Colchicine for Stroke Prevention: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: There has been recent interest in the role of colchicine in cardiovascular diseases, given the implication of inflammation in the pathogenesis of atherothrombosis. This systematic review assessed the role of colchicine in preventing primary or secondary stroke/transient ischemic attack (TIA) in an adult population.

Methods: Four databases were electronically searched: MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), and OpenGrey. Studies were eligible if they reported stroke or TIA incidence as a primary/secondary end point, or as an adverse event. Only case–control studies, cohort studies, and randomized controlled trials (RCTs) were eligible. The primary end point was a pooled estimate using relative risk ratios (RRs) with 95% CIs. Two-sided P values were considered significant if $P < 0.05$. Statistical heterogeneity was assessed by using the Cochrane Q statistic and the Higgin's I^2 statistic. An a priori decision was made to conduct a subgroup analysis based on study type.

Findings: A total of 5 studies were eligible for inclusion: 4 RCTs and 1 cohort study. There were 77 reported stroke/TIA events of a combined 2170 patients. Pooling all studies, stroke incidence was lower in the colchicine versus non-colchicine users (RR, 0.37; 95% CI, 0.22–0.62; $P = 0.0002$). There was no statistical heterogeneity ($\chi^2 = 2.72$; $df = 4$; $P = 0.61$; $I^2 = 0\%$). Pooling 4 RCTs as determined a priori, there was no significant effect of colchicine on stroke incidence (RR, 0.61; 95% CI, 0.17–2.17; $P = 0.57$). Results of the single cohort study suggested that colchicine reduced stroke incidence (RR, 0.33; 95% CI, 0.19–0.59; $P = 0.0002$).

Implications: Colchicine has a potential protective benefit in both primary and secondary stroke/TIA incidence. Current data are inconclusive, likely due to the small sample sizes of available RCTs. Large-scale pragmatic RCTs are required to provide robust evidence in this domain. (*Clin Ther.* 2019;41:582–590) Crown Copyright © 2019 Published by Elsevier Inc. All rights reserved.

Keywords: colchicine, stroke, TIA, transient ischemic attack.

INTRODUCTION

Colchicine is a widely available and well-tolerated drug, known for its anti-inflammatory properties. This alkaloid compound was first identified in 1820 and is the mainstay for medical management of inflammatory conditions such as gout, Familial Mediterranean Fever, and, more recently, acute pericarditis.[1,2] Its anti-inflammatory action is mediated by inhibition of microtubule polymerization to disrupt the cytoskeleton.[3] Colchicine also has direct immunomodulatory effects, particularly inhibition of activation of the NOD-like receptor protein 3 (NLRP3) inflammasome complex[4] and downregulation of pro-inflammatory cytokines.[5]

There has been recent interest in the role of colchicine in cardiovascular diseases, given the implication of inflammation in the pathogenesis of atherothrombosis. However, this relationship was mostly at a hypothetical level.[6] The recent CANTOS (The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial,

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however, showed that attenuating inflammation with a monoclonal antibody targeting interleukin (IL)-1β led to significant reductions in cardiovascular events without affecting lipid levels.[7] This outcome validates the inflammatory hypothesis of atherothrombosis and thus introduces the possibility of new therapeutic targets.

Despite current optimal medical therapy (OMT) that includes antihypertensive agents, antithrombotic agents, and lipid-lowering therapy, the annualized risk of recurrent stroke/transient ischemic attack (TIA) after an index event is still reported up to 3.6%.[8] Hence, there is a need for novel therapies to further reduce stroke risk.

The goal of the present review was to examine the current available evidence to investigate the potential benefits of using colchicine for primary or secondary stroke and TIA prevention in the adult population (>18 years of age).

MATERIALS AND METHODS

Search Strategy

The study results were reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9] Two authors (C.K. and K.V.) independently searched MEDLINE (accessed through Ovid), EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials). Gray literature was searched via OpenGrey. The search terms ("Colchicine" AND ("Stroke" OR "Cardiovascular Disease" OR "Transient Ischemic Attack" OR "Cerebrovascular Disease")) were combined as both key words and exploded MeSH terms (see Supplemental Appendix 1 in the online version at doi:10.1016/j.clinthera.2019.02.003). This approach was supplemented by reviewing reference lists of relevant literature reviews.

Eligibility Criteria

Studies were eligible for selection if they reported stroke or TIA incidence as a primary end point, a secondary end point, or as an adverse event. Strokes from any cause were considered, with both fatal and nonfatal cases included. Case-control, cohort studies, and randomized controlled trials (RCTs) were all eligible. Studies were required to compare colchicine users versus placebo, usual therapy, or no therapy in an adult population. There were no date limitations. Results were limited to English and human subjects only. Case reports and editorials were excluded. Studies with no recorded stroke events were excluded.

