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Colchicine for the primary prevention of cardiovascular events (Review)

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[Intervention Review]

Colchicine for the primary prevention of cardiovascular events

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ABSTRACT

Background

Atherosclerotic cardiovascular diseases (ACVDs), a condition characterised by lipid accumulation in arterial walls, which is often exacerbated by chronic inflammation disorders, is the major cause of mortality and morbidity worldwide. Colchicine, with its first medicinal use in ancient Egypt, is an inexpensive drug with anti-inflammatory properties. However, its role in primary prevention of ACVDs in the general population remains unknown.

Objectives

To assess the clinical benefits and harms of colchicine as primary prevention of cardiovascular outcomes in the general population.

Search methods

We searched the Cochrane Heart Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE (including In-Process & Other Non-Indexed Citations), Ovid Embase, Web of Science, and LILACS. We searched ClinicalTrials.gov and WHO ICTRP for ongoing and unpublished studies. We also scanned the reference lists of relevant included studies, reviews, meta-analyses, and health technology reports to identify additional studies. There were no limitations on language, date of publication, or study setting. The search results were updated on 31 May 2023.

Selection criteria

Randomised controlled trials (RCTs) in any setting, recruiting adults without pre-existing cardiovascular disease. We included trials that compared colchicine versus placebo, non-steroidal anti-inflammatory drugs, corticosteroids, immunomodulating drugs, or usual care. Our primary outcomes were all-cause mortality, non-fatal myocardial infarction, stroke, and adverse events.

Data collection and analysis

Two or more review authors independently selected studies, extracted data, and performed risk of bias and GRADE assessments.

Main results

We identified 15 RCTs (1721 participants randomised; 1412 participants analysed) with follow-up periods ranging from 4 to 728 weeks. The intervention was oral colchicine compared with placebo, immunomodulating drugs, or usual care or no treatment. Due to biases and imprecision, the evidence was very uncertain for all outcomes. All trials but one had a high risk of bias. Five out of seven meta-analyses included fewer than six trials (71.4%). The objectives of the review were to assess cardiovascular outcomes in the general population, but many of the included trials focused on liver disease.

Colchicine compared to placebo

Colchicine may reduce all-cause mortality compared to placebo in primary prevention, but the evidence is very uncertain (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.51 to 0.91; 6 studies, 463 participants; very low-certainty evidence; number needed to treat for an additional beneficial outcome (NNTB) 11, 95% CI 6 to 67). Colchicine may result in little to no difference in non-fatal myocardial infarction, but the evidence is very uncertain (RR 0.87, 95% CI 0.41 to 1.82; 1 study, 100 participants; very low-certainty evidence). Colchicine may not reduce the incidence of stroke, but the evidence is very uncertain (RR 2.43, 95% CI 0.67 to 8.86; 1 study, 100 participants; very low-certainty evidence). Regarding adverse events, colchicine may increase the incidence of diarrhoea (RR 3.99, 95% CI 1.44 to 11.06; 8 studies, 605 participants; very low-certainty evidence; number needed to treat for an additional harmful outcome (NNTH) 10, 95% CI 6 to 17), and may have little to no effect on neurological outcomes such as seizure or mental confusion (RR 0.72, 95% CI 0.31 to 1.66; 2 studies, 155 participants; very low-certainty evidence), but the evidence is very uncertain. The effect of colchicine on cardiovascular mortality is also very uncertain (RR 1.27, 95% CI 0.03 to 62.43; 2 studies, 160 participants; very low-certainty evidence). Colchicine may not reduce post-cardiac procedure atrial fibrillation, but the evidence is very uncertain (RR 0.74, 95% CI 0.25 to 2.19; 1 study, 100 participants). We found no trials reporting on pericardial effusion, peripheral artery disease, heart failure, or unstable angina.

Colchicine compared to methotrexate (immunomodulating drug)

Colchicine may result in little to no difference in all-cause mortality compared to methotrexate, but the evidence is very uncertain (RR 0.42, 95% CI 0.12 to 1.51; 1 study, 85 participants; very low-certainty evidence). We found no trials reporting other cardiovascular outcomes or adverse events for this comparison.

Colchicine compared to usual care or no treatment

The evidence is very uncertain about the effect of colchicine compared with usual care on all-cause mortality in primary prevention (RR 1.07, 95% CI 0.90 to 1.27; 2 studies, 729 participants; very low-certainty evidence). Regarding adverse events, colchicine may increase the incidence of diarrhoea compared to usual care, but the evidence is very uncertain (RR 3.32, 95% CI 1.56 to 7.03; 2 studies, 729 participants; very low-certainty evidence; NNTH 18, 95% CI 12 to 42). No trials reported other cardiovascular outcomes for this comparison.

Authors' conclusions

This Cochrane review evaluated the clinical benefits and harms of using colchicine for the primary prevention of cardiovascular events in the general population. Comparisons were made against placebo, immunomodulating medications, or usual care or no treatment. However, the certainty of the evidence for the predefined outcomes was very low, highlighting the pressing need for high-quality, rigorous studies to ascertain colchicine's clinical impact definitively. We identified numerous biases and inaccuracies in the included studies, limiting their generalisability and precluding a conclusive determination of colchicine's efficacy in preventing cardiovascular events. The existing evidence regarding colchicine's potential cardiovascular benefits or harms for primary prevention is inconclusive owing to the limitations inherent in the current studies. More robust clinical trials are needed to bridge this evidence gap effectively.

PLAIN LANGUAGE SUMMARY

What are the effects of colchicine in preventing cardiovascular events before they ever occur?

Key messages

• The benefits and harms of colchicine in preventing atherosclerotic cardiovascular disease before it ever occurs remain unclear.

• Further research is needed before any strong conclusions can be made.

Colchicine and cardiovascular disease

Atherosclerotic cardiovascular disease (ACVD), a condition marked by lipid accumulation (buildup of fats, cholesterol, and other substances) on the artery walls, which is often made worse by chronic inflammation disorders, is a major cause of death and illness worldwide. Colchicine, first used to treat illness in ancient Egypt, is an inexpensive medication that fights inflammation. It has been used to treat gout, liver diseases, and systemic connective tissue disorders. More recently, researchers have been studying its potential for preventing ACVD.

What did we want to find out?

We wanted to find out colchicine's benefits and harms in preventing ACVD before it ever occurs (primary prevention) in the general population. Primary prevention is all about taking steps to prevent a disease before it even develops, rather than waiting until someone is already sick to start treatment. In the case of ACVD, this is especially important because it is a leading cause of death and disability worldwide. By focusing on prevention, people can be helped to live longer, healthier lives with a resulting reduced burden on healthcare systems. One approach to primary prevention is using immunomodulating medications, which work by modifying the immune system's response. Colchicine is one example of this type of medication.

What did we do?

We looked at the effects of colchicine for primary prevention of ACVD, including heart attacks, strokes, death from cardiovascular causes, and death for any reason. We also looked at unwanted effects such as diarrhoea and neurological events (seizure and mental confusion). We compared and summarised the results of the studies and rated our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We found 15 studies involving 1721 participants with follow-up periods ranging from 4 to 728 weeks, comparing colchicine with placebo (dummy pill), immunomodulating medications, or usual care. Colchicine was taken by mouth as a pill, either once or twice a day, depending on the regimen being followed. The people included in the studies were adults at high risk for developing ACVD, but who had not yet had a major cardiovascular event like a heart attack or stroke. The risk factors considered included age, family history, smoking status, blood pressure, cholesterol levels, and presence of other conditions like diabetes.

Main results

The evidence for the effects of colchicine on preventing cardiovascular events is very uncertain. Although the current evidence does not suggest clear benefits or a reduction in ACVD complications, this conclusion is limited by the quality of the evidence. Further high-quality studies are essential to accurately determine the benefits and harms of colchicine for the primary prevention of ACVD.

What are the limitations of the evidence?

Our confidence in the evidence is very low because of concerns about how some of the studies were conducted, results that differed across studies, and changes to the intended populations or treatments. The studies were very small, and analyses included only a few studies.

How up-to-date is this evidence?

The evidence is current to 31 May 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Colchicine compared with placebo for the primary prevention of cardiovascular events in adults

Colchicine compared with placebo for the primary prevention of cardiovascular events in adults

Patient or population: primary prevention of cardiovascular events in adults
Settings: inpatients and outpatients
Intervention: colchicine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Colchicine			
All-cause mortality Follow-up: median 6.5 years	**292 per 1000**[a]	**199 per 1000** (149 to 266)	**RR 0.68** (0.51 to 0.91)	463 (6 studies)	⊕⊖⊖⊖ **very low**[b,c]
Non-fatal myocardial infarction Follow-up: 4 weeks	**235 per 1000**[d]	**205 per 1000** (96 to 428)	**RR 0.87** (0.41 to 1.82)	100 (1 study)	⊕⊖⊖⊖ **very low**[e,f]
Stroke Follow-up: mean 4 weeks	**59 per 1000**[g]	**297 per 1000** (107 to 822)	**RR 2.43** (0.67 to 8.86)	100 (1 study)	⊕⊖⊖⊖ **very low**[h,i]
Adverse events: diarrhoea Follow-up: median 2.5 years	**10 per 1000**[j]	**39 per 1000** (14 to 108)	**RR 3.99** (1.44 to 11.06)	605 (8 studies)	⊕⊖⊖⊖ **very low**[k,l]
Adverse events: neurological (confusion, seizure) Follow-up: 10 years	**119 per 1000**[m]	**86 per 1000** (37 to 198)	**RR 0.72** (0.31 to 1.66)	155 (2 studies)	⊕⊖⊖⊖ **very low**[n,o]
Cardiovascular mortality Follow-up: median 8 years	**24 per 1000**[p]	**29 per 1000** (0 to 1551)	**RR 1.27** (0.03 to 62.43)	160 (2 studies)	⊕⊖⊖⊖ **very low**[q,r]
Post-cardiac procedure atrial fibrillation Follow-up: 4 weeks	**28 per 1000**[s]	**34 per 1000** (1 to 1000)	**RR 0.74** (0.25 to 2.19)	100 (1 study)	⊕⊖⊖⊖ **very low**[t,u]

Symptoms or intervention related to peripheral artery disease	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Median control risk: 29.2%.
[b]Downgraded two levels due to risk of bias (concerns across most domains).
[c]Downgraded two levels for imprecision: fewer than 300 events.
[d]Median based on the control group risk: 24%.
[e]Downgraded one level for high risk of attrition bias: 29% of withdrawals.
[f] Downgraded two levels due to imprecision: the optimal information size was 5596 participants. The trial's sample size is 1.80% (100/5596). The 95% CI is wide and includes the possibility of no benefit (RR = 1), and the number of events is very low (7.33% (22/300)).
[g]Basal risk is based on the unique included trial: 5.9%.
[h]Downgraded one level for risk of bias: blinding of outcome assessment.
[i]Downgraded two levels due to imprecision. The optimal information size of 200 was not met. The total sample size of 100 represents only 50% of the required information size. The number of events is minimal at 3.3% (10/300). The 95% CI is wide and includes the possibility of no benefit (RR = 1).
[j]Median control risk in 1000: 10.
[k]Downgraded two levels due to high risk of bias for random sequence generation and allocation concealment in 63% of the trials (5/8) plus high risk of attrition bias in all trials.
[l]Downgraded one level due to low number of events (N = 79) and wide 95% CI.
[m]Median control risk: 11.9%.
[n]Downgraded one level due to inadequate allocation concealment and the absence of blinding for both participants and personnel in one trial. Both trials exhibited high risk of detection bias. One trial experienced a loss of more than 12% of its participants.
[o]Downgraded two levels due to imprecision. The optimal information size was 1748, and the total sample size represents 8.86% (155/1748) of this optimal size. Given the low number of events (N = 20), the 95% CI is wide and includes the possibility of no benefit (RR = 1).
[p]Median control risk: 2.4%.
[q]Downgraded a total of three levels due to study limitations (selection, detection, and attrition bias) and inconsistency (I^2 = 73%).
[r]Downgraded two levels for imprecision. The optimal information size required for the trials was 2868. However, the total sample size of both trials only accounted for 5.57% (160/2868) of this size. Additionally, the number of events recorded was very low. Consequently, the 95% CI is quite broad and includes the possibility of no benefit (RR = 1).
[s]Median control risk: 2.8%.
[t] Downgraded one level for risk of bias: blinding of outcome assessment and incomplete outcome data.

[u]Downgraded two levels for imprecise results. The optimal information size for the study was 2696, but the total sample size represents only 3.7% of that (100/2696). Additionally, the number of events observed was very low (N = 12), resulting in a wide 95% CI that includes no benefit (RR = 1).

Summary of findings 2. Colchicine compared with immunomodulating drugs for the primary prevention of cardiovascular events in adults

Colchicine compared with immunomodulating drugs for the primary prevention of cardiovascular events

Patient or population: primary prevention of cardiovascular events in adults
Settings: outpatients
Intervention: colchicine
Comparison: immunomodulating drugs (methotrexate)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Immunomodulating drugs	Colchicine			
All-cause mortality Follow-up: 2 years	**167 per 1000**[a]	**70 per 1000** (20 to 252)	**RR 0.42** (0.12 to 1.51)	85 (1 study)	⊕⊖⊖⊖ **very low**[b,c]
Non-fatal myocardial infarction	Not reported				
Stroke	Not reported				
Adverse events	Not reported				
Cardiovascular mortality	Not reported				
Post-cardiac procedure atrial fibrillation	Not reported				
Symptoms or intervention related to peripheral artery disease	Not reported				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Media control risk based on the trial: 16.7%
[b]Downgraded two levels due to high risk of bias in most domains.
[c]Downgraded two levels for imprecision. The optimal amount of information required was 348. However, the sample size only represents 24.42% (85/348) of the optimal information size. Furthermore, the number of events recorded is minimal. The 95% CI is broad and encompasses no benefit (RR = 1).

Summary of findings 3. Colchicine compared with usual care for the primary prevention of cardiovascular events in adults

Colchicine compared with usual care for the primary prevention of cardiovascular events

Patient or population: primary prevention of cardiovascular events in adults
Settings: outpatients
Intervention: colchicine
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Usual care	Colchicine			
All-cause mortality Follow-up: median 4.5 years	**275 per 1000**[a]	**295 per 1000** (248 to 350)	**RR 1.07** (0.90 to 1.27)	729 (2 studies)	⊕⊖⊖⊖ **very low**[b,c]
Non-fatal myocardial infarction	Not reported				
Stroke	Not reported				
Adverse events Follow-up: median 2.5 years	**15 per 1000**[d]	**48 per 1000** (23 to 102)	**RR 3.32** (1.56 to 7.03)	729 (2 studies)	⊕⊖⊖⊖ **very low**[e,f]
Cardiovascular mortality	Not reported				
Post-cardiac procedure atrial fibrillation	Not reported				

Symptoms or intervention related to peripheral artery disease	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Median control risk: 2.75%.
[b]Downgraded two levels for high risk of bias in most domains in one of the two trials.
[c]Downgraded two levels for imprecision. The ideal amount of information required was 294,174. The total sample size constitutes only 0.24% (729/294,174) of the required amount. The number of occurrences is minimal. The 95% CI is wide-ranging and encompasses no advantage (RR = 1).
[d]Median control risk: 1.5%.
[e]Downgraded two levels for high risk of bias in most domains in one of the two trials.
[f]Downgraded one level due to imprecision. The number of occurrences is very low (N = 37), and the 95% CI is wide. It was not possible to estimate optimal information size due to lack of events in one trial.

BACKGROUND

Description of the condition

Cardiovascular diseases (CVDs) include coronary heart disease (CHD), sudden cardiac death/sudden cardiac arrest, cerebrovascular disease, stroke/transient ischaemic attack, rheumatic heart disease, congenital heart disease, deep venous thrombosis, pulmonary embolism, and peripheral arterial disease. From 1990 to 2019, the prevalence of cases of total CVDs has nearly doubled from 271 million (95% uncertainty interval (UI) 257 to 285 million) to 523 million (95% UI 497 to 550 million), respectively (Roth 2020). In addition, it has been estimated that CVDs caused 18.6 million (95% UI 17.1 to 19.7 million) deaths in 2019 (Roth 2020). Doubtlessly, CVDs yield a high socioeconomic burden on the general population (Flora 2019).

Atherosclerosis, the leading cause of CVDs, is a chronic inflammatory disease with autoimmune foundations resulting from cellular-molecular interactions in the artery wall (Gotlieb 1991). Abundant data link hypercholesterolaemia to atherogenesis, but only recently has it been appreciated that inflammatory mechanisms couple dyslipidaemia to atheroma formation. Leukocyte recruitment and expression of pro-inflammatory cytokines characterise early atherogenesis, and malfunction of inflammatory mediators mutes atheroma formation in mice. Moreover, inflammatory pathways promote thrombosis, a late and dreaded complication of atherosclerosis responsible for myocardial infarctions (MIs) and most strokes. The new appreciation of the role of inflammation in atherosclerosis provides a mechanistic framework for understanding the clinical benefits of lipid-lowering therapies and may eventually furnish new therapeutic targets (Anyfanti 2022; Barrett 2020; Cochain 2017; Eshghjoo 2021; Fazeli 2021; Frostegård 2013; Geovanini 2018; Gisterå 2017; Hansson 2006; Hussain 2020; Kobiyama 2018; Libby 2002; Libby 2019; Liu 2019; Martínez 2018a; Mizuno 2011; Oikonomou 2020; Ozen 2021; Pant 2014; Patel 2022; Rahman 2017; Shi 2010; Veronese 2018; Wolf 2019; Zhu 2018). Individuals with autoimmune disorders, rheumatic arthritis, systemic lupus erythematosus, and osteoarthritis have a higher frequency of cardiovascular events as compared to the healthy population (Croca 2017; Hannawi 2021; Li 2022; Liu 2018; Semb 2017; Vicente 2021; Yalcinkaya 2021). The incidence of MI in people with rheumatoid arthritis seems to be comparable to or higher than in people with diabetes mellitus (Ali 2021; Zhang 2022), therefore rheumatoid arthritis should be considered a prominent risk factor for CVD events (Ferraz-Amaro 2021), and a multidisciplinary team should include cardiologists (Ali 2021).

A potential relationship between a proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and autoimmune disease has been recently noted (Martínez 2018b; Ministrini 2022).

The interrelationship between immunity, inflammation, and atherosclerosis could explain the cardiovascular construct termed residual inflammatory risk (RIR) (Ridker 2018). RIR is defined by the level of high-sensitivity C-reactive protein (hs-CRP) higher than 2 mg/L (Ridker 2018), a well-known biomarker of cardiovascular disease (Liuzzo 1994). The RIR should not be confused with the residual cholesterol risk (low-density lipoprotein cholesterol (LDL-C) higher than 100 mg/dL), residual triglyceride risk (triglycerides higher than 200 mg/dL and high-density lipoprotein cholesterol (HDL-C) lower than 40 mg/dL), residual lipoprotein a risk (Lp(a) higher than 50 mg/dL), and residual thrombotic risk without a predefined biomarker (Ridker 2018). It has been suggested that, in primary prevention, the evaluation of hs-CRP is a useful prognostic factor as much as other conventional measurements of cardiovascular risk (i.e. LDL-C or HDL-C) (Ridker 2018). Subclinical inflammation can be better monitored with hs-CRP (Ridker 2018). Therefore, a decrease in inflammatory burden should decrease the risk of future cardiovascular disease (Whayne 2021). Recently, Kelly and colleagues suggested that colchicine's anti-inflammatory effects show promise in preventing vascular recurrence in coronary disease. The CONVINCE trial aims to extend this hypothesis to non-cardioembolic ischaemic stroke, despite its more diverse aetiologies (Kelly 2024).

Similarly, the concept of residual cardiovascular risk (RCR) has been proposed (Vanuzzo 2011). Hermans and colleagues 2010 defined RCR as the "residual risk of incident vascular events or progression of established vascular damage persisting in patients treated with current evidence-based recommended care. This risk includes established risk factors, such as dyslipidaemia, high blood pressure, hyperglycaemia, inflammation, unhealthy lifestyles, and the risk related to emerging or newer risk factors" (Hermans 2010). The link between inflammation and atherosclerosis has been supported by the use of anti-inflammatory therapies, biological agents, or anti-inflammatory drugs used to treat non-atherosclerotic inflammatory diseases and, hence, reduce cardiovascular events (Arbel 2018; Bäck 2015; Kottoor 2018; Moriya 2019; Roman 2020). Colchicine belongs to the biological agent group of medications (Chistiakov 2018; Dasgeb 2018; Imazio 2016; Thompson 2019; Whayne 2021). Colchicine's prescription in cardiovascular medicine is a novel use for an ancient drug (Chen 2017; Tong 2016). In a recent study, Liu and colleagues analysed several inflammation biomarkers that can be used to predict CVD. They found that high levels of fibrinogen, hs-CRP, interleukin-6 (IL-6), and galectin-3 can be used as specific biomarkers. However, the role of galectin-3 is unclear, and IL-6 is a non-specific inflammation marker (Liu 2023).

Colchicine has been used in gout, familial Mediterranean fever disorders, osteoarthritis (Akman 2018; Alarcón 1981; Aran 2011; Cronstein 2013; Das 2002; Halabe-Cherem 2009; Kiraz 1998; Lazaros 2018; Liantinioti 2018; Meneses 2015; Nuki 2008; Plotz 2022; Richette 2010; Vilardell 1978), dermatological disorders (Kaur 2020; Fujii 2021; Micheletti 2020; Zhao 2022), urological disorders (Akman 2011; Ibrahim 2019; Sinanoglu 2018), hepatology (Gong 2004; Rambaldi 2001), respiratory medicine (Gomer 2010), gastroenterology (Rajapakse 2001; Verne 1997; Verne 2003), and for secondary prevention of cardiovascular outcomes (Fiolet 2021; Imazio 2005a; Imazio 2005b; Imazio 2011a; Imazio 2014a; Imazio 2014a; Imazio 2014b; Maisch 2004; Nidorf 2013; Nidorf 2014; Roubille 2020; Siak 2021; Tardif 2019; Xia 2021). The effect of colchicine is unique since it binds to unpolymerised tubulin hetero dimers, forming a stable complex that effectively inhibits microtubule dynamics, not affecting the glucocorticoid signalling pathway as well as arachidonic acid metabolites production and signal transduction (Deftereos 2013).

