 95 % CI: -1.80-0.06,  $P = 0.07$ ,  $I^2 = 67\%$ ) remained comparable across the two groups.

**Conclusion:** The use of colchicine post-MI reduces the composite of adverse cardiovascular events, and hospitalization urgency but increases adverse gastrointestinal events. However, colchicine does not impact all-cause mortality, cardiac arrest, stroke incidence, incidence of recurrent MI and the levels of hs-CRP. Large scale multicenter RCTs especially with longer follow-up duration are warranted to validate these findings.

## Introduction

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide, with inflammation significantly contributing to the development of MI and prognosis post-MI.<sup>1</sup> Following MI, the inflammatory response initially plays a protective role by removing necrotic debris and promoting tissue repair. However, sustained inflammation can lead to adverse outcomes such as detrimental cardiac remodeling, fibrosis and impaired contractility and ultimately worsening prognosis marked by elevated C-reactive protein (CRP) and interleukin-6 (IL-6).<sup>2,3</sup> Among the anti-inflammatory medications in circulation, colchicine stands out due to its established safety and efficacy in managing other inflammatory disorders such as gout, familial Mediterranean fever and pericarditis.<sup>4,5</sup> Clinical trials have explored its effectiveness in managing other cardiovascular conditions including atrial fibrillation following surgery or ablation, coronary artery disease (CAD), percutaneous coronary interventions and cerebrovascular disease.

Colchicine disrupts cellular functions by binding to tubulin and inhibiting its polymerization, particularly affecting neutrophils.<sup>6,7</sup> It ultimately reduces immune migration to damaged areas, decreases immune cell adhesion to the endothelium and suppresses the secretion of inflammatory molecules.<sup>6,7</sup> Additionally, colchicine inhibits the NLRP3 inflammasome causing a reduction in IL-1 $\beta$  and IL-18. These cytokines drive inflammation and are linked to increased levels of Hs-CRP and IL-6, both of which are markers of inflammation.<sup>6,7</sup> Moreover, colchicine reduces cardiac fibrosis and vascular stenosis by inhibiting the proliferation of myofibroblasts and smooth muscle cells and reduces cardiac remodeling by lowering Matrix metalloproteinase 9 (MMP-9), NADPH oxidase 2 (NOX2) and TGF- $\beta$ 1 (Transforming growth factor beta-1).<sup>6,7</sup>

Formerly published meta-analyses conducted on the following topic recruited a restricted number of trials and also proved to be ineffective in interpreting heterogeneity due to insufficient evidence. Hence, we sought to perform an updated systematic review and meta-analysis to demonstrate the efficacy and adverse effect of colchicine in MI while incorporating recently published randomized control trials. This study will encourage to better guide clinical decisions, optimize treatment strategies and pave the way for further research in this respective area.

## Methods

This review was prospectively registered with Prospero (CRD42024540702). It has been conducted in agreement with the guidelines established in the Cochrane Handbook for Systematic Reviews of Interventions<sup>8</sup> and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>9</sup> Compliance with these guidelines ensures transparent and coherent reviews allowing for global interpretation and reliance.

### Searching of databases

A comprehensive literature search was performed across major electronic databases including PubMed, Scopus, Cochrane Library, Google Scholar, clinical trials.gov. Eligible randomized controlled trials were recognized from beginning through May 2024 by two authors (T.K, Z.A) using the following MeSH (Medical Subject Headings) terms: Myocardial infarction [Mesh] and Colchicine; [Mesh]. Acquired articles were subsequently transferred onto Rayyan.ai. Further information on the comprehensive search results is accessible in the supplementary file. Furthermore, the citation lists of pertinent meta-analyses were manually examined to ensure thorough inclusion of evidence.

### Screening and selection

A transparent evaluation process was established using Rayyan.ai. comprising both initial and subsequent evaluations. A total of 93 articles were retrieved from the databases searched. Following the elimination of 10 duplicates, 83 articles advanced to primary screening. After assessing the title and abstracts, 28 articles remained for additional consideration. A subsequent full-text screening recognized 17 articles for exclusion due to either the lack of intended outcomes or the inclusion of unsuitable population.

Subsequently, 11 RCTs satisfied our inclusion criteria<sup>10-20</sup> (Fig. 1).

### Eligibility criteria

We included adult participants in randomized controlled trials (RCTs) that examined the effects of colchicine treatment, regardless of dosage or mode of administration for certain time duration. The treatment was compared to a placebo or no treatment. Our group of interest included patients who experienced MI, regardless of the type or their diabetic status. More specifically, our main inclusion criteria were as follows: (1) study design: Randomized controlled trials (RCTs); (2) patient population: Patients with MI (both STEMI and NSTEMI) diagnosed by coronary angiography with a follow-up duration of 1 month or more; (3) intervention: colchicine, irrespective of the type, dosing regimen or route of administration; (4) comparator: placebo or standard of care; (5) Outcome: outcomes of interest included; and (6) studies that exclusively discuss MI.

The exclusion criteria were as follows: (1) all study designs other than RCTs, such as quasi-randomized trials and observational studies; (2) studies conducted on animals or children; (3) studies that included patients with any ischemic heart disease rather than specifically focusing on MI; (4) studies with only abstract available; and (5) studies that did not report the specific outcomes of interest. No language or date restrictions were applied.

### Outcomes

A composite of adverse cardiovascular events was our primary outcome. Secondary outcomes included all-cause mortality, adverse gastrointestinal effects, incidence of stroke, incidence of cardiac arrest, incidence of recurrent MI, incidence of urgent re-hospitalization and hs-CRP levels.