Study Selection

Two authors (C.K. and K.V.) independently screened titles and abstracts to identify potential studies. Full-text review was then conducted separately to identify eligible studies. Any disagreement was resolved by discussion between the 2 authors.

Data Extraction

All data was independently extracted from text, tables, and figures by two authors (C.K. and K.V.). Discrepancies between reviewers were resolved with discussion to reach a consensus. The predetermined primary end point was incidence of stroke or TIA.

Risk of Bias Assessment

Two authors (C.K. and K.V.) assessed methodologic quality within RCTs in collaboration. The Cochrane Risk of Bias tool[10] was used to objectively assess 6 specific domains: random sequence allocation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, completeness of outcome data, and selective reporting.

Statistical Analysis

The primary end point of stroke incidence was pooled using an a priori determined random effects model. An a priori decision was made to conduct subgroup analysis based on the different study designs. Relative risk (RR) was used as the summary effect with 95% CIs. Two-sided P values were used and considered significant if $P < 0.05$. Statistical heterogeneity was to be assessed by using the Cochrane Q statistic and the Higgins I^2 statistic. Publication bias was assessed by examining funnel plot asymmetry using Egger's regression test. An a priori decision was made to only assess publication bias if at least 10 studies were included to ensure asymmetry tests were adequately powered.[11]

All analyses were performed by using Review Manager (RevMan version 5.3; Cochrane Collaboration, Oxford, United Kingdom) and Stata MP (Stata Statistical Software: Release 14; StataCorp LP, College Station, Texas).

RESULTS

A total of 1242 unique records were identified through initial searching. From these, 1207 records were

excluded by screening the title and abstract. From the 35 remaining records, 5 were deemed eligible for inclusion in the meta-analysis after full-text review. Of these, 4 records were RCTs,[12–15] and the remaining record was a retrospective cohort study.[16] These findings are summarized in the accompanying PRISMA flowchart (Figure 1). There was no disagreement between authors.

Characteristics of the 5 included studies are summarized in the Table.[12–16] Male subjects were more prevalent across all study populations. Colchicine dosing protocol was reported by 4 of 5 studies and differed between each study. Follow-up periods varied from 32 days to 3 years.

Overall, the risk of bias was low in all 6 domains across all RCTs (Figure 2) (see Supplemental Appendix 2 for detailed risk of bias assessment in the online version at doi:10.1016/j.clinthera.2019.02.003). One RCT was assessed to be at high risk of performance bias. There were no other domains in any RCT that were high risk of bias.

The eligible studies were pooled together in a meta-analysis as shown in Figure 3. Stroke incidence was lower in the colchicine group compared with non-colchicine users (RR, 0.37; 95% CI, 0.22−0.62; $P = 0.0002$). There was no statistical heterogeneity in the Cochrane Q test ($\chi^2 = 2.72$; $df = 4$; $P = 0.61$) or Higgin's I^2 test ($I^2 = 0\%$). Pooling 4 RCTs as determined a priori, there was no significant effect of colchicine on the incidence of stroke (RR, 0.61; 95% CI, 0.17−2.17; $P = 0.57$). There was no statistical heterogeneity in the RCT subgroup analysis ($\chi^2 = 2.02$; $df = 3$; $P = 0.57$; $I^2 = 0\%$). There was only 1 cohort study in the cohort subgroup analysis, which showed that colchicine reduced stroke incidence (RR, 0.33; 95% CI, 0.19−0.59; $P = 0.0002$). Testing statistical heterogeneity was not applicable in this subgroup because there was only 1 included study.

A funnel plot depicting the 5 included studies is shown in Figure 4. Funnel plot asymmetry was not investigated due to the small number of included studies, as determined a priori.

DISCUSSION

The proposed mechanism of colchine's stroke protective effects is via its anti-inflammatory action that reduces plaque progression and destabilization. Key components of atherosclerosis pathogenesis are the NLRP3 inflammasome complex and IL-1 pro-atherogenic cytokine family.[17] The NLRP3 inflammasome is a cytosolic multiprotein complex that is assembled in myeloid cells (eg, neutrophils and monocytes) upon exposure to stress stimuli such as cholesterol crystals.[18] Assembly of the NLRP3 inflammasome complex results in the caspase-1−dependent upregulation of atherogenic IL-1β and IL-18 cytokines, which are predictive of future cardiovascular events. Colchicine inhibits NLRP3 inflammasome activation via several proposed mechanisms such as direct monocyte caspase-1 inhibition and inhibition of colocalization inflammasome complex proteins.[17,18] Colchicine is also believed to have direct inhibitory cellular effects via cytoskeletal disruption. By binding to the highly expressed α- and β-tubulin proteins in neutrophils and macrophages, it inhibits a range of cellular processes, including adhesion, rolling, phagocytosis, and cytokine secretion.[19]

