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Colchicine for prevention of cardiovascular events (Review)

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[Intervention Review]

Colchicine for prevention of cardiovascular events

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ABSTRACT

Background

Colchicine is an anti-inflammatory drug that is used for a wide range of inflammatory diseases. Cardiovascular disease also has an inflammatory component but the effects of colchicine on cardiovascular outcomes remain unclear. Previous safety analyses were restricted to specific patient populations.

Objectives

To evaluate potential cardiovascular benefits and harms of a continuous long-term treatment with colchicine in any population, and specifically in people with high cardiovascular risk.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ClinicalTrials.gov, WHO International Clinical Trials Registry, citations of key papers, and study references in January 2015. We also contacted investigators to gain unpublished data.

Selection criteria

Randomised controlled trials (parallel-group or cluster design or first phases of cross-over studies) comparing colchicine over at least six months versus any control in any adult population.

Data collection and analysis

Primary outcomes were all-cause mortality, myocardial infarction, and adverse events. Secondary outcomes were cardiovascular mortality, stroke, heart failure, non-scheduled hospitalisations, and non-scheduled cardiovascular interventions. We conducted predefined subgroup analyses, in particular for participants with high cardiovascular risk. .

Main results

We included 39 randomised parallel-group trials with 4992 participants. Colchicine had no effect on all-cause mortality (RR 0.94, 95% CI 0.82 to 1.09; participants = 4174; studies = 30; I^2 = 27%; moderate quality of evidence). There is uncertainty surrounding the effect of

colchicine in reducing cardiovascular mortality (RR 0.34, 95% CI 0.09 to 1.21, I^2 = 9%; participants = 1132; studies = 7; moderate quality of evidence). Colchicine reduced the risk for total myocardial infarction (RR 0.20, 95% CI 0.07 to 0.57; participants = 652; studies = 2; moderate quality of evidence). There was no effect on total adverse events (RR 1.52, 95% CI 0.93 to 2.46; participants = 1313; studies = 11; I^2 = 45%; very low quality of evidence) but gastrointestinal intolerance was increased (RR 1.83, 95% CI 1.03 to 3.26; participants = 1258; studies = 11; I^2 = 74%; low quality of evidence). Colchicine showed no effect on heart failure (RR 0.62, 95% CI 0.10 to 3.88; participants = 462; studies = 3; I^2 = 45%; low quality of evidence) and no effect on stroke (RR 0.38, 95% CI 0.09 to 1.70; participants = 874; studies = 3; I^2 = 45%; low quality of evidence). Reporting of serious adverse events was inconsistent; no event occurred over 824 patient-years (4 trials). Effects on other outcomes were very uncertain. Summary effects of RCTs specifically focusing on participants with high cardiovascular risk were similar (4 trials; 1230 participants).

Authors' conclusions

There is much uncertainty surrounding the benefits and harms of colchicine treatment. Colchicine may have substantial benefits in reducing myocardial infarction in selected high-risk populations but uncertainty about the size of the effect on survival and other cardiovascular outcomes is high, especially in the general population from which most of the studies in our review were drawn. Colchicine is associated with gastrointestinal side effects based on low-quality evidence. More evidence from large-scale randomised trials is needed.

PLAIN LANGUAGE SUMMARY

Effects and safety of long-term use of colchicine on heart disease

Background

Colchicine is a very old, inexpensive treatment. It has strong effects against inflammation and is widely used in inflammatory diseases like gout. There are many studies on colchicine in inflammatory diseases. Inflammation is also an important component for the development of heart attacks or strokes. Some recent studies have shown that colchicine may have positive effects on heart disease.

Review question

We aimed to review all available studies evaluating longer-term use of colchicine. We wanted to describe the benefits and harms for people with or without established coronary heart disease. We looked at all studies that lasted at least six months, that included adults, and that compared health effects of colchicine use with the use of any other treatment. We took a closer look at people with previous heart issues.