In June 2023, the US Food and Drug Administration (FDA) approved colchicine for the secondary prevention of cardiovascular events in certain high-risk patients with coronary artery disease (FDA 2023). This approval was based on results from several randomised controlled trials (RCTs) evaluating colchicine's effectiveness in

secondary cardiovascular disease prevention (Deftereos 2013; Nidorf 2013; Nidorf 2020; Opstal 2022; Tardif 2019; Tong 2020). A Cochrane review to comprehensively assess the clinical benefits and potential harms of colchicine in this context is currently underway (Ebrahimi 2023).

This Cochrane review's scope was the use of colchicine for the primary prevention of cardiovascular outcomes in the general population.

Description of the intervention

Colchicine is a tricyclic alkaloid extracted from *Colchicum autumnale* and *Gloriosa superba* (Finkelstein 2010; Imazio 2021; Karamanou 2018). The drug is administered in either solid or liquid oral dosage form (FDA 2021a; FDA 2021b). It is rapidly absorbed in the gastrointestinal tract (Finkelstein 2010), and is mainly metabolised in the liver. Colchicine's main targets are the leukocytes (white blood cells) (Chappey 1993). The drug's half-life is between 41 and 46 hours for leukocytes and 49 hours for plasma (Chappey 1993). Colchicine binds to albumin at ~40% (Sabouraud 1994), and is excreted unchanged as metabolites in the faeces (about 80%), and 10% to 20% are excreted in the urine (Liantinioti 2018). Colchicine's dosage must be reduced and closely monitored in patients with relevant hepatic or renal dysfunction (Cocco 2010; Curiel 2012; Hung 2005; Imai 2020). Thus, those receiving colchicine must be monitored closely, especially elderly patients with kidney failure (Anonymous 2008; Ho 2019).

Colchicine has a narrow therapeutic index (Essame 2020; Finkelstein 2010; Ghawanmeh 2020), and its toxicity is associated with a poor prognosis (Essame 2020; Finkelstein 2010). Cytochrome P3A4 and P-glycoprotein metabolise colchicine; thus, any drug that binds these proteins influences the colchicine's pharmacokinetics (Borron 1996; Nuki 2008; Slobodnick 2015). Several drugs inhibit colchicine metabolism, including: macrolides (mainly clarithromycin), antiretroviral therapy, broad-spectrum oral antifungal agent (ketoconazole, etc.), grapefruit juice, histamine H2-antagonists (cimetidine), steroids (hydrocortisone, dexamethasone), selective serotonin reuptake inhibitors (fluoxetine, paroxetine), calcium-channel blockers (verapamil, diltiazem), and immuno-suppressors (cyclosporine A and tacrolimus are potent inhibitors). Prescribers must be aware of colchicine's drug interactions to reduce the likelihood of fatal and non-fatal side effects (Amanova 2014; Borron 1996; Dahan 2009; Davis 2013; Imai 2020; Magro 2021; Rollot 2004; Slobodnick 2015; Stewart 2020; Villa Zapata 2020). Colchicine increases the rate of diarrhoea and gastrointestinal adverse events that precede liver, sensory, muscle, infectious, and haematological adverse events or death (Stewart 2020). Recently, Dubé and colleagues described two genomic regions associated with gastrointestinal events in individuals treated with colchicine. It may benefit some patients with genetic predispositions to lower tolerability of treatment with colchicine (Dubé 2021).

A major concern is the inconsistency and errors in the available information on how colchicine interacts with other medications, leading to recommendations that might do more harm than good. Recently, a paper sought to clarify which drug interactions with colchicine are genuinely harmful, challenging the prevailing guidance of simply lowering colchicine doses when used with certain other drugs, a strategy that could result in either toxicity or inadequate treatment effectiveness (Hansten 2021). Recently, Gómez-Lumbreras and colleagues analysed the FDA Adverse Event Reporting System (FAERS) database to investigate potential drug interactions with colchicine, focusing on CYP3A4 and P-glycoprotein inhibitors. Their study identified multiple safety signals for combinations of colchicine with these inhibitors. The researchers recommend avoiding such combinations or closely monitoring patients when co-prescription is unavoidable (Gómez Lumbreras 2023). Therefore, this work underscores the importance of considering drug interactions in colchicine therapy, particularly with CYP3A4/P-gp inhibitors. It points to the need for cautious prescribing practices and suggests areas for further research to optimise colchicine use.

How the intervention might work

Colchicine's interaction with proteins such as tubulin, cytochrome P450, and P-glycoprotein elucidates its dual roles in clinical outcomes and pharmacokinetics (Slobodnick 2015). Its binding to tubulin is central to both its therapeutic and adverse effects, while its interactions with cytochrome P450 and P-glycoprotein are key to understanding its pharmacokinetic behaviour.

The drug's primary mechanism involves inhibiting the functions of microtubules (Wilson 1976), essential components of the eukaryotic cytoskeleton (Bershadsky 1988). These structures are crucial for cell division, shape, motility, and intracellular transport (Forkosh 2020; Janke 2020; Morton 1999; Roll-Mecak 2020; Taylor 1965). Colchicine's specific target, tubulin, comprises alpha and beta subunits. Its binding to tubulin disrupts microtubule assembly, leading to a disassembly that underpins its anti-inflammatory actions (Chaldakov 2018; Forkosh 2020; Terkeltaub 2009). This inhibitory effect is believed to mediate colchicine's beneficial impacts on various cell types involved in inflammation, such as macrophages, platelets, endothelial cells, and especially neutrophils (Cerquaglia 2005; Cronstein 1995; Hu 2021; Imazio 2016; Leung 2015; Liang 2019; Paschke 2013; Perico 1996; Pircher 2019; Rudolph 1977). These cells are central to the inflammatory process and thus to the early stages of atheroma plaque formation (d'Alessandro 2020; Ma 2019; Nording 2020; Schrottmaier 2020), suggesting colchicine's potential in the primary prevention of cardiovascular events (Tsivgoulis 2018).

Adding to this, the interplay of monocytes, neutrophils, and the NLRP3 inflammasome within these cells plays a crucial role in the inflammation associated with atherosclerosis, with cholesterol crystals activating the NLRP3 inflammasome to produce key inflammatory mediators (Martínez 2018a; Martínez 2018b). Additionally, the work by Reglero-Real and colleagues emphasises the importance of endothelial cell autophagy in modulating inflammation, suggesting that colchicine may also exert effects on endothelial cell architecture, thereby influencing leukocyte migration and further underscoring its comprehensive anti-inflammatory properties in CVD management (Reglero-Real 2021).

Why it is important to do this review

This review is critical for the following reasons. First, according to a Cochrane review, there is uncertainty about the benefits and risks of colchicine in the general population (Hemkens 2016). Of the 39 RCTs included in Hemkens 2016, 82% (32/39) came from populations with chronic liver diseases, renal and primary amyloidosis, gout, Behçet's syndrome, or idiopathic pulmonary

fibrosis. Furthermore, several trials reported no cardiovascular risk profile. Therefore, this Cochrane review is required to assess colchicine's clinical benefits and risks in the primary prevention of cardiovascular events in people with or without cardiovascular risk factors.

Second, numerous non-Cochrane systematic reviews emphasise the use of colchicine to prevent atrial fibrillation (AF) after cardiac procedures. Some include both levels of prevention (Lennerz 2017; Papageorgiou 2017; Salih 2017; Trivedi 2014; Verma 2015; Wang 2016). However, these meta-analyses show inconsistencies in the measure of the effect of the intervention (i.e. odds ratio or risk ratio), reported funnel plots with fewer than 10 RCTs, lacked assessment of the risk of bias in the included trials, or used out-of-date assessment scales without information about the certainty of the evidence. It was therefore necessary to specify the role of colchicine in the primary prevention of cardiovascular events with Cochrane's methodology.

Third, it is necessary to conduct a critical appraisal of trials in the primary prevention of post-pericardiotomy syndrome (Finkelstein 2002; Imazio 2010) and early postoperative pericardial and pleural effusions (Imazio 2011b; Meurin 2015). According to the information reported in the clinical practice guidelines of international scientific societies, there is uncertainty about the role of colchicine in the primary prevention of AF post-cardiac surgery (Calkins 2017; January 2014; Kirchhof 2016). Fourth, there is uncertainty about the role of colchicine in the scope of the primary prevention of cardiovascular events in rheumatological diseases, which have an inflammatory nature with a strong link with atherogenesis. Therefore, critical appraisal of the RCTs is necessary to determine the certainty of the evidence and obtain firm conclusions to facilitate better decision-making in clinical and epidemiological practice.

OBJECTIVES

To assess the clinical benefits and harms of colchicine as primary prevention of cardiovascular outcomes in the general population.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of publication status. We only included RCTs with a parallel design and a minimum follow-up of one year. The one-year minimum follow-up is based on the premise that cardiovascular events require enough time to develop. The exception was for studies that included people with post-cardiac procedure AF, in which case there was no minimum follow-up requirement.

We excluded non-randomised clinical trials. We did not apply any limitations on language or country. We included studies reported as full text, those published as abstract only, and unpublished data. We excluded cross-over and cluster-randomised trials, as they are unsuitable due to the nature of the clinical conditions where colchicine is prescribed and its pharmacodynamic properties, especially its very long elimination half-life.

We carefully analysed whether trials were published in predatory journals (beallslist.net/). A predatory journal is an exploitive for-profit publication model that promises a quick and easy publishing process with supposedly high editorial and publishing standards; however, it lacks quality control, transparency, and impact factor, threatening the foundation of evidence-based research (Van Nuland 2017).

For future updates, we will not exclude any trial published in a predatory journal; however, we will conduct a sensitivity analysis.

Types of participants

We only included adults (aged 18 years or more), regardless of gender, without a known history of cardiovascular outcomes (MI, unstable angina, heart failure, stroke, pericardial effusion, AF, and peripheral arterial disease). We included participants with any risk factor for cardiovascular outcomes (i.e. blood hypertension, obesity, dyslipidaemia, diabetes mellitus, and chronic kidney diseases).

We also included pregnant women. However, we did not report information about this population because we identified no trials that included pregnant participants.

For future updates, if we identify an RCT including participants with or without a history of cardiovascular outcomes, we plan to check whether there was information by subgroup. If there is no report, the trial will be excluded. However, we will contact the lead author before making a final decision.

Types of interventions

We only included the intervention as monotherapy, given at any dosage. We did not pool all eligible comparators; we considered each as a different comparison. For the purposes of the review, and in the absence of a standard definition of usual care, we accepted the following quote: "It can include the routine care received by patients for prevention or treatment of diseases" (Gellman 2013).

1. Intervention

Colchicine is only administered orally. We only considered colchicine given alone (monotherapy), regardless of colchicine dosage.

2. Control

- Placebo.
- Non-steroidal anti-inflammatory drugs (NSAIDs): indomethacin, celecoxib, mefenamic acid, naproxen, etoricoxib, ibuprofen, diclofenac, and high-dose aspirin.
- Corticosteroids: dexamethasone, prednisone, deflazacort, prednisolone, and any other drug that met the criteria of this class of drugs.
- Immunomodulating drugs: cyclophosphamide, methotrexate, D-penicillamine, and any other medication that met the criteria of this class of drugs.
- Usual care.

The current version of the review includes only the following comparisons.

- Colchicine versus placebo.
- Colchicine versus immunomodulating drugs.

- Colchicine versus usual care (including unreported control or no intervention/treatment).

We plan to include comparisons between colchicine and NSAIDs and corticosteroids for future updates, as there are currently no trials comparing colchicine with these medications.

We accepted co-interventions, including treatment of complications, if they were administered equally to all intervention arms.

Types of outcome measures

Reporting in the trial one or more of the outcomes listed in this review was not an inclusion criterion for the review. We tried to access the trial protocol or contact the trial authors to ascertain all measured outcomes, even if unreported. Relevant trials that measured these outcomes but did not report their results or are not reported in a usable format are included in the narrative. We did not exclude any RCTs solely based on the reporting of the outcome data.

We reported the number of people with at least one event for all outcomes that could occur more than once in a trial participant.

We assessed all outcomes at maximum follow-up.

Primary outcomes

- All-cause mortality.
- Non-fatal MI.
- Stroke. We included either acute ischaemic stroke or intracerebral haemorrhage. However, clinical diagnosis with imaging was an eligibility criterion.
- Adverse events: we prioritised:
  - gastrointestinal (diarrhoea);
  - liver (jaundice);
  - kidney (acute renal failure);
  - neurological (seizure, mental confusion);
  - multiorgan failure.

Secondary outcomes

- Cardiovascular mortality
- Post-cardiac procedure AF
- Pericardial effusion
- Symptoms or intervention related to peripheral artery disease
- Heart failure
- Unstable angina

We excluded economic costs as an outcome of this Cochrane review. However, economic costs are mentioned in the Discussion in a narrative form.

Search methods for identification of studies

Electronic searches

We identified relevant trials through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 5), in the Cochrane Library.
- MEDLINE Ovid (including In-Process & Other Non-Indexed Citations, from 1946 to 31 May 2023).
- Embase Ovid (from 1980 to 31 May 2023).
- LILACS (BIREME) (Latin American and Caribbean Health Sciences Literature) (from 1982 to 31 May 2023).

The preliminary search strategy for MEDLINE (Ovid) was adapted for use in the other databases (Appendix 1). The Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2019) was applied to MEDLINE (Ovid) and adaptations of it to other databases, except CENTRAL.

We searched all databases from their inception to the present and did not restrict the language of publication or publication status.

We did not perform a separate search for adverse events of colchicine used to treat any disease. We considered the adverse events described in the included studies only.

Searching other resources

We searched in Web of Science (WOS) CPCI-S (Conference Proceedings Citation Index-Science) to include conference abstracts (31 May 2023).

We conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) for ongoing or unpublished trials (31 May 2023).

We searched the following regulatory data websites.

- European Medicines Agency (EMA) (www.ema.europa.eu/en/homepage) (31 May 2023).
- US Food and Drug Administration (FDA) (www.fda.gov/drugs) (31 May 2023).

Three review authors (AMC, EAB, RR) checked the reference lists of all primary studies and review articles for additional references.

We also examined any relevant retraction statements and errata for included studies. We did not find retractions on RCTs.

Data collection and analysis

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008a).

Selection of studies

Three review authors (AMC, DM, ACP) independently screened the titles and abstracts identified by the search for potential relevance, coding each study as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. A fourth review author was asked to arbitrate (RH) in the case of disagreement. We retrieved the full-text study reports/publications, and three review authors (DM, CMA, RR) independently screened the full texts, identified studies for inclusion, and determined and recorded reasons for exclusion of the ineligible studies. We resolved disagreements through discussion or consultation with a fourth review author (JBS). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow

diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. Four review authors (AMC, RR, DM, MGV) extracted study characteristics from the included studies. Two review authors (AC, CMA) checked the data extraction. We extracted the following study characteristics.

- Methods: study design, the total duration of the study, follow-up period, details of any 'run in' period, number of study centres and location, and study setting.
- Participants: number (N) randomised, N lost to follow-up/withdrawn, N analysed, age (as reported by trialist), sex, body mass index (BMI) (it is relevant to determine obesity diagnosis), hs-CRP level, pertinent details for comorbidities, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: trial's registration number, conduction dates, a priori sample estimation, financial disclosures, other disclosures, funding/support, and publication in a predatory journal.

One review author (AMC) transferred data to RevMan (RevMan 2024). Two review authors (MGV, RR) double-checked that data had been entered correctly by comparing the data presented in the systematic review with the data extraction form. Another review author (DM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

One review author (AMC) assessed the risk of bias in each trial using Cochrane's RoB 1 tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008b). Three other review authors (MGV, DM, JBDeS) independently re-checked the risk of bias in each trial. We discussed any discrepancies between review authors and achieved consensus on the final assessment.

We assessed the following domains as low, high, or unclear risk of bias.

- Randomisation
- Concealment of allocation.
- Blinding (of participants, personnel, and outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other bias

Definitions of the domains are listed in Appendix 2.

Measures of treatment effect

Data for all outcomes in this Cochrane review were dichotomous, therefore we analysed all outcomes using risk ratio (RR) with 95% confidence intervals (CIs).

Unit of analysis issues

The unit of analysis in this Cochrane review was the participant. The time of the analysis was the longest established in each trial. In the case of trials with multiple arms, we combined the groups to yield a single pair-wise comparison.

Dealing with missing data

Due to the scarcity of data and flaws in the methodologies of the trials, we did not conduct missing data analysis. Therefore, for future updates, we will assess the percentage of dropouts for each included trial and for each intervention group and will evaluate whether an intention-to-treat (ITT) analysis had been performed or could have been performed from the available published information. We will try to contact the study authors to answer any questions arising from this issue.

To undertake an ITT analysis, we will seek data from the trial authors about the number of participants in treatment groups, irrespective of their compliance and whether they were later thought to be ineligible, otherwise excluded from treatment, or lost to follow-up.

We will include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios.

- Extreme-case analysis favouring the experimental intervention ('best-worse' case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator (Hollis 1999).
- Extreme-case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator (Hollis 1999).

We will use Stata software to assess the impact of the missing data (Stata).

Assessment of heterogeneity

We initially detected the presence of heterogeneity from visual assessment of the forest plots.

We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials due to heterogeneity rather than sampling error (Higgins 2003). We assumed that 50% to 90% may represent substantial heterogeneity (Deeks 2019). For a proper interpretation of the I^2, we followed the following recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*: "The importance of the observed value of I^2 depends on (1) magnitude and direction of effects, and (2) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2: uncertainty in the value of I^2 is substantial when the number of studies is small)." (Deeks 2019). However, we considered statistical heterogeneity present if I^2 exceeded 70% (Deeks 2019).

Assessment of reporting biases

For future updates, if there are 10 or more randomised clinical trials for the outcome, we will use the contour-enhanced funnel plot to differentiate asymmetry due to publication bias from those due to other factors (Sterne 2011). We will assess the likelihood of publication bias with Harbord's test (Sterne 2011). We will use Stata statistical software to produce conventional and contour funnel plots (Stata).

Data synthesis

We followed the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* to summarise study characteristics and prepare for synthesis (McKenzie 2019). When data pooling was not feasible, we showed the information as a narrative summary of the evidence presented in either text or tabular form. For future updates, if there is evidence that an effect exists in at least one study, we plan to use an albatross plot with combined P values (Harrison 2017; McKenzie 2019). The albatross plot requires a two-sided P value, sample size, and direction of effect (or, equivalently, a one-sided P value and sample size) for each result (Harrison 2017; McKenzie 2019).

We performed meta-analyses with 95% CIs using a random-effects model. For future updates, in the case of statistical heterogeneity (I^2 > 70%), we will report the prediction interval (Deeks 2019; IntHout 2016; Riley 2011). If there is simultaneous statistical heterogeneity and three or more trials, we will determine the 95% prediction interval, which takes into account the whole distribution of the effects (Riley 2011). Prediction intervals in meta-analysis show the expected range of true effects in similar studies (Borenstein 2017; IntHout 2016). The prediction interval will show the distribution of the true effect sizes, which does not mean precision of the mean of the effect sizes (Borenstein 2009; Borenstein 2017). We will estimate the 95% prediction interval using Stata (Kontopantelis 2010; Stata).

Regardless of the overall risk of bias, RCTs contributed to the primary analyses when available. We conducted meta-analysis using RevMan software (RevMan 2024). We estimated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) only for outcomes where evidence suggested benefit or harm. We followed Cochrane methodology (Schünemann 2019b). We used GraphPad to estimate NNTB and NNTH (GraphPad 2024).

Subgroup analysis and investigation of heterogeneity

For future updates, if there are 10 or more RCTs for the outcome, and an I^2 is greater than 70%, we will conduct a meta-regression using Stata (Stata). We hypothesise that the following covariates could explain the potential statistical heterogeneity: rheumatological disorders (rheumatoid arthritis or gout), cardiovascular risk factors, hs-CRP level, and rheumatoid arthritis (Deeks 2019).

We plan to carry out the following subgroup analyses.

- Participants with rheumatological disorders (rheumatoid arthritis or gout) compared to participants without rheumatological disorders (hypothesis: participants with rheumatological disorders may have a higher risk of cardiovascular outcomes).
- Participants with cardiovascular risk factors (diabetes mellitus, blood hypertension, chronic kidney disease) compared to participants without cardiovascular risk factors (hypothesis: participants with cardiovascular risk factors have a higher risk of cardiovascular outcomes).
- Participants with hs-CRP levels higher than 2 mg/L versus participants with levels ≤ 2 mg/L (hypothesis: higher hs-CRP could suppose a higher risk of cardiovascular outcomes).

We will conduct the subgroup analysis for all outcomes. We will use the formal test for subgroup differences in Review Manager (RevMan 2024) and base our interpretation on this.

Sensitivity analysis

We plan to conduct the following sensitivity analyses for future updates, if possible.

- Trials with a low risk of bias compared to trials with an unclear or high risk of bias.
- A fixed-effect meta-analysis compared to a random-effects model meta-analysis.
- Trials without industry support compared to trials with industry support, given that trials with industry support tend to report positive effects.
- Trials not published in predatory journals compared to trials published in predatory journals, given that trials published in predatory journals tend to report positive effects.

We plan only to conduct these analyses for the primary outcomes.

We will use the overall risk of bias for a study result rather than specific domains. We will judge whether there is a difference between the primary and sensitivity analyses by comparing P values changes.

Summary of findings and assessment of the certainty of the evidence

We created a summary of the findings tables using the predefined outcomes in this Cochrane review (all-cause mortality, non-fatal MI, stroke, adverse events, cardiovascular mortality, post-cardiac procedure AF, and symptoms or intervention related to peripheral artery disease). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it relates to the RCTs that contribute data to the meta-analyses for the predefined outcomes (Atkins 2004; Guyatt 2008). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a), employing GRADEpro GDT software (GRADEpro GDT). As listed in Types of interventions, each comparison has a separate summary of findings table. We justified all decisions to downgrade the certainty of the evidence using footnotes and made comments to aid the reader's understanding of the review where necessary.

Two review authors (AMC, MGV) independently assessed the certainty of the evidence, with disagreements resolved by discussion or by involving a third review author (RR). Judgements were justified, documented, and incorporated into the reporting of results for each outcome.

We used the GRADE Working Group's statements to communicate findings combining size and certainty of an acceptable effect (Santesso 2020).

