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ORIGINAL RESEARCH

Colchicine in the Management of Acute Coronary Syndrome: A Meta-analysis

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ABSTRACT

Introduction: Colchicine, thought to exert its effect via reduction of inflammation, has recently been studied in patients following acute coronary syndromes (ACS). We performed a meta-analysis of all available randomized controlled trials (RCTs) in this high-risk cohort, evaluating efficacy and safety.

Methods: MEDLINE, PubMed, EMBASE, clinical trial registries, and select conference proceedings were searched for RCTs comparing colchicine to placebo in patients following ACS. The primary outcome was trial-defined major adverse cardiovascular events (MACE). Secondary endpoints included stroke, myocardial infarction (MI), all-cause and cardiovascular death, and urgent revascularization. Analysis was performed at the longest available clinical follow-up.

Results: Two RCTs with a pooled sample size of 5540 patients with 2778 (50.1%) receiving colchicine and 2762 (49.9%) placebo were included. In order to maximize consistency, composite efficacy endpoints between trials were modified. Compared to placebo, patients receiving colchicine had reduction in study-defined composite endpoint (5.5% vs. 7.6%) OR 0.67 (95% CI 0.46–0.98, $p = 0.04$, $I^2 = 46\%$). Similarly, there was a significant reduction in cerebrovascular accidents (OR 0.31, 95% CI 0.14–0.69, $p = 0.004$, $I^2 = 0\%$) and repeat revascularization OR 0.36 (95% CI 0.14–0.90, $p = 0.03$, $I^2 = 54\%$). There was no difference between cardiovascular death (OR 0.92, 95% CI 0.52–1.62, $p = 0.78$, $I^2 = 0\%$), non-cardiovascular death OR 1.27 (95% CI 0.72–2.24, $p = 0.41$, $I^2 = 0\%$), MI at longest available follow-up OR 0.89 (95% CI 0.67–1.17, $p = 0.39$, $I^2 = 0\%$) or resuscitated cardiac arrest OR 0.88 (95% CI 0.32–2.43, $p = 0.81$, $I^2 = 0\%$) in those receiving colchicine.

Conclusions: These data suggest colchicine, in addition to guideline-directed medical therapy following acute coronary syndrome reduces MACE, cerebrovascular accidents, and rates of urgent revascularization at 2 years of follow-up.

Keywords: Colchicine; Acute coronary syndrome; Myocardial infarction; MACE

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Key Summary Points

Despite improvements in medical therapy, there is ongoing morbidity and mortality following an acute coronary syndrome (ACS).

Recent data have explored the utility of colchicine, a broadly acting anti-inflammatory therapy, to improve outcomes amongst patients with ACS with favorable outcomes.

We performed an updated meta-analysis with modified primary endpoints from our groups study exploring the utility of colchicine amongst patients with recent ACS.

We found that the early administration of colchicine led to reduced rates of major adverse cardiac events.

We await the results of the CLEAR SYNERGY trial to provide more data on the role of colchicine amongst patients with recent ACS.

INTRODUCTION

Acute coronary syndromes remain a major cause of morbidity and mortality worldwide despite improving treatment in recent decades [1]. The role of revascularization, anti-thrombotic, cholesterol lowering, and anti-anginal therapy are now widely accepted as mainstay therapy in patients with coronary artery disease and have seen significant improvement in clinical outcomes [2–4].

Recent studies investigating the use of anti-inflammatory agents have shown promise. Colchicine, an inexpensive and widely available agent with decades of clinical experience, has recently emerged as an adjunct therapy in the treatment of patients with coronary artery disease. It is a broadly acting sophisticated anti-inflammatory therapy that antagonizes the NOD-Like Receptor Protein 3 (NLRP3) inflammasome and cholesterol crystal-induced inflammation [5, 6].

A growing body of evidence supporting the role of colchicine in the management of acute coronary syndromes is emerging. The recent COLCOT and COPS randomized controlled trials have both shown a reduction in ischemic cardiovascular events with the daily use of colchicine in patients who have presented with an acute coronary syndrome [7, 8]. Additionally, the benefit of early administration of colchicine has been studied in ST-segment-elevation myocardial infarction (STEMI), with colchicine showing reduced myocardial infarct size as measured by volume of scar on cardiac MRI and creatine kinase [9]. Although early results are promising, long-term data are still lacking.

