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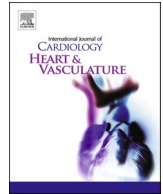
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Risk of coronary artery disease in patients with gout on treatment with Colchicine: A systematic review and meta-analysis

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ABSTRACT

Background: Colchicine has anti-inflammatory properties, but its utility in improving cardiovascular outcomes has been disputed. Here, we study the impact of colchicine on cardiovascular outcomes in patients with gout with and without coronary artery disease (CAD).

Methods: Medline, Web of Science and Cochrane Central Register of Controlled Trials were systematically searched to identify relevant studies. Primary outcomes included myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Secondary outcomes included stroke and all-cause mortality.

Results: We included 4 observational studies comprising 10,026 patients with gout on treatment with colchicine. There was no significant difference in the risk of myocardial infarction (risk ratio [RR] 0.71; 95% confidence interval [CI], 0.36–1.39), need for PCI, or need for CABG, between patients on colchicine and those not receiving colchicine. Colchicine was associated with a significantly lower risk of all-cause mortality (RR 0.58; 95% CI 0.43–0.79).

Conclusion: Non-randomized studies suggest that risk of MI, stroke and revascularization is not higher in gout patients treated with colchicine compared to gout patients without colchicine treatment.

1. Introduction

Inflammation is known to play a major role in the pathogenesis and progression of coronary artery disease (CAD). [1] However, the use of anti-inflammatory drugs in CAD have demonstrated mixed results. In the Cardiovascular Reduction Inflammation Trial (CIRT), the use of methotrexate did not result in fewer cardiovascular (CV) events compared with placebo among patients with stable atherosclerosis. [2] On the other hand, the monoclonal antibody canakinumab, was shown to reduce CV outcomes when compared to placebo (CANTOS) in those with previous myocardial infarction (MI). [3] Considering this, scientists have been in search of a cost effective and safe anti-inflammatory therapy with favorable effects on the CV system. Colchicine fits this profile and has been under study in recent years. Colchicine inhibits neutrophil migration and the NLRP3 inflammasome. [4] Importantly, it acts not only against urate crystals in gouty joints, but also against

cholesterol crystals in atherosclerotic coronary arteries. [4] Colchicine also decreases the production of the inflammatory marker IL-6 in acute coronary syndrome (ACS). [5] Thus, the interest in colchicine remains, and it has been studied repeatedly in those with CAD. However, the results have been mixed. The LoDoCo trial randomly assigned 0.5 mg a day of colchicine versus no colchicine in patients with stable coronary disease already receiving aspirin and/or clopidogrel and statins. [6] The trial showed a reduction in the risk of CV events. [6] This is in contrast to the COLCOT trial, where recruited patients within 30 days after a MI were randomized to colchicine 0.5 mg daily versus placebo. [7] Colchicine was not found to be superior in reducing individual outcomes of mortality, MI, or cardiac arrest. [7] To supplement these findings, we performed this meta-analysis to assess CV outcomes in patients with gout treated with colchicine compared to those who did not receive colchicine. The findings of this analysis will further support whether colchicine is beneficial or not in patients with or without CAD.

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2. Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and meta-Analyses (PRISMA) guidelines. [8] Medline, Web of Science and Cochrane Central Register of Controlled Trials were searched from database inception through January 2021 using the following combination of keywords: gout OR gouty arthritis or uric acid calculi AND colchicine AND myocardial infarction OR coronary artery disease OR coronary heart disease OR coronary atherosclerosis. No time restriction was placed on the search; however, language was restricted to English. We also searched trial registries, <https://www.clinicaltrialresults.org>, www.clinicaltrials.gov, abstracts, and presentations from major CV proceedings. All citations retrieved from the search were transferred to EndNote X7.5 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania). Reference manager and duplicates were removed.

All citations were screened by one reviewer (MUS). Eligible studies reported on the risk or prevalence of MI or CAD in patients with gout treated with colchicine. We included randomized and non-randomized studies. Exclusion criteria include colchicine use for secondary prevention of CAD or gout patients not on colchicine.

The primary endpoints were MI, need for percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG). Secondary outcomes included stroke and all-cause mortality.

Data on year of publication, study design, inclusion criteria, primary endpoints, and follow-up duration was extracted using a standardized data extraction form. Risk of bias was assessed using the Modified Newcastle-Ottawa scale for observational studies [9], which assesses 3 domains: patient selection, comparability, and outcome assessment. The methodological quality of a study was graded as high or low based on whether the study had adequate adjustment for confounders, which we judged to be the most critical domain affecting the outcome of myocardial infarction. [10] Table 1 and Fig. 1 shows the risk of bias assessment.