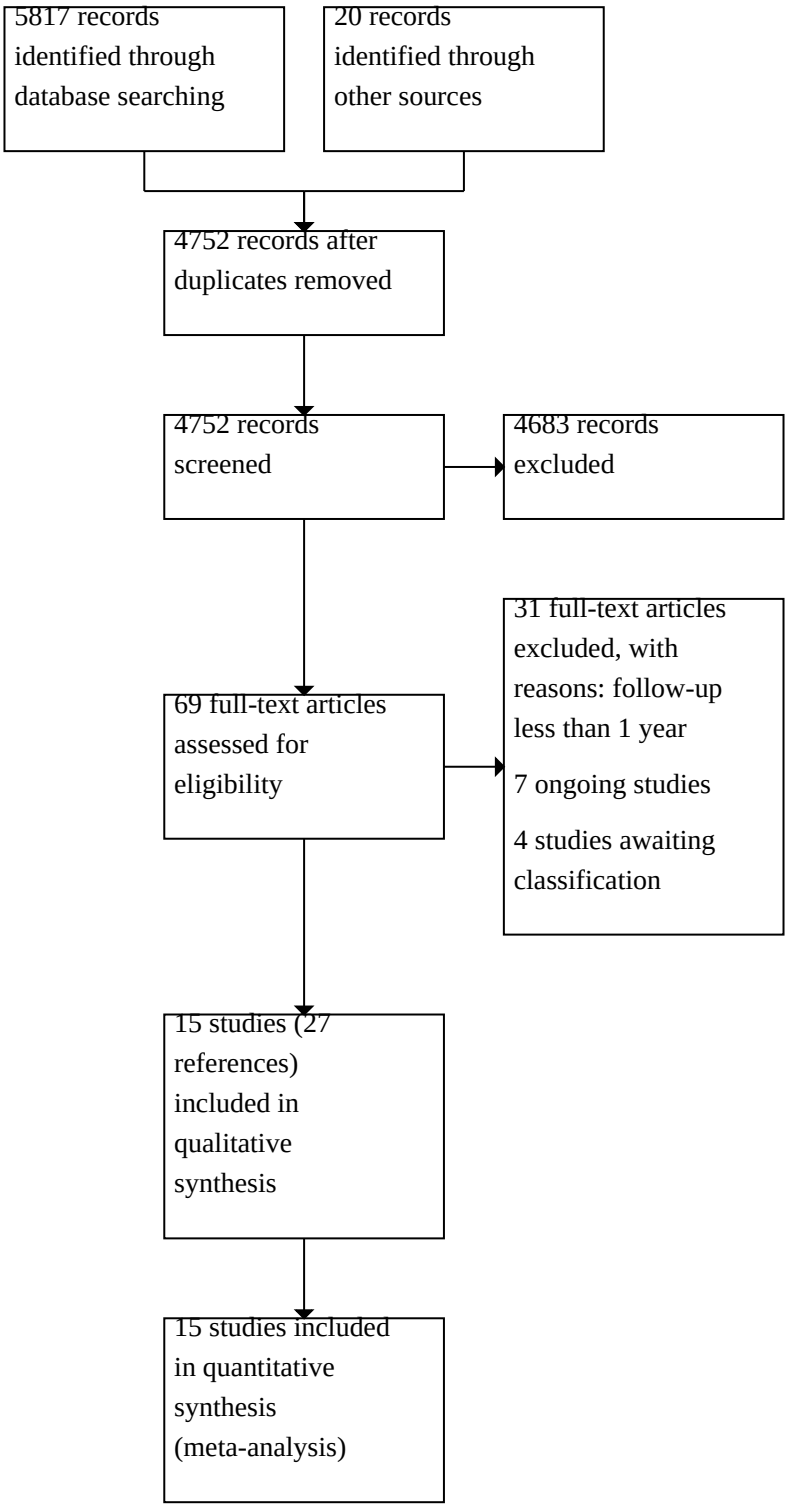
RESULTS

Description of studies

Results of the search

This Cochrane review searched for the studies twice. The Cochrane Heart Group conducted the first search (15 November 2022), and the library personnel at the Universidad Francisco de Vitoria (Madrid, Spain) performed the second search (up to 31 May 2023). In total, we retrieved 5837 studies from 5 databases, 2 clinical trials registers, and 2 databases of regulatory data (see Electronic searches; Searching other resources). Once duplicates were removed, we reviewed 4752 titles and abstracts, of which 69 records were identified as potentially relevant. We excluded 31 studies (see reasons for exclusion in Characteristics of excluded studies). We classified four studies as awaiting classification and seven as ongoing (see Studies awaiting classification and Ongoing studies). Fifteen clinical trials (27 records) encompassing 1721 randomised participants met our stringent inclusion criteria (see Characteristics of included studies). The selected trials include Bessissow 2018; Bodenheimer 1988; Buligescu 1989; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001. The evidence is current to 31 May 2023. For a comprehensive overview of our search and selection process, please refer to the flow diagram in Figure 1.

Figure 1. Study flow diagram.



See the preliminary MEDLINE (Ovid) search strategy in Martí-Carvajal 2022.

Included studies

Methods

Design and comparison groups

All trials had a parallel design with two comparison groups.

Duration of trials

- Twelve out of 15 trials (80%) disclosed the study's duration, averaging 4.04 years, ranging from one year to 11 years. The median duration was 2.5 years (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1999; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001).
- Three trials did not mention the study's duration.

Follow-up period

The follow-up for participants varied between 4 and 728 weeks, with an average duration of 223.86 weeks and a median of 156 weeks.

Run-in period

No trials reported a run-in period.

Trial location and centres

- All trials were conducted in a single country, as follows: Canada (Bessissow 2018), Greece (Nikolaidis 2006), Mexico (Kershenobich 1988), Portugal (Cortez-Pinto 2002), Romania (Buligescu 1989), Spain (Sainz 1992), Sweden (Olsson 1995), Taiwan (Lin 1996; Wang 1994), Turkey (Yurdakul 2001), the UK (Warnes 1987) and the USA (Bodenheimer 1988; Kaplan 1986; Kaplan 1999; Morgan 2005).
- Eight out of 15 trials (53.33%) were single-centre studies (Bessissow 2018; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Nikolaidis 2006; Wang 1994; Warnes 1987; Yurdakul 2001).
- Three trials (20%) were multicentre (Bodenheimer 1988; Morgan 2005; Olsson 1995).
- Four trials did not specify the number of centres involved (Buligescu 1989; Cortez-Pinto 2002; Lin 1996; Sainz 1992).

Trial setting

- Fourteen trials (93.33%) were conducted in outpatient settings.
- Only one trial was conducted in both inpatient and outpatient settings (Bessissow 2018).

Participants

Diseases

Liver diseases emerged as the predominant focus of the review, featured in 86.67% (13/15) of the studied trials, and encompassed a variety of conditions: primary biliary cholangitis 26.67% (4/13) (Bodenheimer 1988; Kaplan 1986; Kaplan 1999; Warnes 1987), alcoholic liver cirrhosis 13.33% (2/13) (Buligescu 1989; Kershenobich 1988), non-alcoholic liver cirrhosis 13.33% (2/13) (Cortez-Pinto 2002; Morgan 2005), alcoholic liver disease (Sainz 1992), chronic hepatitis B (Lin 1996), chronic liver disease (Nikolaidis 2006), hepatitis B virus-related postnecrotic cirrhosis (Wang 1994), and primary sclerosing cholangitis (Olsson 1995).

Outside the realm of liver diseases, the review also included a trial centred on cardiovascular disease, specifically perioperative AF (Bessissow 2018). Additionally, we included a study on systemic connective tissue disorders focused on Behçet's syndrome (Yurdakul 2001). Notably, non-cardiovascular diseases were the predominant subject of the trials, with only one study exclusively from the cardiovascular field (Bessissow 2018).

Randomised participants

The total number of randomised participants was 1721. The average number of participants in the included trials was 114.77, with a standard deviation (SD) of 125.03. The 95% CI for the mean ranged from 45.49 to 183.97. The median number of participants was 84.

Analysed participants

Twelve trials reported participant withdrawals. The total number of analysed participants was 1412. Consequently, the average number of analysed participants was 117.66, with an SD of 137.67. The 95% CI for this mean ranged from 38.87 to 194.66, and the median number of participants was 83.5 (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Olsson 1995; Wang 1994; Warnes 1987; Yurdakul 2001). The percentage of withdrawals was 17.95%.

Participant age

Eleven trials provided data on participant age. The mean age was 49.93 years, with an SD of 10.42 years. The 95% CI for the mean age ranged from 45.57 to 54.28 years. The median age was 51 years (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Wang 1994; Yurdakul 2001).

Participant gender

Twelve studies provided data regarding the gender distribution of participants. The mean proportion of male participants was 57.04%, with an SD of 32.91%. The 95% CI for the mean ranged from 31.42% to 68.66%. The median value was 60.75% (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Wang 1994; Yurdakul 2001).

None of the included trials provided information regarding participants' body mass index, hs-CRP levels, or history of chronic kidney disease. Only one trial detailed baseline data on the history of hypertension, diabetes mellitus, and tobacco use (Bessissow 2018). Another trial documented history related to dyslipidaemia (Kaplan 1999). Six trials presented data on participants with a history of autoimmune diseases (Bodenheimer 1988; Kaplan 1986; Kaplan 1999; Nikolaidis 2006; Olsson 1995; Yurdakul 2001). A further two trials discussed cardiovascular risk factors (Bessissow 2018; Kaplan 1999).

Inclusion criteria

Fourteen trials (93.33%) reported inclusion criteria (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001). One trial (6.67%) reported no information regarding inclusion criteria (Buligescu 1989).

Exclusion criteria

Ten trials (66.67%) reported exclusion criteria (Bessissow 2018; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Wang 1994; Yurdakul 2001). Four trials (26.67%) did not report exclusion criteria (Bodenheimer 1988; Olsson 1995; Sainz 1992; Warnes 1987). In the remaining trial (6.67%) this information was unclear (Buligescu 1989).

Interventions

Intervention

All trials administered colchicine orally. Of the 15 trials:

- eight trials (53.33%) used a dose of 1 mg (Buligescu 1989; Cortez-Pinto 2002; Kershenobich 1988; Lin 1996; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994);
- five trials (33.33%) used a dose of 0.6 mg (Bessissow 2018; Bodenheimer 1988; Kaplan 1986; Kaplan 1999; Morgan 2005);
- one trial used a dose of 0.5 mg (Warnes 1987);
- one trial allowed a flexible dose of 1 to 2 mg (Yurdakul 2001).

Regarding frequency, colchicine was administered:

- twice-daily in six trials; (Bessissow 2018; Bodenheimer 1988; Kaplan 1986; Kaplan 1999; Morgan 2005; Warnes 1987);
- once-daily in four trials (Buligescu 1989; Olsson 1995; Sainz 1992; Yurdakul 2001);
- once-daily but only five days a week in five trials (Cortez-Pinto 2002; Kershenobich 1988; Lin 1996; Nikolaidis 2006; Sainz 1992).

The average duration of administration across 14 trials was 211.81 weeks, with an SD of 190.91 weeks. The range spanned from a minimum of 1.42 weeks to a maximum of 728 weeks, with a median of 156 weeks. Notably, Morgan 2005 had a variable duration, prescribing colchicine between 104 and 312 weeks.

Control

- Placebo: 10 trials (66.66%) compared colchicine with a placebo (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kershenobich 1988; Morgan 2005; Olsson 1995; Wang 1994; Warnes 1987; Yurdakul 2001).
- NSAIDs, including indomethacin, celecoxib, mefenamic acid, naproxen, etoricoxib, ibuprofen, diclofenac, and high-dose aspirin: not reported in any trial.
- Corticosteroids, including dexamethasone, prednisone, deflazacort, prednisolone, and other drugs that fit the corticosteroid classification: not reported in any trial.
- Immunomodulating drugs, including cyclophosphamide, methotrexate, D-penicillamine, and others that met this class's criteria: one trial compared colchicine with methotrexate (Kaplan 1999).
- Usual care: we adopted this approach because the participants assigned to the control group would likely have received usual care. There is uncertainty about whether usual care was consistently defined or administered, which affects the reliability of the knowledge obtained. We also included under this category:
  - unreported control: two trials did not adequately describe the nature of the control group/condition (Buligescu 1989; Lin 1996). One trial was an abstract (Buligescu 1989);
  - no intervention: two trials reported that the control group "... did not receive antifibrotic treatment", indicating no intervention for these participants. However, the specific treatment or conditions for the control group were not detailed (Nikolaidis 2006; Sainz 1992).

Outcomes

Primary outcomes

The 15 included trials reported an average of 4.06 primary outcomes (SD 3.32). The range spanned from a minimum of 1 to a maximum of 13 outcomes, with a median of 4. The 95% CI for the mean ranged from 2.22 to 5.90.

Predefined primary outcomes

- All-cause mortality: reported by 11 trials (73.33%) (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Olsson 1995; Wang 1994; Warnes 1987). Four trials did not report information on this outcome (Buligescu 1989; Nikolaidis 2006; Sainz 1992; Yurdakul 2001).
- Non-fatal MI: reported by one trial (Bessissow 2018).
- Stroke: reported by one trial (Bessissow 2018).
- Adverse events: 13 trials (86.66%) provided data (Bessissow 2018; Bodenheimer 1988; Buligescu 1989; Cortez-Pinto 2002; Kaplan 1986; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Wang 1994; Warnes 1987; Yurdakul 2001). Two trials offered no data (Kaplan 1999; Sainz 1992).

Secondary outcomes

The 15 included trials reported an average of 5.12 secondary outcomes (SD 3.44). Outcomes ranged from 2 to 11, with a median of 3.5. The 95% CI for the mean was between 2.24 to 8.0.

Predefined secondary outcomes

- Cardiovascular mortality: reported by two trials (Kaplan 1999; Kershenobich 1988).
- Post-cardiac procedure AF: reported by one trial (Bessissow 2018).
- Pericardial effusion: not reported by any trial.
- Symptoms or intervention related to peripheral artery disease: not reported by any trial.
- Heart failure: not reported by any trial.
- Unstable angina: not reported by any trial.

Notes

Trial registration number

Out of 15 trials, only Bessissow 2018 provided a registration number. The remaining 14 trials did not provide this information.

Trial dates

- Start dates: six trials indicated the trial start date, ranging from 1979 to 2014 (Bessissow 2018; Cortez-Pinto 2002; Kershenobich 1988; Lin 1996; Morgan 2005; Yurdakul 2001).
- Finish dates: five trials reported conclusion dates between 1993 and 2015 (Bessissow 2018; Cortez-Pinto 2002; Lin 1996; Morgan 2005; Yurdakul 2001), while Kershenobich 1988 did not specify an end date.

- Nine trials did not provide information on the dates trials were conducted (Bodenheimer 1988; Buligescu 1989; Kaplan 1986; Kaplan 1999; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987).

A priori sample size estimation

Five trials conducted their research with a predetermined sample size (Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Morgan 2005; Wang 1994). Ten trials did not report this information.

Financial disclosure

- Six trials disclosed no financial ties.
- Two trials were sponsored by a drug company (Bodenheimer 1988; Kaplan 1986).
- Seven trials received funding from a governmental scientific organisation.

Sponsorship

- Two trials were sponsored by a drug company (Bodenheimer 1988; Kaplan 1986).
- Five trials were funded by government or public organisations.
- Two trials received backing from mixed public and private entities.
- Six trials did not clarify their sponsorship.

Ethical committee approval

Eleven trials confirmed receiving ethical committee approval. Four trials did not provide this information (Buligescu 1989; Lin 1996; Nikolaidis 2006; Sainz 1992).

Predatory journal

No trials were published in predatory journals.

See Figure 1 and Characteristics of included studies.

Excluded studies

We excluded 31 studies because the follow-up was less than one year (Agzarian 2018; Ahern 1987; Ahmadieh 2015; Aisen 2001; Akriviadis 1990; Aktulga 1980; Amirpour 2016; Basak 1993; Borstad 2004; Da Cunha 2006; Das 2002; Davis 2021; Deftereos 2013; Døssing 2023; Ediz 2012; Fish 1997; Grimaitre 2000; Hays 2021; Korkerdsup 2022; Lenior 2001; Leung 2018; Levine 2022; Meek 1990; Meurin 2015; Safarinejad 2004; Samuels 2020; Schnebel 1988; Simmons 1990; Taghavi 2010; Trinchet 1989; Wuttiputhanun 2022).

See Characteristics of excluded studies for details.

Ongoing studies

We identified seven ongoing trials (EUCTR2018-002114-13; IRCT138808062641N1; NCT02442921; NCT03693781; NCT04160117; NCT05175274; NCT05802992). These trials are being conducted in Canada (NCT04160117), China (NCT05175274; NCT05802992), France (EUCTR2018-002114-13), Israel (NCT02442921), and Italy (NCT03693781). The conditions being studied include immunoglobulin A (IgA) vasculitis (France), amyotrophic lateral sclerosis (Italy), diabetic nephropathy (Israel), pulmonary vein isolation (Canada), high risk of coronary artery disease (China), and multiple myeloma (China). Colchicine dosages ranged from 0.005 mg/kg/day to 1.2 mg. The number of study centres involved in each trial ranged from 1 to 32. Most studies are small, single-centre trials, except for the French study on IgA vasculitis, which involves 32 centres. In summary, these studies demonstrate research interest in exploring colchicine as a treatment for a diverse range of conditions, with studies spanning multiple countries and evaluating various colchicine dosing regimens. The size and scale of the trials range considerably. See Characteristics of ongoing studies for details.

Studies awaiting classification

Four studies are awaiting classification. We were not able to obtain the full text for two studies (Parise 1995; Reinhardt 1986). Conen 2023 and Eikelboom 2022 were categorised as studies awaiting classification following peer review. See Characteristics of studies awaiting classification for details.

Risk of bias in included studies

Risk of bias summaries are shown in Figure 2 and Figure 3; for further details see Characteristics of included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

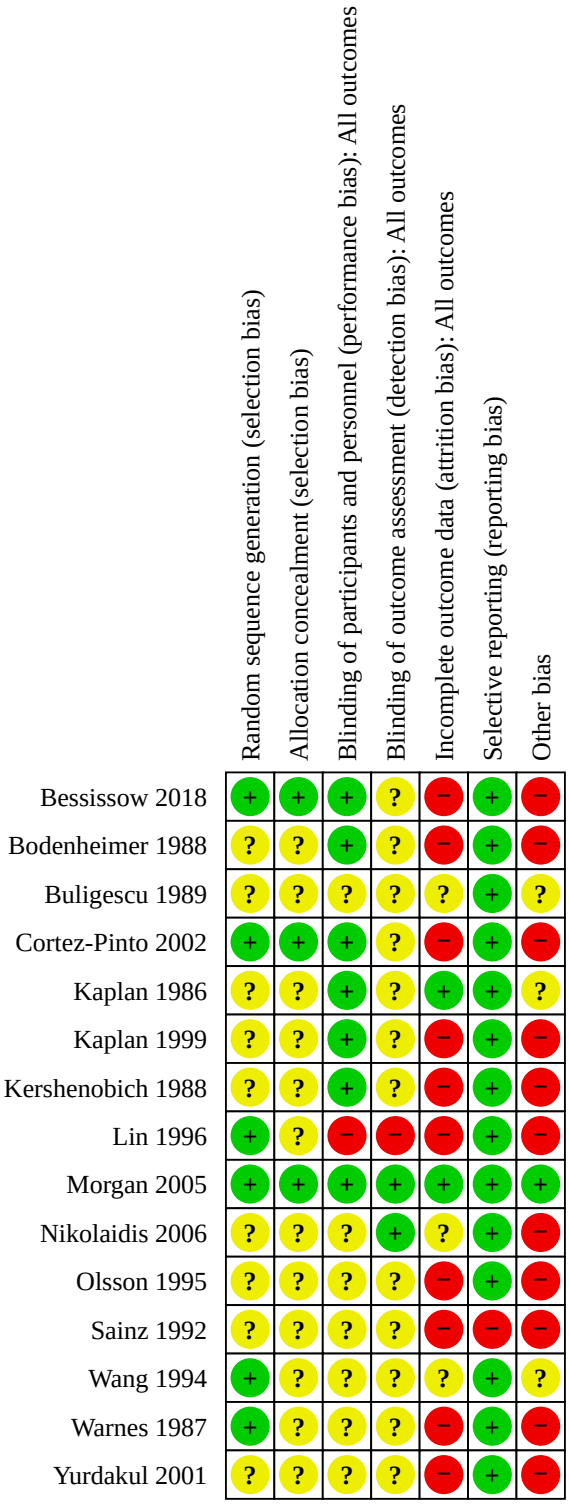
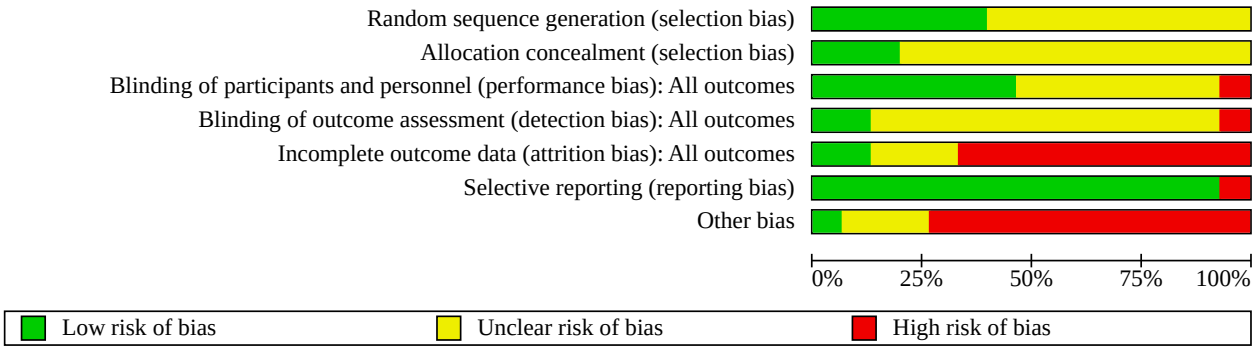


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation (randomly assigning participants to groups) was adequately carried out in 6 of the 15 trials (40%) (Bessissow 2018; Cortez-Pinto 2002; Lin 1996; Morgan 2005; Wang 1994; Warnes 1987), leading to a judgement of low risk of selection bias. The remaining nine trials had unclear reporting on their sequence generation, resulting in a judgement of unclear risk (Bodenheimer 1988; Buligescu 1989; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Nikolaidis 2006; Olsson 1995; Sainz 1992; Yurdakul 2001)

Only three trials (20%) were considered to have performed allocation concealment to minimise selection bias properly (Bessissow 2018; Cortez-Pinto 2002; Morgan 2005). The other 12 trials had unclear reporting on concealment methods, resulting in a judgement of unclear risk of bias (Bodenheimer 1988; Buligescu 1989; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001).