This inflammatory process in atherosclerotic disease has been noted in patients with coronary artery disease. Blood samples from patients with acute coronary syndrome (ACS) were found to have significantly elevated IL-1β, IL-6, and IL-18 levels compared with healthy control subjects.[20] Furthermore, in patients with ACS and those with stable coronary artery disease, these pro-inflammatory cytokines were all found to be at higher levels in the coronary sinus compared with arterial and venous levels. Colchicine was found to significantly lower transcoronary levels of all 3 pro-inflammatory cytokines. This finding may explain why a recent computed tomography angiography study reported a significant reduction in coronary low attenuation plaque volume in colchicine plus OMT users versus OMT alone users.[21] These results were independent of high-dose statin therapy. A 2016 Cochrane review showed that patients receiving colchicine therapy were significantly less likely to have a recurrent myocardial infarction (RR, 0.20; $P = 0.003$).[22] This summary estimate was derived from 2 studies[14,23] and was deemed to be of "moderate" quality as per the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.[24] The pathophysiology of myocardial infarction and ischemic stroke are fundamentally similar: plaque rupture leading to arterial thrombotic occlusion. Primary and secondary preventative therapy for both conditions is also similar, relying on antiplatelet agents and statins.

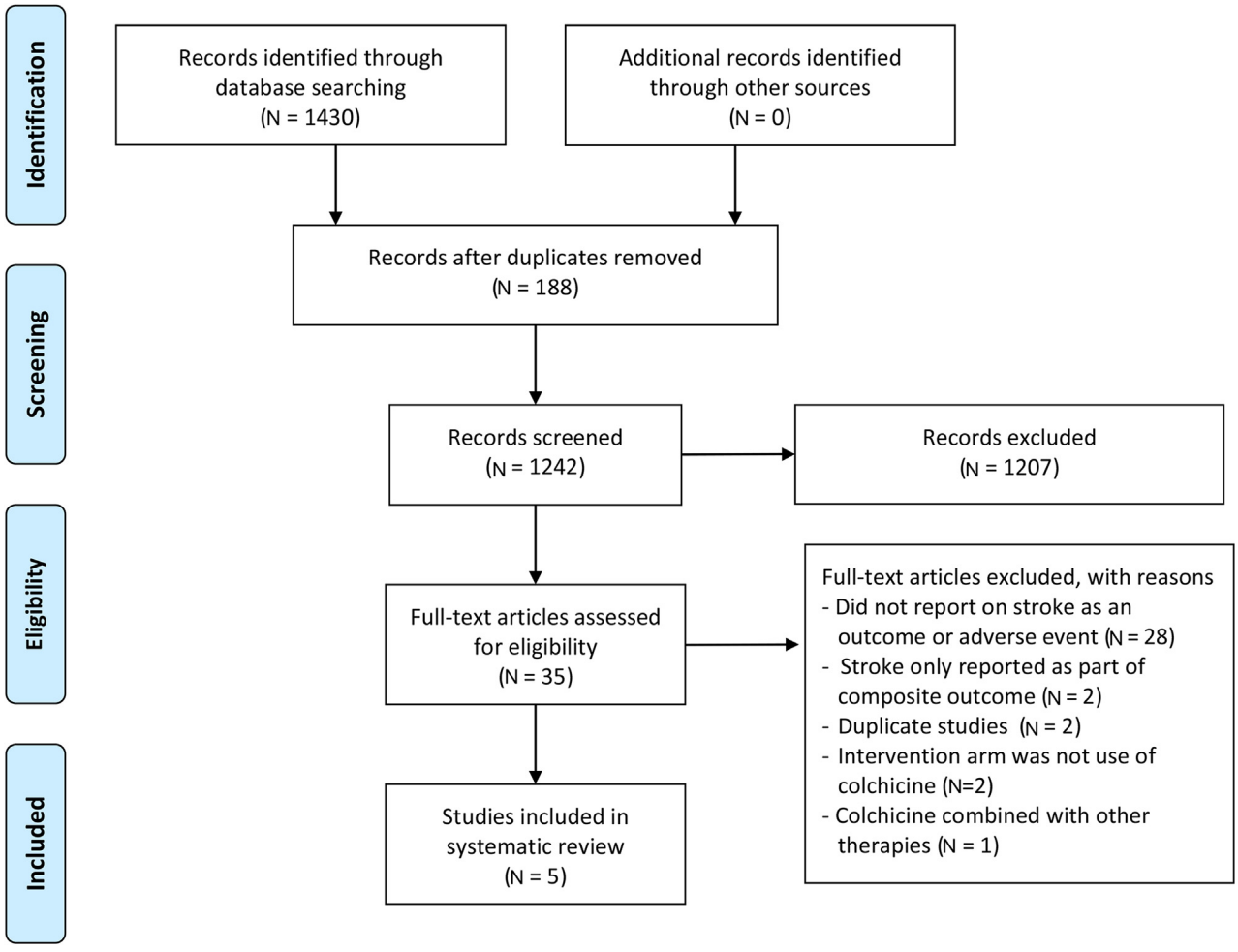

Figure 1. Search strategy per Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Given this similarity, we hypothesized that colchicine therapy would improve plaque stability and reduce the incidence of stroke/TIA.