Key results

We included 39 trials with 4992 participants in our analyses. Four trials included 1230 participants in total with heart disease. Colchicine treatment had no effect on death from any cause. There is uncertainty around the effect of colchicine on cardiovascular (heart-related) death. Results showed that cardiovascular death may be reduced, but this was not clear because some of our analyses showed a reduced risk while others did not. The risk for myocardial infarctions (heart attacks) was reduced, but this finding was based on only two studies and a total of 22 events. Colchicine did not clearly increase the risk of total harms but colchicine increased the risk for gastrointestinal intolerance, which was typically described as mild and short-lived. We found no clear effects on strokes, heart failure, emergency hospitalisations or unplanned invasive cardiac treatments.

Four of the 39 studies reported that they systematically looked for serious side effects linked to use of colchicine. Serious side effects can be life-threatening or require hospitalisation. No participant in these four studies was reported to have such a serious side effect. This means that possible serious side effects seem to be relatively rare: for example, the results indicate that among 800 people who are treated for one year, none would suffer a serious side effect. However, we have some concerns about the certainty of this result, because the reporting of serious harms in the studies was not ideal; for example, because the definitions of serious adverse events differed between studies, and it was not always clear what would be considered a serious adverse event. We found no difference in effects of colchicine in people at high cardiovascular risk.

The evidence is current to January 2015.

Conclusions

Overall, we found that further research would probably change our assessment of the benefits and harms of colchicine. Our findings should therefore be interpreted with caution. However, new treatments in heart diseases are urgently needed. Although there is much uncertainty around the benefits and harms of colchicine treatment, it may be associated with cardiovascular benefits, especially on myocardial infarction. We therefore think that large high-quality clinical trials should be conducted to further investigate colchicine in heart disease.

Summary of findings 1. Colchicine compared to any control treatment for prevention of cardiovascular events

Colchicine compared to any control treatment for prevention of cardiovascular events

Patient or population: any patient population and people with high cardiovascular risk
Settings: any
Intervention: Colchicine
Comparison: Any control treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Any control treatment	Colchicine				
Mortality (all-cause) Follow-up: 0.5 - 14 years	**193 per 1000**	**182 per 1000** (157 to 211)	**RR 0.94** (0.82 to 1.09)	4174 (30 studies)	⊕⊕⊕⊖ **moderate** [1]	
	Patients with high cardiovascular risk					
	32 per 1000	**17 per 1000** (8 to 36)	**RR 0.54** (0.26 to 1.14)	1230 (4 studies)	⊕⊕⊕⊖ **moderate** [1]	Follow-up: 0.5 - 3 years
Mortality (cardiovascular) Follow-up: 0.5-14 years	**27 per 1000**	**9 per 1000** (2 to 32)	**RR 0.34** (0.09 to 1.21)	1132 (7 studies)	⊕⊕⊕⊖ **moderate** [1]	
	Patients with high cardiovascular risk					
	31 per 1000	**8 per 1000** (1 to 81)	**RR 0.25** (0.02 to 2.66)	754 (2 studies)	⊕⊕⊖⊖ **low** [2,3]	Follow-up: 0.5 - 3 years
Myocardial Infarction (total) Follow-up: mean 3 years	**58 per 1000**	**12 per 1000** (4 to 33)	**RR 0.20** (0.07 to 0.57)	652 (2 studies[4])	⊕⊕⊕⊖ **moderate** [5]	Most evidence provided by a single study
	Patients with high cardiovascular risk					
	Study population		**RR 0.20** (0.07 to 0.57)	532 (1 study)	⊕⊕⊕⊖ **moderate** [5]	Evidence provided by a single study. Follow-up: mean 3 years Please see footnote[6]
	72 per 1000	**18 per 1000** (5 to 41)				