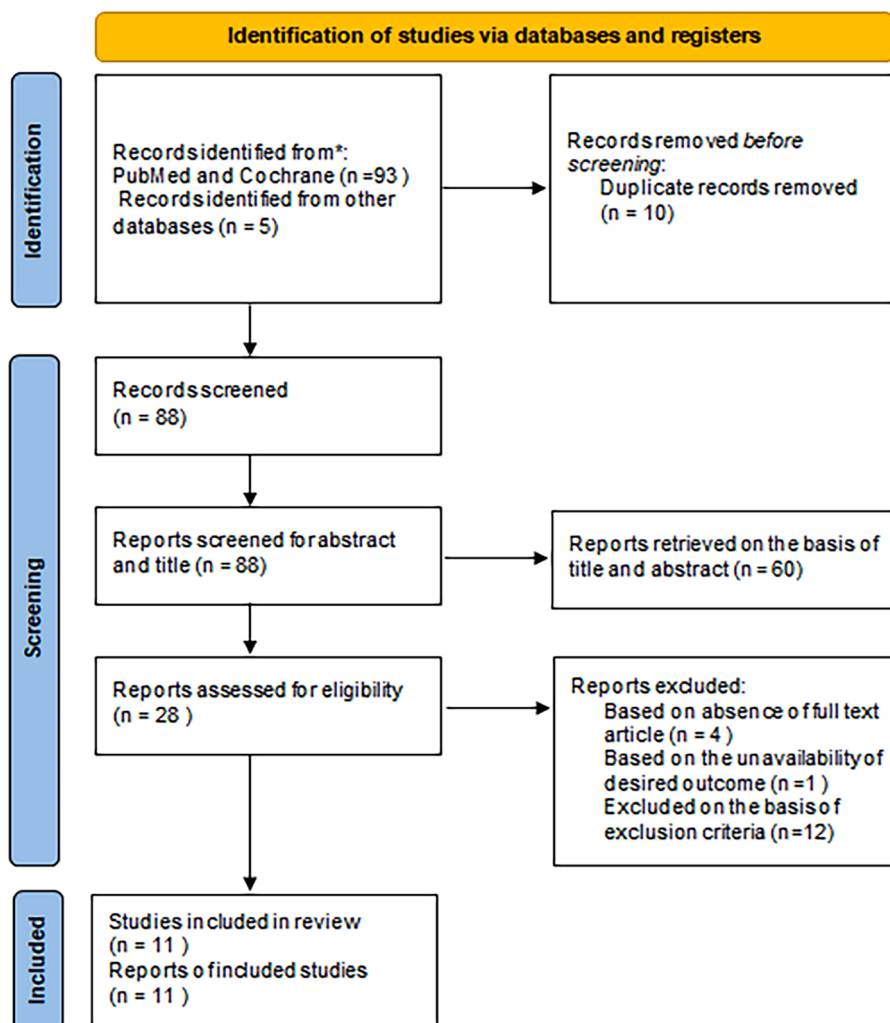


Fig. 1. PRISMA 2020 flowchart of the study selection process.

### Risk of bias assessment

Two authors (A.Y and Z.A) independently evaluated the risk of bias in the included studies using the revised Cochrane Risk of Bias Tool for RCTs (RoB 2.0).<sup>21</sup> Bias was assessed using the following five domains: (1) bias from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Risk of bias for each included study was categorized as either high, low or some concerns of bias. Any discrepancies regarding the risk of bias were settled by consensus (Fig. 2).

### Data extraction

Two authors were involved in creating a standardized data extraction form to collect relevant data from the included studies. Study information extracted included: author names, study design, and sample size. Baseline characteristics were recorded and included age, body mass index (BMI), smoking status, hypertension, diabetes, dyslipidemia, follow-up duration for colchicine. Outcomes extracted included adverse cardiovascular events, adverse gastrointestinal events, all-cause mortality, incidence of stroke, incidence of cardiac arrest, incidence of recurrent MI, hs-CRP levels and hospitalization urgency.

### Statistical analysis

Statistical analysis were performed using Review Manager (RevMan) version 5.4.1, in line with recommendations from the Cochrane Collaboration and the PRISMA guidelines. Outcomes were analyzed using a random effects model (DerSimonian and Laird) and summary estimates were reported as pooled risk ratios (RR) and mean differences (MD) with 95 % confidence intervals (CI). Statistical heterogeneity was quantified with Higgin  $I^2$  statistics. Heterogeneity was defined as low, moderate or high based on  $I^2$  values of 25 %, 50 % and 75 % respectively. The value of analysis was performed on an intention-to-treat basis. A two-sided p-value of 0.05 was considered significant. Publication bias for the primary outcome was visually assessed with funnel plots. Moreover, due to limited number of studies (fewer than 10) for each outcome, we excluded the application of Egger's regression test to analyze publication bias.<sup>8</sup>

### Certainty of evidence assessment

Certainty of evidence was assessed using the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluations) which evaluates five key considerations: risk of bias, inconsistency, indirectness, imprecision and publication bias. Each body of evidence was rated as being of high, moderate, low or very low certainty.<sup>22,23</sup>

## Results

Eleven RCTs<sup>10-20</sup> exactly matched our PICOS and inclusion criteria (Fig. 1 PRISMA flowchart). In these RCTs, 7161 patients with MI were involved in the randomization process out of which 3546 (49.51 %) were allocated to colchicine and 3591 (50.14 %) received placebo. There was a considerable variation in terms of follow-up duration, ranging from 5 days to greater than 1 year. Characteristics of the included trials and patient baseline characteristics are summarized in Table 1.