The present pooled analysis of 4 RCTs and 1 retrospective cohort study suggest that patients taking colchicine are less likely to experience ischemic stroke/TIA compared with those who are not (RR, 0.37; 95% CI, 0.22−0.62; $P = 0.0002$). A subgroup analysis of only RCTs, however, did not reach statistical significance for this effect ($P = 0.44$).

The retrospective cohort study had a much larger sample size (N = 1002), with a significant weight on the overall summary effect (83.3%). An a priori subgroup analysis of this cohort study found colchicine users to be at almost 3 times less risk of ischemic stroke/TIA compared with non-colchicine counterparts (RR, 0.37; 95% CI, 0.19−0.59). Although this result is promising, the study had large baseline differences between the control and colchicine groups, representing substantial selection bias. Of note, patients in the non-colchicine group at baseline had significantly higher prevalence of end-stage renal disease compared with colchicine users (17.4% vs 12.2%, respectively; $P = 0.02$), Furthermore, non-colchicine users had significantly lower statin use (15.6% vs 49.7%; $P < 0.0001$). This

Table. Baseline characteristics of included studies.

Characteristic	Deftereos et al,[12] 2013	Imazio et al,[13] 2014	Nidorf et al,[14] 2013	Raju et al,[15] 2012	Solomon et al,[16] 2016
Study design	RCT	RCT	RCT	RCT	Retrospective cohort study
Participants	196	360	532	80	1002
Population	Diabetic patients who underwent PCI with BMS	Postcardiac surgery patients	Stable CAD patients	In-hospital patients with ACS or acute ischemic stroke	Patients with a gout diagnosis
Follow-up period	6 mo (all)	3 mo (all)	3 y (median)	32 d (median)	16.5 mo (median)
Colchicine dosing	0.5 mg BID	≥70 kg: 0.5 mg BID <70 kg: 0.5 mg daily	0.5 mg daily	1 mg daily	Not specified
Study characteristics					
Age, mean (SD), Y	63.6 (7.0)	67.5 (10.6)	66.5 (9.4)	57.2 (10)	72.6 (11.5)
Male, %	65	69	89	89	84
Ever-smoker, %	38	52	5	79	62
Hypertension, %	49	66	—	43	52
Diabetes, %	100	22	30	16	38

ACS = acute coronary syndrome; BMS = bare-metal stent; CAD = coronary artery disease; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

finding is concerning for confounding bias because statins are proven to reduce both primary and secondary cardiovascular events.[25,26] Hence, the cohort study results should be interpreted with caution.

Stroke incidence was 1.36% and 4.87% in the colchicine group and control group, respectively. The control group had a low event rate compared with figures in large population studies (8.3% in the United States[27] among adults aged ≥65 years, 7.6% in Singapore[28] among adults aged ≥60 years). One possible explanation is that many patients included in this meta-analysis were already receiving therapy for other comorbidities that would reduce stroke risk. Aspirin use was prevalent in ~40% of all patients in the cohort study[16]; 95% of patients in the study by Nidorf et al[14] were already taking a high-dose statin. Furthermore, 3 of the 5 studies[12–14] had a short follow-up duration (6, 3, and 1 month, respectively), which may have artificially reduced the event rate.

There was substantial clinical heterogeneity within the RCT subgroup analysis. As seen from the Table, there were vastly different study populations and primary outcomes across the included studies. Stroke/TIA was a secondary outcome in 2 studies[13,14] and reported as an adverse event in the other 2 studies.[12,15] Methodologic heterogeneity was also evident between included RCTs, such as differences between dosing regimens and duration of follow-up. Given the large heterogeneity across the 4 RCTs, it was very unlikely that a true effect size would encompass all the included studies. Hence, a random effects approach was appropriately implemented, as determined a priori. There was no statistical heterogeneity overall or within subgroups. However, this result should be interpreted with caution, as both the Cochrane Q statistic and the Higgins I^2 statistic have poor power to detect true heterogeneity when there are a small number of included studies.[29,30]

A key limitation in this meta-analysis was that no included trial investigated stroke/TIA as the primary end point. In 2 studies, stroke was reported as an adverse event rather than a deliberate secondary end