While prior meta-analyses have examined the role of colchicine in more chronic cardiovascular disease, there has not been a specific assessment in an extended follow-up ACS cohort. Therefore, we performed a meta-analysis of randomized controlled trials that studied the effects of early colchicine administration in patients who present with acute coronary syndromes compared to placebo at longest available follow-up.

METHODS

Study Endpoints and Selection Criteria

Pre-specified primary and secondary endpoints were determined prior to literature search. The primary endpoint was the study-defined combination of major adverse cardiovascular events (MACE). Secondary endpoints included all-cause mortality, cardiovascular death, myocardial infarction (MI), stroke, and need for revascularization. Study criteria for inclusion were as follows: (1) Randomized controlled trials (RCT), (2) studies comparing those receiving colchicine vs. placebo, (3) studies reporting clinical endpoints, (4) at least 1 year of follow-up.

Studies were excluded if the primary study population was not acute coronary syndrome.

Literature Search

A comprehensive search of all electronic literature was conducted from inception through to August 2021. PubMed, MEDLINE, and EMBASE databases and Google Scholar, along with conference proceedings and online clinical trial registries, were searched with no restrictions. Searches were performed using Medical Subject Heading (MeSH) and keywords that included, but were not limited to; 'coronary artery disease', 'acute coronary syndrome', 'colchicine', 'coronary artery disease'. The study protocol was prospectively registered with PROSPERO (CRD42021236504) and adhered to the Preferred Reporting Items For Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. An example search strategy for the MEDLINE database and results are provided in Supplementary Table S1.

Two review authors (JN and OM) independently conducted searches based on the prespecified selection criteria to identify potential trials for inclusion. All citations returned were first screened at title/abstract level to determine suitability for inclusion. Full-text articles and/or conference proceedings were then retrieved and reviewed with studies meeting the inclusion criteria included in the analysis. Additionally, reference lists of the eligible trials were searched for identification of further potential trials to be included. The individual patient inclusion and exclusion criteria for the included trials are provided in Supplementary Table S2.

Data Extraction

Two authors (JN and OM) independently extracted data. Baseline patient characteristics, treatment variables, cardiovascular risk factors, sample size of trials, dosage and duration of colchicine, and clinical follow-up data were recorded. The senior author (JL) subsequently verified the extracted data with discrepancies resolved by consensus.

Bias Assessment

Risk of bias for each trial in the analysis was assessed independently by two review authors (JN and OM) using the Cochrane Collaboration Assessment Tool [11], providing reasons for judgment at a study level. Full details on the risk of bias assessment are presented in Supplementary Fig. S1.

Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan) version 5.3 in line with recommendations from the Cochrane Collaboration and the PRISMA guidelines. Outcomes were analyzed using a Peto random effect models and summary estimates reported as pooled odds ratios (OR) with 95% confidence intervals (CI). Statistical heterogeneity was quantified with the I^2 statistic. Heterogeneity was defined as low, moderate, or high based on I^2 values of 25, 50, and 75%, respectively [12]. Analysis was performed on an intention-to-treat basis. Publication bias was estimated visually by funnel plot assessment. A two-sided p value of < 0.05 was considered significant.

RESULTS

As shown in Fig. 1, the search returned two studies of the 74 articles initially screened. These two RCTs included 5540 patients, with 2778 (50.1%) patients receiving colchicine and 2762 (49.9%) patients receiving placebo. The two trials included were the COLCOT and COPS trials, both of which were multi-center randomized trials with mean duration of follow-up of 22.6 and 24 months, respectively. Characteristics of the included trials are outlined in Supplementary Table S3 with summary patient characteristics at baseline shown in Table 1. In brief, 19.4% of patients were female, with 20% having diabetes mellitus and 30.6% being current smokers. Follow-up was available in 96% of study participants in COPS and 98.1% in COLCOT. With regard to colchicine dosing, study participants in COPS received 0.5 mg twice