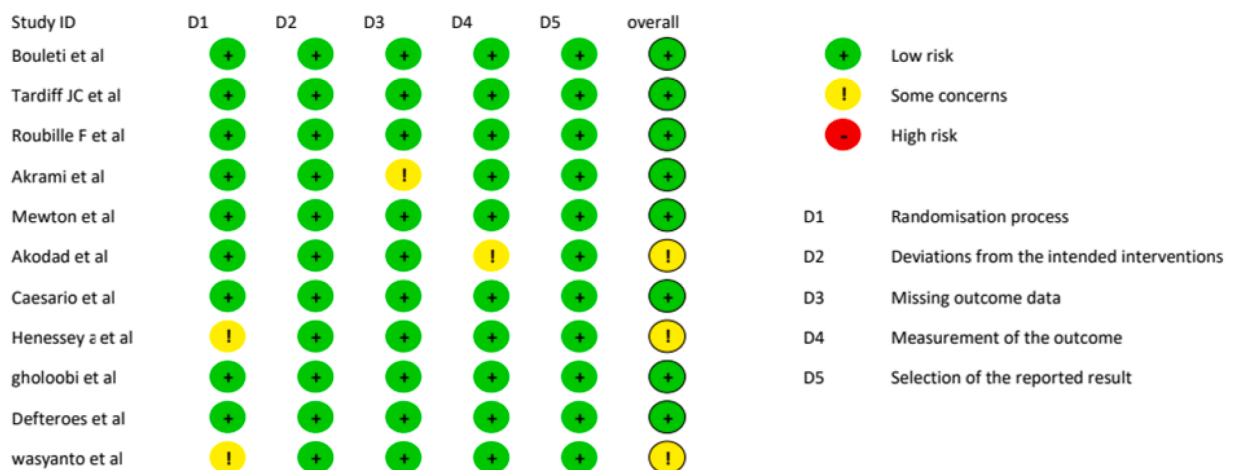


Fig. 2. Quality assessment of included trials Forest plots.

## Patient Characteristics

The detailed characteristics of included studies and patients have been outlined in [Table 1](#). Across the included trials, the mean age of participants ranged from approximately 56 to 62 years. Gender distribution was relatively balanced across colchicine and placebo arms. In terms of comorbidities, the prevalence of diabetes varied across studies, with percentages ranging from approximately 9 % to 52 % in the colchicine group and 13 % to 45 % in the placebo group. However, one study recruited all patients with type 2 diabetes. Similarly, the prevalence of hypertension varied across studies ranging from 25 % to 72 %. Likewise, the percentage of smokers varied between 29 % to 73 % across studies. These differences reflect variations in patient demographics and recruitment criteria across trials. However, most baseline characteristics generally appeared well-balanced between the placebo and colchicine groups in all the studies indicating careful randomization.

## Clinical outcomes

The incidence of adverse cardiovascular events was our primary outcome, while secondary outcomes included all-cause mortality, incidence of adverse gastrointestinal events, incidence of cardiac arrest, incidence of recurrent MI, hospitalization urgency, stroke incidence and levels of hs-CRP.

### Primary outcome

#### Incidence of adverse cardiovascular events

Adverse cardiovascular events included cardiovascular death, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina, heart failure, unstable angina, ACS, and ventricular arrhythmias. Seven out of eleven studies<sup>10-16</sup> reported adverse cardiovascular events. Our meta-analysis demonstrated a statistically significant reduction in the composite of major adverse cardiovascular events in patients receiving colchicine versus placebo (RR = 0.75, CI = 0.60-0.94,  $P = 0.01$ ,  $I^2 = 47\%$ ), as shown in [Fig. 3\(a\)](#). On conducting sensitivity analysis, excluding one specific study<sup>13</sup> caused the heterogeneity to fall to 0 % (Supplementary Figure S1). The overall quality of evidence was evaluated to be moderate due to some concerns about inconsistency across studies ([Table 2](#)).

### Secondary outcomes

#### All-cause mortality

Eight out of eleven studies<sup>10-16,19</sup> reported all-cause mortality out of which 3 studies<sup>11,12,16</sup> reported no deaths at all. This meta-analysis revealed no statistically significant difference in mortality rates between the colchicine and placebo groups (RR = 1.00, CI = 0.72-1.39,  $P = 0.98$ ,  $I^2 = 0\%$ ) as seen in [Fig. 3\(b\)](#). The overall quality of evidence was evaluated to be high due to the absence of any significant concerns in the GRADE domains ([Table 2](#)).

#### Incidence of adverse gastrointestinal events

Seven out of eleven studies<sup>11-17</sup> reported adverse gastrointestinal side effects. Adverse gastrointestinal events included diarrhea, nausea, vomiting and flatulence. Our meta-analysis shows a statistically significant increase in gastrointestinal events between the colchicine and placebo groups (RR = 1.86, CI = 1.14-3.02,  $P = 0.01$ ,  $I^2 = 79\%$ ) as seen in [Fig. 3\(c\)](#). The overall quality of evidence was evaluated to be moderate due to high heterogeneity ([Table 2](#)).