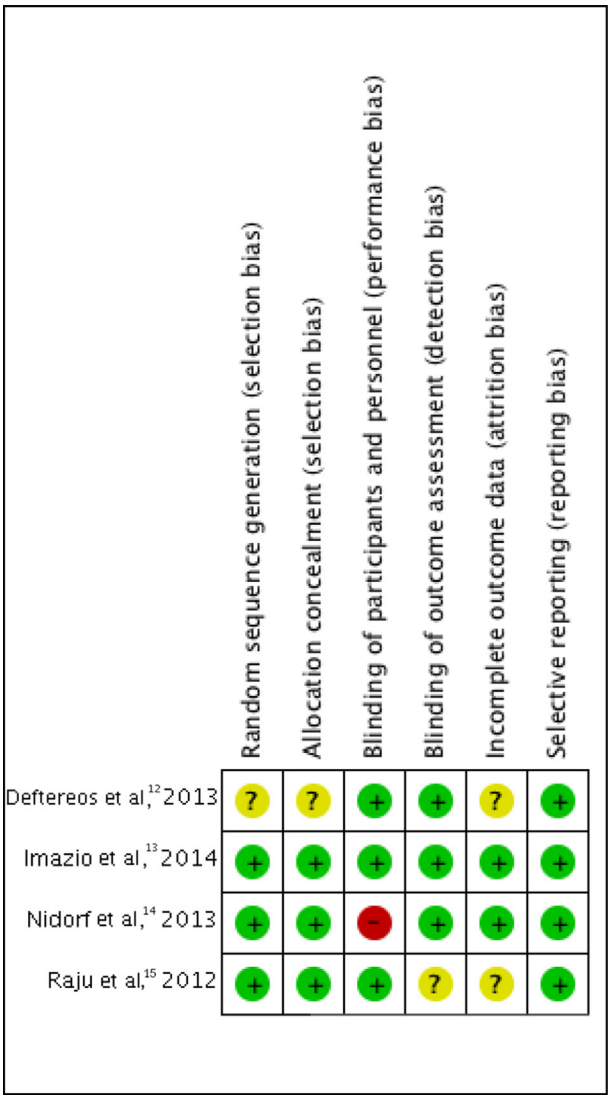

Figure 2. Summary of risk of bias assessment of all 4 randomized controlled trials.

point. This approach may explain the large clinical and methodologic heterogeneity. Only one study[14] specified that stroke events were of ischemic etiology, whereas the others[12,13,15] did not differentiate between stroke subtypes. This is a significant limitation, as current evidence[31] suggests an association only between raised inflammatory markers and ischemic stroke. There were a very small number of stroke/TIA events in all RCTs in which data were available. Another issue was the short duration of follow-up in 3 of the 4 RCTs. As seen in the Table, the second longest follow-up duration was 6 months; the shortest period was 32 days. Given the low incidence rate of stroke, we require longer follow-up times to attain more meaningful data in terms of the impact of colchicine in stroke prevention. As discussed earlier, the cohort study was at high risk of selection bias. The authors identified that non-colchicine users in this study were more likely to be unwell.[16]

Another issue with regard to this meta-analysis is the lack of generalizability of results. The RCTs recruited from a relatively low comorbid elderly population. Patients with significant hepatic and kidney disease were often excluded. Nidorf et al[14] excluded patients who were clinically unstable within 6 months of recruitment. Two studies[12,14] subjectively excluded patients who were perceived to be noncompliant with follow-up before randomization. These narrow inclusion criteria can limit our ability to interpret these results in the context of real-world practice. More pragmatic clinical trials and broader real-world cohort designs would be useful.

The present review used 2 independent reviewers and followed the PRISMA guidelines to minimize reporting bias.[9] There may be some risk of bias due to incomplete retrieval of data. Two studies[32,33] identified in our search strategy had stroke as part of a composite end point in an RCT study with colchicine and non-colchicine study arms. However, we were unable to access data from these studies, and hence unable to add relevant data to this review. We were unable to conduct an additional subgroup analysis for stroke subtypes due to the small number of events and limited availability of stroke subtyping data.

To our knowledge, this study is the largest and most comprehensive meta-analysis to date that investigates the possible role of colchicine in stroke prevention. There are 2 previous reviews with accompanying meta-analyses that examine the cerebrovascular protective effects of colchicine.[22,34] One study[23] in the Cochrane review[22] was not included in our meta-analysis, as there was no incidence of stroke in either study arm. Neither review assessed cohort studies.