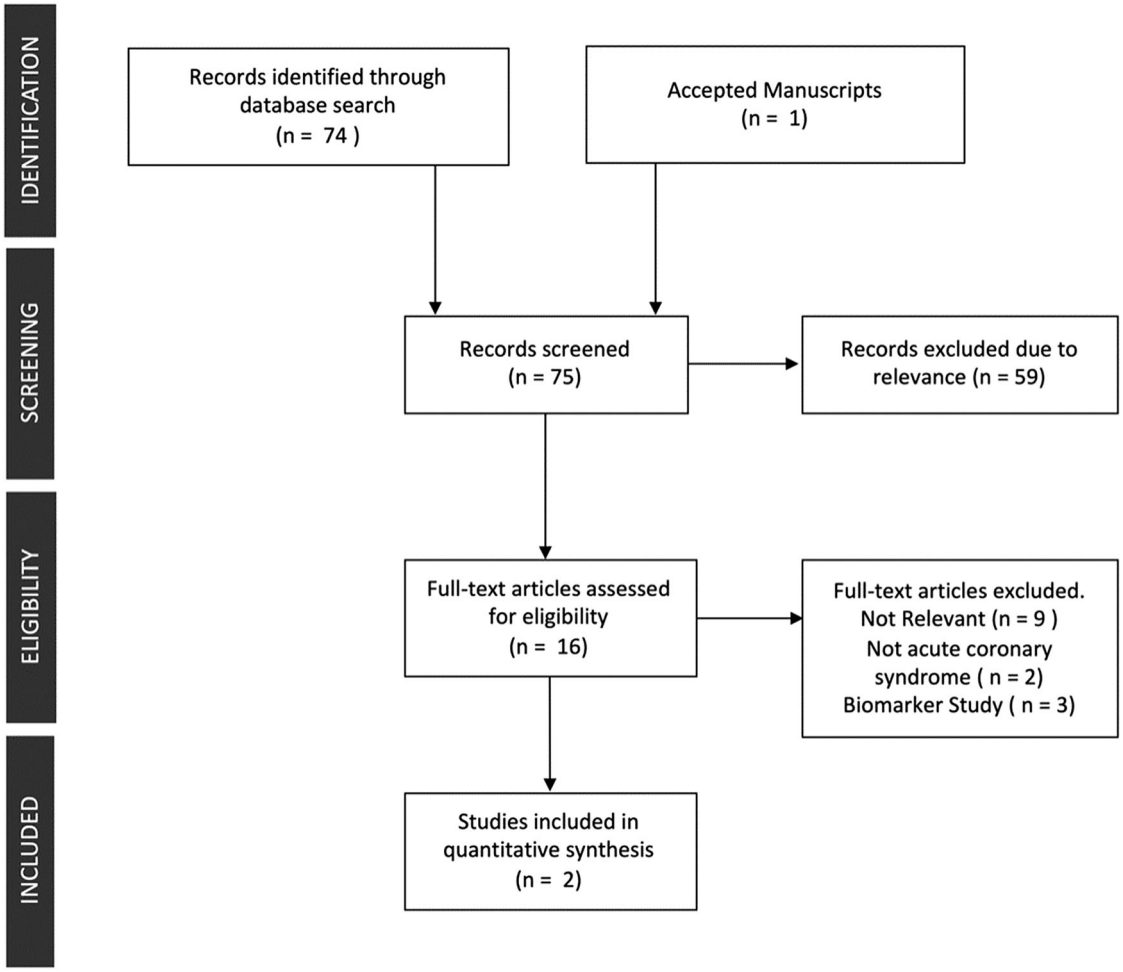


Fig. 1 Study flow chart. PRISMA statement flow diagram of review process and study selection

Table 1 Patient baseline demographics

Study	Age (years)	Male	Smoker	HTN	HChol	Diabetes	Family Hx	STEMI	NSTEMI
COPS 2020	60/60	81/78	32/37	51/50	46/46	19/19	45/36	48/53	48/44
COLCOT 2019	61/61	80/82	30/30	50/52	NR/NR	20/21	NR/NR	NR/NR	NR/NR