#### Incidence of stroke

Four out of eleven studies<sup>10,14-16</sup> reported stroke incidence. The analysis revealed no statistically significant reduction in stroke incidence among patients receiving colchicine compared to those receiving placebo (RR = 0.45, CI = 0.17-1.19,  $P = 0.11$ ,  $I^2 = 36\%$ ) as seen in [Fig. 3\(d\)](#). After performing sensitivity analysis, statistical significance was achieved by excluding one study<sup>16</sup> as seen in Supplementary Figure S2. The overall quality of evidence was evaluated to be moderate due to some heterogeneity ([Table 2](#)).

#### Incidence of cardiac arrest

Three out of eleven studies<sup>14-16</sup> reported on the incidence of cardiac arrests. No statistically significant difference in the incidence of cardiac arrest between the colchicine and placebo groups was found (RR = 0.81, CI = 0.33-1.95,  $P = 0.63$ ,  $I^2 = 0\%$ ) as seen in [Fig. 3\(e\)](#). The overall quality of evidence was evaluated to be high due to the absence of any significant concern in the GRADE domains ([Table 2](#)).

#### Incidence of recurrent MI (MI)

Six out of eleven studies<sup>11-16</sup> reported on the incidence of recurrent MI. There was no statistically significant difference in the incidence of recurrent MI between the colchicine and placebo groups (RR = 0.78, 95 % CI = 0.57-1.06,  $P = 0.11$ ,  $I^2 = 11\%$ ) as seen in [Fig. 3\(f\)](#). The overall quality of evidence was evaluated to be high due to the absence of any significant concern within the GRADE domains ([Table 2](#)).

#### Hospitalization urgency

Three out of eleven studies<sup>12,14,15</sup> reported on hospitalization urgency. Patients receiving colchicine demonstrated a statistically

**Table 1**  
Baseline characteristics of patients.

Author name	TYPE	Parameters	Sample Size	Age, years	Smoking, n%	Diabetes mellitus, n (%)	Hypertension, n (%)	Dyslipidemia, n (%)	BMI, n (%)	Follow-up (months)
Bouleti C et al. <sup>12</sup>	RCT	Colchicine	101	59.0 ± 10.6	44(43.6)	12/101 (11.9)	30(29.7)	29/101 (28.7)	27.3 ± 5.0	12 months
		Placebo	91	60.9 ± 10.4	39(42.9)	13/91 (14.3)	29 (31.9)	34/91 (37.4)	26.9 ± 4.4	
Tardif JC et al. <sup>17</sup>	RCT	Colchicine	2366	60.6 ± 10.7	708 (29.9)	462 (19.5)	1185 (50.1)	NA	28.2 ± 4.8	NA
		Placebo	2379	60.5 ± 10.6	708 (29.8)	497 (20.9)	1236 (52.0)	NA	28.4 ± 4.7	
Roubille F et al. <sup>16</sup>	RCT	Colchicine	462	62.5 ± 10.4	127(27.5)	462	337(72.9)	NA	29.7 ± 5.1	NA
		Placebo	497	62.4 ± 10.7	122(24.5)	497	381(76.7)	NA	30.2 ± 5.2	
Hennessy et al. <sup>14</sup>	RCT	Colchicine	111	:61 ± 13.6	77 (65 %)	27(23 %)	64 (54 %)	NA	28(25-30)	1 months
		Placebo	113	61 ± 12.5	67 (57 %)	25 (21 %)	48(41 %)	NA	28(26-30)	
akodad et al. <sup>13</sup>	RCT	Colchicine	23	60.1 ± 13.1	17 (73.9)	3 (13.0)	9 (39.1)	8 (34.8)	NA	1 Month
		Placebo	21	59.7 ± 11.4	14 (66.7)	3 (14.3)	10 (47.6)	8 (38.1)	NA	
Wasyanto et al. <sup>20</sup>	RCT	Colchicine	16	57.87	13 (41)	3(9)	8 (25)	3(9)	NA	5 Days
		Placebo	16	52.87	10 (31)	4(13)	7(22)	1(3)	NA	
.Deftereos et al. <sup>21</sup>	RCT	Colchicine	74	58 ± 12.72	13 (17)	13 (17)	31 (40)	44 (57)	27.1 (25.3–30.7)	5 Days
		Placebo	77	58 ± 8.98	19 (26)	19 (26)	29(39)	35 (47)	27.1 (24.6–30.8)	
Gholoobi et al. <sup>22</sup>	RCT	Colchicine	75	60.87 ± 7.9	40 (53.3 %)	40 (53.3 %)	NA	197.58 ± 35.56	NA	1 Month
		Placebo	75	61.97 ± 5.4	34(45.3 %)	40 (53.3 %)	NA	219.46 ± 37.74	NA	
Mewton et al. <sup>18</sup>	RCT	Colchicine	101	59.0 ± 10.6	12/101 (11.9)	12/101 (11.9)	30(29.7)	29/101 (28.7)	27.3 ± 5.0	2 Month
		Placebo	91	60.9 ± 10.4	13/91 (14.3)	13/91 (14.3)	29(31.9)	34/91 (37.4)	26.9 ± 4.4	
Caesario et al. <sup>19</sup>	RCT	Colchicine	92	56.43 ± 8.96	32 (34.8 %)	32 (34.8 %)	53 (57.6 %)	78 (84.7 %)	1.73 ± 0.32	3 Month
		Placebo	104	55.47 ± 9.68	43 (41.3 %)	43 (41.3 %)	69 (66.3 %)	83 (79.8 %)	1.69 ± 0.24	
Akrami et al. <sup>15</sup>	RCT	Colchicine	122	56.9 ± 7.56	27 (22.5)	27 (22.5)	52(43.3)	37 (30.8)	NA	6 Month
		Placebo	129	56.89 ± 7.45	32 (24.8)	32 (24.8)	59(45.7)	36 (27.9)	NA	