We extracted or calculated a risk ratio (RR) and 95 % confidence intervals (CI) from each study. RRs were pooled using a random effect model to account for between study variance. [14] The I^2 -statistic was quantified to measure heterogeneity with values > 25 %, 50 %, and 75 % consistent with low, moderate, and high degrees of heterogeneity, respectively. [15] Review Manager Software v5.4 was used for the analysis. P-values < 0.05 were considered to be statistically significant. Certainty in the evidence (i.e., confidence in the final estimates), was assessed using the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation) based on the risk of bias,

Table 1
Risk of bias assessment of the included studies.

Modified Newcastle Ottawa Scale	Included studies			
	Crittenden, 2012	Shah, 2020	Ju, 2020	Solomon, 2016
Selection	4	3	4	4
Comparability	0	2	0	1
Adjustment	Unadjusted	Standardized mean difference was calculated between groups to verify the balance of covariates	The outcome assessed was unadjusted	Adjusted for age, gender and race. Unadjusted for other co- morbidities
Outcome	2	3	2	2
Total	6	8	6	7

Legend: For selection, the highest score was 4 based on representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and outcome of interest at the start of the study; for comparability, the highest score was 2 based on comparability of the cohort; and for outcome, the highest score was 3 based on assessment of outcome, follow-up period, and adequacy of the follow-up.

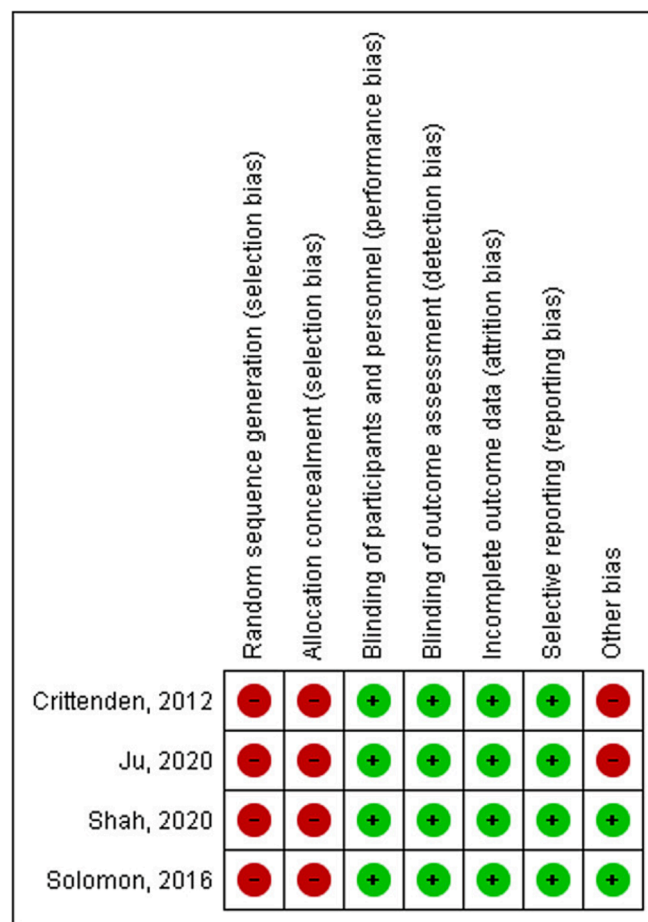


Fig. 1. Risk of bias summary in the included studies.

imprecision, indirectness, inconsistency, and publication bias. [16].

3. Results

Of 69 potential articles screened, 4 studies [11–13,17] comprising 10,026 patients with gout were included (Fig. 2). Of these, 6,800 patients were treated with colchicine and 3,426 were not. There was no mention of the dosage of colchicine used in these studies. All studies included were observational (non-randomized). Baseline characteristics of the included studies are provided in Table 2. Three studies provided information on the uric acid status of the populations studied. [12,13,17] There was no difference in serum urate levels between patients on colchicine versus not on colchicine (7.8 ± 2.1 vs 7.5 ± 2.1 mg/dL) in the study by Crittenden et al. [12] In the studies by Solomon et al. and Shah et al., those on colchicine had higher urate levels versus those not on colchicine (8.4 ± 2.8 vs 7.1 ± 2.9 mg/dL; $p = 0.003$, 8.3 ± 2.0 vs 7.6 ± 2.4 ; $p = 0.006$). [13,17] Two studies did not specify the follow-up period [11,12]. Overall mean age across both groups was 69.3 (Table 3). The mean age could not be obtained for the outcome measured in one study. [11] Table 4 demonstrates the outcomes of included studies with the number of events.