Blinding

We assessed seven trials as having a low risk of performance bias (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Morgan 2005). Seven other trials had unclear reporting about blinding of participants and personnel, resulting in a judgement of unclear risk of bias (Buligescu 1989; Nikolaidis 2006; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001). The remaining trial had a high risk of performance bias related to lack of blinding (Lin 1996).

Regarding detection bias, we assessed two trials that appropriately reported on blinding of outcome assessment as at low risk of bias (Morgan 2005; Nikolaidis 2006). Twelve trials had unclear reporting about blinding of outcome assessment, leading to a judgement of unclear risk of detection bias (Bessissow 2018; Bodenheimer 1988; Buligescu 1989; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Olsson 1995; Sainz 1992; Wang 1994; Warnes 1987; Yurdakul 2001). We assessed one trial as having a risk of detection bias (Lin 1996).

Incomplete outcome data

Attrition bias refers to systematic differences between groups due to the withdrawal or exclusion of participants during a study. Assessment of this type of bias depends on whether trials appropriately report participant dropouts and exclusions.

We assessed two trials as at low risk of attrition bias, as they had less than 12% dropout rates and provided sufficient details on withdrawals or exclusions (Kaplan 1986; Morgan 2005).

We assessed three trials as at unclear risk of attrition bias, as they did not report adequate information about participant withdrawals and exclusions (Buligescu 1989; Nikolaidis 2006; Wang 1994).

We assessed 10 trials as at high risk of attrition bias. Each trial lost over 12% of its participants during the study, exceeding the acceptable threshold for dropout rates (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1999; Kershenobich 1988; Lin 1996; Olsson 1995; Sainz 1992; Warnes 1987; Yurdakul 2001).

Selective reporting

Given that the included trials studied liver diseases and other soft-tissue conditions, we assessed whether they reported expected outcomes for colchicine treatment (such as death or adverse events, particularly diarrhoea or neuropathies). In summary, we assessed 14 out of 15 included trials as having a low risk of reporting bias (Bessissow 2018; Bodenheimer 1988; Buligescu 1989; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Wang 1994; Warnes 1987; Yurdakul 2001).

We assessed one trial as at high risk of bias due to missing data, as there was an absence of adverse event reporting (Sainz 1992).

Other potential sources of bias

We assessed one trial as at low risk of other bias (Morgan 2005). The main biases identified in this review were design and confusion biases due to inadequate sample size estimation and high attrition rates. Financial disclosure issues also raised concerns about potential conflicts of interest, but insufficient information prevented a definitive risk assessment.

Overall risk of bias

Given the considerations noted above, we assessed all trials but one, Morgan 2005, as at high risk of bias.

Effects of interventions

See: **Summary of findings 1** Colchicine compared with placebo for the primary prevention of cardiovascular events in adults; **Summary of findings 2** Colchicine compared with immunomodulating drugs for the primary prevention of cardiovascular events in adults; **Summary of findings 3** Colchicine compared with usual care for the primary prevention of cardiovascular events in adults

1. Colchicine versus placebo

See Summary of findings 1.

Primary outcomes

All-cause mortality

Meta-analysis of six trials comparing colchicine versus placebo suggests that colchicine may reduce all-cause mortality in primary prevention, but the evidence is very uncertain (52/241 (21.6%) versus 69/222 (31.1%); RR 0.68, 95% CI 0.51 to 0.91; Tau^2 = 0.00; I^2 = 0%; 6 studies, 463 participants; very low-certainty evidence; Analysis 1.1). The evidence is very uncertain due to limitations in design and execution and low number of events. The NNTB was 11 (95% CI 6 to 67), which means that colchicine treatment is estimated to benefit 1 in every 11 participants treated. However, the 95% CI (6 to 67) indicates substantial uncertainty in this estimate. The true effect could range from being highly effective (benefiting 1 in 6 participants) to marginally effective (benefiting 1 in 67 people), suggesting more research may be needed for a more precise estimate (Cortez-Pinto 2002; Kaplan 1986; Kershenobich 1988; Olsson 1995; Wang 1994; Warnes 1987).

Non-fatal MI

One trial comparing colchicine versus placebo suggests that colchicine may have little to no effect on non-fatal MI in primary prevention, but the evidence is very uncertain (10/49 (20.40%) versus 12/51 (23.52%); RR 0.87, 95% CI 0.41 to 1.82; Tau^2 = 1.09; 1 study, 100 participants; very low-certainty evidence; Analysis 1.2). The evidence is very uncertain due to limitations in design and execution and imprecision: small sample size regarding the optimal information size and very low number of events, the 95% CI is broad and includes no effect (RR = 1) (Bessissow 2018).

Stroke

The evidence from one trial comparing colchicine with placebo suggests that colchicine may not reduce the incidence of stroke in primary prevention, but the evidence is very uncertain (7/49 (14.3%) versus 3/51 (5.9%); RR 2.43, 95% CI 0.67 to 8.86; 1 study, 100 participants; very low-certainty evidence; Analysis 1.3). We downgraded the certainty of the evidence one level for risk of bias related to blinding of outcome assessment, and two levels for imprecision. The optimal information size of 200 was not met, and the total sample size of 100 represents only 50% of the required information size. The number of events is very small at 3.3% (10/300), and the 95% CI is wide and includes no benefit (RR = 1) (Bessissow 2018).

Adverse events

Gastrointestinal (diarrhoea)

Meta-analysis of eight trials comparing colchicine with placebo suggests that colchicine may increase the incidence of diarrhoea in primary prevention, but the evidence in very uncertain (57/309 (18.4%) versus 22/296 (7.4%); RR 3.99, 95% CI 1.44 to 11.06 ; Tau^2 = 0.94; I^2 = 51%; 8 studies, 605 participants; very low-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence two levels due to concerns with random sequence generation, allocation concealment, performance bias, detection bias, and attrition bias. We downgraded one level due to a low number of adverse events (79), and the 95% CI is wide despite excluding no benefit (RR = 1). The NNTH was 10 (95% CI 6 to 17), meaning that about 1 in every 10 people will be harmed by the treatment (Bessissow 2018; Bodenheimer 1988; Cortez-Pinto 2002; Kaplan 1986; Kershenobich 1988; Olsson 1995; Warnes 1987; Yurdakul 2001).

Neurological (seizure, mental confusion)

Meta-analysis of two trials comparing colchicine with placebo suggests that colchicine may have little to no effect on neurological outcomes such as seizure or mental confusion in primary prevention, but the evidence is very uncertain (8/79 (10.1%) versus 11/76 (14.5%); RR 0.72, 95% CI 0.31 to 1.66; Tau^2 = 0.0; I^2 = 0%; 2 studies, 155 participants; very low-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence one level for risk of bias due to inadequate allocation concealment, performance bias issues, detection bias issues, and potential attrition bias. We also downgraded two levels due to imprecision. The optimal information size was 1748, and the total sample size represents 8.86% (155/1748) of this optimal size. Given the low number of events (N = 20), the 95% CI is wide and includes the possibility of no benefit (RR = 1) (Cortez-Pinto 2002; Wang 1994).

Secondary outcomes

Cardiovascular mortality

Meta-analysis of two trials assessing colchicine versus placebo suggests that colchicine may have little to no effect on cardiovascular mortality in primary prevention, but the evidence is very uncertain (4/84 (4.76%) versus 2/76 (2.6%); RR 1.27, 95% CI 0.03 to 62.43; Tau^2 = 5.63; I^2 = 71%; 2 studies, 160 participants; very low-certainty evidence; Analysis 1.5). We downgraded the certainty of the evidence a total of three levels due to risk of bias (concerns with selection, detection, and attrition bias), inconsistency (I^2 = 71%), and imprecision (small number of events and wide CI). The optimal information size required for the trials was 2868. However, the total sample size of both trials only accounted for 5.57% (160/2868) of this size. Additionally, the number of events recorded was very low. Consequently, the 95% CI is quite broad and includes the possibility of no benefit (RR = 1) (Kaplan 1986; Kershenobich 1988).

Post-cardiac procedure AF

The evidence from one trial comparing colchicine to placebo suggests that colchicine may not reduce post-cardiac procedure AF in primary prevention, but the evidence is very uncertain (5/49 (10.2%) versus 7/51 (13.7%); RR 0.74, 95% CI 0.25 to 2.19; 1 study, 100 participants; very low-certainty evidence; Analysis 1.6). We downgraded the certainty of the evidence one level due to concerns with detection and attrition bias and two levels for imprecise results. The optimal information size for the study was 2696, but the total sample size only represents 3.7% of that (100/2696). Additionally, the number of events observed was very low (N = 12), resulting in a wide 95% CI that includes no benefit (RR = 1) (Bessissow 2018).

We acknowledge a limitation in our analyses: studies classified as primary prevention may include a small percentage of individuals with pre-existing cardiovascular disease.

No trials provided data about pericardial effusion, symptoms or intervention related to peripheral artery disease, heart failure, and unstable angina.

2. Colchicine versus immunomodulating drugs

See Summary of findings 2.

Primary outcomes

All-cause mortality

The evidence from one trial comparing colchicine with methotrexate (immunomodulating drug) suggests that colchicine may have little or no effect on all-cause mortality, but the evidence is very uncertain (3/43 (7%) versus 7/42 (16.7%); RR 0.42, 95% CI 0.12 to 1.51; 1 study, 85 participants; very low-certainty evidence; Analysis 2.1). We downgraded the certainty of the evidence two levels for high risk of bias in several domains, including sequence generation, allocation concealment, blinding of outcome assessment, and incomplete outcome data, and downgraded further for imprecision. The optimal amount of information required was 348. However, the sample size only represents 24.42% (85/348) of the optimal information size. Furthermore, the number of events recorded is minimal. The 95% CI is broad and encompasses no benefit (RR = 1) (Kaplan 1999).

No trials provided data about the following outcomes: non-fatal MI, stroke, and adverse events.

Secondary outcomes

No trials provided data about the following outcomes: cardiovascular mortality, post-cardiac procedure AF, pericardial effusion, symptoms or intervention related to peripheral artery disease, heart failure, and unstable angina.

3. Colchicine versus usual care

See Summary of findings 3.

Primary outcomes

All-cause mortality

The evidence for the effect of colchicine on all-cause mortality in primary prevention is very uncertain (141/374 (37.7%) versus 132/355 (37.2%); RR 1.07, 95% CI 0.90 to 1.27; $Tau^2 = 0.00$; $I^2 = 0\%$; 2 studies, 729 participants; very low-certainty evidence; Analysis 3.1). We downgraded the certainty of the evidence due to limitations in design and execution (concerns across most domains) and two levels for imprecision (small number of events and wide CI). The ideal amount of information required was 294,174. The total sample size comprises only 0.24% (729/294,174) of the required amount. The number of occurrences is minimal. The 95% CI is broad and encompasses no advantages (RR = 1) (Buligescu 1989; Morgan 2005).

Adverse events

Gastrointestinal (diarrhoea)

Meta-analysis of two trials comparing colchicine with usual care or no intervention suggests that colchicine may increase the incidence of diarrhoea, but the evidence is very uncertain (29/374 (7.75%) versus 8/355 (2.25%); RR 3.32, 95% CI 1.56 to 7.03; $Tau^2 = 0.00$; $I^2 = 0\%$; 2 studies, 729 participants; very low-certainty evidence; Analysis 3.2). We downgraded the certainty of the evidence two levels due to limitations in design and execution (concerns across most domains) and one level for imprecision. The number of occurrences was very low (N = 37), and the 95% CI was wide. The NNTH was 18 (95% CI 12 to 42), which means that, on average, for every 18 people treated with colchicine instead of usual care, 1 additional adverse outcome might occur. The 95% CI suggests that the true NNTH could be as low as 12 or as high as 42 (Buligescu 1989; Morgan 2005).

No trials provided data about the following outcomes: non-fatal MI and stroke.

Secondary outcomes

No trials provided data about the following outcomes: cardiovascular mortality, post-cardiac procedure AF, pericardial effusion, symptoms or intervention related to peripheral artery disease, heart failure, and unstable angina.

DISCUSSION

Summary of main results

This comprehensive Cochrane review assesses the potential clinical advantages and drawbacks of using colchicine to prevent primary cardiovascular disease outcomes in the general population. We included 15 RCTs, collectively involving 1721 participants. The included studies compared the effects of colchicine against placebo, immunomodulating drugs (specifically methotrexate), and usual care.

Summary of the characteristics of included trials:

- Methods:
  - Most trials (80%) reported study duration, which averaged 4.04 years.
  - Follow-up varied, with an average of 223.86 weeks.
  - None of the trials were international.
  - 53.33% were single-centre studies, and 20% multicentre.
- Participants:
  - Liver diseases were the primary focus in 86.67% of trials.
  - The total number of randomised participants was 1721, while the total number of analysed participants was 1412.
  - The mean age of participants was 49.93 years.
  - The mean proportion of male participants was 57.04%.
  - Only a few trials provided details on participants' medical history.
- Interventions:
  - All trials administered colchicine orally, while doses varied (ranging from 0.5 mg to 2 mg).
  - The average duration of colchicine administration was 211.81 weeks.
  - Most trials (66.66%) compared colchicine with placebo.
- Outcomes:
  - Trials reported an average of 4.06 primary outcomes.
  - All-cause mortality was reported in 73.33% of trials.
  - The trials reported an average of 5.12 secondary outcomes.

- Notes:
  - Only one trial provided a registration number.
  - A predetermined sample size was present in 33.33% of trials.
  - No trials were identified as published in predatory journals.

Regarding the effect of the intervention, we show the following summary:

- Colchicine versus placebo: we performed four meta-analyses, three of which included few studies.
  - Primary outcomes:
    - All-cause mortality: six trials contributed to this analysis. The evidence is very uncertain due to limitations in design and execution (Analysis 1.1). The NNTB was 11 (95% CI 6 to 67), which means that colchicine treatment is estimated to benefit 1 in every 11 participants treated. However, the 95% CI (6 to 67) indicates substantial uncertainty in this estimate. The true effect could range from being highly effective (benefiting 1 in 6 participants) to marginally effective (benefiting 1 in 67 people), suggesting that more research may be needed for a more precise estimate.
    - Non-fatal MI: evidence from one trial is very uncertain due to limitations in design and execution (Analysis 1.2).
    - Stroke (Analysis 1.3): the evidence was derived from a single trial and is very uncertain due predominantly to limitations in design and execution.
    - Adverse events:
    - gastrointestinal (diarrhoea) (Analysis 1.4): eight trials contributed to this meta-analysis. The evidence is very uncertain due predominantly to design flaws across most trials. The NNTH was 10 (95% CI 6 to 17), which means that about 1 in every 10 people will be harmed by the treatment;
    - neurological (seizure, mental confusion) (Analysis 1.4): the evidence was based on two trials and is very uncertain due predominantly to limitations in design and execution.
  - Secondary outcomes:
    - Cardiovascular mortality: two trials were included. The evidence is very uncertain due predominantly to limitations in design and execution (Analysis 1.5).
    - Post-cardiac procedure AF: evidence from one trial is very uncertain due to limitations in design and execution (Analysis 1.6).
- Colchicine versus immunomodulating drugs:
  - All-cause mortality: one trial compared colchicine with methotrexate. The evidence is very uncertain due to limitations in design and execution (Analysis 2.1).
- Colchicine versus usual care:
  - All-cause mortality: evidence from two trials is very uncertain due to design limitations and imprecision (Analysis 3.1).
  - Adverse events: gastrointestinal (diarrhoea): four trials contributed data to this outcome. The evidence is very uncertain due to design flaws and imprecision (Analysis 3.2). The NNTH was 18 (95% CI 12 to 42), which means that, on average, for every 18 people treated with colchicine instead of usual care, 1 additional adverse outcome might occur. The 95% CI suggests that the true NNTH could be as low as 12 or as high as 42.

Overview:

- The comparison of colchicine to placebo yielded most of our data, spanning four distinct meta-analyses. However, three of these meta-analyses contained only a few studies.
- The confidence level across all comparisons and outcomes remains very low, due largely to challenges in the trial designs and their execution, coupled with the non-specificity of the findings.
- We found no studies that compared colchicine with either NSAIDs or corticosteroids.

For details, see Summary of findings 1; Summary of findings 2; Summary of findings 3.

Overall completeness and applicability of evidence

This Cochrane review shows that when colchicine is compared with placebo, immunomodulating drugs, or standard care (or the absence of a specific comparison), it appears to offer negligible to no clinical advantages in the primary prevention of cardiovascular disease outcomes. However, this conclusion is limited by the very low certainty of the evidence, and therefore warrants cautious interpretation.

This discussion offers insights into the concerns about the indirectness of the trials concerning the primary review question. The section explains how the existing evidence base, while valuable, may not be directly aligned with evaluating colchicine for primary cardiovascular disease prevention.

Our systematic review found a pronounced discrepancy between the sample sizes utilised in the trials and the optimal information size required to empower the studies adequately. Across three comparison types - colchicine versus placebo, colchicine versus immunomodulating agents, and colchicine versus standard care or no comparator - we pinpointed 10 outcomes for which the certainty of evidence was downgraded by one or two levels due to imprecision. The downgrading stemmed from small sample sizes, sparse events, and wide CIs encompassing potential null effects. Notably, only 5 of 15 trials, a mere 33%, reported conducting sample size calculations a priori (Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Morgan 2005; Wang 1994). This elicits two critical concerns: first, the lack of rigorous sample size considerations raises ethical questions (Gelfond 2011), as many trials may have inadequately balanced risks and benefits for participants. Second, it casts uncertainty on whether prespecified hypotheses were properly evaluated in numerous trials, amplifying the susceptibility to type I and II errors. The obvious lack of a priori sample size calculations from the analysed evidence is troubling and threatens the validity of the conclusions (Peduzzi 1988).

Since we included trials studying liver diseases and other soft-tissue conditions in this Cochrane review of colchicine for primary prevention of cardiovascular events, we focused on whether these trials reported their expected outcomes (such as death or adverse events, particularly diarrhoea or neuropathies). As these trials were not designed for cardiovascular outcomes, it is not surprising that 14 out of 15 included trials were rated as having low risk of reporting bias for their intended outcomes (Bessissow 2018; Bodenheimer 1988; Buligescu 1989; Cortez-Pinto 2002; Kaplan 1986; Kaplan 1999; Kershenobich 1988; Lin 1996; Morgan 2005; Nikolaidis 2006; Olsson 1995; Wang 1994; Warnes 1987; Yurdakul 2001). However, the absence of evidence regarding cardiovascular events in these trials does not mean evidence of absence of colchicine effects

in primary cardiovascular prevention (Altman 1995). Therefore, studies specifically evaluating whether colchicine, when used in non-cardiovascular conditions, may offer benefits in primary prevention of cardiovascular events are needed. Atherosclerosis and other cardiovascular diseases are significantly influenced by inflammatory processes, suggesting that anti-inflammatory therapies could reduce cardiovascular events. While colchicine has traditionally been used for acute short-term treatment of gout flares and familial Mediterranean fever episodes, its application in cardiovascular disease requires long-term administration, as atherosclerosis in primary prevention needs sustained treatment to effectively reduce cardiovascular risk (Deftereos 2013; Deftereos 2022; Mohammadnia 2023).

1. Colchicine versus placebo

Trials comparing colchicine with placebo raise significant doubts about its efficacy for primary prevention of cardiovascular disease. However, due to the very low certainty of the evidence, these conclusions should be interpreted cautiously, considering the inherent design and execution limitations and suboptimal sample sizes. Such deficiencies are known to diminish the strength and dependability of systematic reviews and meta-analyses (Ioannidis 2005; Ioannidis 2008). The studies also exhibit biases in allocation and blinding, leading to further reservations (Savovic 2012). Hence, the real-world applicability of such evidence remains ambiguous. We acknowledge a limitation in our analyses: studies classified as primary prevention may include a small percentage of individuals with pre-existing cardiovascular disease.

2. Colchicine versus immunomodulating drugs

The sole study comparing colchicine with immunomodulating drugs, notably methotrexate, raises concerns regarding its all-cause mortality outcomes. Single studies, particularly those laden with biases, are often viewed cautiously, and there is a consensus on the need for more comprehensive research to solidify findings (Ioannidis 2005; Ioannidis 2008). The vast gap between the study's sample size and the desired optimal information size weakens the strength of the evidence. Determining the target difference for the primary outcome is crucial when calculating the sample size for an RCT. It is essential to provide a more robust rationale for the target difference and enhance its documentation (Cook 2015).

3. Colchicine versus usual care or no comparison

Trials comparing colchicine with standard care or without a defined comparator present a palpable level of uncertainty. This effect is primarily attributed to biases and data inaccuracies, typical shortcomings that erode the value of systematic reviews (Miller 2022). Given that the sample sizes fall significantly short of the ideal, the evidence's utility in guiding clinical decisions remains dubious.

In essence, we sought to spotlight the gap between actual and optimal sample sizes; elicit ethical concerns regarding participant risk-benefit balance; explain how this heightens error susceptibility; and underscore the alarming absence of a priori calculations, which could compromise the conclusions' credibility. The researchers from Difference ELicitation in TriAls (DELTA) have crafted a comprehensive set of guidelines that are a valuable addition and are likely to enhance the design and reporting of trials (Bell 2018). There has been a strong push to recognise the ethical importance of statistical standards, and 10 core principles have been proposed. These principles guide statistics' responsible and ethical application in clinical and translational studies (Gelfond 2011).

Primary prevention therapies that are deemed effective usually meet several key criteria: (1) they show efficacy in populations that are at a relatively low risk; (2) they ensure safety during long-term usage; (3) they prove to be cost-effective; and (4) they are easily accessible, often in the form of a daily oral pill (Samuel 2020). Colchicine appears to fit these criteria well. From an economic standpoint, low-dose colchicine has been recognised as a leading cost-saving approach for the secondary prevention of cardiovascular diseases (Samuel 2021). The findings of this Cochrane review emphasise the need for well-designed, adequately powered RCTs to conclusively determine the efficacy and harms of colchicine in primary prevention of cardiovascular events. However, we have not conducted a formal economic evaluation.

Regarding both NNTB and NNTH, we advise readers to exercise caution. These clinical measures are derived from meta-analyses that may include studies with varying follow-up periods. This variation is crucial for correct interpretation of the results.

Quality of the evidence

We conducted GRADE assessments on the outcomes from both meta-analyses and non-pooled trials. We assessed the evidence as of very low certainty. We based this conclusion on the small sample sizes (even after meta-analysis), which resulted in wide CIs with a low precision of the estimate for the intervention effects. Additionally, high risk of bias arose from inadequate randomisation methods, a lack of blinding, high attrition, and significant loss to follow-up. Our analysis revealed issues with randomisation and allocation concealment in many trials. Specifically, 60% (9 out of 15) had ambiguities in their random sequence generation, while 73.3% (11 out of 15) had unclear allocation concealment. As Martí-Carvajal 2018 has noted, these discrepancies can undermine the effectiveness of clinical research. Such issues inflate the intervention effect size estimates and increase inconsistency between trials that report subjectively assessed outcomes (Pereira 2011; Savovic 2012).