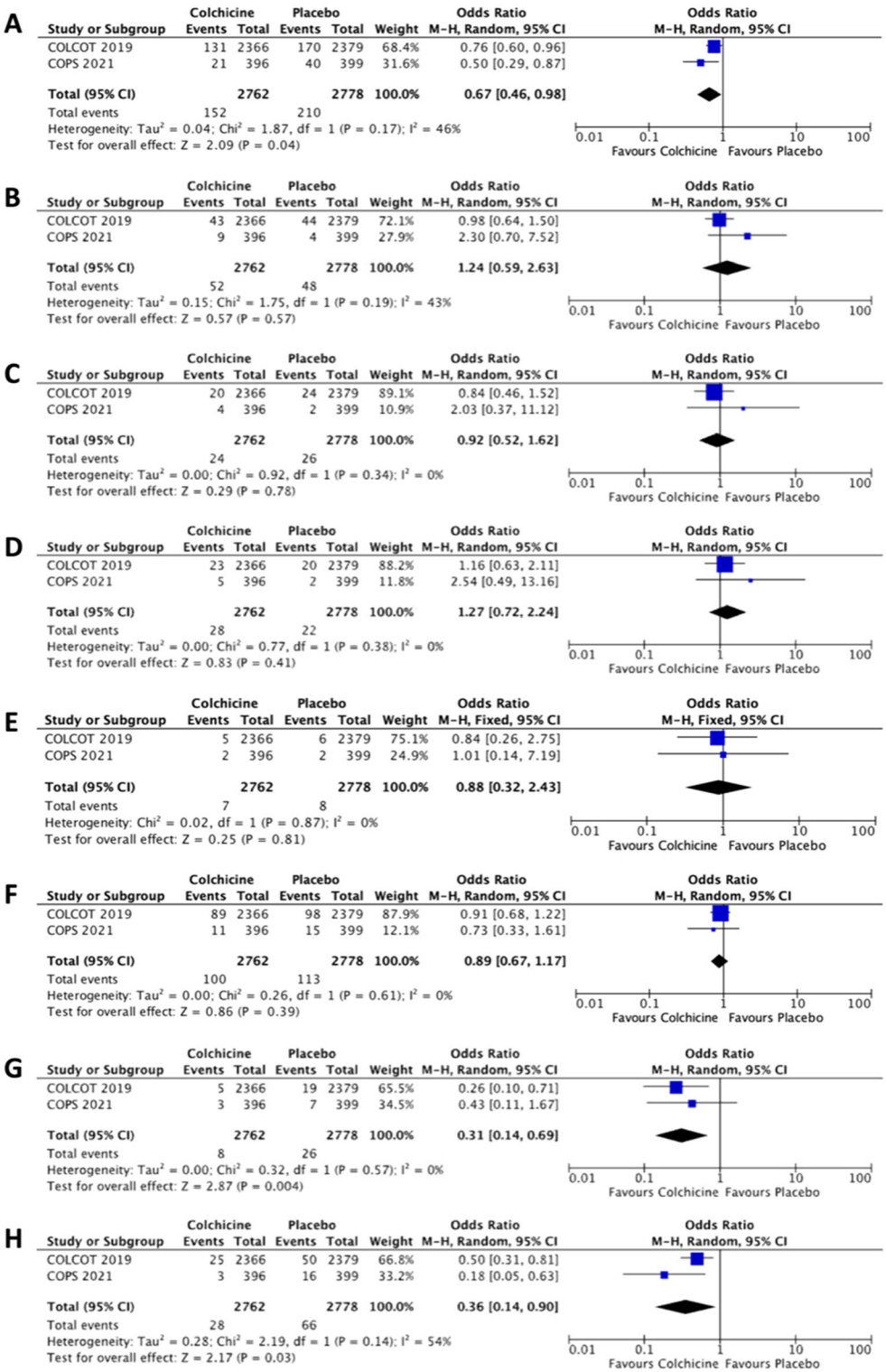
(Colchicine/Placebo) (%)

PCI percutaneous coronary intervention, *HTN* hypertension, *HChol* hypercholesterolemia, *MI* myocardial infarction, *NR* not-reported, *NA* not applicable, *LVEF* left ventricular ejection fraction, *CABG* coronary artery bypass grafting, *ACS* acute coronary syndrome

daily for 1 month and then 0.5 mg daily for the remaining 11 months. Patients enrolled in COLCOT received 0.5 mg daily for the duration of the study.