Three studies reported all-cause mortality with a total of 9510 patients. [11–13] Pooled results identified a significantly lower risk of all-cause mortality in patients with gout on colchicine compared with the non-colchicine group (RR 0.58; 95 % CI 0.43–0.79; Fig. 3).

All studies included MI as one of the outcomes. Pooled results of the 4 studies showed no difference in the risk of MI in gout patients on colchicine when compared to those not on colchicine (RR 0.71; 95 % CI 0.36–1.39; Fig. 4). [11–13,17].

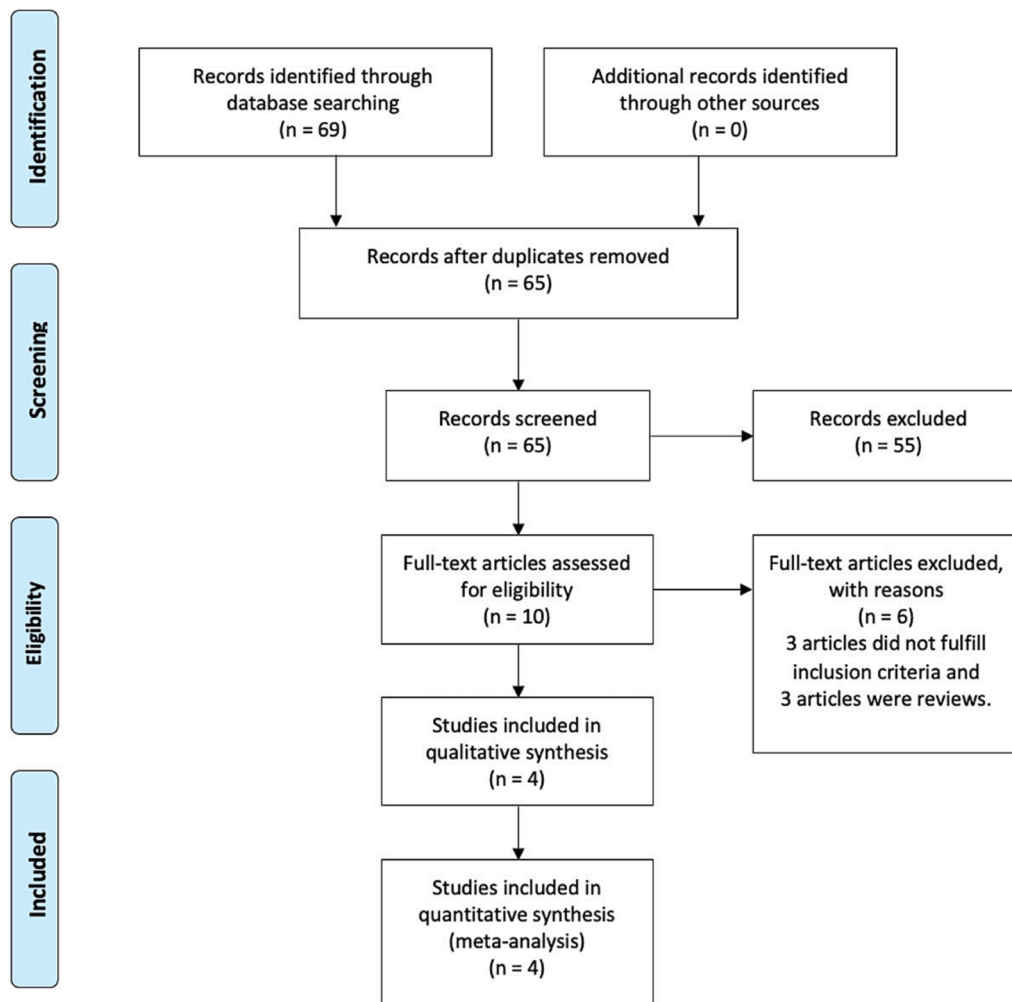


Fig. 2. The Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) flow diagram of the included studies.

Table 2

Baseline characteristics of the included studies.