	Assumed 1-year risk					
	25 per 1000	**6 per 1000** (2 to 14)				
Adverse event (total) Follow-up: 0.5 - 14 years	**Study population**		**RR 1.52** (0.93 to 2.46)	1313 (11 studies)	⊕⊖⊖⊖ **very low** [1,7,8]	No study in participants with high cardiovascular risk reported on total adverse events.[9]
	89 per 1000	**135 per 1000** (83 to 219)				
	Assumed 1-year risk					
	89 per 1000	**135 per 1000** (83 to 219)				
Adverse event (gastrointestinal) Follow-up: 0.5 - 14 years	**Study population**		**RR 1.83** (1.03 to 3.26)	1258 (11 studies)	⊕⊕⊖⊖ **low** [8,12]	Please see footnote[9]
	132 per 1000	**242 per 1000** (136 to 431)				
	Assumed 1-year risk					
	132 per 1000	**242 per 1000** (136 to 430)				
Adverse event (serious) Follow-up: mean 824 patient-years	See comment	See comment	Not estimable	472 (4 studies)	⊕⊕⊖⊖ **low** [10,11]	No illustration of comparative risks due to very uncertain assumed risks[10,11]
Heart failure (total) Follow-up: 0.5 - 3 years	See comment	See comment	**RR 0.62** (0.10 to 3.88)	426 (3 studies)	⊕⊕⊖⊖ **low** [3,4,5]	No illustration of comparative risks due to very uncertain assumed risks
Stroke (total) Follow-up: 0.5 - 3 years	See comment	See comment	**OR 0.38** (0.09 to 1.70)	874 (3 studies)	⊕⊕⊖⊖ **low** [3,4,5]	No illustration of comparative risks due to very uncertain assumed risks

*The basis for the **assumed risk** is the mean control group risk across studies if not otherwise stated in comments/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; **OR**: Peto Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Confidence interval is compatible with participant-relevant benefit and harm.
[2]Small number of events therefore downgraded for imprecision.
[3]Substantial imprecision because confidence interval compatible with major harm and major benefit.
[4]One study without events.
[5]Effect based on small number of events.
[6]For balancing benefits and harms using absolute risk measures (1-year risk), we extrapolated the 1-year risk of myocardial events assuming that the risk is constant over the entire follow-up.
[7]High risk for attrition bias in 5 of 10 studies.
[8]Visual inspection of funnel plot shows asymmetry; lack of small studies reporting lower adverse event rates with colchicine than with comparator (the rate of adverse events with colchicine may appear too high due to bias).
[9]For balancing benefits and harms using absolute risk measures (1-year risk), we assumed that all adverse events observed over the entire follow-up accumulate within the first year of treatment.
[10]Only four studies reported on serious adverse events (zero events in approximately 800 patient-years). In many other studies events occurred (e.g. deaths) that could be regarded as serious adverse events.
[11]No indication for publication bias, but reporting quality very limited.
[12]Substantial between-study heterogeneity (I^2 = 74%) without plausible explanation.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the leading cause of death worldwide (WHO 2011). CVD is a class of diseases that affect the heart and blood vessels. CVD includes coronary heart disease and cerebrovascular disease, both diseases of the blood vessels supplying the heart or brain with oxygenated blood. One important pathophysiologic mechanism of CVD is the development of atherosclerotic lesions, so called 'plaques' (Libby 2013; Shah 2003; Shah 2009). These lesions may cause chronic ischaemia and subsequent organ damage leading, for example, to heart failure. However, such plaques may also rupture and cause acute thrombotic events such as myocardial infarctions or strokes (Libby 2013; Shah 2003; Shah 2009). The mechanisms leading to destabilisation of atherosclerotic plaques and subsequent rupture are not completely understood, but inflammatory processes seem to play an important role (Libby 2013; Shah 2009). This is based on observations that inflammatory cells concentrate at ruptured plaques (Carr 1997; Libby 2013), and there is strong evidence that raised blood levels of inflammatory markers (C-reactive protein) are associated with increased risk of coronary events (Emerging Risk Factors Collaboration 2010).

Description of the intervention

Colchicine is a very old, inexpensive drug with strong anti-inflammatory effects (Niel 2006; Terkeltaub 2009). Extracts from autumn crocus (*Colchicum autumnale*) have been used for centuries to treat acute gout (Cocco 2010; Rodnan 1970; Terkeltaub 2009). In the 18th century, an alkaloid was identified as the active pharmaceutical ingredient of this plant, which became known as colchicine and which since then has been widely used for treatment of gout (Rodnan 1970; Schlesinger 2004).