Clinical Outcomes

Both studies reported a composite as their primary endpoint. In order to equalize pooling of composite efficacy endpoints between trials, the


A
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 131 2366 170 2379 68.4% 0.76 [0.60, 0.96]
COPS 2021 21 396 40 399 31.6% 0.50 [0.29, 0.87]
Total (95% CI) 2762 2778 100.0% 0.67 [0.46, 0.98]
Total events 152 210
Heterogeneity: Tau² = 0.04; Chi² = 1.87, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 2.09 (P = 0.04)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
B
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 43 2366 44 2379 72.1% 0.98 [0.64, 1.50]
COPS 2021 9 396 4 399 27.9% 2.30 [0.70, 7.52]
Total (95% CI) 2762 2778 100.0% 1.24 [0.59, 2.63]
Total events 52 48
Heterogeneity: Tau² = 0.15; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%
Test for overall effect: Z = 0.57 (P = 0.57)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
C
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 20 2366 24 2379 89.1% 0.84 [0.46, 1.52]
COPS 2021 4 396 2 399 10.9% 2.03 [0.37, 11.12]
Total (95% CI) 2762 2778 100.0% 0.92 [0.52, 1.62]
Total events 24 26
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.78)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
D
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 23 2366 20 2379 88.2% 1.16 [0.63, 2.11]
COPS 2021 5 396 2 399 11.8% 2.54 [0.49, 13.16]
Total (95% CI) 2762 2778 100.0% 1.27 [0.72, 2.24]
Total events 28 22
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
E
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
COLCOT 2019 5 2366 6 2379 75.1% 0.84 [0.26, 2.75]
COPS 2021 2 396 2 399 24.9% 1.01 [0.14, 7.19]
Total (95% CI) 2762 2778 100.0% 0.88 [0.32, 2.43]
Total events 7 8
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.81)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
F
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 89 2366 98 2379 87.9% 0.91 [0.68, 1.22]
COPS 2021 11 396 15 399 12.1% 0.73 [0.33, 1.61]
Total (95% CI) 2762 2778 100.0% 0.89 [0.67, 1.17]
Total events 100 113
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
G
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 5 2366 19 2379 65.5% 0.26 [0.10, 0.71]
COPS 2021 3 396 7 399 34.5% 0.43 [0.11, 1.67]
Total (95% CI) 2762 2778 100.0% 0.31 [0.14, 0.69]
Total events 8 26
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo
H
Colchicine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
COLCOT 2019 25 2366 50 2379 66.8% 0.50 [0.31, 0.81]
COPS 2021 3 396 16 399 33.2% 0.18 [0.05, 0.63]
Total (95% CI) 2762 2778 100.0% 0.36 [0.14, 0.90]
Total events 28 66
Heterogeneity: Tau² = 0.28; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 2.17 (P = 0.03)
0.01 0.1 1 10 100
Favours Colchicine Favours Placebo

◀**Fig. 2** Clinical outcomes. Forest plot displaying summary odds ratio (OR) and 95% confidence interval (CI) for **A** study composite primary endpoint, **B** all-cause death, **C** cardiovascular death, **D** non-cardiovascular death, **E** resuscitated cardiac arrest, **F** myocardial infarction, **G** cerebrovascular accident, and **H** repeat evascularization

primary endpoint of COPS, our groups study, were modified to match the COLCOT definition of MACE. With these amendments, we found that in patients presenting with an acute coronary syndrome, there was a significant reduction in the equalized composite endpoint in patients receiving colchicine compared to placebo (5.5 vs. 7.6%) with an OR of 0.67 (95% CI 0.46–0.98, $p = 0.04$, $I^2 = 46\%$) (Fig. 2A). When assessing type of death, there was no significant difference between all-cause death (OR 1.24, 95% CI 0.59–2.63, $p = 0.57$, $I^2 = 43\%$) (Fig. 2B), cardiovascular death (OR 0.92, 95% CI 0.52–1.62, $p = 0.78$, $I^2 = 0\%$) (Fig. 2C), non-cardiovascular death (OR 1.27, 95% CI 0.72–2.24, $p = 0.41$, $I^2 = 0\%$) (Fig. 2D), or resuscitated cardiac arrest (OR 0.88, 95% CI 0.32–2.43, $p = 0.81$, $I^2 = 0\%$) (Fig. 2E) in those receiving colchicine versus placebo respectively.