Author, Year	Study Design	Inclusion Criteria	Endpoints	Follow-up duration	Other treatments	Exclusion Criteria
Crittenden, 2012	Cross-sectional study	Patients with gout on colchicine between August 2007 to July 2008 at a single center	Primary: myocardial infarction Secondary: all-cause mortality, CRP level	N/A	Allopurinol	NR
Ju, 2020	Retrospective cohort study	Patients with gout or were prescribed xanthine oxidase inhibitors between January 2013 to December 2017 at 9 hospitals and 47 outpatient clinics	Primary: composite of hospitalization due to heart failure, MACE Secondary: all-cause mortality	NR	Xanthine oxidase inhibitors	Patients under 18 years old, history of MACE or heart failure before first gout diagnosis, or on any xanthine oxidase inhibitors before first gout diagnosis.
Shah, 2020	Retrospective cohort study	Patients with gout and/or hyperuricemia between January 2000 to December 2009 at a single center	Primary: myocardial infarction	8 years	Allopurinol	Patients under 45 or over 85 years old, female, or history of cardiovascular disease
Solomon, 2016	Retrospective cohort study	Patients with gout between 2006 and 2011 at a single center	Primary: first event of myocardial infarction, stroke, or transient ischemic attack Secondary: primary outcome with subsequent revascularization procedure (PCI, CABG), all-cause mortality	Median 1.31 years	Allopurinol	NR

Legend: CRP c-reactive protein, N/A not applicable, NR not reported, MACE major adverse cardiovascular events, PCI percutaneous coronary intervention, CABG coronary artery bypass graft.

Table 3

Age and sex of included patients.

Study	Group	Sex			Age			
		Male	Female	Both	Mean	SD	Median	Range
Crittenden, 2012	Colchicine	574	2	576	71.3	11.8	NR	NR
	No Colchicine	706	6	712	71.3	11.9	NR	NR
Ju, 2020	Colchicine	NR	NR	5277	NR	NR	NR	NR
	No Colchicine	NR	NR	1937	NR	NR	NR	NR
Shah, 2020	Colchicine	446	0	446	64.0	9.0	NR	NR
	No Colchicine	276	0	276	64.0	10.0	NR	NR
Solomon, 2016	Colchicine	319	182	501	72.2	10.6	NR	NR
	No Colchicine	319	182	501	73.0	12.3	NR	NR

Legend: NR not reported.

Table 4

Outcomes from the included studies with number of events and p-values.

Author, Year	Outcomes	Colchicine	No colchicine	P-value
Crittenden, 2012	Myocardial infarction	7/576	19/712	0.03
	All-cause mortality	23/576	36/712	0.76
	C-reactive protein	2.5 (4.6)	3.4 (5.6)	0.24
Ju, 2020	Heart failure hospitalization	419/5277	142/1937	NR
	Myocardial infarction	160/5277	54/1937	NR
	Cardiovascular death	9/5277	3/1937	NR
	stroke	183/5277	73/1937	NR
	All-cause mortality	1162/5277	673/1937	NR
Shah, 2020	Myocardial infarction	8/446	3/276	0.55
	Percutaneous coronary intervention	11/446	6/276	NR
	Coronary artery bypass graft	5/446	2/276	NR
Solomon, 2016	Myocardial infarction	18/501	45/501	NR
	Stroke	9/501	35/501	NR
	Transient ischemic attack	6/501	10/501	NR
	All-cause mortality	43/501	103/501	NR
	Coronary artery bypass graft	7/501	3/501	NR
	Percutaneous coronary intervention	26/501	34/501	NR

Legend: NR not reported.

Two studies reported PCI as an outcome with a total of 1724 patients.

[13,17] Pooled results did not show a significant difference in PCI between colchicine and no colchicine in patients with gout (RR 0.83; 95 % CI 0.53–1.29; Fig. 4).

Two studies reported CABG as an outcome with a total of 1724 patients. [13,17] Pooled results from these studies revealed no significant difference in CABG between the two groups (RR 1.98; 95 % CI 0.70–5.58; Fig. 4).

Two studies reported stroke as an outcome with a total of 8,216 patients. [11,13] Pooled results identified no statistical difference in the risk of stroke among gout patients on colchicine when compared to gout patients not on colchicine (RR 0.51; 95 % CI 0.15–1.78; Fig. 3).

The sensitivity analysis of the pooled findings after the exclusion of the unadjusted data from the studies by Crittenden et al and Ju et al showed results consistent with the overall RR of MI (RR 0.71; 95 % CI 0.18–2.78; Fig. 5). [11,12] The Chi-squared test for sub-group differences was also non-significant ($p = 0.92$). Furthermore, the sensitivity analysis of the pooled findings after the exclusion of the studies that did not include patients with baseline CAD showed results contrary to the overall RR of MI in favor of patients treated with colchicine (RR 0.41; 95 % CI 0.26–0.65; Fig. 6). The Chi-squared test for sub-group differences was also significant ($p < 0.01$). [12,13].