Given this evidence, we cannot draw any definitive conclusions, and readers should exercise caution when using it to inform decisions or policies. Conducting more rigorous and relevant studies would improve the certainty of the evidence. Such studies should address existing uncertainties and provide more precise and consistent estimates of intervention or phenomenon effects (Santesso 2020; Schünemann 2019a).

In this review, we did not assess the impact of missing data on the intervention effect using best-worst- and worst-best-case scenarios, and Gamble-Hollis analysis. Please refer to Summary of findings 1, Summary of findings 2, and Summary of findings 3 for a comprehensive assessment and the rationale behind our ratings.

Potential biases in the review process

Our comprehensive Cochrane review analysed 15 RCTs. However, despite their number, these RCTs addressed only a subset of the clinically relevant outcomes (Summary of findings 1; Summary of findings 2; Summary of findings 3). This indicates that specific outcomes of potential interest or relevance might not have been

covered. The certainty of the evidence for several of these outcomes was categorised as 'very low' based on the GRADE approach, raising concerns about the reliability of the evidence (Summary of findings 1; Summary of findings 2; Summary of findings 3).

A pivotal limitation emerged: none of the RCTs directly evaluated colchicine for the primary prevention of core cardiovascular events, the central focus of our review. This means that the included trials left our primary research question unanswered. In the face of these gaps, we synthesised the best available data from various endpoints. While this approach is a testament to our commitment to making the most of available data, it is crucial to understand that indirect evidence might not carry the same weight as direct evidence.

Our review underscores a fundamental principle in scientific research: the difference between 'absence of evidence' and 'evidence of absence'. It is imperative not to interpret the lack of direct evidence as an indication that an intervention is ineffective (Altman 1995).

Publication bias poses a grave threat that can undermine research literature (Howland 2011). Researchers widely recognise that publication bias and outcome reporting bias distort drug efficacy and harms. These biases exaggerate benefits and understate risks. The aim is to enable unbiased analysis and derive undistorted efficacy and safety conclusions. However, most trial data remain unpublished, indicating extensive, persistent publication bias (Howland 2011). In this review, we cannot reliably judge the presence or absence of publication bias without comprehensive data. Robust methodology mandates at least 10 RCTs per outcome to gauge publication bias, but fewer commonly exist. Thus, publication bias degrades the evidence base and should be spotlighted as a top priority for reform through proactive transparency initiatives and policies (Dwan 2013; Ioannidis 2010; Thornton 2000).

In closing, our Cochrane review exemplifies rigorous methodology and steadfast commitment to evidence-based principles despite inherent constraints within the available literature. We uncompromisingly optimised the data synthesis to derive maximally meaningful clinical inferences guiding physicians. Our frank acknowledgement of limitations demonstrates dedication to transparency alongside tireless efforts to offer the current best evidence. Manifesting the Cochrane spirit, we challenged assumptions through exhaustive critical appraisal. Our review incisively illuminates the realities of suboptimal evidence while foiling biases threatening meaningful analysis. With rigour yet thoughtful nuance, our review synthesises the highest attainable level of evidence. We present clinicians with the most valid and insightful conclusions achievable from the present data. Through fortitude and unwavering scientific integrity, our review overcomes limitations to stand as an authoritative reference for optimising clinical practice and patient care.

Agreements and disagreements with other studies or reviews

A 2016 Cochrane review by Hemkens 2016 synthesised 39 RCTs with 4992 participants comparing colchicine treatment for at least six months versus control. The review concluded that the benefits and harms of colchicine treatment remained highly uncertain, particularly for cardiovascular outcomes in primary prevention. The authors found no conclusive evidence that colchicine provided substantial benefits for reducing MI, even in high-risk groups. The review linked colchicine to gastrointestinal side effects, but this evidence was of low quality.

It is important to note that the Hemkens review did not include the more recent COLCOT (Tardif 2019) and LoDoCo2 (Nidorf 2020) trials, which provided evidence on the potential benefits of colchicine in secondary prevention of cardiovascular events. However, as our current review focuses specifically on the use of colchicine in primary prevention, the findings from the COLCOT and LoDoCo2 trials are not directly applicable to our scope.

The Hemkens review authors called for well-designed, large-scale RCTs enrolling participants with elevated cardiovascular risk to determine any benefits versus harms of colchicine definitively. Despite differences in trial design, follow-up duration, inclusion criteria, and objectives between the Hemkens review and our current review, the results are similar for primary prevention outcomes.

Our review aims to provide an updated assessment of the benefits and harms of colchicine in primary prevention of cardiovascular events, taking into account the available evidence from RCTs focusing on this specific population.

Shah and colleagues conducted a study to investigate the use of colchicine in male gout participants and its potential link to the development of coronary artery disease (CAD). This topic holds significance because of established connections between inflammation, gout, and CAD. Although retrospective studies come with their own challenges, they can offer valuable preliminary data for subsequent research. The research team employed a Cox proportional hazards model to address potential biases and confounding factors. However, it should be noted that by excluding female patients, Shah and colleagues might have limited the generalisability of the findings. Focusing solely on a single veterans' affairs (VA) health system might render the results less relevant to non-US veterans. The study had a relatively small sample size, which could account for the non-significant trends observed. Nevertheless, Shah and colleagues identified a trend towards reduced CAD with colchicine use, a promising observation. They also found a notable association between colchicine and lower CAD rates in individuals without chronic kidney disease, suggesting a possible interaction between renal status and the effects of colchicine. Shah and colleagues transparently and appropriately concluded that more comprehensive prospective research is needed. Future research would benefit from considering potential confounders like other medications, lifestyle choices, and comorbidities; investigating adverse events; and delving into the effects of varying colchicine dosages and durations. In conclusion, while the findings are intriguing, one must approach them cautiously due to the study's limitations. Shah and colleagues recommend more research, ideally encompassing female gout patients and a wider range of non-VA populations (Shah 2020).

The evidence presented in the study by Shah and colleagues includes weaknesses that stem from the inherent limitations of the research design and methods employed. The retrospective cohort structure relies on data not initially meant for research purposes, making it prone to bias and confounding that cannot be fully accounted for. Moreover, excluding female participants undermines the study's ability to make broadly generalisable

claims, as the findings may not extend to the entire population of interest. While retrospective analyses have value in generating hypotheses and preliminary observations, their constructed evidence should be interpreted cautiously. More robust research frameworks incorporating diverse perspectives and mitigating systematic biases would provide firmer evidential foundations for advancing knowledge and practice. Ultimately, thoughtful critique of research structure and composition is vital to properly contextualise the constructed evidence and determine the most appropriate applications of the findings.

AUTHORS' CONCLUSIONS

Implications for practice

This Cochrane review evaluated the clinical benefits and harms of using colchicine for the primary prevention of cardiovascular events in the general population. Comparisons were made against placebo, immunomodulating medications, or usual care or no intervention. However, the certainty of evidence for the predefined outcomes was very low, highlighting the pressing need for high-quality, rigorous studies to ascertain colchicine's clinical impact definitively. We identified numerous biases and inaccuracies in the included studies, limiting their generalisability and precluding a conclusive determination of colchicine's efficacy in preventing cardiovascular events. The existing evidence is inconclusive regarding colchicine's potential cardiovascular benefits or harms for primary prevention, given the limitations in the current studies. It is crucial for the research community to conduct more robust clinical trials to bridge this evidence gap effectively.

Implications for research

While colchicine, a long-established medication, is acknowledged for its anti-inflammatory properties, its role in the primary prevention of cardiovascular diseases remains unknown. This warrants further elucidation through bespoke clinical trials. A core challenge for this Cochrane review was the divergence between the incorporated studies' primary outcomes and our analysis's goal, that is delineating colchicine's efficacy in cardiovascular disease prevention. Most trials did not focus on cardiovascular outcomes, preventing any clear-cut conclusions. There is a need for trials that focus on colchicine's effects on cardiovascular outcomes. Broadening the review to include secondary or subgroup analyses from more extensive trials might yield richer insights. Future research should focus on elucidating the mechanisms underlying colchicine's anti-inflammatory effects in the context of atherosclerosis (Buckley 2024).

This review accentuates the pressing imperative for forward-looking studies that directly probe colchicine's promise in forestalling cardiovascular diseases.

To bolster the robustness of outcomes, trials should adhere to a universally agreed set of core outcomes, thereby reducing outcome reporting bias (Clarke 2007). Committing to well-established standards, encompassed in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Chan 2013a; Chan 2013b) and CONSORT statements, will uplift the quality of intervention and adverse event documentation. Crafting future trials harmoniously with the guidelines proposed by the Foundation of Patient-Centered Outcomes Research is indispensable (Parry 2021). Adopting these practices is crucial to impeding the proliferation of mediocre biomedical research (Chalmers 2009; Ioannidis 2014).

In 2015, Roberts and colleagues cast a discerning spotlight on the shortcomings ingrained in the healthcare knowledge apparatus, emphasising the rampant biases and the deluge of inferior trials in the medical literature (Roberts 2015). Our review stands as a testament to this assertion.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bessissow 2018

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 1 year 4. Follow-up period: 30 days (approx. 4 weeks) 5. Run-in period: not stated

Bessissow 2018 *(Continued)*

6. Run-in period time: not applicable
7. Multicentre (number of centres): yes (2)
8. International: no
9. Country: Canada
10. Study setting: inpatient and outpatient

Participants	1. Type of disease: perioperative atrial fibrillation (POAF) in lung resection surgery 2. Diagnosis criteria: "new-onset atrial fibrillation developing after induction of anesthesia until the end of follow-up." (supplementary material page 1) 3. Severity: not stated 4. Total randomised: 100 participants a. Colchicine: 49 b. Placebo: 51 5. Number lost to follow-up/withdrawn (%): 29 (29) a. Colchicine: 14 (28.6) b. Placebo: 15 (29.4) 6. Total analysed: 100 participants a. Colchicine: 49 b. Placebo: 51 7. Age, years, mean (SD) a. Colchicine: 68.9 (7.5) b. Placebo: 68.3 (7.4) 8. Sex, male % (males/total) a. Colchicine: 32.6 (16/49) b. Placebo: 56.8 (29/51) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: included 12. Inclusion criteria: a. All participants ≥ 55 years of age in sinus rhythm undergoing resection of a tumour in the lung (malignant, benign, or unknown) during the study period. 13. Exclusion criteria: a. Participants in AF or atrial flutter just prior to surgery b. Participants undergoing only minor thoracic interventions or procedures (i.e., chest tube insertion, needle pleural/lung biopsy, minor chest-wall surgeries, or mediastinoscopy). c. Participants with contraindications to colchicine (i.e., allergy, myelodysplastic disorders, pregnancy, or estimated glomerular filtration rate [e-GFR] <30 ml/min/1.73m2) d. Participants not expected to take oral medications for >24 hours after surgery (e.g., esophagectomy) e. Participants taking non-study colchicine before surgery
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: Pharmascience c. Dose: 0.6 mg, twice daily for 10 days d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: 0.6 mg, twice daily for 10 days c. Administration route: oral 3. Co-intervention: not stated. 4. Prohibited medications: not stated.
Outcomes	1. Primary (baseline to day 30)

Bessissow 2018 *(Continued)*

a. New onset perioperative atrial fibrillation (POAF) of any duration.

2. Secondary (baseline to day 30)
   a. Death
   b. Myocardial injury after noncardiac surgery (MINS)
   c. Myocardial infarction after MINS
   d. Stroke and transient ischaemic attack (TIA)
   e. Clinically important bradycardia
   f. Clinically important hypotension
   g. Life-threatening bleeding
   h. Serious adverse events
   i. Sepsis/infections
   j. Non-infectious diarrhoea
   k. Length of hospital stay

Notes	1. Trial registration number: COPAF131001* 2. Date of trial conduction: April 2014 to April 2015 3. A priori sample size estimation: not stated 4. Financial disclosure: supported by grants from the Canadian Institutes of Health Research, Physicians Services Incorporated and the Division of General Internal Medicine at McMaster University. 5. Disclosure comment: "none declared" (page 950, main reference) 6. Ethical committee approved: yes 7. Published in a predatory journal: no *Not stated in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... via an Interactive Web Randomization System (IWRS) maintained by the coordinating centre at the Population Health Research Institute (PHRI) in Hamilton, Ontario." page 946.
Allocation concealment (selection bias)	Low risk	Quote: "... via an Interactive Web Randomization System (IWRS) maintained by the coordinating centre at the Population Health Research Institute (PHRI) in Hamilton, Ontario." page 946.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Colchicine was (...) undertook drug over-encapsulation (i.e. to make an identical appearing placebo), labelling, packaging and shipping." page 496.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to judge "high" or "low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Randomised: 100 a. Colchicine: 49 b. Placebo: 51 2. Withdrawals: 29 a. Colchicine: 14 (28.57%) b. Placebo: 15 (29.4%) Note: page 950.

Bessissow 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trialists reported the main clinical predefined outcomes in this review.
Other bias	High risk	Design bias and confusion biases. The combination of lack of a priori sample size and high risk of attrition yielded these biases. The ethics of an RCT design starts with the estimation of the sample size for comparing the hypothesis. And, the attrition bias generates distortion of the original sample size either quantitatively or qualitatively.

Bodenheimer 1988

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 5 years 4. Follow-up period: 4 years (208 weeks) 5. Run-in period: not stated 6. Run-in period time: not apply 7. Multicentre (number of centres): yes (2) 8. International: no 9. Country: the USA 10. Study setting: outpatient
Participants	1. Type of disease: primary biliary cirrhosis (currently known as primary biliary cholangitis NIDDK 2021) 2. Diagnosis criteria: liver biopsy confirmed 3. Severity: "...all four stages of the disease were represented." (page 125) 4. Total randomised: 57 participants a. Colchicine: 28 b. Placebo: 29 5. Number lost to follow-up/withdrawn (%): 10 (17.54) a. Colchicine: 5 (17.85) b. Placebo: 5 (17.24) 6. Total analysed: 47 participants a. Colchicine: 23 b. Placebo: 24 7. Age, years, mean a. Colchicine: 53 b. Placebo: 51 8. Sex, male % (males/total) a. Colchicine: 7.1 (2/28) b. Placebo: 10.3 (3/29) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. History of chronic cholestatic liver disease and liver biopsy results compatible with primary biliary cirrhosis. 13. Exclusion criteria: not stated
Interventions	1. Intervention a. Drug: Colchicine

Bodenheimer 1988 *(Continued)*

	b. Pharmaceutical laboratory: Eli Lilly and Company (Indianapolis, USA) c. Dose: 0.6 mg, twice daily for 4 years d. Administration route: oral 2. Comparison/Control a. Drug: placebo (composition not stated) b. Dose: twice daily for 4 years c. Administration route: oral 3. Co-intervention: cholestyramine, calcium, and vitamins. 4. Prohibited medications: not stated
Outcomes	• Alkaline phosphatase (baseline through year 4) • ALT (baseline through year 4) • Bilirubin (baseline through year 4) • IgM (baseline through year 4) • Pathologic stage of the disease (baseline through year 4)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: Eli Lilly and Company supplied the drug and placebo 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomization process produced two subject cohorts..." page 125. Insufficient information to judge a "High" or "Low" risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The design of our trial was that of a double-blind, randomized evaluation of colchicine (...) twice daily compared with an identically appearing placebo." page 125
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Total sample: 57 a. Colchicine: 28 b. Placebo: 29 2. Withdrawals: 17.54 % (10/57) due to non-compliance. a. Colchicine: 17.85 % (5/28) b. Placebo:17.24 % (5/29)
Selective reporting (reporting bias)	Low risk	This trial reported all-cause mortality and gastrointestinal adverse events (diarrhoea).
Other bias	High risk	Design bias: no information about sample size estimation *a priori*.

Bodenheimer 1988 *(Continued)*

	Confusion bias: high attrition bias yielded qualitative and quantitative distortion of the original sample size.

Buligescu 1989

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: not stated 4. Follow-up period: 3 years (156 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): not stated 8. International: no 9. Country: Romania 10. Study setting: outpatient
Participants	1. Type of disease: liver cirrhosis 2. Diagnosis criteria: not stated 3. Severity: not stated 4. Total randomised: 180 participants a. Colchicine: 100 b. Control: 80 5. Number lost to follow-up/withdrawn (%): not stated 6. Total analysed: not stated 7. Age, years: not stated 8. Sex: not stated 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: not stated 13. Exclusion criteria: not stated
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg daily for 3 years d. Administration route: oral 2. Comparison/Control a. The trial did not adequately describe the nature of the control group/condition. b. Dose: not stated c. Administration route: not stated 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	• Serum bilirubin • Alkaline phosphatase • AST/ALT • Serum albumin • Serum gamma globulins

Buligescu 1989 *(Continued)*

- Prothrombin time (PT)
- Risk if jaundice
- Mortality

Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. The ethical committee approved: not stated 7. Published in a predatory journal: no 8. Data gathered from conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…by a prospective randomized clinical trial..." page S12 Comment: insufficient information to judge as "high" or "low" risk of bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "…by a prospective randomized clinical trial..." page S12 Comment: insufficient information to judge as "high" or "low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient information to judge as "high" or "low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to judge as "high" or "low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1. Randomised: 180 2. Colchicine: 100 3. Usual care: 80 There was no information about dropouts.
Selective reporting (reporting bias)	Low risk	Reported adverse event (diarrhoea) in four participants. Trial did not mention the occurrences by comparison groups.
Other bias	Unclear risk	Comment: insufficient information to judge as "high" or "low" risk of bias.

Cortez-Pinto 2002

Study characteristics

Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 11 years 4. Follow-up period: 10 years (520 weeks) 5. Run-in period: not stated

Cortez-Pinto 2002 *(Continued)*

6. Run-in period time: not applicable
7. Multicentre (number of centres): not stated
8. International: no
9. Country: Portugal
10. Study setting: outpatient

Participants	1. Type of disease: alcoholic liver cirrhosis 2. Diagnosis criteria: biopsy-proven liver cirrhosis and alcohol intake history 3. Severity: Child-Pugh A or B 4. Total randomised: 62 participants a. Colchicine: 31 participants b. Placebo: 31 participants 5. Number lost to follow-up/withdrawn (%): 33 (53.2) a. Colchicine: not stated b. Placebo: not stated 6. Total analysed: 55 participants a. Colchicine: 29 b. Placebo: 26 7. Age, years, mean (SD) a. Colchicine: 53.2 (8.5) b. Placebo: 54.4 (9.1) 8. Sex, male % (males/total) a. Colchicine: 93.1 (27/29) b. Placebo: 84.6 (22/26) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. Biopsy-proven liver cirrhosis b. Age 18 to 65 years old c. Well-documented history of previous daily alcohol intake exceeding 40 g of ethanol in women and 60 g in men for more than 5 years d. Other causes of liver disease were excluded 13. Exclusion criteria: a. Other liver diseases b. Child-Pugh class C c. Serum bilirubin > 10 mg/dL d. Gastrointestinal bleeding in the previous 15 days e. Refractory ascites f. Serious illness (renal or cardiac failure, neoplasia)
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg daily, 5 days/week for 10 years d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: once daily, 5 days/week for 10 years c. Administration route: oral 3. Co-intervention: not stated 4. Prohibited medications: not stated

Cortez-Pinto 2002 *(Continued)*

Outcomes	1. Primary (baseline through year 10) a. Death from any cause b. Gastrointestinal bleeding c. Ascites d. Encephalopathy e. Jaundice 2. Secondary (baseline through year 10) a. AST b. ALT c. GGT d. Bilirubin e. Albumin
Notes	1. Trial registration number: not stated 2. Date of trial conduction: 1989 to 2000. 3. A priori sample size estimation: yes 4. Financial disclosure: a grant from the Center of Nutrition and Metabolism (RUN 437) partially supported the study. 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "(...) according to a computer-generated randomization list (blocks of four)". Page 378.
Allocation concealment (selection bias)	Low risk	Quote: "(...) according to a computer-generated randomization list (blocks of four)". Page 378.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...colchicine or a placebo identical in appearance, prepared at the hospital pharmacy." (...) The study drugs were coded and distributed to the patient by the hospital pharmacy. At no time were the treatment codes disclosed for any patient, attending physicians or investigators". Page 378
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Total sample: 62 a. Colchicine: 31 b. Placebo: 31 2. Total withdrawal: 33 (53%) participants before the 10 years follow-up mark, no distinction between groups. Page 379
Selective reporting (reporting bias)	Low risk	This trial reported all-cause mortality and gastrointestinal adverse events (diarrhoea).
Other bias	High risk	Confusion bias: the high attrition rate (60% over 10 years) poses a substantial risk of bias that could distort the original sample composition and undermine the study's internal validity.

Kaplan 1986

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: not stated 4. Follow-up period: 2 years (104 weeks)* 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): no 8. International: no 9. Country: the USA 10. Study setting: outpatient *Data from the "double-blind" phase of the study, the first 2 years
Participants	1. Type of disease: primary biliary cirrhosis (currently known as primary biliary cholangitis NIDDK 2021) 2. Diagnosis criteria: biopsy-proven primary biliary cirrhosis 3. Severity: histologic stages 1 to 4 of primary biliary cirrhosis 4. Total randomised: 60 participants a. Colchicine: 30 b. Placebo: 30 5. Number lost to follow-up/withdrawn (%): 10 (16.67) a. Colchicine: 5 (16.67) b. Placebo: 5 (16.67) 6. Total analysed: 57 participants a. Colchicine: 28 b. Placebo: 29 7. Age, years: average age not stated 8. Sex, male % (males/total) a. Colchicine: 6.67 (2/30) b. Placebo: 3.33 (1/30) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. Clinical history and biochemical profile consistent with primary biliary cirrhosis b. Positive test for antimitochondrial antibody c. Liver biopsy consistent with primary biliary cirrhosis d. Patency of the biliary ducts by radiographic or ultrasonographic evidence 13. Exclusion criteria: a. End-stage liver disease b. Debilitating cardiovascular disease
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: Eli Lilly and Company (Indianapolis, USA) c. Dose: 0.6 mg twice daily for 2 years* d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: twice daily for 2 years* c. Administration route: oral

Kaplan 1986 *(Continued)*

3. Co-intervention: cholestyramine
4. Prohibited medications: not stated

*Data from the "double-blind" phase of the study, the first 2 years

Outcomes	1. Primary (baseline to year 2) a. Treatment failure rate 2. Secondary (baseline to year 2) a. Albumin b. PT c. Symptom score d. Clinical score e. Bilirubin f. Cholesterol g. Alkaline phosphatase h. "Aminotransferase" (page 1450) i. Liver histology scores j. Cumulative mortality due to liver failure
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: yes 4. Financial disclosure: Eli Lilly and Company supplied the medication and placebo 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias. Page 1449.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias. Page 1449.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Colchicine and placebo had identical appearance. Page 1449.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias. Page 1449.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. Total sample: 60 a. Colchicine: 30 b. Placebo: 30 2. Withdrawals: 5 % (3/60) a. Colchicine: 6.66 % (2/30) b. Placebo: 3.33 % (1/30)
Selective reporting (reporting bias)	Low risk	Reported information about all-cause mortality, cardiovascular mortality (myocardial infarction) and adverse events.