Overall, we believe the current evidence surrounding the use of colchicine in stroke prevention is of "low" quality, as per the GRADE Working Group grades of evidence.[24] This implies that further research is very likely to have an important impact on our confidence in the summary estimate of effect and is likely to change the estimate. Although our results showed a reduced risk of stroke in colchicine

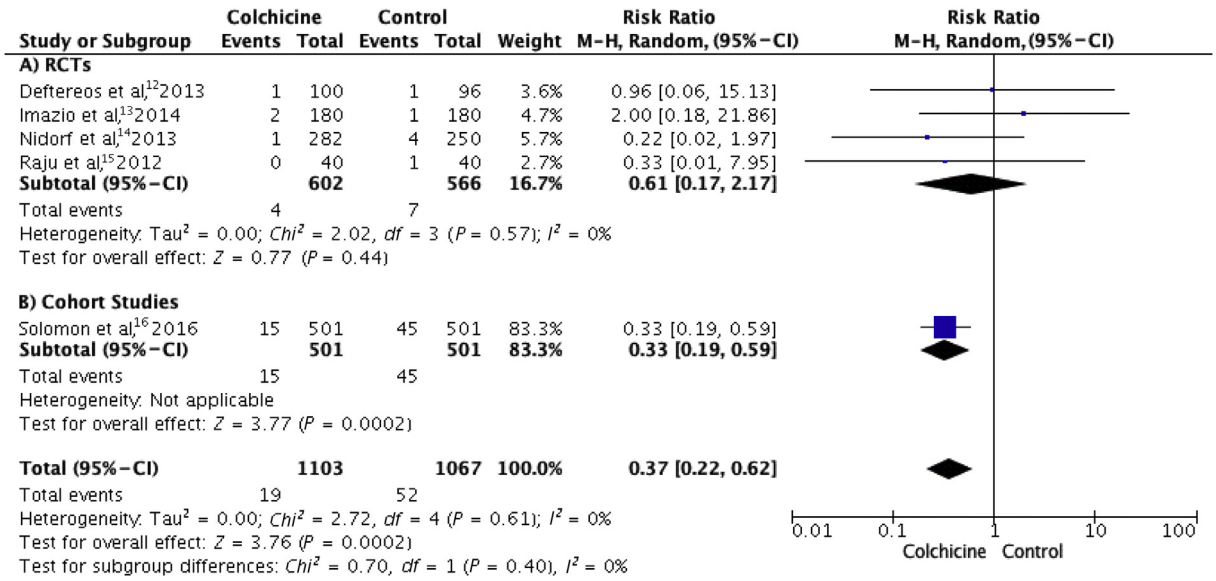

Figure 3. Pooled stroke incidence across all 5 studies with CIs. Divided into 2 subgroups: (A) randomized controlled trials (RCTs); and (B) cohort studies.

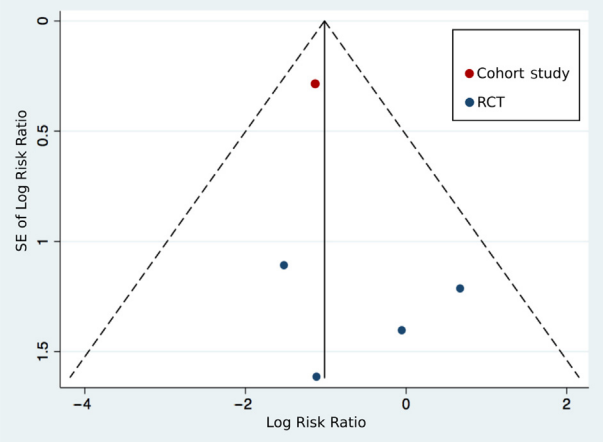

Figure 4. Funnel plot for all 5 included studies. RCTs = randomized controlled trials.

users, this finding was not reproducible in the RCT subgroup analysis. We believe that the lack of significance in this subanalysis likely represents a type II error due to the paucity of available data.

Four large upcoming randomized trials that would provide more clarity in this space are the CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-Cardioembolic Stroke) trial, LoDoCo2 (Low Dose Colchicine for Secondary Prevention in Stable Coronary Heart Disease) trial, COACS (Colchicine for Acute Coronary Syndromes) trial, and COPS (Colchicine in Patients With Acute Coronary Syndromes) trial.[35–38] CONVINCE is a European study that aims to evaluate the effectiveness of low-dose colchicine in preventing recurrence of nonfatal ischemic stroke.[35] The study will observe 2623 participants over 60 months. The LoDoCo 2 trial is an Australian-based study that aims to investigate the time to first occurrence of nonfatal stroke (as part of a composite end point) in patients with stable coronary artery disease receiving low-dose colchicine.[36] It addresses the pitfalls of the original LoDoCo trial, with a larger sample size and double-blind randomization. The COACS trial is an Italian-based, multicenter, double-blinded RCT that aims to investigate the effects of low-dose colchicine in post-ACS patients, focusing on overall mortality, new ACS, and ischemic stroke incidence.[37] The Australian-based COPS trial is similar, aiming to investigate the incidence of ACS, ischemic-driven revascularization, and nonembolic stroke in post-ACS patients after 1

year of follow-up.[38] The authors' goal is to recruit 1009 patients; they have currently recruited 770.