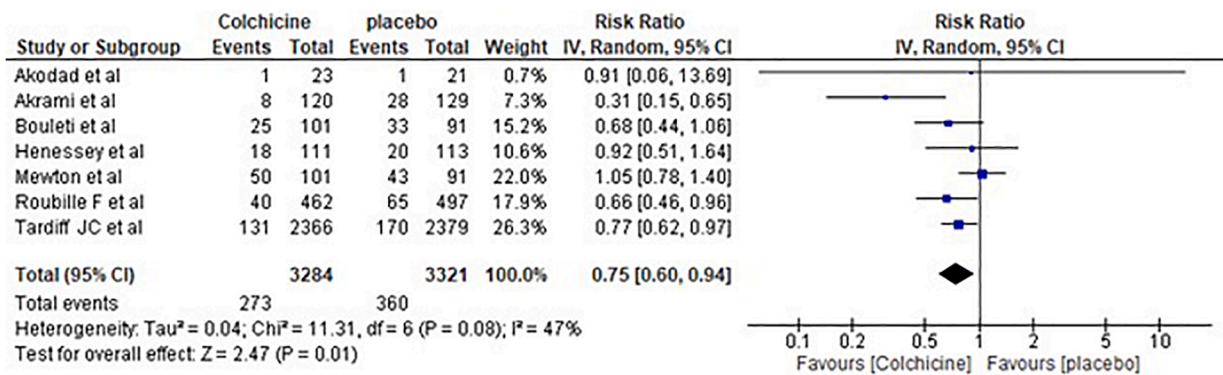


Fig. 3(a). Forest plot showing summary risk ratio and 95 % CI for adverse cardiovascular events.

Table 2

Grading of recommendations assessment, development, and evaluation (GRADE) summary of findings.

Outcomes	Risk of bias	inconsistency	indirectness	imprecision	Publication bias	Certainty
Adverse cardiovascular events	not serious	serious	not serious	not serious	NA	⊕⊕⊕○ Moderate
Hs-CRP	serious	serious	not serious	not serious	undetected	⊕⊕○○ Low
All-cause mortality	not serious	not serious	not serious	not serious	undetected	⊕⊕⊕⊕ High
Incidence of stroke	not serious	serious	not serious	not serious	undetected	⊕⊕⊕○ Moderate
Incidence of cardiac arrest	not serious	not serious	not serious	not serious	undetected	⊕⊕⊕⊕ High
Hospitalization urgency	not serious	not serious	not serious	not serious	undetected	⊕⊕⊕⊕ High
Adverse gastrointestinal effects	not serious	serious	not serious	not serious	undetected	⊕⊕⊕○ Moderate
Incidence of recurrent MI	not serious	not serious	not serious	not serious	undetected	⊕⊕⊕⊕ High

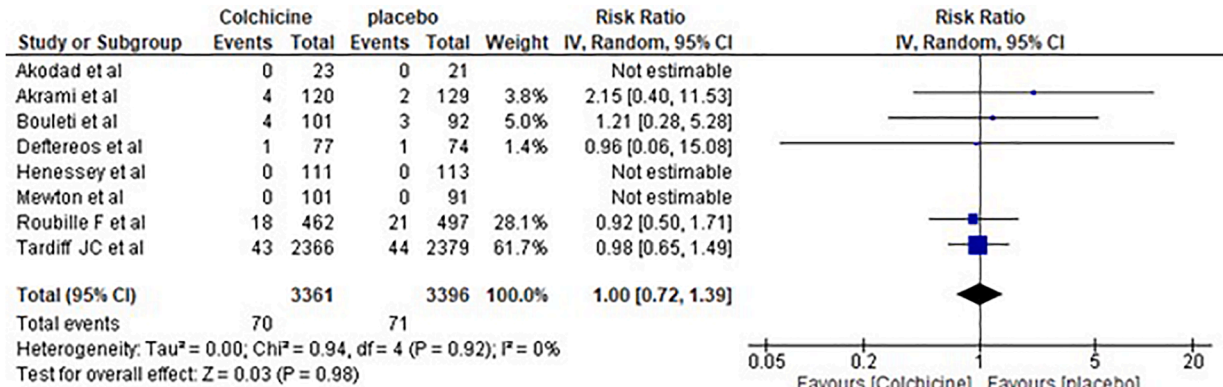


Fig. 3(b). Forest plots showing summary risk ratio and 95 % CI for All-cause mortality.

significant reduction in hospitalization urgency compared to those receiving a placebo ( $RR = 0.46$ , 95 %  $CI = 0.31-0.68$ ,  $P = 0.0001$ ,  $I^2 = 0\%$ ) as seen in Fig. 3(g). The overall quality of evidence was evaluated to be high due to the absence of any significant concern within the GRADE domains (Table 2).

#### High-sensitive C-reactive protein

Six out of eleven studies<sup>11,12,16,18-20</sup> reported on high sensitive C-reactive protein. Our meta-analysis showed no statistically significant difference in hs-CRP levels in patients receiving colchicine compared to those receiving placebo ( $MD = -0.87$ , 95 %  $CI = -1.80-0.06$ ,  $P = 0.07$ ,  $I^2 = 67\%$ ) as seen in Fig. 3(h). The overall quality of evidence was evaluated to be low due to the inclusion of some studies of small sample size, hence giving rise to potential bias and heterogeneity (Table 2).