In addition to gout, colchicine is also used for treatment of several other diseases, including familial Mediterranean fever (FMF), Behçet's disease, primary biliary cirrhosis, and pericarditis (Cocco 2010; Terkeltaub 2009). The complex molecular and cellular mechanisms of action of colchicine and its pharmacological properties have recently been systematically reviewed by Terkeltaub 2009. While the mechanism of action against diverse diseases is not completely understood, over recent years the understanding of how and under what circumstances colchicine can be used to treat diverse clinical conditions has continuously evolved (Terkeltaub 2009). Colchicine's anti-inflammatory action is strongly related to its effects on leukocytes by modifying their adhesion, migration, cytokine production and secretion (Cronstein 2006; Niel 2006; Terkeltaub 2009).

Colchicine has a relatively narrow therapeutic window and high inter-individual pharmacokinetic variability (Niel 2006; Terkeltaub 2009; Yang 2010). Despite its widespread use in treatment of gout, there is limited evidence allowing assessment of the optimal dosage of colchicine for this condition. A Cochrane review published in 2006 identified only a single randomised controlled trial (RCT) comparing colchicine to placebo (with 42 participants), and no trial comparing colchicine to non-steroidal anti-inflammatory drugs (NSAIDs) or to other treatments (Schlesinger 2006). In this trial, acute gout was treated with a regimen of 1 mg of oral colchicine followed by 0.5 mg every two hours until symptoms were relieved or adverse effects occurred. The participants received a mean dose of 6.7 mg colchicine and all those in the active treatment group had gastrointestinal side effects (diarrhoea or vomiting), while five control participants developed nausea but without diarrhoea or vomiting (Ahern 1987). A recent RCT including 185 participants explored the comparative effectiveness of such a high-dose treatment for acute gout (here 4.8 mg over six hours, i.e. 1.2 mg initially and 0.6 mg every hour) with a low-dose regimen (1.8 mg over one hour, i.e. 1.2 mg initially and 0.6 mg one hour later) and with placebo (Terkeltaub 2010). The gout-related benefits of treatment (pain reduction) were similar in both active treatment regimens. However, while with the high-dose regimen 77% of participants had diarrhoea (19% severe), 77% nausea, and 17% vomiting, with low-dose treatment 23% of participants had diarrhoea (none severe), 4% nausea and none had vomiting (placebo: 14%, 5%, 0% respectively). Serious adverse events did not occur in this study.

Low-dose colchicine for the treatment and prevention of pericarditis has been shown to be effective in several RCTs without providing indications of severe adverse effects occurring in the first six months of treatment (Imazio 2012c). The daily dose used in five trials was 0.5 to 1.0 mg and 1.5 mg/day in one trial. Among 684 participants with a maximum follow-up of six months, gastrointestinal intolerance was the most frequent side effect and no severe adverse events were reported (Imazio 2012c).

In people with increased risk for cardiovascular events, low-dose colchicine treatment is a novel and non-standard treatment approach. It has been evaluated as continuous treatment over six months in doses of 0.5 mg/day (Nidorf 2013), and 1 mg/day (Deftereos 2013). An earlier trial used colchicine after coronary angioplasty at a dose of 1.2 mg/day over six months (O'Keefe 1992). Side effects in these studies were predominantly gastrointestinal, with other reported adverse effects including myalgia, myositis, and muscle cramps, and a small number of cases of increased creatine kinase levels, rash, accelerated hair loss, alopecia, itch, peripheral neuritis, and death (Deftereos 2013; Nidorf 2013; O'Keefe 1992).

How the intervention might work

Colchicine might inhibit the inflammatory mechanisms leading to the development or destabilisation of atherosclerotic plaques. Colchicine treatment was associated with a decrease of high-sensitivity C-reactive protein in people with stable coronary artery disease (Nidorf 2007), but this was not observed in a randomised trial of participants with acute coronary syndrome or acute stroke (Raju 2012).