Kaplan 1986 *(Continued)*

Other bias	Unclear risk	Financial disclosure: Eli Lilly and Company supplied the medication and placebo. However, we lack evidence whether Eli Lilly and Company had any role in the design, conduct, analysis, or reporting of the study, if any of the study authors had financial ties or conflicts of interest related to Eli Lilly and Company, or the study authors maintained full control over the data and decision to publish. Insufficient information to judge as "High" or "Low" risk of bias.

Kaplan 1999

Study characteristics

Methods

1. Study design: parallel
2. Number of arms: 2 arms
3. Duration: 2 years
4. Follow-up period: 6 years*
5. Run-in period: not stated
6. Run-in period time: not applicable
7. Multicentre (number of centres): no
8. International: no
9. Country: the USA
10. Study setting: outpatient
11. Article is an interim analysis of the first 2 years of the study

Participants

1. Type of disease: Primary biliary cirrhosis (currently known as primary biliary cholangitis NIDDK 2021)
2. Diagnosis criteria: biopsy-proven primary biliary cirrhosis
3. Severity: not stated
4. Total randomised: 87 participants ("Two withdrew from the study immediately after randomization before they received any drugs" page 1175)
   a. Colchicine: 43
   b. Methotrexate: 42
5. Number lost to follow-up/withdrawn (%): unclear
   a. Colchicine: unclear
   b. Methotrexate: unclear
6. Total analysed: 83 participants
   a. Colchicine: unclear
   b. Methotrexate: unclear
7. Age, years, mean (SE)
   a. Colchicine: 51 (1.4)
   b. Methotrexate: 51 (1.5)
8. Sex, male % (males/total)
   a. Colchicine: 2.3 (1/43)
   b. Methotrexate: 4.8 (2/42)
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: it includes patients with high cholesterol
12. Inclusion criteria:
    a. Clinical history and biochemical profile consistent with primary biliary cirrhosis
    b. Serum alkaline phosphatase level of at least 2 times greater than the upper limit of normal
    c. Serum bilirubin level not greater than 10 mg/dL
    d. Liver biopsy performed within 12 months of entry consistent with or diagnostic of primary biliary cirrhosis
    e. Radiological or ultrasonic evidence that the bile ducts were patent

Kaplan 1999 *(Continued)*

13.Exclusion criteria:
   a. End-stage liver disease
   b. History of alcohol abuse
   c. Administration of drugs associated with chronic liver disease
   d. Contemplation of pregnancy
   e. Other serious medical illnesses
   f. Signs of hypersplenism

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: Eli Lilly and Co. (Indianapolis, USA) c. Dose: 0.6 mg twice daily for 6 years d. Administration route: oral 2. Comparison/Control a. Drug: Methotrexate b. Pharmaceutical laboratory: Lederle Laboratories (Pearl River, USA) c. Dose: 15 mg/week; taken 5 mg every 12 hours for 6 years d. Administration route: oral 3. Co-intervention: ursodeoxycholic acid (Ciba-Geigy Corp), cholestyramine, colestipol 4. Prohibited medications: not stated
Outcomes	• Incidence of death or liver transplant (baseline through year 2) • Fatigue (baseline through year 2) • Pruritus (baseline through year 2) • Bilirubin (baseline through year 2) • Alkaline phosphatase (baseline through year 2) • Albumin (baseline through year 2) • PT (baseline through year 2) • IgM (baseline through year 2) • ALT (baseline through year 2) • AST (baseline through year 2) • Cholesterol (baseline through year 2) • Liver histology (baseline through year 2) • Treatment success (baseline through year 2)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: yes 4. Financial disclosure: grants from the National Institutes of Health Center for Research Resources, Gastroenterologic Research in Absorptive and Secretory Processes Digestive Disease Center, and Lederle Laboratories supported the study. 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no *Note: this article is an interim analysis of the first 2 years of the study. However, we do not know if the final results have been published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned by a single study monitor..." page 1174

Kaplan 1999 *(Continued)*

		Insufficient information to judge as "High" or "Low" risk of bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned by a single study monitor..." page 1174 Insufficient information to judge as "High" or "Low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the patients and investigators were blinded to the treatment assignments." Page 1174 Quote: "Each patient was to remain in the double-blind phase of the study for 6 years or until clear evidence of disease progression or drug toxicity was detected and the treatment was judged a failure." Page 1174 Quote: "Colchicine and identical-appearing placebo ..., and methotrexate and identical-appearing placebo..." Page 1174 The trial authors did not describe how the double-blind was conducted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Original randomised: 87 (four did not receive treatment or were referred to transplantation). • Colchicine: 43 • Methotrexate: 42 However, there is inconsistency in the total number in the comparison groups. (Page 1176, Table 1). Withdrawals: 10. However, there was no discrimination by comparison group.
Selective reporting (reporting bias)	Low risk	This trial reported all-cause mortality and two adverse events: gastrointestinal (diarrhoea) and neurological complications (pneumonitis).
Other bias	High risk	Confusion bias which is based on the explanation for graded as high risk for attrition bias.

Kershenobich 1988

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: not stated 4. Follow-up period: "up to 14 years" (page 1709) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): no 8. International: no 9. Country: Mexico 10. Study setting: outpatient
Participants	1. Type of disease: liver cirrhosis 2. Diagnosis criteria: history, physical examination, and biochemical or histological evidence (page 1709)

Kershenobich 1988 *(Continued)*

3. Severity: Child-Turcotte-Pugh A, B and C
4. Total randomised: 100 participants
   a. Intervention: 54
   b. Control: 46
5. Number lost to follow-up/withdrawn (%): 19 (19)
   a. Intervention: 10 (18.5)
   b. Control: 9 (19.6)
6. Total analysed: 100 participants
   a. Intervention: 54
   b. Control: 46
7. Age, years, mean (SE)
   a. Intervention: 49.7 (1.52)
   b. Control: 50.8 (1.74)
8. Sex, male % (males/total)
   a. Intervention: 46.3 (24/54)
   b. Control: 54.3 (25/46)
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
    a. Liver cirrhosis by history, physical examination, and biochemical or histological evidence.
    b. Age: 18 years or older.
13. Exclusion criteria:
    a. Gastrointestinal bleeding or encephalopathy in the previous two weeks.
    b. Total serum bilirubin above 171 µmol/L (10 mg/dL)
    c. Serum albumin below 220 µmol/L (1.5 g/dL)
    d. Severe concomitant disease
    e. Inability to attend the study site regularly

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily, 5 days a week for 14 years d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: 1 mg once daily, 5 days a week for 14 years c. Administration route: oral 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	1. Primary (baseline up to year 14) a. Death 2. Secondary (baseline up to year 14) a. Cause of death b. Histological characteristics
Notes	1. Trial registration number: not stated 2. Date of trial conduction: 1979 - not stated 3. A priori sample size estimation: No. "the required sample sized was not estimated..." (page 1712) 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. Ethical committee approved: yes

Kershenobich 1988 *(Continued)*

7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was carried out by one of us who was based in an institution separate from the Instituto Nacional de la Nutricion Salvador Zubiran." page 1710 Comment: insufficient information to judge as "high" or "low" risk of bias. The random sequence generation procedure is unknown.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was carried out by one of us who was based in an institution separate from the Instituto Nacional de la Nutricion Salvador Zubiran." page 1710 Comment: insufficient information to judge as "high" or "low" risk of bias. The random sequence generation procedure is unknown.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: " were randomly assigned to receive either colchicine (...) or a placebo that was identical in appearance, for five days a week. (...) At no time did he come into contact with any of the patients in the study or disclose the treatment code for any patient to the attending physicians. He prepared coded supplies of colchicine and placebo and made these available to the clinicians for each new patient at entry and every two months thereafter". Page 1710.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to judge as "high" or "low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Total sample: 100 a. Colchicine: 54 b. Placebo: 46 2. Total withdrawals: 19% (19/100) a. Colchicine: 18.51% (10/54) b. Placebo: 19.56% (9/46)
Selective reporting (reporting bias)	Low risk	Reported all-cause mortality in both comparison groups, including fatal myocardial infarction in the placebo group.
Other bias	High risk	Confusion bias: the follow-up's median was greater in the colchicine group (42 months) than the placebo group (12 months). Furthermore, the high risk of attrition bias modifies the original sample.

Lin 1996

Study characteristics

Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 4 years 4. Follow-up period: 4 years (208 weeks) 5. Run-in period: no stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): not stated

Lin 1996 *(Continued)*

8. International: no
9. Country: Taiwan
10. Study setting: outpatient

Participants	1. Type of disease: chronic hepatitis B 2. Diagnosis criteria: seropositive for hepatitis B surface antigen (HBsAg) and abnormal serum aminotransferase for more than 6 months 3. Severity: not stated 4. Total randomised: 66 participants ("One patient was excluded 2 month after entry..." Page 963) a. Intervention: 38 b. Control: 27 5. Number lost to follow-up/withdrawn (%): 8 (12.1) a. Intervention: 3 (7.9) b. Control: 5 (18.5) 6. Total analysed: 57 participants a. Intervention: 35 b. Control: 22 7. Age, years, mean (SD) a. Intervention: 39.9 (9.06) b. Control: 39.6 (13.28) 8. Sex, male % (males/total) a. Intervention: 86.8 (33/38) b. Control: 88.9 (24/27) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. Clinically and pathologically documented chronic hepatitis B b. Positive hepatitis B surface antigen (HBsAg) and abnormal serum aminotransferase for over 6 month. c. Histological evidence of bridging hepatic necrosis (BHN) or one episode of hepatitis accompanied by elevation in serum alpha fetoprotein (AFP) greater than 100 ng/ml 13. Exclusion criteria: a. Age under 25 years b. Pregnancy c. Renal insufficiency d. History of idiosyncrasy to colchicine e. "Cardiopulmonary decompensation" (page 962) f. Signs or symptoms of hepatic failure
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily, 5 days per week for 4 years d. Administration route: oral 2. Comparison/Control: none 3. Co-intervention: not stated 4. Prohibited medications: steroids and antiviral agents (only prohibited for the control group, page 962)
Outcomes	1. Primary (baseline to year 4) a. Incidence of liver cirrhosis 2. Secondary (baseline to year 4) a. Incidence of acute exacerbation of hepatitis b. Biochemical test

Lin 1996 *(Continued)*

	c. Adverse events
Notes	1. Trial registration number: not stated 2. Date of trial conduction: October 1989 to September 1993 3. A priori sample size estimation: not stated 4. Financial disclosure: grants from the National Science Council of the Republic of China funded the study. 5. Disclosure comment: not stated 6. Ethical committee approved: not stated 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence table was done before the start of the trial.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial reported as open. Also, control group did not receive matching intervention (page 962)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial reported as open. Also, control group did not receive matching intervention (page 962)
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Total sample: 66 (one patient withdrawn in the placebo group due to liver histology showing cirrhosis). a. Colchicine: 38 b. No treatment: 27 2. Total withdrawal: 12.30 % (8/65) a. Colchicine: 7.89 %(3/38) b. No treatment: 18.51 %(5/27) c. Imbalance: 10.62
Selective reporting (reporting bias)	Low risk	This trial reported all-cause mortality and gastrointestinal adverse events (diarrhoea).
Other bias	High risk	Design bias: no information about sample size estimation *a priori* Confusion bias: high imbalance between comparison groups distorted the original sample size as qualitative as quantitative.

Morgan 2005

Study characteristics

Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 6 years

Morgan 2005 *(Continued)*

4. Follow-up period: 6 years (312 weeks)
5. Run-in period: not stated
6. Run-in period time: not applicable
7. Multicentre (number of centres): yes (13)
8. International: no
9. Country: the USA
10. Study setting: outpatient

Participants	1. Type of disease: Alcoholic liver cirrhosis 2. Diagnosis criteria: histological evidence, long history of alcohol use and exclusion of other causes. 3. Severity: Advance, Child-Turcotte-Pugh score ≥ 7 (Class B or C) 4. Total randomised: 549 participants a. Intervention: 274 b. Control: 275 5. Number lost to follow-up/withdrawn (%): 0 a. Intervention: 0 b. Control: 0 6. Total analysed: 549 participants a. Intervention: 274 b. Control: 275 7. Age, years, mean (SD) a. Intervention: 55.2 (8) b. Control 55.9 (7.6) 8. Sex, male % (males/total) a. Intervention: 97.5 (267/274) b. Control: 98.6 (271/275) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. Alcoholic cirrhosis by histological evidence, long history of alcohol use and exclusion of other causes b. Child-Turcotte-Pugh score ≥ 7 (Class B or C) 13. Exclusion criteria: a. Gastrointestinal bleeding in the previous 28 days, requiring transfusion b. Illicit drug use in the previous 12 months c. HIV infection d. Cancer in the previous 10 years e. Serum creatinine > 1.5 mg/dL f. Total white blood cells count < 3500/mL g. 70 years or older h. Serious chronic disease i. No home telephone
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 0.6 mg twice daily for 24 months up to 72 months d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: twice daily for 24 months up to 72 months c. Administration route: oral

Morgan 2005 *(Continued)*

	3. Co-intervention: oral multivitamin supplement 4. Prohibited medications: not stated
Outcomes	1. Primary (baseline to year 6) a. Death from any cause 2. Secondary (baseline to year 6) a. Death from liver disease b. Liver function status c. Histological improvement d. Adverse events
Notes	1. Trial registration number: not stated 2. Date of trial conduction: August 1994 to August 2000 3. A priori sample size estimation: yes 4. Financial disclosure: the Veterans Affairs Cooperative Studies Program funded the study 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patient enrollment and random assignment to treatment was by telephone call to the data-coordinating center". Page 883.
Allocation concealment (selection bias)	Low risk	Quote: "Patient enrollment and random assignment to treatment was by telephone call to the data-coordinating center". Page 883.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the patients, the nurses administering the treatment, nor the physicians assessing the outcomes were aware of the treatment group assignment until all data analysis was complete." page 883. Quote: "Study medications were dispensed by each VA Pharmacy from prepackaged kits matched to the treatment ID number." page 883
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "adjudication committee consisting of 3 hepatologists reviewed blinded/redacted medical records." page 884
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. Randomised: 549 a. Colchicine: 275 b. Placebo: 274
Selective reporting (reporting bias)	Low risk	Reported all-cause mortality and adverse events.
Other bias	Low risk	We did not find evidence of other bias.

Nikolaidis 2006

Study characteristics

Methods	1. Study design: parallel

Nikolaidis 2006 *(Continued)*

2. Number of arms: 2 arms
3. Duration: 1 year
4. Follow-up period: 1 year (52 weeks)
5. Run-in period: not stated
6. Run-in period time: not applicable
7. Multicentre (number of centres): no
8. International: no
9. Country: Greece
10. Study setting: outpatient

Participants	1. Type of disease: Chronic liver disease 2. Diagnosis criteria: liver biopsy-proven chronic active disease (page 282) 3. Severity: not stated 4. Total randomised: 38 participants a. Intervention: 21 participants b. Control: 17 participants 5. Number lost to follow-up/withdrawn (%): not reported 6. Total analysed: unclear 7. Age, years, median (range) a. Intervention: 49 (20 to 70) b. Control 53 (33 to 69) 8. Sex, male % (males/total) a. Intervention: 57.1 (12/21) b. Control: 64.7 (11/17) 9. BMI: not stated 10. hs-CRP basal level: not stated 11. Participants with cardiovascular risk factors: not stated 12. Inclusion criteria: a. Chronic liver disease proven by liver biopsy 13. Exclusion criteria: a. Age < 20 or > 70 years old b. Pregnancy c. Malignancies d. Renal, cardiopulmonary, haematological, neurological or collagen disease e. Diabetes mellitus f. Hyper/hypothyroidism g. Child class C
Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily for 5 days per week, for 12 months d. Administration route: oral 2. Comparison/Control: none 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	• Biochemical parameters (baseline to months 12 and 24) ◦ Serum immunoglobins ◦ Serum aminoterminal peptide of procollagen III ◦ CD4 ◦ CD8 • Bridging necrosis (baseline to months 12 and 24)

Nikolaidis 2006 *(Continued)*

	• Adverse events (baseline to months 12 and 24)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly..." (page 282) Comment: insufficient information to judge as "High" or "Low" risk of bias.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Liver biopsies were taken (...) were evaluated by two pathologists (...) who were blinded to treatment groups" (page 282)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is no report about withdrawals.
Selective reporting (reporting bias)	Low risk	Trial author declared lack of any adverse event.
Other bias	High risk	Design bias: lack of an *a priori* sample size estimation.

Olsson 1995

Study characteristics

Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 3 years 4. Follow-up period: 3 years (156 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): yes (not stated) 8. International: no 9. Country: Sweden 10. Study setting: outpatient
Participants	1. Type of disease: Primary sclerosing cholangitis

Olsson 1995 *(Continued)*

2. Diagnosis criteria: "typical cholangiographic appearance" (page 1199)
3. Severity: not stated
4. Total randomised: 84 participants
   a. Intervention: 44 participants
   b. Control: 40 participants
5. Number lost to follow-up/withdrawn (%): 10 (11.9)
   a. Intervention: 8 (18.2)
   b. Control: 2 (5)
6. Total analysed: 84 participants
   a. Intervention: 44
   b. Control: 40
7. Age, years, mean (95% CI)
   a. Intervention: 39.5 (36.2 to 42.7)
   b. Control: 43.7 (40.1 to 47.3)
8. Sex, male % (males/total)
   a. Intervention: 61.4 (27/44)
   b. Control: 72.5 (29/40)
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
    a. Primary sclerosing cholangitis by "typical cholangiographic appearance" (page 1199)
13. Exclusion criteria: not stated

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily for 3 years d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: once daily for 3 years c. Administration route: oral 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	1. Primary (baseline to year 3) a. Mortality b. Incidence of liver transplantation 2. Secondary (baseline to year 3) a. Clinical changes: pain, fever and pruritus b. Biochemical changes c. Histological changes
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no
Risk of bias	

Olsson 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " The randomization procedure was performed for each center using the sealed envelope technique." page 1999 Comment: there is no description procedure to conduct a random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: " The randomization procedure was performed for each center using the sealed envelope technique." page 1999 Comment: there is no description of whether the sealed envelope was opaque.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The results of a double-blind,..." page 1999 Comment: Insufficient information to judge as "High" or Low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge as "High" or "Low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Randomised: 84 a. Colchicine: 44 b. Placebo: 40 2. Withdrawals: 11.9% (10/84) a. Colchicine: 18% (8/44) b. Placebo: 5% (2/40) 3. Imbalance: 13% 4. Reasons were reported.
Selective reporting (reporting bias)	Low risk	Reported all-cause mortality and one case of diarrhoea as a side effect in the colchicine group.
Other bias	High risk	Design bias: there was no *a priori* sample size estimation. Confusion bias due to distortion due to imbalance loss between comparison groups.

Sainz 1992

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 2 years 4. Follow-up period: 2 years (104 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): not stated 8. International: no 9. Country: Spain 10. Study setting: outpatient
Participants	1. Type of disease: alcoholic liver disease

Sainz 1992 *(Continued)*

2. Diagnosis criteria: alcohol consumption > 80 g/day for > 5 years and histological evidence of alcoholic liver lesion
3. Severity: not stated
4. Total randomised: 54 participants
   a. Intervention: 28 participants
   b. Control: 26 participants
5. Number lost to follow-up/withdrawn (%): 14 (25.9)
   a. Intervention: 4 (14.3)
   b. Control: 10 (35.7)
6. Total analysed: not stated
7. Age: not stated
8. Sex: not stated
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
    a. Alcohol consumption > 80 g/day for > 5 years
    b. Histological evidence of alcoholic liver lesion
13. Exclusion criteria: not stated

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily, 5 days a week, for 2 years d. Administration route: oral 2. Comparison/Control: none 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	• Disease complications (baseline to year 2) • Amino-terminal type III procollagen peptide (baseline to year 2) • Histological changes (baseline to year 2)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. Ethical committee approved: not stated 7. Published in a predatory journal: no 8. Data gathered from conference proceeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias. (page 56)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.

Sainz 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Total sample: 54 a. Colchicine: 28 b. Control: 26 2. Withdrawal: 25.92% (14/54) a. Colchicine: 14.2 % (4/28) b. Control: 38.46 % (10/26) c. Imbalance: 24.26 (38.46 - 14.2). 3. No information about the reasons for withdrawals.
Selective reporting (reporting bias)	High risk	No information about any adverse events.
Other bias	High risk	Design bias: no information about *a priori* sample size estimation. Confusion bias: the large number of withdrawals distorted the original sample size.