#### Quality assessment of included studies

Eight out of eleven studies<sup>10,13-17,19,20</sup> were found to be of low risk of bias and three studies<sup>11,12,18</sup> were found to have some concerns of bias due to some issues in the randomization process, reporting or measurement of outcomes (Fig. 1).



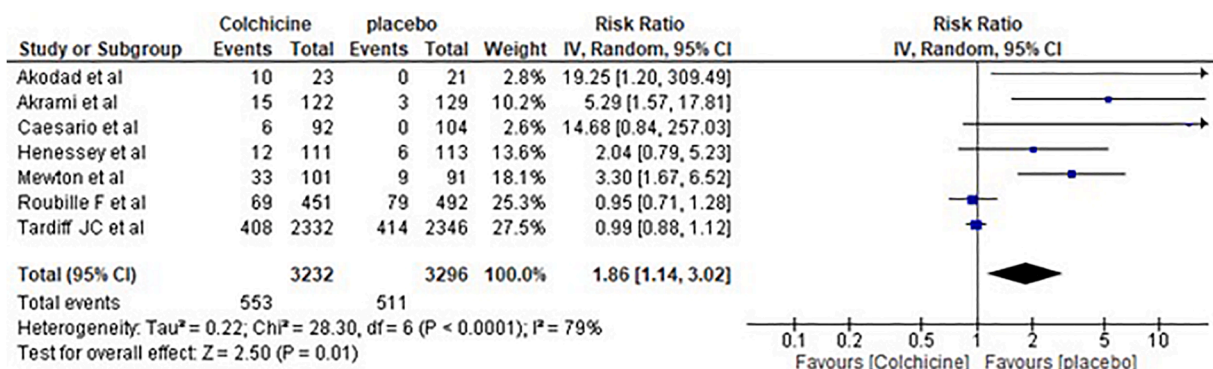


Fig. 3(c). Forest plot showing summary risk ratio and 95 % CI for GI adverse effect.

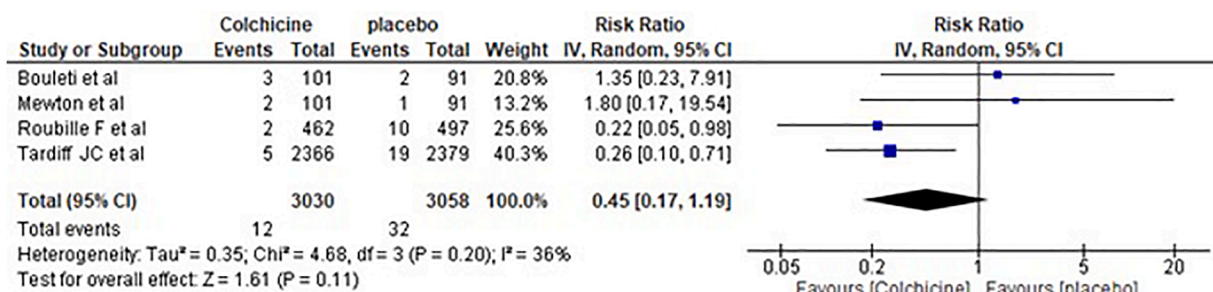


Fig. 3(d). Forest plot showing summary risk ratio and 95 % CI for stroke incidence.

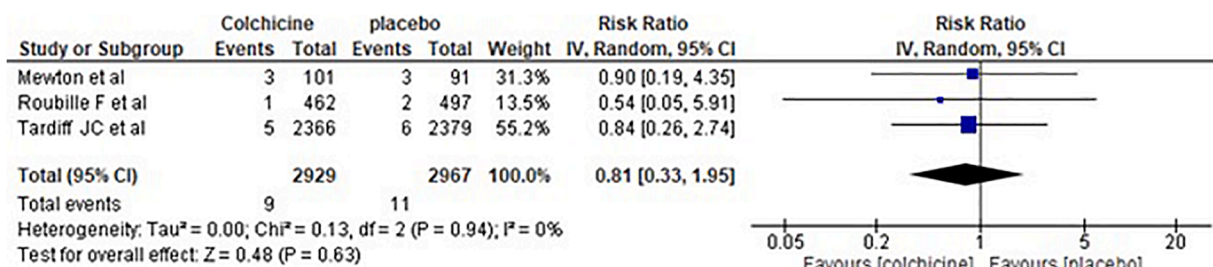


Fig. 3(e). Forest plot showing summary risk ratio and 95 % CI for cardiac arrest.

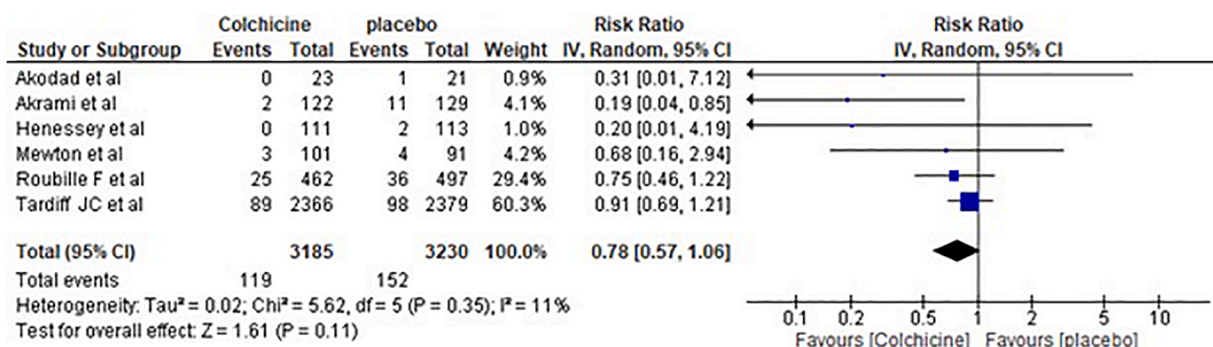


Fig. 3(f). Forest plot showing summary risk ratio and 95 % CI for recurrent MI.