Both trials reported events with regards to vascular outcomes. In patients receiving colchicine, there was no difference in regard to rates of myocardial infarction at longest available follow-up with an OR of 0.89 (95% CI 0.67–1.17, $p = 0.39$, $I^2 = 0\%$) (Fig. 2F). There was, however, a significant reduction in the rates of cerebrovascular accidents (OR 0.31, 95% CI 0.14–0.69, $p = 0.004$, $I^2 = 0\%$) (Fig. 2G) and repeat revascularization (OR 0.36, 95% CI 0.14–0.90, $p = 0.03$, $I^2 = 54\%$) (Fig. 2H) in patients receiving colchicine. A numerical summary of the findings is outlined in Table 2.

Publication Bias

The authors abandoned the planned assessment of publication bias given there were less than ten studies in the meta-analysis.

DISCUSSION

This contemporary meta-analysis evaluated randomized studies which evaluated the impact of colchicine administration in patients presenting with an acute coronary syndrome. The addition of colchicine to optimal guideline-directed medical therapy was shown to reduce the adjusted composite endpoint of major adverse cardiovascular events, rates of cerebrovascular events, and the need for urgent coronary revascularization, but did not result in any difference in all cause or cardiovascular mortality. Colchicine is an inexpensive drug with a favorable safety profile that has potential long-term benefits when used early in patients specifically presenting with acute coronary syndromes.

The studies included in this meta-analysis, COLCOT and COPS, had comparable inclusion criteria, patient demographics, and follow-up periods however had a higher proportion of male patients ($\sim$ 80%) in both studies. The pooled results demonstrated a reduction in the adjusted composite endpoint of major cardiovascular events, which was primarily driven by a reduction in ischemic stroke and urgent revascularization, both of which showed a statistically significant reduction with the use of colchicine. However, despite not reaching statistical significance, there was a large numerical reduction in myocardial infarction with the use of colchicine. Importantly, given our group conducted the COPS trial, we were able to adjust our combined primary endpoint to include resuscitated cardiac arrest, which brought it in line with COLCOT and is the first time that this specific data have been published. This substantially increases the reliability of the analysis compared to others who have post hoc adjusted composites of the primary endpoint based on limited published data and then undertaken analysis. This gives our study reliability and novelty, along with analysis at 2 years of follow-up.

Both COPS and COLCOT initiated treatment with colchicine either prior to discharge (COPS) or within 30 days of index event (COLCOT). Moreover, a prespecified analysis of time to

Table 2 Study outcomes

	COPS		COLCOT	
	Colchicine, *N* = 396	**Placebo, *N* = 399**	**Colchicine, *N* = 2366**	**Placebo, *N* = 2379**
Equalized primary composite endpoint: Cardiovascular mortality, resuscitated arrest, myocardial infarction, ischemic stroke, urgent revascularization				
Events, *N* (%)	21 (5.3%)	40 (10.0%)	126 (5.3%)	164 (6.9%)
Combined events, *N* (%)	Colchicine 152 (5.5%)		Placebo 210 (7.6%)	
Summary OR (95% CI)	0.67 (0.46–0.98)			
Cardiovascular death				
Events, *N* (%)	4 (1.0%)	2 (0.5%)	20 (0.8%)	24 (1.0%)
Combined events, *N* (%)	Colchicine 24 (0.9%)		Placebo 26 (0.9%)	
Summary OR (95% CI)	0.92 (0.52–1.62)			
Resuscitated cardiac arrest				
Events, *N* (%)	2 (2.3%)	2 (1.0%)	5 (1.6%)	6 (1.8%)
Combined events, *N* (%)	Colchicine 7 (0.25%)		Placebo 8 (0.29%)	
Summary OR (95% CI)	0.88 (0.32–2.43)			
All-cause death				
Events, *N* (%)	9 (2.3%)	4 (1.0%)	43 (1.6%)	44 (1.8%)
Combined events, *N* (%)	Colchicine 52 (1.9%)		Placebo 48 (1.7%)	
Summary OR (95% CI)	1.24 (0.59–2.63)			
Myocardial infarction				
Events, *N* (%)	11 (2.8%)	15 (3.8%)	89 (3.8%)	98 (4.1%)
Combined events, *N* (%)	Colchicine 100 (3.7%)		Placebo 125 (4.5%)	
Summary OR (95% CI)	0.89 (0.67–1.17)			
Cerebrovascular accident				
Events, *N* (%)	3 (0.8%)	7 (1.8%)	5 (0.2%)	19 (0.8%)
Combined events, *N* (%)	Colchicine 8 (0.3%)		Placebo 26 (0.9%)	
Summary OR (95% CI)	0.31 (0.14–0.69)			
Urgent revascularization				
Events, *N* (%)	3 (0.8%)	16 (4.0%)	25 (0.9%)	50 (1.8%)
Combined events, *N* (%)	Colchicine 28 (1.0%)		Placebo 66 (2.4%)	
Summary OR (95% CI)	0.36 (0.14–0.90)			