Wang 1994

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 10 years* 4. Follow-up period: 10 years* (520 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): no 8. International: no 9. Country: Taiwan 10. Study setting: outpatient *The study was designed for a 5-year double-blind period and 5-year post-treatment follow-up (page 873).
Participants	1. Type of disease: hepatitis B virus-related postnecrotic cirrhosis 2. Diagnosis criteria: histological evidence or "compatible clinical features, biochemical data and sonographic findings." (Page 873) 3. Severity: not stated 4. Total randomised: 100 participants a. Intervention: 50 participants b. Control: 50 participants 5. Number lost to follow-up/withdrawn (%): 9 (9) a. Intervention: 2 (4) b. Control: 7 (14)

Wang 1994 *(Continued)*

6. Total analysed: varies with each outcome
   a. Intervention: varies with each outcome
   b. Control: varies with each outcome
7. Age, years, mean (range)
   a. Intervention: 60 (32 to 79)
   b. Control: 59 (36 to 80)
8. Sex, male % (males/total)
   a. Intervention: 94 (47/50)
   b. Control: 94 (47/50)
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
    a. Hepatitis B surface antigen (HBsAg)-positive cirrhosis
13. Exclusion criteria:
    a. End-stage liver cirrhosis
    b. Episodes of variceal bleeding or hepatic encephalopathy in the previous 2 weeks
    c. Concomitant debilitating illness
    d. Unable to attend clinic regularly

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 1 mg once daily for 5 years d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: once daily for 5 years c. Administration route: oral 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	• Death (baseline to end of follow-up) • Biochemical liver test (baseline to end of follow-up) • Ultrasonographic status (baseline to end of follow-up) • Histologic progression (baseline to end of follow-up)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: yes 4. Financial disclosure: a grant from the National Science Council of the Republic of China funded the study. 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were then randomly (...) by random numbers. The random numbers were computer generated and arranged in numerical order and divided in two." Page 873

Wang 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was carried out by a nurse who assisted in the patients' follow-up and file management" Page 873
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...receive either 1 mg of colchicine daily or an identical placebo by random numbers." (...) Neither the patients nor the physicians knew which treatment was given." Page 873 Quote: "Randomization was carried out by a nurse who assisted in the patients' follow-up and file management" Page 873 Comment: it is unclear the full involvement the nurse in charge of the randomisation had with the participants' clinical assessments.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...receive either 1 mg of colchicine daily or an identical placebo by random numbers." (...) Neither the patients nor the physicians knew which treatment was given." Page 873 Quote: "Randomization was carried out by a nurse who assisted in the patients' follow-up and file management" Page 873 Comment: it is unclear the full involvement the nurse in charge of the randomisation had with the participants' clinical assessments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1. Total sample: 100 a. Colchicine: 50 b. Placebo: 50 2. Withdrawals: 9% (9 /100). a. Colchicine: 4 % (2/50) b. Placebo: 14 % (7/50) c. Imbalance: 10
Selective reporting (reporting bias)	Low risk	This trial reported all-cause mortality and two types of adverse events: gastrointestinal (diarrhoea) and liver complications (jaundice, ascites).
Other bias	Unclear risk	Insufficient information to judge a "High" or "Low" risk of bias.

Warnes 1987

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 18 months 4. Follow-up period: 18 months (78 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): no 8. International: no 9. Country: the UK 10.Study setting: outpatient
Participants	1. Type of disease: primary biliary cirrhosis (currently known as primary biliary cholangitis NIDDK 2021) 2. Diagnosis criteria: liver histology compatible with primary biliary cirrhosis 3. Severity: not stated 4. Total randomised: 64 participants

Warnes 1987 *(Continued)*

a. Intervention: 34 participants
b. Control: 30 participants
5. Number lost to follow-up/withdrawn (%): 10 (15.6)
a. Intervention: 8 (23.5)
b. Control: 2 (6.7)
6. Total analysed: varies with each outcome
a. Intervention: varies with each outcome
b. Control: varies with each outcome
7. Age, years: not stated
8. Sex: not stated
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
a. Liver histology compatible with, or diagnostic of, primary biliary cirrhosis
b. Raised serum alkaline phosphatase
c. Positive anti-mitochondrial antibody test
13. Exclusion criteria: not stated

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: not stated c. Dose: 0.5 mg twice daily for 12 months d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose twice daily for 12 months c. Administration route: oral 3. Co-intervention: not stated 4. Prohibited medications: not stated
Outcomes	• Death (baseline to month 18) • Side effects (baseline to month 12) • Biochemical liver tests (baseline to month 12) • Immunological test (baseline to month 12) • Histological changes (baseline to month 12)
Notes	1. Trial registration number: not stated 2. Date of trial conduction: not stated 3. A priori sample size estimation: not stated 4. Financial disclosure: not stated 5. Disclosure comment: not stated 6. Ethical committee approved: yes 7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " by reference to random tables." page 2

Warnes 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to judge "high" or "low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient information to judge "high" or "low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote "The study was double-blind." page 2
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Randomised: 64 a. Colchicine: 34 b. Placebo: 30 2. Withdrawals: 16% (10/64) a. Colchicine: 23 % (8/34) b. Placebo: 7 % (2/30)
Selective reporting (reporting bias)	Low risk	Reported information about all-cause mortality and adverse events.
Other bias	High risk	Design bias: no *a priori* sample size estimation. Confusion bias: high-risk attrition bias, which distorts the quality of the original sample size.

Yurdakul 2001

Study characteristics	
Methods	1. Study design: parallel 2. Number of arms: 2 arms 3. Duration: 2 years 4. Follow-up period: 2 years (104 weeks) 5. Run-in period: not stated 6. Run-in period time: not applicable 7. Multicentre (number of centres): no 8. International: no 9. Country: Turkey 10. Study setting: outpatient
Participants	1. Type of disease: Behçet's syndrome 2. Diagnosis criteria: not stated 3. Severity: active disease 4. Total randomised: 120 participants a. Intervention: 60 participants b. Control: 60 participants 5. Number lost to follow-up/withdrawn (%): 36 (30) a. Intervention: 18 (30) b. Control: 18 (30) 6. Total analysed: 116 participants a. Intervention: 58 b. Control: 58

Yurdakul 2001 *(Continued)*

7. Age, years, mean (SD)
   a. Intervention
      i. Female: 26.7 (4.8)
      ii. Male: 27 (5.5)
   b. Control
      i. Female: 27.2 (5.5)
      ii. Male: 27.3 (5.3)
8. Sex, male % (males/total)
   a. Intervention: 51.7 (30/58)
   b. Control: 51.7 (30/58)
9. BMI: not stated
10. hs-CRP basal level: not stated
11. Participants with cardiovascular risk factors: not stated
12. Inclusion criteria:
   a. "Consecutive patients" (page 2687)
   b. 18 to 35 years of age
   c. Active disease
   d. Disease duration ≤ 2 years
   e. Live at a travel distance from the study centre
13. Exclusion criteria:
   a. Use of immunosuppressant agents, steroids or colchicine in the previous 6 months
   b. Organ involvement requiring immunosuppression
   c. Had eye disease, especially with retinal involvement

Interventions	1. Intervention a. Drug: Colchicine b. Pharmaceutical laboratory: F. Frik Pharmaceutical Company Limited (Istanbul, Turkey) c. Dose: 1 to 2 mg a day (adjust to body weight) for 2 years d. Administration route: oral 2. Comparison/Control a. Drug: Placebo (composition not stated) b. Dose: daily for 2 years c. Administration route: oral 3. Co-intervention: local treatment for ulcers and paracetamol or NSAIDs for joint pains 4. Prohibited medications: not stated
Outcomes	1. Primary (baseline to year 2) a. Complete absence of: i. Oral ulceration ii. Genital ulcers iii. Erythema nodosum iv. Follicular lesions v. Arthritis 2. Secondary (baseline to year 2) a. Differences in the mean number of mucocutaneous lesions or joints with arthritis b. Other symptoms of the disease c. Adverse events
Notes	1. Trial registration number: not stated 2. Date of trial conduction: November 1991 to November 1995 3. A priori sample size estimation: not stated 4. Financial disclosure: TUBITAK (Turkish Scientific and Technical Research Council) and the Research Fund of the University of Istanbul supported the study. F. Frik Pharmaceutical Company Limited (Istanbul, Turkey) provided the drug and the placebo.

Yurdakul 2001 *(Continued)*

5. Disclosure comment: not stated
6. Ethical committee approved: yes
7. Published in a predatory journal: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomization was done separately for each sex." Page 2687 Comment: insufficient information to judge "high" or "low" risk of bias.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to judge the "high" or "low" risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: " All participating physicians were blinded to the patient's allocation to the study arms." Page 2687 Comment: insufficient information to judge "high" or "low" risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Adverse effects were recorded by questioning patients regarding loss of appetite, nausea, abdominal pain, and diarrhea or any other symptom volunteered by the patient at each visit." Page 2687. Comments: no information regarding other outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Randomised: 120 a. Colchicine: 60 b. Placebo: 60 2. Withdrawals at 18 months: 30% (84/120) a. Colchicine: 30% (42/60) b. Placebo: 30% (42/60) Reported several reasons to explain the withdrawals.
Selective reporting (reporting bias)	Low risk	This trial reported two types of adverse events: gastrointestinal (loss of appetite, nausea, abdominal pain, diarrhoea) and neurological complications (intracranial hypertension).
Other bias	High risk	Design bias: no *a priori* sample size estimation. Confusion bias: high-risk attrition bias distorts the quality and quantity of the original sample size.

- AF: atrial fibrillation
- ALT: alanine transaminase
- AST: aspartate aminotransferase
- BMI: body mass index
- GGT: gamma-glutamyl transferase
- HBsAg: hepatitis B surface antigen
- hs-CRP: high-sensitivity C-reactive protein
- IgM: immunoglobulin M
- MINS: myocardial injury after non-cardiac surgery
- NSAIDs: non-steroidal anti-inflammatory drugs
- POAF: perioperative atrial fibrillation
- PT: prothrombin time

- PTT: partial thromboplastin time
- SD: standard deviation
- SE: standard error
- TIA: transient ischaemic attack

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agzarian 2018	Follow-up less than 1 year
Ahern 1987	Follow-up less than 1 year
Ahmadieh 2015	Follow-up less than 1 year Quote "The patients were followed for 6 months." page e171
Aisen 2001	Follow-up less than 1 year
Akriviadis 1990	Follow-up less than 1 year Quote "During a 4-month follow-up period ..." Source: https://pubmed.ncbi.nlm.nih.gov/2199290/
Aktulga 1980	Follow-up less than 1 year
Amirpour 2016	Follow-up less than 1 year
Basak 1993	Follow-up less than 1 year
Borstad 2004	Follow-up less than 1 year
Da Cunha 2006	Follow-up less than 1 year
Das 2002	Follow-up less than 1 year
Davis 2021	Follow-up less than 1 year
Deftereos 2013	Follow-up less than 1 year
Døssing 2023	Follow-up less than 1 year
Ediz 2012	Follow-up less than 1 year
Fish 1997	Follow-up less than 1 year
Grimaitre 2000	Follow-up less than 1 year (2 months)
Hays 2021	Follow-up less than 1 year
Korkerdsup 2022	Follow-up less than 1 year
Lenior 2001	Follow-up less than 1 year
Leung 2018	Follow-up less than 1 year
Levine 2022	Follow-up less than 1 year

Study	Reason for exclusion
Meek 1990	Follow-up less than 1 year (2 months)
Meurin 2015	Follow-up less than 1 year
Safarinejad 2004	Follow-up less than 1 year
Samuels 2020	Follow-up less than 1 year
Schnebel 1988	Follow-up less than 1 year
Simmons 1990	Follow-up less than 1 year
Taghavi 2010	Follow-up less than 1 year
Trinchet 1989	Follow-up less than 1 year
Wuttiputhanun 2022	Follow-up less than 1 year

Characteristics of studies awaiting classification *[ordered by study ID]*

Conen 2023

Methods	Randomised controlled trial conducted at 45 sites in 11 countries
Participants	Patients aged 55 years or older and undergoing major non-cardiac thoracic surgery
Interventions	Oral colchicine 0.5 mg twice daily or matching placebo
Outcomes	Perioperative atrial fibrillation and myocardial injury after non-cardiac surgery (MINS), sepsis or infection, and non-infectious diarrhoea
Notes	

Eikelboom 2022

Methods	Open-label, 2 × 2 factorial, randomised, controlled trial conducted at 48 clinical sites in 11 countries
Participants	Patients in the community aged 30 years and older with symptomatic, laboratory confirmed COVID-19 who were within 7 days of diagnosis and at high risk of disease progression
Interventions	Colchicine versus usual care
Outcomes	Hospitalisation or death
Notes	

Parise 1995

Methods	
Participants	
Interventions	
Outcomes	
Notes	We were not able to find the full-text article.

Reinhardt 1986

Methods	
Participants	
Interventions	
Outcomes	
Notes	We were not able to find the full-text article.

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2018-002114-13

Study name	Efficacy of Colchicine to prevent skin relapses in adult's IgA vasculitis
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 264 4. Phase: III 5. Country: France
Participants	1. Age: 18 years to 85 years 2. Sex: Both 3. Inclusion criteria: a. IgA-V recently diagnosed (< 20 days since skin biopsy) and defined by: i. Histologically proven small vessels vasculitis with IgA deposits IgA Vasculitis ii. Purpura and/or involvement of at least one organ among kidney, joint, or intestinal tract 4. Exclusion criteria: a. Severe renal IgA vasculitis: impaired renal function, defined as an eGFR < 60 ml per minute per 1.73 m2 (MDRD or CKD-EPI formula)-proteinuria/creatiniuria> 1g/l- Uncontrolled blood pressure (systolic blood pressure > 170 mmHg, diastolic blood pressure > 100 mmHg) b. Severe digestive IgA vasculitis:- intussusception- massive gastrointestinal haemorrhage- intestinal ischaemia- perforation- abdominal pain persisting more than one day (EVA > 5) and unresponsive to standard analgesics (level 1 or 2). c. Prior (< 3 months) immunosuppressive or corticosteroid therapy) Additional cutaneous, and/or digestive and/or chronic renal diseases; e) HIV and B and C Chronic hepatitis; f) Pregnancy or breast feeding or women without sufficient contraception among women of childbearing; g) Known allergy or intolerance to study medication or any of its excipients (lactose, saccharose); h) Contraindication to colchicine such as:- severe hepatic insufficiency- combination with a

EUCTR2018-002114-13 *(Continued)*

	macrolide (except spyramicin),- combination with pristinamycin; i) Participation in another interventional trial; j) Patient having not signed an informed consent; k) Patient without Social Security System Insurance
Interventions	• Experimental: 1. COLCHICINE OPOCALCIUM 1 mg, oral • Control: 1. Placebo
Outcomes	• Primary: 1. Number of patients who have presented at least one cutaneous relapse in the colchicine group versus the placebo group, 6 months after inclusion. Cutaneous relapse is defined by reappearance of palpable purpura with lower limb predominance and not related to thrombocytopenia. • Secondary: 1. Time (in days) to first cutaneous relapse 2. Number of cutaneous relapses per patients at M6 and M12 3. Rate of patients who have presented at least a severe cutaneous relapse at M0, M6 and M12- 36 4. 36-item Short-form Health Survey (SF-36) score at M6 and M12 5. Rate of patients displaying at least one work stoppage related to IgAV between M0 and M12 and number of days of work stoppage per patient. 6. Rate of patient who consulted in emergency for IgA relapse or new organ involvement between M0 and M12. 7. Adverse events associated with Colchicine and compliance at M3 and M6 8. Clinical, biological and histological candidate predictors at diagnosis.
Starting date	1. Date of first enrolment: 2019-05-24 2. Date of registration: 2019-03-26
Contact information	1. DRCI Hôpital Saint Louis 2. Address: 1 av Claude Vellefaux, Paris 75010, France 3. Telephone:+331 44 84 17 33 4. Email: cecile.kedzia@aphp.fr 5. Affiliation: ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS (APHP)
Notes	https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002114-13/FR#A

IRCT138808062641N1

Study name	The effectiveness of 1 mg/day Colchicine in the treatment of patients with ocular involvement in Behcet's Disease
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 80 4. Phase: IV 5. Country: Iran
Participants	1. Age: 17 years to 70 years 2. Sex: Both 3. Inclusion criteria: a. Diagnosed Behcet's disease according to Iran's diagnostic tree criteria, signing the informed consent, not being pregnant or breast feeding, no history of malignancy, age more than 16, posterior uveitis or retinitis in latest ophthalmological visit

IRCT138808062641N1 *(Continued)*

	4. Exclusion criteria: a. blood dyscrasia, pregnancy, low compliance
Interventions	• Experimental: 1. Colchicine 1 mg/day during one year orally • Control: 1. placebo
Outcomes	• Primary (total following time is 12 months in 5 visits): 1. Decrease/or not relapsing of ocular inflammatory index: 3 months • Secondary: 1. decrease/or not relapsing ocular IBDDAM: 3 months 2. retinal inflammatory index: 3 months 3. posterior chamber inflammatory index: 3 months
Starting date	1. Date of first enrolment: 2010-01-21 2. Date of registration: 2020-08-13
Contact information	1. Fereydoun Davatchi 2. Address: Iran (Islamic Republic of) 3. Telephone: +98 21 8802 6956 4. Email: davachif@sina.tums.ac.ir 5. Affiliation: Rheumatology Research Center, Tehran University of Medical Sciences
Notes	https://en.irct.ir/trial/2453

NCT02442921

Study name	The Effect of Colchicine Treatment on the Progression of Proteinuria in Patients With Diabetic Nephropathy
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 40 4. Phase: II 5. Country: Israel
Participants	1. Age: ≥18 years 2. Sex: Both 3. Inclusion criteria: a. Patients with diabetes mellitus, age >18 years old, able to sign an informed consent. b. Haemoglobin A1c in the range of 6-9%, stable for last year (0.5±) c. Blood creatinine lower than 2 mg/dL. d. Blood pressure lower than 140/90 mmHg on stable anti-hypertensive treatment for at least 3 months. e. Treated with ACE or angiotensin II receptor blocker, unless contraindicated 4. Exclusion criteria: a. Malignancy or significant heart, lung or liver disease. b. Any gastrointestinal disease, inflammatory bowel disease, malnutrition (BMI under 18) c. Psychiatric disease d. Any muscle disease, history of rhabdomyolysis, myopathy or myositis. e. Any disease causing renal injury/proteinuria apart from diabetes mellitus

NCT02442921 *(Continued)*

	f. Any inflammatory or autoimmune disease g. Any infection during the last month.
Interventions	1. Experimental: a. 2 mg of colchicine 2. Control: a. Placebo
Outcomes	• Primary: 1. Change of urinary protein excretion (mg/24 h) from baseline to 18 months. [Time Frame: From baseline to 18 months (end of trial)]
Starting date	1. Date of first enrolment: 2015-05-13 2. Date of registration: 2015-04-30
Contact information	1. Shaye Kivity, MD 2. Address: Ramat Gan, Israel, 52621 3. Telephone: +970526668134 4. Email: kivitys@gmail.com 5. Affiliation: Sheba Medical Center
Notes	https://classic.clinicaltrials.gov/ct2/show/NCT02442921

NCT03693781

Study name	Proteostasis and ALS: protocol for a phase II, randomised, double-blind, placebo-controlled, multi-centre clinical trial for colchicine in ALS (Co-ALS)
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: a. Intervention 1: 18. b. Intervention 2: 18. c. Control group: 18. 4. Phase: II 5. Country: Italy
Participants	1. Age: 18 years to 80 years 2. Sex: Both 3. Inclusion criteria: • Patients diagnosed with a laboratory-supported, clinically 'probable' or 'definite' ALS according to the Revised El Escorial criteria. • Sporadic ALS. • ALS phenotypes: classic or bulbar. • Disease duration from symptom onset no longer than 18 months at the screening visit. • Patients treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening. • Patients with a weight of >50 kg and a BMI of ≥18. • Patients with an FVC ≥65% predicted normal value for gender, height and age at the screening visit. • Patients able and willing to comply with study procedures as per protocol. • Patients able to understand and capable of providing informed consent at screening visit prior to any protocol-specific procedures.

NCT03693781 *(Continued)*

	• Use of *highly effective* contraception for both men and women. 4. Exclusion criteria: • Prior use of colchicine. • Prior allergy/sensitivity to colchicine. • Receiving colchicine or other anti-inflammatory drugs (such as corticosteroids, methotrexate, antineoplastic, interleukin 1–1b antagonist, tumour necrosis factor-alpha inhibitor). • Receiving food or co-medications, such as strong–moderate cytochrome P450 3A4 inhibitors that will result in elevated plasma levels of colchicine. • Inflammatory disorders (systemic lupus erythematosus, rheumatoid arthritis and connective tissue disorder), chronic infections (HIV and hepatitis B or C infections) or significant history of malignancy.
Interventions	• Experimental: 1. Colchicine 0.01 mg/kg/day + riluzole. 2. Colchicine 0.005 mg/kg/day + riluzole. • Control: 1. Placebo + riluzole.
Outcomes	• Clinical assessment ◦ Periodic clinical assessment will be performed at defined time points by: ■ Overall survival from randomisation to date of documented death or tracheostomy or non-invasive ventilation (NIV) >22 hours/day. ■ Survival rate at weeks 30, 42 and 54. ■ Forced vital capacity score from baseline to weeks 8, 18, 30, 42 and 54. • Quality of life assessment ◦ Determination of quality of life as perceived by patients with ALS will be investigated by comparing ALS assessment questionnaire (ALSAQ-40) from baseline to weeks 8, 30 and 54.
Starting date	1. Date of first enrolment: 2019-04-10 2. Date of registration: 2018-10-03
Contact information	1. Jessica Mandrioli 2. Address: -- 3. Telephone: -- 4. Email: -- 5. Affiliation: Azienda Ospedaliero Universitaria dì Modena
Notes	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6549675/ https://classic.clinicaltrials.gov/ct2/show/NCT03693781

NCT04160117

Study name	Impact of Short-course Colchicine Versus Placebo After Pulmonary Vein Isolation (IMPROVE-PVI): A Pilot Study
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 200 4. Phase: III 5. Country: Canada

NCT04160117 *(Continued)*

Participants	1. Age: ≥ 18 years 2. Sex: Both 3. Inclusion criteria: a. Symptomatic atrial fibrillation and planned catheter-guided first or repeat ablation (pulmonary vein isolation) for atrial fibrillation (radiofrequency or cryoablation energy; concomitant ablation of the cavotricuspid isthmus and other lesions left at the discretion of the treating physician) b. Written informed consent 4. Exclusion criteria: a. Ablation for left atrial tachycardia or isthmus-dependent atrial flutter only (i.e. without pulmonary vein isolation) b. Administration of a strong inhibitor of CYP3A4 or p-gp (clarithromycin, erythromycin, telithromycin, cyclosporine, ketoconazole or itraconazole) c. Known hypersensitivity to colchicine d. Serious gastrointestinal disease (severe gastritis or diarrhoea) e. Clinically overt hepatic disease f. Severe renal disease (eGFR < 30ml/min/1.73m2) g. Clinically significant blood dyscrasia (e.g., myelodysplasia) h. Absolute indication for or ongoing treatment with colchicine i. Pregnant or breastfeeding women, or women of child-bearing potential who do not use a highly effective form of birth control
Interventions	• Experimental: 1. Colchicine 0.6 mg • Control: 1. Placebo
Outcomes	• Primary: 1. Average monthly enrolment rate 2. Compliance with study treatment 3. Rate of complete follow-up at 6 months • Secondary: 1. Rate of non-infectious diarrhoea 2. Rate of signs and symptoms of pericarditis 3. Recurrence of atrial fibrillation within the first 2 weeks after catheter ablation 4. Recurrence of atrial fibrillation between 10 and 15 weeks after catheter ablation 5. Rate of patients with composite clinical endpoint 6. Rate of all-cause mortality (24 months)
Starting date	1. Date of first enrolment: 2020-01-14
Contact information	1. Alex Benz 2. Address: 3. Telephone: 905-521-2100 4. Email: IMPROVE-PVI@phri.ca 5. Affiliation: Hamilton Health Sciences Corporation - Hamilton General Hospital
Notes	https://clinicaltrials.gov/study/NCT04160117?a=5