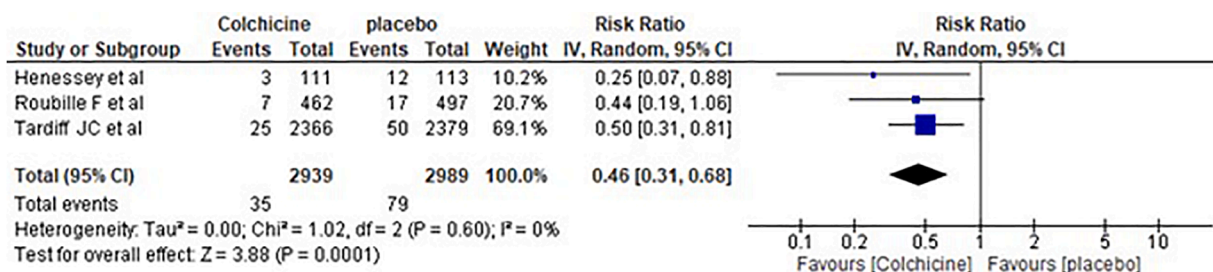


Fig. 3(g). Forest plot showing summary risk ratio and 95 % CI for hospitalization urgency.

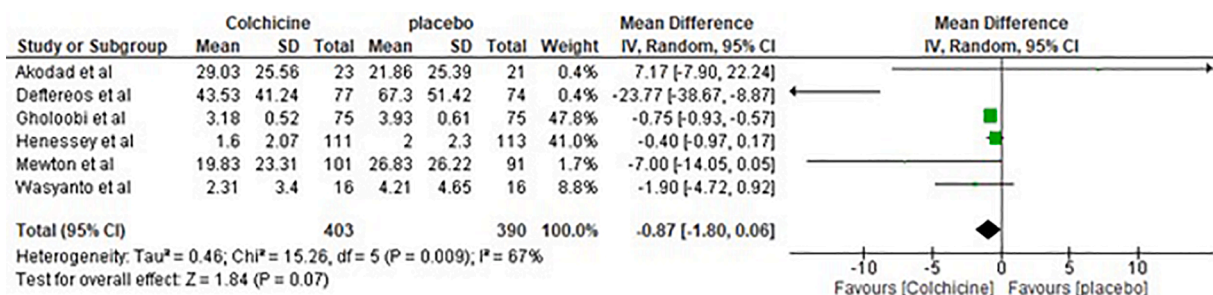


Fig. 3(h). Forest plot showing mean difference (MD) and 95 % CI for Hs-CRP.

### Publication bias

Assessment of publication bias through funnel plot visualization for the primary outcome suggested that there was no evidence of publication bias, with minimal or no funnel plot asymmetry (Supplementary Figures S3).

### Discussion

This updated meta-analysis of 7161 patients with MI provides a comprehensive evaluation of the effects of colchicine versus no colchicine. The findings reveal that colchicine is associated with a reduction in the risk of a composite of adverse cardiovascular events including cardiovascular death, resuscitated cardiac arrest, MI, stroke, urgent hospitalization, heart failure, unstable angina, ACS and ventricular arrhythmias. Additionally, we found that colchicine causes a reduction in hospitalization urgency but increases the risk of adverse gastrointestinal effects. Despite these benefits, colchicine is not shown to impact all-cause mortality, stroke incidence, incidence of cardiac arrest, incidence of recurrent MI or levels of hs-CRP. GRADE assessment demonstrated that most of the outcomes have moderate to high certainty except hs-CRP which has low certainty due to inconsistency and risk of bias. Adverse cardiovascular events, adverse gastrointestinal events, and incidence of stroke exhibited moderate certainty owing to inconsistency. On the other hand, incidence of cardiac arrest, incidence of recurrent MI, hospitalization urgency, and all-cause mortality exhibited high certainty, indicating the strength of evidence and consistency across the studies (Table 2).

### Colchicine and cardiovascular outcomes

Over the past several years, multiple trials have explored colchicine's efficacy in chronic CAD and ACS, however, results regarding cardiovascular events have been variable. Our meta-analysis is heavily influenced by the significant weighting of the COLCOT trial which showed a significantly lower primary composite endpoint in post-MI patients treated with colchicine (HR: 0.77,  $p = 0.02$ ).<sup>15</sup> Notably, this effect in COLCOT was predominantly driven by reductions in stroke and urgent cardiovascular revascularization, with no impact on mortality. In contrast, the influential COPS trial which focused more broadly on patients with any ACS (and thus excluded from our meta-analysis) did not show a reduction in the composite and instead found increased mortality.<sup>24</sup>

In our meta-analysis, we found a reduction in the composite cardiovascular endpoint, with the only significant effect being in the urgent cardiovascular revascularization category. However, this category was only measured in three of the included studies and was largely influenced by the COLCOT trial.<sup>15</sup> The efficacy we observed in terms of cardiovascular outcomes exceeds that of the COPS trial which included all ACS, possibly suggesting colchicine's greater role in more acute inflammatory heightened conditions. Earlier administration of colchicine in all trials may show even greater reductions in cardiovascular events, as evidenced by the separate time-to-treatment analysis of COLCOT.<sup>25</sup>