CONCLUSIONS

Colchicine is shown to have potential to reduce rates of stroke and improve patient outcomes. Current data are limited, and large-scale pragmatic RCTs are thus required to provide robust evidence in this domain.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

Dr. Patel was involved in conceptualization and methodology. Drs. Khandkar and Vaidya were involved in validation, formal analysis, investigation, data curation, and writing of the original draft. Dr. Khandkar was involved in sourcing software. Dr. Patel was involved in visualization, supervision, and project administration. All authors were involved in reviewing and editing of the manuscript.

REFERENCES

1. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rep*. 2008;10:218.
2. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) endorsed by: the European association for Cardio-thoracic Surgery (EACTS). *Eur Heart J*. 2015;36:2921–2964.
3. Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. *Am J Med*. 2015;128:461–470.
4. Deftereos S, Giannopoulos G, Papoutsidakis N, et al. Colchicine and the heart: pushing the envelope. *J Am Coll Cardiol*. 2013;62:1817–1825.
5. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J*. 2014;35:1782–1791.
6. Vaidya K, Martínez G, Patel S. The role of colchicine in acute coronary syndromes. *Clin Ther*. 2019;41:11–20.
7. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
8. Park JH, Ovbiagele B. Optimal combination secondary prevention drug treatment and stroke outcomes. *Neurology*. 2015;84:50–56.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. The PG: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLOS Med*. 2009;6:e1000097.
10. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343.
11. Higgens J, Green S. *10.4.1 Funnel Plots, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011.
12. Deftereos S, Giannopoulos G, Raisakis K, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol*. 2013;61:1679–1685.
13. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. *JAMA*. 2014;312:1016–1023.
14. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61:404–410.
15. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. *J Thromb Thrombolysis*. 2012;33:88–94.
16. Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. The effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. *Ann Rheum Dis*. 2016;75:1674–1679.
17. Martinez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. *Atherosclerosis*. 2018;269:262–271.
18. Robertson S, Martinez GJ, Payet CA, et al. Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP3 inflammasome monocyte activation. *Clin Sci (Lond)*. 2016;130:1237–1246.
19. Tsivgoulis G, Katsanos AH, Giannopoulos G, et al. The role of colchicine in the prevention of cerebrovascular ischemia. *Curr Pharm Des*. 2018;24:668–674.
20. Martinez GJ, Robertson S, Barraclough J, et al. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. *J Am Heart Assoc*. 2015;4:e002128.
21. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imag*. 2018;11:305–316.
22. Hemkens LG, Ewald H, Gloy VL, et al. Colchicine for prevention of cardiovascular events. *Cochrane Database Syst Rev*. 2016;1:CD011047.

23. Yurdakul S, Mat C, Tuzun Y, et al. A double-blind trial of colchicine in Behcet's syndrome. *Arthritis Rheum*. 2001;44:2686–2692.
24. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394.
25. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
26. Ramos R, Garcia-Gil M, Comas-Cufi M, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol*. 2016;67:630–640.
27. Centers for Disease Control and Prevention (CDC). Prevalence of stroke—United States, 2006-2010. *MMWR Morbid Mortal W*. 2012;61:379–382.
28. Teh WL, Abdin E, Vaingankar JA, et al. Prevalence of stroke, risk factors, disability and care needs in older adults in Singapore: results from the WiSE study. *BMJ Open*. 2018;28:e020285.
29. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
30. Huendo-Medina T, Johnson B. In: BMJ, ed. *I2 is Subject to the Same Statistical Power Problems as Cochran's Q*. BMH Publishing Group; 2007.
31. Woodward M, Lowe GD, Campbell DJ, et al. Associations of inflammatory and hemostatic variables with the risk of recurrent stroke. *Stroke*. 2005;36:2143–2147.
32. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. *Circulation*. 2011;124:2290–2295.
33. Nochaiwong S, Ruengorn C, Panyathong S, Nanta S. Association of colchicine with primary and secondary cardiovascular events in peritoneal dialysis patients: a propensity score analysis. *Value Health*. 2014;17:A757.
34. Verma S, Eikelboom JW, Nidorf SM, et al. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovas Disor*. 2015;15:96.
35. US National Library of Medicine. *NCT02898610—CONVINCE—(COlchicine for preventioN of Vascular Inflammation in Non-CardioEmbolic Stroke)—A Randomised Clinical Trial of Low-Dose Colchicine for Secondary Prevention after Stroke*. 2016.
36. Australian and New Zealand Clincal Trials Registry. ACTRN12614000093684— The LoDoCo2 trial: a randomised controlled trial on the effect of low dose colchicine for secondary prevention of cardiovascular disease in patients with established. *Stable Coronary Artery Disease*. 2014.
37. US National Library of Medicine. *NCT01906749—Colchicine for Acute Coronary Syndromes (COACS)*. 2013.
38. Australian and New Zealand Clincal Trials Registry. *ACTRN12615000861550—The Australian COPS Trial—COlchicine in Patients with Acute Coronary Syndromes*. 2015.