The included studies were observational with variable methodological quality with increased risk of selection and confounding bias. Two studies did not adjust for confounders and therefore had high risk of confounding bias [11,12], whereas another study only adjusted for age, sex, and race. [13] There was high risk of selection bias in all the four studies given the lack of randomization and blinding. We were unable to

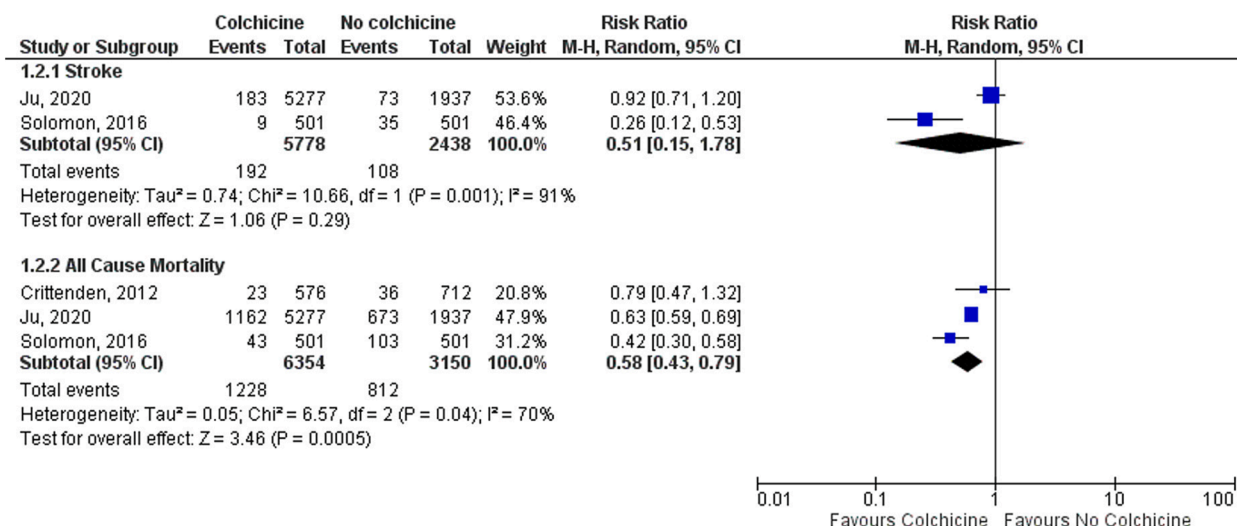


Fig. 3. Forest plot for all-cause mortality and stroke comparing gout patients on colchicine versus not on colchicine. Legend: The pooled risk ratio with 95% confidence intervals were calculated using a random effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% confidence interval for each study's risk ratio. The diamond signifies the pooled risk ratio; the diamond center denotes the point estimate and the width denotes the 95% confidence interval.