Contrary to other studies, our study did not show a significant reduction in the incidence of stroke. This finding is influenced by the inclusion of newer additional RCTs specifically in patients post-MI. The recent 2024 CONVINC trial, published in the LANCET, which investigated the role of colchicine in patients with previous non-cardioembolic ischemic stroke also showed no significant reduction in

recurrent ischemic stroke.<sup>26</sup> Moreover, unlike some other studies which showed increased non-cardiovascular mortality without a clear cause, we did not find any excess mortality associated with colchicine use. This discrepancy may be due to low event numbers and insufficient power in other studies. Despite cardiac MRI studies showing colchicine's ability to reduce infarct size post-MI, we observed no difference in cardiac arrest.<sup>27</sup> Given that colchicine also affects transcriptional level, longer therapy may be needed to observe its full effect. We anticipate that the CLEAR SYNERGY trial with a 3.5-year follow-up will help clarify many of these findings (ClinicalTrials.gov identifier: NCT03048825).

### *Colchicine and inflammatory biomarkers*

The benefits of colchicine on cardiovascular outcomes theoretically stem from its role in modulating inflammation. During an MI event, cellular necrosis and inflammatory responses are initiated, thereby raising inflammatory biomarkers such as CRP produced in response to pro-inflammatory cytokines such as IL-6.<sup>28</sup> Studies have shown that elevated CRP following MI is associated with an increased risk of major adverse cardiovascular events and mortality, while other anti-inflammatory agents like canakinumab have been shown to reduce these events.<sup>29,30</sup>

Despite the known anti-inflammatory properties of colchicine including its ability to stabilize plaques<sup>31</sup>, our meta-analysis did not find a significant difference in hs-CRP levels between groups. This may be due to multitude of factors such as timings of CRP measurement, as levels peak immediately following MI and may vary if taken at different points across studies; potential imbalance in comorbidities and infection rates more so in small RCTs; underlying chronic inflammation within the population thereby limiting CRP reduction with colchicine; and heterogeneity between studies. Given that colchicine affect many cellular pathways, other markers of inflammation may be more suitable for assessing its effects than CRP alone.

### *Adverse effects of colchicine*

With colchicine's antimitotic activity, highly proliferative tissues are at greatest risk of adverse effects. The most common side effects are gastrointestinal such as diarrhea, nausea and vomiting. Our meta-analysis shows almost a two-fold increase in gastrointestinal side effects in the colchicine group, concordant with another meta-analysis with 14,188 patients.<sup>32</sup> However, the meta-analysis by Diaz-Arocutipa et al. with 6005 patients did not show a significant difference in gastrointestinal side effects between groups.<sup>33</sup> The discrepancy may be attributed to the inclusion of recent studies in our review that focused on shorter follow-up periods, during which gastrointestinal side effects are more prominent. Rarer and more severe side effects, such as myelotoxicity and sepsis, were not explored in this meta-analysis due to insufficient reporting in other trials.

### *Strengths and Limitations*

Our meta-analysis specifically focuses on patients post-MI, in contrast to many other reviews that focus on general CAD. We employed broad inclusion criteria encompassing all types of MI, making this one of the largest meta-analyses on this topic known to date. Data were collected from recent studies with better methodological rigor and a true randomization process, thus excluding any potential confounding bias from quasi-randomized studies. Furthermore, we evaluated the quality of evidence using the GRADE approach to enhance our confidence in the findings.

However, there are limitations to consider. Firstly, variability in patient sample sizes, disease severity, colchicine dosing, timing of administration and follow-up durations introduces heterogeneity and potential bias. Many of the included studies also had small sample sizes which may affect conclusions drawn. Secondly, the composite outcome in the included RCTs comprised of different cardiovascular events. Thirdly, we were unable to stratify data by variables such as gender, age and specific intervention details due to lack of access to the original data. Finally, most trials excluded those with significant heart and renal failure which makes the application of our findings in clinical practice more uncertain.

### **Conclusion**

In conclusion, the addition of colchicine in combination with guideline-directed medical therapy reduces the composite of adverse cardiovascular events, and hospitalization urgency but increases adverse gastrointestinal events like diarrhea in patients with myocardial infarction. However, the addition of colchicine doesn't seem to individually impact all-cause mortality, incidence of cardiac arrest, incidence of recurrent MI, levels of hs-CRP, or cerebrovascular accidents like stroke. Identifying which patients are most likely to benefit from colchicine along with long-term benefits of the colchicine highlights the need of further large scale RCTs to evaluate the robustness of colchicine in patients with myocardial infarction.

### **Author contribution**

A.Y, Z.A; contributed to the conception or design of the work. A.Y, Z.A, T.K contributed to the acquisition, analysis, or interpretation of data for the work. All authors help in drafting the manuscript. S.M, A.K, H.R, A.Y critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Ethical Approval

Since this is a review article of previously published studies, ethical approval is not required.

## Consent to participate

Not Applicable.

## Data availability statement

The data underlying this article are available in the article and its online supplementary material.

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The manuscript has not previously been presented at a meeting, published in abstract form in the proceedings of a meeting, or posted on a preprint server. No reference or previously published material protected by copyright is used in the manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.cpcardiol.2024.102878](https://doi.org/10.1016/j.cpcardiol.2024.102878).

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