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APPENDIX 1. MEDLINE (OVID) SEARCH ALGORITHM

1. colchicine.tw
2. exp COLCHICINE/
3. exp STROKE/
4. exp CARDIOVASCULAR DISEASE/
5. exp. TRANSIENT ISCHEMIC ATTACK/
6. exp. CEREBROVASCULAR DISEASE/
7. (random: or clinical trial or cohort or observational).mp.
8. (1 or 2) and (3 or 4 or 5 or 6) and 7
9. 8 not conference abstract.pt
10. limit 9 to english language
11. remove duplicates from 10

APPENDIX 2. DETAILED RISK OF BIAS ASSESSMENT OF ALL INCLUDED RANDOMIZED CONTROLLED TRIALS (RCTS)

Defteros et al.

Bias	Author judgement	Supporting reasoning
Random Sequence Allocation	Unclear risk	The authors do no mention the method of randomisation in the paper
Allocation concealment	Unclear	As above, there is no mention the randomisation process in the trial
Blinding of participants and personnel	Low risk	The authors mention that the trial is double blinded
Blinding of outcomes assessment	Low risk	The authors mention, "captured IVUS data, identified only by serial number, were analysed offline".
Incomplete outcome data	Unclear risk	The authors employed a modified intention-to-treat analysis. - "all patients who received at least 1 dose of study treatment were included in the analysis" - "Of 222 eligible consented patients…196[88%] completed the study procedures." Only these 196 patients were analysed
Selective reporting	Low risk	The study reported appropriately on all pre-specified outcomes

Imazio et al.

Bias	Author judgement	Supporting reasoning
Random Sequence Allocation	Low risk	The authors mention that participants were "randomly assigned to treatment groups by a central computer-based automated sequence"
Allocation concealment	Low risk	The authors mention that "allocation concealment was achieved by using opaque sealed envelopes, sequentially numbered containers, and centralised randomization"
Blinding of participants and personnel	Low risk	Double blinded trial

(*continued on next page*)

Imazio et al. (*Continued*)

Bias	Author judgement	Supporting reasoning
Blinding of outcomes assessment	Low risk	Authors mention that "data gathered by all authors were…analysed at the Cardiology Department of Maria Vittoria Hospital, Torino, Italy, after blinded adjudication of events"
Incomplete outcome data	Low risk	All 360 patients who were randomized were included in analysis, and there were no losses to follow up
Selective reporting	Low risk	The authors appropriately reported on all pre-specified outcomes, and chose relevant outcomes for their patient population

Nidorf 2013 et al.

Bias	Author judgement	Supporting reasoning
Random Sequence Allocation	Low risk	Authors mention that "the randomization sequence was computer generated"
Allocation concealment	Low risk	The authors mention that the randomization sequence was "concealed from investigators at all times". However they do not mention how this was done.
Blinding of participants and personnel	High risk	Neither patients nor investigators were blinded, as "investigators and patients were advised in writing of the treatment group to which the patient had been assigned"
Blinding of outcomes assessment	Low risk	Authors mention that "all outcomes were evaluated by an experienced adjudicator blinded to the treatment allocation"
Incomplete outcome data	Low risk	All 532 patients were included in intention-to-treat analysis. The pre-specified minimum follow-up period of 2 years was met for all patients.
Selective reporting	Low risk	Authors appropriately reported on all pre-specified outcomes, and addressed clinically relevant outcomes

Raju et al.

Bias	Author judgement	Supporting reasoning
Random Sequence Allocation	Low risk	Authors mention using "computer generated randomization with variable block sizes"
Allocation concealment	Low risk	Authors mention that the drug was issued to each participant "immediately after randomization using sequentially numbered bottles". This as done by an independent pharmacist.
Blinding of participants and personnel	Low risk	The study drugs were over-encapsulated by an independent pharmacist to appear identical, "thereby blinding investigators, study coordinator, and patients"
Blinding of outcomes assessment	Unclear	Patients had a follow up appointment at 30 days, however it unclear whether the evaluators at this point were blinded
Incomplete outcome data	Unclear	There was dropout rate of 7.5% (6/80) after randomization. The authors do not mention employing intention-to-treat analysis.
Selective reporting	Low risk	The authors appropriately reported on all pre-specified and clinically relevant outcomes.