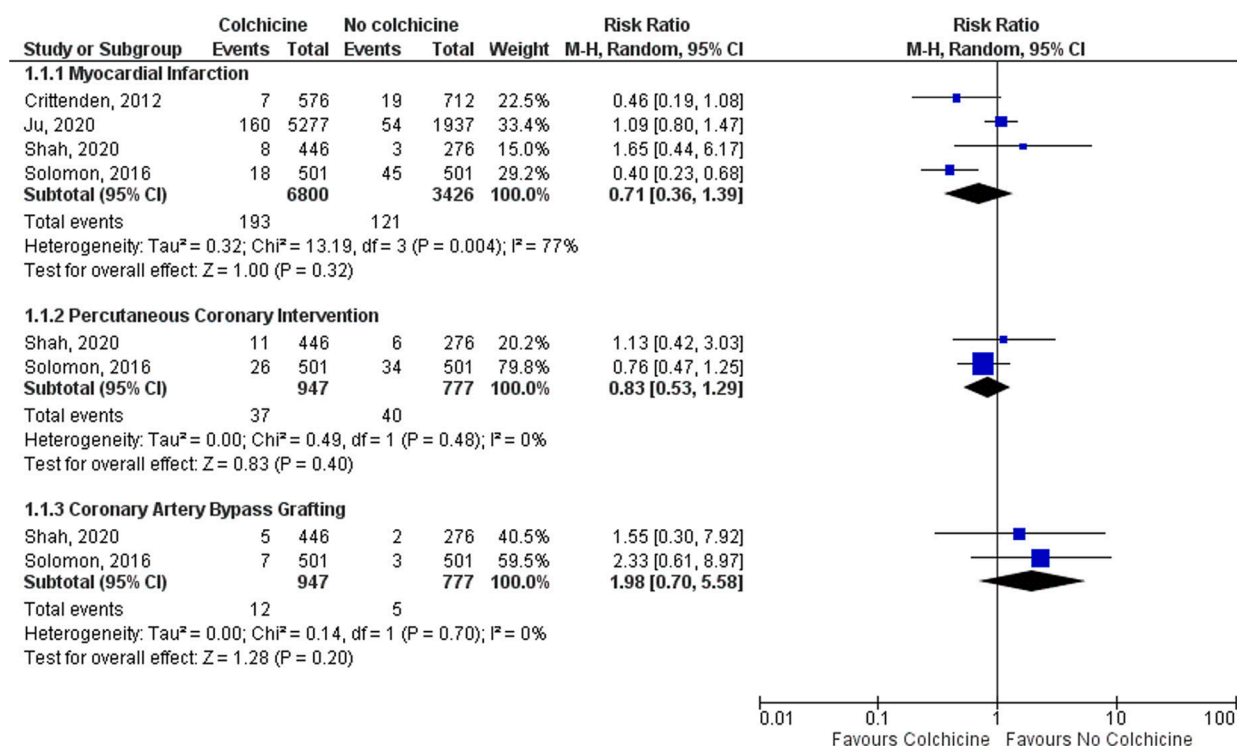


Fig. 4. Forest plot for primary outcomes comparing gout patients on colchicine versus not on colchicine. Legend: The pooled risk ratio with 95% confidence intervals were calculated using a random effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% confidence interval for each study's risk ratio. The diamond signifies the pooled risk ratio; the diamond center denotes the point estimate and the width denotes the 95% confidence interval.

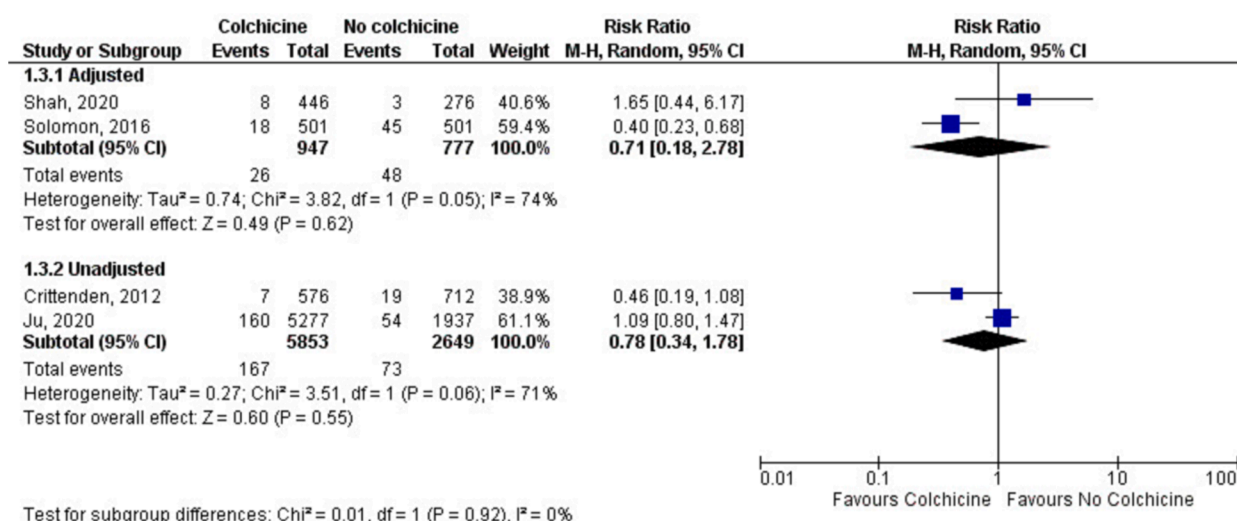


Fig. 5. Forest plot for myocardial infarction comparing gout patients on colchicine versus not on colchicine in adjusted and unadjusted subgroups. Legend: The pooled risk ratio with 95% confidence intervals were calculated using a random effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% confidence interval for each study's risk ratio. The diamond signifies the pooled risk ratio; the diamond center denotes the point estimate and the width denotes the 95% confidence interval.

statistically evaluate publication bias due to the small number of included studies. The estimates were precise for MI, stroke, and all-cause mortality (large number of events). Whereas PCI and CABG analyses had <100 events. There was no indirectness or evidence of publication bias. Heterogeneity was noted among the included studies. The quantified I^2 value for each individual outcome investigated are as follows: all-cause mortality 70 % (moderate), MI 77 % (high), PCI 0 % (minimal), CABG 0 % (minimal), stroke 91 % (high). Overall, the certainty in the estimates in all the 5 outcomes was judged to be low.