NCT05175274

Study name	Colchicine Use for Primary Prevention in People at High Risk of Coronary Artery Disease
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 6792 4. Phase: III 5. Country: China
Participants	1. Age: 40 years to 70 years 2. Sex: Both 3. Inclusion Criteria: • At least 3 risk factors for CAD. • GFR > 90 mmol/L. • Patients are not pre-diagnosed with CAD, which is defined by negative results of CT coronary angiography. 1. Exclusion Criteria: • Patients with any pre-existing diagnosis of coronary artery disease. • Other cardiovascular diseases such as peripheral vascular disease, congestive heart failure and cardiomyopathy. • Cerebrovascular diseases such as cerebral thrombosis and cerebral haemorrhage. • Currently on treatment with colchicine. • Patients who are known to be allergic to colchicine. • Chronic symptomatic heart failure within the last year and known reduced ejection fraction (LVEF ≤ 40%), documented before recruitment. • Severe hepatic impairment (Child-Pugh class C) at the time of inclusion into the trial. • Any other non-cardiovascular diseases, such as active malignancy requiring treatment at the time of screening or with a life expectancy of fewer than two years based on the investigator's clinical judgement.
Interventions	• Experimental: a. Colchicine 0.5 mg every 24 hours for 3 years • Control: a. Placebo
Outcomes	• Primary: 1. The incidence of CAD [Time Frame: 3 years]: collect the incidence of CAD during the follow-up time. CAD is defined with the positive stress test, ST depression in ECG with typical symptoms of myocardial ischaemia, and progression to myocardial infarction. To further detect patients with occult CAD, the rest of the asymptomatic patients will be subjected to CT coronary angiography, in which CAD is defined with over 50% diameter stenosis in a major coronary artery. 2. Occurrence of adverse events in both groups [Time Frame: 3 years]: collect the occurrence of adverse events in both groups during the drug use. Adverse events include gastrointestinal, liver, haematology, muscle, neurology, other sensory, infectious and death. • Secondary: 1. MACE events [Time Frame: 3 years]: to assess the occurrence of myocardial infarction, stroke and death from cardiovascular causes during the follow-up time.
Starting date	1. Date of first enrolment: 2022-01-03 2. Date of registration: 2020-08-13
Contact information	1. Mengmei Li, MD 2. Address: Qingdao, Shandong, China, 266042 3. Telephone: 0086053284961672 4. Email: Sjogen@163.com

NCT05175274 *(Continued)*

	5. Affiliation: Qingdao Central Hospital
Notes	https://classic.clinicaltrials.gov/ct2/show/NCT05175274 Estimated Primary Completion Date: March 1, 2028 Estimated Study Completion Date: July 1, 2028 Sponsors and Collaborators: Qingdao Central Hospital Qingdao Municipal Hospital

NCT05802992

Study name	A Single-center Clinical Trial to Evaluate the Efficacy and Safety of Colchicine Combined With Conventional Therapy in Multiple Myeloma Patients
Methods	1. Study type: Interventional study 2. Study design: Parallel 3. Target sample size: 30 4. Phase: III 5. Country: China
Participants	1. Age: 18 years to 80 years 2. Sex: Both 3. Inclusion criteria: a. Clinical diagnosis of multiple myeloma b. Have received at least one-line treatment c. Must be able to swallow tablets 4. Exclusion criteria: a. Resistance to or intolerance to therapeutic agents such as bortezomib or lenalidomide b. Allergy to the experimental drug or its ingredients c. Has invaded the central nervous system d. Severe cardiovascular, liver and kidney failure, severe chronic obstructive pulmonary disease (COPD), and moderate to severe asthma e. Active hepatitis B or C infection f. HIV seropositivity g. Is participating in other clinical trial or has participated in other clinical trials within the past two weeks h. Other factors that the researchers determined were not suitable for the trial
Interventions	• Experimental: 1. Colchicine • Control: 1. Lenalidomide
Outcomes	• Primary: 1. Changes of the level of Serum M protein before and after treatment [60 months] 2. Changes of the proportion of bone marrow plasma cells before and after treatment 3. Changes of the level of SPEP and UPEP before and after treatment 4. Changes of the level of Serum FLC before and after treatment • Secondary: 1. Changes of the level of Serum M protein before and after treatment 2. Changes of the level of CBC before and after treatment

NCT05802992 *(Continued)*	3. Changes of the level of Serum M protein before and after treatment 4. Changes of the ECOG score before and after treatment.
Starting date	1. Date of first enrolment: 2020-09-01 2. Date of registration: 2022-03-30
Contact information	1. Hongming Huang 2. Address: China 3. Telephone: +8615006281688 4. Email: hhmmmc@163.com 5. Affiliation: Hospital of Nantong University
Notes	https://clinicaltrials.gov/study/NCT05802992

- ACE: angiotensin converting enzyme inhibitors
- ALS: amyotrophic lateral sclerosis
- BMI: body mass index
- BD: Behçet's disease
- CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
- CAD: coronary artery disease
- CBC: complete blood count
- eGFR: estimated glomerular filtration rate
- ECG: electrocardiogram
- ECOG: Eastern Cooperative Oncology Group
- EVA: escala análoga visual (visual analogue scale)
- FLC: free light chains
- FVC: forced vital capacity
- GFR: glomerular filtration rate
- IgA: immunoglobulin A
- IBDDAM: Iranian BD dynamic measure
- LVFE: left ventricular ejection fraction
- MACE: major adverse cardiovascular events
- MDRD: modification of diet in renal disease
- SPEP: serum protein electrophoresis
- ST: ST segment
- UPEP: urine protein electrophoresis

DATA AND ANALYSES

Comparison 1. Colchicine versus placebo

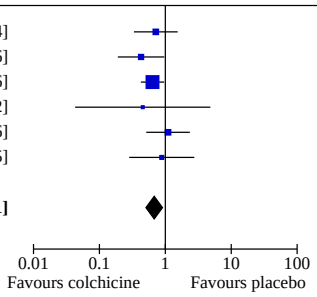
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	6	463	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.91]
1.2 Non-fatal myocardial infarction	1	100	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.41, 1.82]
1.3 Stroke	1	100	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.67, 8.86]

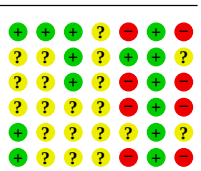
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Adverse events	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Gastrointestinal (diarrhoea)	8	605	Risk Ratio (M-H, Random, 95% CI)	3.99 [1.44, 11.06]
1.4.2 Neurological (seizure, confusion)	2	155	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.66]
1.5 Cardiovascular mortality	2	160	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.03, 62.43]
1.6 Post-cardiac procedure atrial fibrillation	1	100	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.25, 2.19]

Analysis 1.1. Comparison 1: Colchicine versus placebo, Outcome 1: All-cause mortality

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cortez-Pinto 2002	8	29	10	26	14.3%	0.72 [0.33 , 1.54]
Kaplan 1986	6	30	14	30	12.7%	0.43 [0.19 , 0.96]
Kershenobich 1988	21	54	28	46	50.6%	0.64 [0.43 , 0.96]
Olsson 1995	1	44	2	40	1.5%	0.45 [0.04 , 4.82]
Wang 1994	11	50	10	50	14.4%	1.10 [0.51 , 2.36]
Warnes 1987	5	34	5	30	6.5%	0.88 [0.28 , 2.75]
Total (Wald[a])		**241**		**222**	**100.0%**	**0.68 [0.51 , 0.91]**
Total events:	52		69			

Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 3.20, df = 5 (P = 0.67); I² = 0%





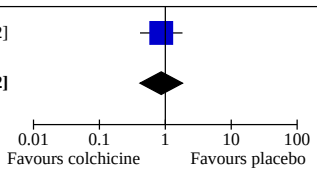
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Colchicine versus placebo, Outcome 2: Non-fatal myocardial infarction

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bessissow 2018	10	49	12	51	100.0%	0.87 [0.41 , 1.82]
Total		**49**		**51**	**100.0%**	**0.87 [0.41 , 1.82]**
Total events:	10		12			

Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

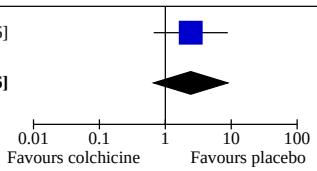


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Colchicine versus placebo, Outcome 3: Stroke

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bessissow 2018	7	49	3	51	100.0%	2.43 [0.67 , 8.86]
Total		**49**		**51**	**100.0%**	**2.43 [0.67 , 8.86]**
Total events:	7		3			

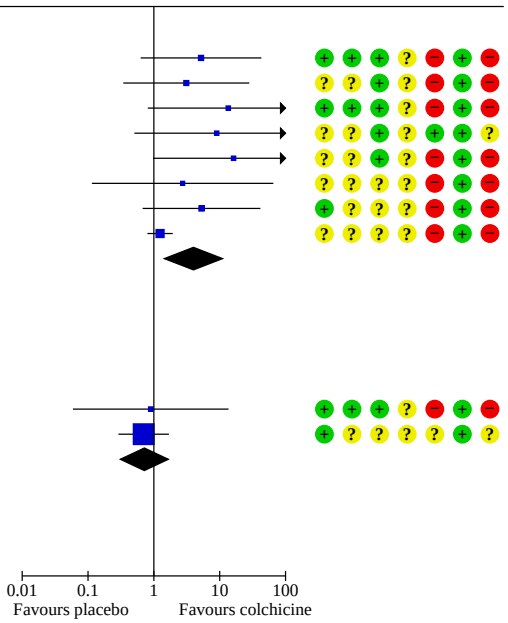
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Colchicine versus placebo, Outcome 4: Adverse events

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Gastrointestinal (diarrhoea)						
Bessissow 2018	5	49	1	51	12.9%	5.20 [0.63 , 42.96]
Bodenheimer 1988	3	28	1	29	12.3%	3.11 [0.34 , 28.12]
Cortez-Pinto 2002	7	29	0	26	9.0%	13.50 [0.81 , 225.38]
Kaplan 1986	4	30	0	30	8.7%	9.00 [0.51 , 160.17]
Kershenobich 1988	9	54	0	46	9.0%	16.24 [0.97 , 271.59]
Olsson 1995	1	44	0	40	7.6%	2.73 [0.11 , 65.24]
Warnes 1987	6	34	1	30	13.2%	5.29 [0.68 , 41.51]
Yurdakul 2001	22	41	19	44	27.3%	1.24 [0.80 , 1.93]
Subtotal (Wald[a])		**309**		**296**	**100.0%**	**3.99 [1.44 , 11.06]**
Total events:	57		22			
Test for overall effect: Z = 2.66 (P = 0.008)						
Heterogeneity: Tau² (DL[b]) = 0.94; Chi² = 14.35, df = 7 (P = 0.05); I² = 51%						
1.4.2 Neurological (seizure, confusion)						
Cortez-Pinto 2002	1	29	1	26	9.5%	0.90 [0.06 , 13.62]
Wang 1994	7	50	10	50	90.5%	0.70 [0.29 , 1.69]
Subtotal (Wald[a])		**79**		**76**	**100.0%**	**0.72 [0.31 , 1.66]**
Total events:	8		11			
Test for overall effect: Z = 0.78 (P = 0.44)						
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for subgroup differences: Chi² = 6.50, df = 1 (P = 0.01), I² = 84.6%						



Footnotes

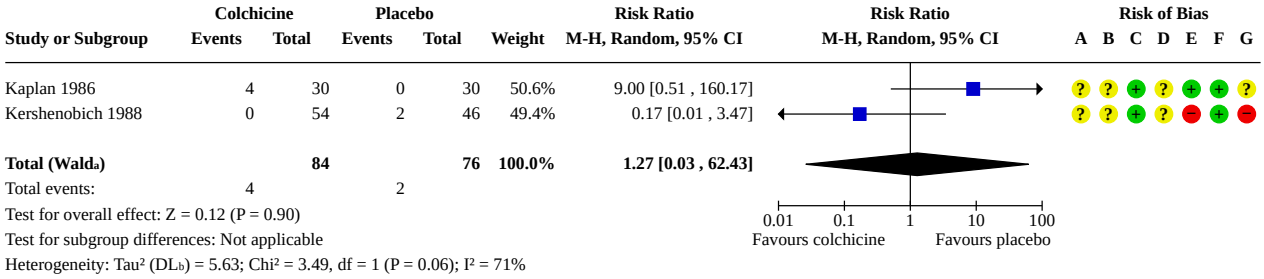
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Colchicine versus placebo, Outcome 5: Cardiovascular mortality



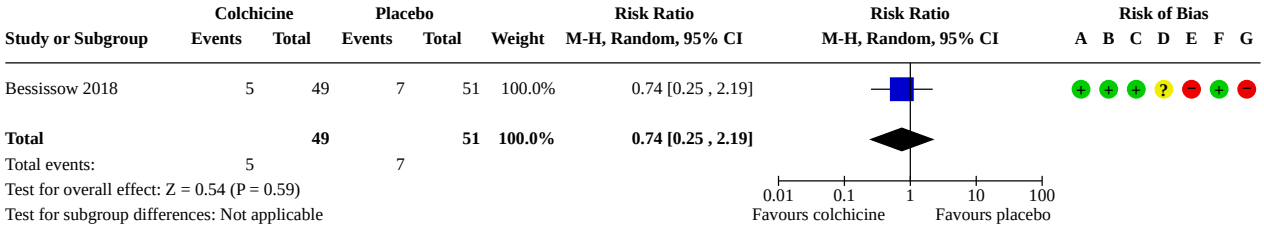
Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Kaplan 1986	4	30	0	30	50.6%	9.00 [0.51 , 160.17]	? ? + ? + + ?
Kershenobich 1988	0	54	2	46	49.4%	0.17 [0.01 , 3.47]	? ? + ? − + −
Total (Wald[a])		**84**		**76**	**100.0%**	**1.27 [0.03 , 62.43]**	
Total events:	4		2				

Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 5.63; Chi² = 3.49, df = 1 (P = 0.06); I² = 71%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Colchicine versus placebo, Outcome 6: Post-cardiac procedure atrial fibrillation



Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Bessissow 2018	5	49	7	51	100.0%	0.74 [0.25 , 2.19]	+ + + ? − + −
Total		**49**		**51**	**100.0%**	**0.74 [0.25 , 2.19]**	
Total events:	5		7				

Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

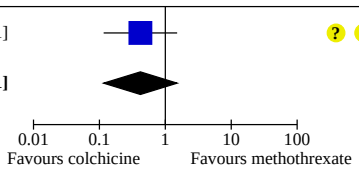
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Colchicine versus immunomodulating drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1	85	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.12, 1.51]

Analysis 2.1. Comparison 2: Colchicine versus immunomodulating drugs, Outcome 1: All-cause mortality

Study or Subgroup	Colchicine Events	Colchicine Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Kaplan 1999	3	43	7	42	100.0%	0.42 [0.12 , 1.51]	? ? + ? − + −
Total		**43**		**42**	**100.0%**	**0.42 [0.12 , 1.51]**	
Total events:	3		7				



Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

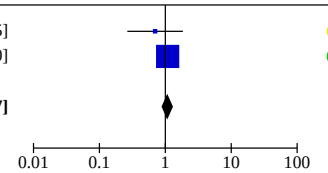
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Colchicine versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	2	729	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]
3.2 Adverse events	2	729	Risk Ratio (M-H, Random, 95% CI)	3.32 [1.56, 7.03]

Analysis 3.1. Comparison 3: Colchicine versus usual care, Outcome 1: All-cause mortality

Study or Subgroup	Colchicine Events	Colchicine Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Buligescu 1989	7	100	8	80	3.2%	0.70 [0.27 , 1.85]	? ? ? ? ? + ?
Morgan 2005	134	274	124	275	96.8%	1.08 [0.91 , 1.30]	+ + + + + + +
Total (Wald[a])		**374**		**355**	**100.0%**	**1.07 [0.90 , 1.27]**	
Total events:	141		132				



Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%

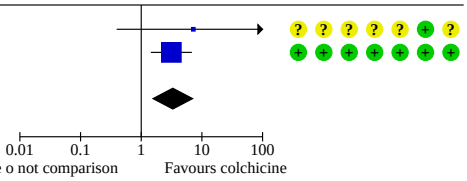
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Colchicine versus usual care, Outcome 2: Adverse events

Study or Subgroup	Colchicine Events	Colchicine Total	Usual care or no comparison Events	Usual care or no comparison Total	Weight	Risk Ratio M-H, Random, 95% CI
Buligescu 1989	4	100	0	80	6.7%	7.22 [0.39 , 132.11]
Morgan 2005	25	274	8	275	93.3%	3.14 [1.44 , 6.83]
Total (Wald[a])		**374**		**355**	**100.0%**	**3.32 [1.56 , 7.03]**
Total events:	29		8			

Test for overall effect: Z = 3.13 (P = 0.002)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. Search strategies

CENTRAL
#1 MeSH descriptor: [Colchicine] this term only
#2 colchicine
#3 #1 or #2

MEDLINE Ovid
1 Colchicine/ (14911)
2 Colchicine.tw. (16798)
3 1 or 2 (21877)
4 randomized controlled trial.pt. (580762)
5 controlled clinical trial.pt. (95098)
6 randomized.ab. (582385)
7 placebo.ab. (233297)
8 clinical trials as topic.sh. (200559)
9 randomly.ab. (395442)
10 trial.ti. (273844)
11 4 or 5 or 6 or 7 or 8 or 9 or 10 (1485150)
12 exp animals/ not humans.sh. (5064943)
13 11 not 12 (1366379)
14 3 and 13 (828)

Embase Ovid
1 colchicine/ (31979)
2 Colchicine.tw. (18985)
3 1 or 2 (35495)
4 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (5888817)
5 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not

(comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9097)
6 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.) (326829)
7 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (20377)
8 (Systematic review not (trial or study)).ti. (227083)
9 (nonrandom$ not random$).ti,ab. (17955)
10 ("Random field$" or (random cluster adj3 sampl$)).ti,ab. (4262)
11 (review.ab. and review.pt.) not trial.ti. (1037611)
12 "we searched".ab. and (review.ti. or review.pt.) (44391)
13 ("update review" or (databases adj4 searched)).ab. (54873)
14 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1120827)
15 Animal experiment/ not (human experiment/ or human/) (2325530)
16 or/5-15 (3948874)
17 4 not 16 (5204655)
18 3 and 17 (3252)
19 limit 18 to embase (2260)

Web of Science (WOS)
Colchicine (Topic) and (random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*) (Topic)

LILACS
Colchicine

ClinicalTrials.gov
Study type: Interventional Studies (Clinical Trials)
Intervention/treatment: Colchicine

WHO ICTRP
Intervention: Colchicine

Appendix 2. Domains for assessing of risk of bias in the included studies

Random sequence generation

- Low risk of bias: the allocation sequence was generated by a computer or random number table, drawing of lots, tossing of a coin, shuffling of cards or throwing dice.
- High risk of bias: a system involving dates, names, or admittance numbers was used for the allocation of participants. These studies are known as quasi-randomised and were excluded from the review.
- Unclear risk of bias: the trial was described as randomised, but the method used for the allocation sequence generation was not mentioned.

Allocation concealment

- Low risk of bias: the allocation of participants involved a central independent unit, on-site locked computer, identical-appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- High risk of bias: the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised, the latter of which were excluded from the review.
- Unclear risk of bias: the trial was described as randomised, but the method used to conceal the allocation was not mentioned.

Blinding (or masking)

We assessed each trial as low, high, or unclear risk of bias for:

- blinding of participant to treatment allocation;
- blinding of clinician (person delivering treatment) to treatment allocation;
- blinding of outcome assessor to treatment allocation.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described, or it was specified that there were no dropouts or withdrawals.

- High risk of bias: the number or reasons for dropouts and withdrawals were not described.
- Unclear risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

We further examined the percentage of dropouts overall in each trial and per randomisation arm, and evaluated whether intention-to-treat analysis was performed or could be performed from the published information.

Selective outcome reporting

Low risk of bias: either of the following:

- the study protocol is available, and all the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way;
- the study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified.

High risk of bias: any one of the following:

- not all the study's prespecified primary outcomes have been reported;
- one or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified;
- one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- the study report fails to include results for a key outcome that would be expected to have been reported for the study.

Unclear risk of bias: insufficient information.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.

We considered trials in which there was adequate random sequence generation, allocation concealment, blinding, and handling of incomplete outcome data, and the study was free of selective outcome reporting and other bias, as at overall low risk of bias.

We consider trials in which one of the domains was at high or unclear risk of bias as at overall high risk of bias.

HISTORY

Protocol first published: Issue 6, 2022

CONTRIBUTIONS OF AUTHORS

Conceiving the review: the Cochrane Heart Group selected the title for this review through an internal editorial decision-making process among the group's editors.
Designing the review: all authors
Co-ordinating the review: AMC
Designing the electronic search strategy: the Cochrane Heart Group's Information Specialist and AMC
Screening search results: AMC, DM, ACP, MGV, EA, RH
Obtaining copies of trials: AMC, MGV, DM
Appraising quality of papers: AMC, MGV, DM, JBDeS, RR
Extracting data from papers: AMC, MGV, DM
Data management for the review: AMC, MGV, DM
Entering data into RevMan: AMC
Analysis of data: AMC, MGV, RR
Summary of findings: AMC, MGV, DM, CMA, ER
Interpretation of data: all authors
Writing the review: AMC, MGV, CMA, JBDeS
Draft the final review: all authors
Guarantor for the review: AMC

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- Iberoamerican Cochrane Center, Barcelona, Spain

  Academic.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We requested permission from the Cochrane Heart Group to use RoB 1 instead of RoB 2 for risk of bias assessment in accordance with the protocol.
- Based on a suggestion from Dr Tjerk SJ Opstal (clinical reviewer), we improved the writing of the How the intervention might work section.
- We estimated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) according to Cochrane methodology (Schünemann 2019b). We used GraphPad to estimate NNTB and NNTH (GraphPad 2024).