N number, *OR* odds ratio

treatment in the COLCOT supported a premise of earlier administration of colchicine within 3 days. Thus, early administration of colchicine appears to be important in reducing future events.

The original COPS trial reported an increase in all-cause death (8 vs. 1, $P = 0.017$) with the use of colchicine. At that time, we recognized the possibility of a type 1 error, given the small number of events. Recognizing that, as the study drug was discontinued at 12 months in COPS, the extended results over 24 months demonstrated this difference became non-significant (9 vs. 4, $p = 0.17$). This meta-analysis provides reassurance as to the safety of colchicine when administered in the acute phase of an ACS.

Both studies reported a similarity in adverse events between colchicine and placebo groups. Gastrointestinal (GI) adverse events, commonly associated with the use of colchicine, occurred at similar rates in the colchicine and placebo groups. The COPS study, which had twice the dose of colchicine administered initially (0.5 mg twice daily compared to 0.5 mg daily), reported a 23% incidence of GI events, compared to COLCOT, which reported a 17.5%. Dose-related comparison in GI adverse events is limited however due to the presence of similar rates of GI events in the placebo group in both studies. The incidence of GI events in these studies is comparable to what is commonly reported with the use of colchicine [13]. The COLCOT trial detected an increased rate of pneumonia with the colchicine arm (21 vs. 9, $p = 0.03$). While it could be theorized that this difference is explained by immunosuppressive properties of colchicine, this effect was not observed in COPS with no significant differences in other infections or septic shock. Although a different patient population, a systematic review on the use of colchicine did not find a greater rate of infection [13]. Overall, these findings support that colchicine has an acceptable safety profile and given it was discontinued after 1 year, further analysis on side-effects was neither warranted nor possible.

Colchicine is an efficacious, cost-effective, and safe drug. Similar to canakinumab in the CANTOS trial, its mechanisms in cardiovascular disease hinge on the interaction between atherosclerosis and inflammation. The NLRP3 inflammasome is a cytoplasmic protein complex that promotes the formation of proinflammatory interleukins, including IL-1β [14, 15] with NLRP3 inflammasomes an important component in the development of atherosclerotic disease. Animal studies support this with Duewell et al. showing that NLRP3-deficient mice, when fed a high-cholesterol diet, had significantly less atherosclerosis [14]. The presence of cholesterol crystals are themselves triggers for the activation of the NLRP3 inflammasome and do so in a dose-dependent manner, establishing the relationship between inflammation and cholesterol metabolism [15].

Inhibitors of angiotensin-converting enzyme (ACE) and beta-blockers have both been shown to be efficacious when initiated early in patients presenting with acute coronary syndromes. ACE inhibitors exert their effect through a reduction of neurohormonal activation and thus favorably alter ventricular remodeling. Meta-analysis of over 100,000 patients showed a significant benefit with ACE inhibitor use with a 7% reduction in 30-day mortality [16, 17]. Similarly, beta-blockers, through their reduction of myocardial workload and oxygen demand, heart rate, blood pressure, catecholamine levels, and decrease of myocardial demand, have been shown to have a mortality benefit of up to 23% in long-term trials [18–21]. However, the importance of this effect has been met with controversy, as many older trials pre-date the era of statin and coronary reperfusion therapy, where beta-blockers have had equivocal benefit [22]. In fact, the ongoing DANBLOCK trial seeks to investigate the benefit of beta-blockers in patients post myocardial infarction with preserved ejection fraction [23]. In contrast to the modes of action of beta-blockers and ACE inhibitors, colchicine alters patient prognosis by modifying conditions that would portend a risk of plaque rupture, through its anti-inflammatory action. Although our results did not show mortality benefit, they revealed a significant 32% reduction in adjusted MACE, along with a 69% reduction in CVA and 67% reduction in the need for urgent revascularization with little risk of medication side effects. These