However, recently published results from RCTs on prevention of cardiovascular events suggest a considerable benefit of low-dose colchicine treatment in people at increased risk of cardiovascular events (Deftereos 2013; Nidorf 2013). Nidorf 2013 analysed in a RCT with blinded outcome assessment 532 participants with stable coronary disease who were treated with colchicine 0.5 mg/day or no colchicine. Median follow-up was three years. The primary outcome (a combined endpoint of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardio-embolic ischaemic stroke) was significantly reduced with colchicine treatment (hazard ratio (HR) 0.33; 95% confidence interval (CI) 0.18 to 0.59; P < 0.001; number needed to treat for an additional beneficial outcome (NNTB): 11). Deftereos 2013 analysed in a placebo-controlled, double-blinded study 222 participants with diabetes undergoing

a percutaneous coronary intervention (PCI) with a bare-metal stent (BMS). Colchicine treatment (1 mg/day) over six months significantly reduced the risk for in-stent restenoses (odds ratio (OR) 0.38, 95% CI 0.18 to 0.79, P = 0.007, NNTB: 6).

Why it is important to do this review

While recent studies (Deftereos 2013; Nidorf 2013) suggest a considerable benefit of low-dose colchicine treatment, their results are inconsistent with previous findings where no benefit for prevention of restenosis after coronary angioplasty was demonstrated (O'Keefe 1992).

There is thus far no systematic review of the available evidence on the effects of colchicine treatment on cardiovascular events that would allow a valid assessment of the potential long-term benefits and harms of this intervention for primary and secondary prevention of cardiovascular events. Safety analyses in previous reviews did not consider all the randomised evidence on adverse effects, but were restricted to specific indications of colchicine, e.g. familial Mediterranean fever (Wu 2015), gout (Van Echteld 2014), pericarditis (Alabed 2014; Imazio 2012c; Imazio 2014c; Raval 2015), atrial fibrillation (Trivedi 2014), liver fibrosis and cirrhosis (Rambaldi 2005), or primary biliary cirrhosis (Gong 2004). However, many side effects, such as gastrointestinal intolerance, are probably unrelated to the underlying condition, and potential effects on arteriosclerosis are not necessarily related to the indication for which colchicine was used.

OBJECTIVES

To evaluate potential cardiovascular benefits and harms of a continuous long-term treatment with colchicine in any population, and specifically in people with high cardiovascular risk.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), cluster- and pseudo-randomised controlled trials for inclusion. We included studies published as full-text or abstract, and unpublished data. From randomised cross-over trials, only data from the first phase were eligible for inclusion. We excluded 'N of 1' trials and non-randomised (observational) research.

Types of participants

We included trials in adults (aged 18 years and over) with any condition or disease.

Types of interventions

We included trials comparing treatment with colchicine for any condition or any disease on a continuous basis (treatment over at least six months at any dose and with any type of application) with no or any other treatment (including usual care or placebo) not containing colchicine. We accepted any co-interventions, provided they were identical in the compared study groups and not part of the randomised treatment.

Types of outcome measures

For all outcomes we used the number of participants, not the number of events.

Primary outcomes

1. All-cause mortality
2. Myocardial infarction
3. Adverse events (total, gastrointestinal, serious)

Colchicine is typically intended to be used as lifelong treatment of a chronic condition. Thus we required a sufficient treatment duration to allow valid assessment of the long-term benefits and harms. We therefore included only trials reporting on any of these outcomes at least six months after randomisation.

Following the US Food and Drug Administration (FDA) definition, we considered an adverse event or suspected adverse reaction "serious" if:

"it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse" (FDA 2013).

If adverse events were reported as "serious" but the definition was unclear we considered and reported these outcomes.

Secondary outcomes

1. Cardiovascular mortality
2. Stroke
3. Heart failure
4. Non-scheduled hospitalisations (all-cause and due to cardiovascular reasons)
5. Non-scheduled cardiovascular interventions (percutaneous coronary intervention (PCI)/angioplasty or coronary artery bypass graft).

We planned not to include studies reporting only on secondary outcomes and not on any of the primary outcomes (but this was never the case).

We accepted any definition of myocardial infarction, stroke or heart failure, and separately assessed total, fatal, and non-fatal events.