3.1. Discussion

Due to its anti-inflammatory properties, colchicine has been postulated to have beneficial effects in atherosclerotic coronary disease patients. This is particularly true in the prevention of ACS, the pathophysiology of which revolves around plaque rupture and the inflammatory cascade that follows. A recent meta-analysis by Ullah et al. [18] revealed that colchicine offers no significant reduction in major adverse cardiovascular events (MACE) with a potential for increased risk

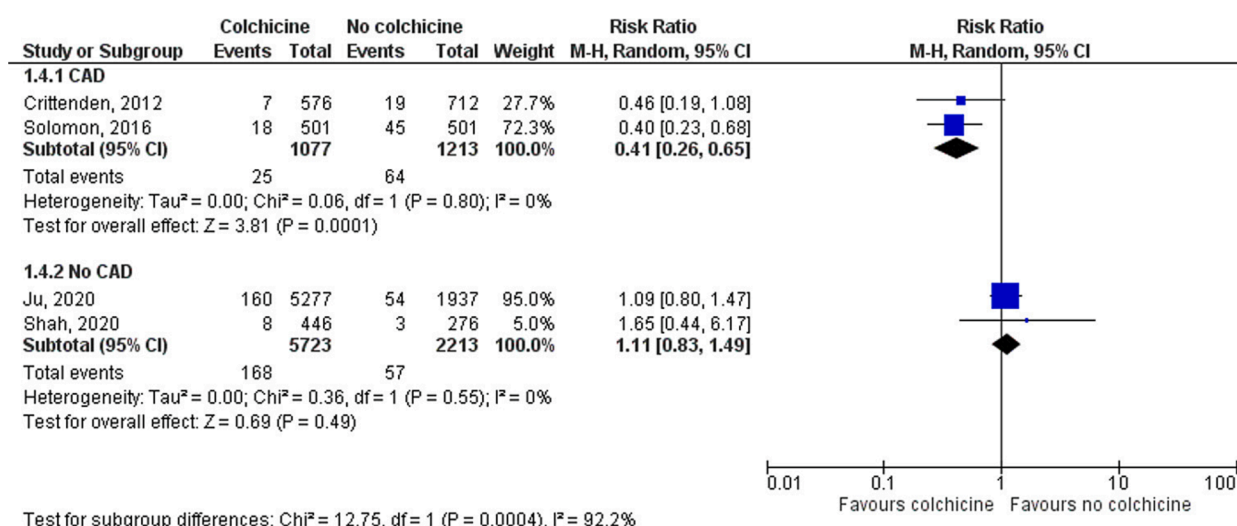


Fig. 6. Forest plot for myocardial infarction comparing gout patients on colchicine versus not on colchicine in studies that did not include patients with coronary artery disease. Legend: The pooled risk ratio with 95% confidence intervals were calculated using a random effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% confidence interval for each study's risk ratio. The diamond signifies the pooled risk ratio; the diamond center denotes the point estimate and the width denotes the 95% confidence interval.

of gastrointestinal adverse effects in patients with stable and unstable CAD. The aim of our *meta*-analysis is to study the effects of colchicine in patients with gout on the incidence of acute CV events. Therefore, only patients with gout were included, which is contrary to Ullah et al. The results reveal that colchicine use in patients with gout did not reduce the incidence of MI, stroke, or rates of revascularization compared to those not treated with colchicine. This is similar to the results of the *meta*-analysis conducted by Ullah et al.

In recent years, multiple trials have investigated the effect of colchicine on CV outcomes in patients with CAD. The LoDoCo trial identified 532 individuals with established CAD receiving anti-platelets and a statin and randomly assigned participants in a 1:1 manner to either colchicine 0.5 mg daily or no colchicine. The results showed that colchicine significantly reduced the incidence of ACS in patients with established CAD. [6] However, the study suffered from low power and was without a placebo arm, thus, it was only observer blinded. The COLCOT trial addressed these design limitations and investigated the effects of colchicine in patients with stable CAD within one month of MI. Colchicine was found to be beneficial in reducing MACE. However, on analyzing individual endpoints of mortality, MI and cardiac arrest, colchicine was not superior to placebo. There was a difference in the primary efficacy composite endpoint of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization. This is secondary to the increased risk of stroke and angina in the placebo group. [7].