data suggest that colchicine may be of benefit post ACS; however, prior to being incorporated into guidelines, it would be prudent to await the results of the CLEAR SYNERGY trial with 7000 patients and COLCARDIO-ACS trial with 3000 patients assessing similar outcomes also in an acute coronary syndrome cohort.

LIMITATIONS

This meta-analysis confers greater confidence in the efficacy and safety of colchicine when used early in patients presenting with acute coronary syndrome. These results, however, must be viewed with regard to their limitations. Firstly, long-term follow-up periods are currently not available. With only 2 years of data published, the optimal duration of treatment and long-term benefit is still not known. Longer follow-up periods are necessary to establish the long-term efficacy. Second, there were differences in the definition of primary outcome between the two trials. Although we attempted to minimize heterogeneity through the adjustment of outcomes to be more consistent with each other, it must be noted that there are differences in the original trial outcomes and that only two studies are included in this analysis.

CONCLUSIONS

In patients presenting with an acute coronary syndrome, these data suggest that the addition of colchicine commenced during index hospitalization, in combination with guideline directed medical therapy reduces rates of major adverse cardiovascular events, cerebrovascular accidents, and need for revascularization compared to standard therapy alone.

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Author Contributions. JL: Designed study, involved in initial manuscript writing and all further versions of the paper. AB: Provided appraisal of paper and all further versions of manuscript.JN: Performed initial literature review, statistical analysis, wrote initial version of manuscript.DT: Provided appraisal of paper and all further versions of manuscript.OM: Provided appraisal of paper and all further versions of manuscript.All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Disclosures. Jason Nogic, Ojas Mehta, David Tong, Adam J. Brown, and Jamie Layland have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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

REFERENCES

1. Vedanthan R, Seligman B, Fuster V. Global perspective on acute coronary syndrome: a burden on the young and poor. Circ Res. 2014;114(12): 1959–75.

2. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289–367.

3. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60(24):e44–164.

4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Rev Esp Cardiol (Engl Ed). 2017;70(12):1082.

5. Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep. 2014;16(9):435.

6. Martinez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis. 2018;269:262–71.

7. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505.

8. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian cops randomized clinical trial. Circulation. 2020;142(20):1890–900.

9. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation. 2015;132(15):1395–403.

10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339: b2700.

11. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343: d5928.

12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.

13. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2020;22(1):28.

14. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature. 2010;464(7293):1357–61.

15. Rajamaki K, Lappalainen J, Oorni K, Valimaki E, Matikainen S, Kovanen PT, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. PLoS ONE. 2010;5(7): e11765.

16. Franzosi MG. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation. 1998;97(22):2202–12.

17. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. Am J Med. 2003;115(6):473–9.

18. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S, et al. Early intravenous beta-blockers in patients with acute coronary syndrome–a meta-analysis of randomized trials. Int J Cardiol. 2013;168(2):915–21.

19. Safi S, Sethi NJ, Nielsen EE, Feinberg J, Jakobsen JC, Gluud C. Beta-blockers for suspected or diagnosed acute myocardial infarction. Cochrane Database Syst Rev. 2019;12:CD012484.

20. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. JAMA. 1988;260(14):2088–93.

21. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta blockade after myocardial infarction:

systematic review and meta regression analysis. BMJ. 1999;318(7200):1730–7.

22. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med. 2014;127(10): 939–53.

23. Kristensen AMD, Bovin A, Zwisler AD, Cerquira C, Torp-Pedersen C, Botker HE, et al. Design and rationale of the Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction: study protocol for a randomized controlled trial. Trials. 2020;21(1):415.