The recently published LoDoCo2 trial [19] studied the effect of low dose 0.5 mg colchicine on the risk of CV events. A total of 5522 patients with chronic coronary disease without gout were recruited. 2762 in the colchicine group and 2760 in the placebo group were followed for a mean period of 28.6 months. The use of colchicine resulted in a significant decrease in the primary composite outcome of MI, stroke, CV death, and ischemia driven coronary revascularization. There was a decrease in the incidence of MI (hazard ratio [HR] 0.70; 95 % CI 0.53–0.93; $p < 0.01$) and MI or ischemia driven coronary revascularization (HR 0.67; 95 % CI 0.55–0.83; $p < 0.01$). The study did not include baseline data on lipids and blood pressure, which limits outcome reporting based on risk factor profile. The trial also had a lower-than-expected female participation.

The studies included in our *meta*-analysis highlight the unclear utility of colchicine in reducing adverse cardiac outcomes in patients with gout. Crittenden et al [12] compared colchicine users to non-users with

gout and found that those treated with colchicine had a lower prevalence of MI (RR 0.46, $p = 0.03$). In 2016, Solomon et al [13] compared colchicine users to non-users in a 1:1 ratio with 501 subjects in each group. The study demonstrated that those treated with colchicine had a reduced incidence rate of the composite primary outcome of MI, stroke, and transient ischemic attack compared to non-users. There was a statistically significant reduction in the incidence of MI and stroke when evaluated individually amongst colchicine users. In 2020, Ju et al's study [11] performed a sub-group analysis on the concurrent use of colchicine with xanthine oxidase inhibitors. It showed that colchicine users had lower all-cause mortality (HR 0.67; 95 % CI 0.59–0.77; $p < 0.01$), but there was no difference in the risk of developing non-fatal MI, stroke, or CV death. A longer duration of colchicine use was associated with a statistically significantly lower risk of hospitalization for heart failure (HR 0.75, 95 % CI 0.59–0.94; $p = 0.01$). In the retrospective study led by Shah et al [17], no difference in the incidence of MI was found when comparing colchicine users and non-users. This study used data from the Veteran Affairs population, comprising only of men, which severely limits the generalizability and the external validity of the study. Since the landmark LoDoCo, COLCOT, and LoDoCo2 trials included patients with CAD, we performed a sensitivity analysis and identified that the pooled findings of the two studies that included patients with CAD showed a decreased risk of MI when on colchicine. There appears to be a correlation between colchicine use and decreased risk of ACS in patients with established CAD as identified in some landmark trials [6,19] and the sensitivity analysis in this review. This may be due to the anti-inflammatory properties of colchicine which is evident mostly in patients with risk factors for atherosclerotic CAD.

Despite the mixed results thus far, the utility of colchicine in improving cardiovascular outcomes in those with CAD remains of great interest. Further trials similar to LoDoCo2 would provide further insight. The CLEAR-SYNERGY trial is an ongoing large randomized controlled trial comparing colchicine 0.5 mg twice daily versus placebo in 4000 ST-elevation MI patients receiving a SYNERGY stent (ClinicalTrials.gov NCT03048825). This trial is underway to study the benefits of colchicine and spironolactone in patients with MI.

3.2. Limitations

There are several limitations worth noting. Two studies [12,17] did not include females, limiting the generalizability of this *meta*-analysis.

All studies included were observational in design and lacked randomization, which increases the possibility of selection bias and confounding. The included studies were heterogenous with regards to the population studied, outcomes reported, and concomitant medications utilized for the treatment of gout. Additionally, there was no mention of the dose of colchicine used in the studies included.

4. Conclusion

The objective of this systematic review and *meta*-analysis was to identify if the risk of CAD is greater in patients with gout treated with colchicine compared to those without. Taking into account the observational nature of available studies, the combined data suggests that the rate of MI, stroke, and revascularization procedures are not different in gout patients treated with colchicine when compared to gout patients not treated with colchicine. However, in patients with gout and established CAD, the use of colchicine is associated with decreased risk of MI.

Ethics approval and consent to participate.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was a *meta*-analysis that did not require approval from our institutional review board. This article does not contain any studies with animals performed by any of the authors.

Availability of data and materials.

Data is safely kept in a password protected security system at Thomas Jefferson University Hospital. The datasets used and/or analysed during the current study are de-identified and available from the corresponding author on reasonable request.

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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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