We planned to comment on data on quality of life or economic costs in the Discussion section in a narrative form (but there were no data in any eligible study).

We did not consider composites of any of the primary or secondary outcomes.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 30 January 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1 of 12, 2015) on the Cochrane Library
- MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE and OLDMEDLINE (Ovid, 1946 to 30 January 2015)
- EMBASE (embase.com 1947 to 15 May 2014) and EMBASE Classic + EMBASE (Ovid, 1947 to 30 January 2015)

We adapted the search strategy for MEDLINE (Ovid) (see Appendix 1) for use in the other databases. We slightly modified the Cochrane precision-maximising RCT filter (Lefebvre 2011) to increase sensitivity and applied it to MEDLINE (Ovid) and adaptations of it to the other databases, except for CENTRAL. We imposed no restriction on language of publication.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), using the term "colchicine" (last updated search on 22 January 2015).

We conducted the searches with the support of an experienced professional librarian.

Searching other resources

We checked reference lists of all eligible primary studies for additional references. We contacted the investigators of 29 studies (in the remaining cases we could not identify any contact details). We asked for information on unreported outcomes, missing outcome data, and unpublished studies. We sent them our extractions and bias assessments for review. Authors of 13 studies responded.

We used the citation search in Web of Science (Thomson Reuters) to identify potentially relevant articles citing key papers in this area of research: Deftereos 2013; Nidorf 2013; O'Keefe 1992.

Data collection and analysis

Selection of studies

Two review authors (from LGH, HE, VLG, AA, KKO, DG, AJN, MB) independently screened titles and abstracts of all the potential studies for inclusion, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We resolved disagreements by consensus or with a third review author (LGH or MB). We retrieved the full-text study reports/publications, and two review authors (from LGH, HE, VLG, AA, KKO, DG, AJN or MB) independently screened the full texts and identified studies for inclusion. We identified ineligible studies and recorded the reasons for exclusion. Four studies published in languages in which none of the authors are fluent (Portuguese, Chinese, and Turkish) were evaluated by external native-speaking review authors experienced in trial methodology. We subsequently excluded three of them (LGH or MB confirmed reasons for exclusion).

One review author (HE or DG) screened citations and references of the included studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (LGH or MB). We identified and excluded database duplicates and collated multiple publications of the same study with relevant information, so that each study rather than each publication is the unit of interest in the review. We did not consider publications on included studies that did not contain any further pertinent information, but we explicitly report them in the list of excluded publications. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a Characteristics of excluded studies table.

Data extraction and management

We used a pre-tested electronic data collection form for study characteristics and outcome data, which was piloted on at least one study in the review. One review author (AA or HE) extracted study characteristics from included studies, and a second review author (DG) verified the extractions. One review author (HE) extracted information on funding, and a second review author (LGH) spot-checked it. We extracted the following study characteristics:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, condition or disease, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: notable conflicts of interest of trial authors, funding information.

Two review authors (from LGH, HE, VLG, AA, KKO) independently extracted outcome data from included studies. The study published in Portuguese was extracted by an external native-speaking review author experienced in trial methodology and a second review author (LGH) verified translated key items. In the Characteristics of included studies table, we noted if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third review author (LGH or MB). Two review authors (AA, HE) transferred data into the Review Manager 5 (RevMan 2014) file. One review author (DG) double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. Another review author (LGH) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (HE, AJN) independently assessed the risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They resolved any disagreements by discussion or by involving another review author (LGH, DG). An external native-speaking review author experienced in trial methodology evaluated the study published in Portuguese, and another review author (LGH) confirmed the judgement.

We assessed the risks of bias according to the following domains.

1. Random sequence generation (selection bias)

2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)
7. Other bias.

We graded each potential source of bias as being at high, low or unclear risk of bias and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the protocol published in the Cochrane Library (Hemkens 2014a) and registered with PROSPERO (Hemkens 2014b). There were no major protocol deviations.

Measures of treatment effect

We analysed dichotomous data as odds ratios and risk ratios with 95% confidence intervals.

We undertook meta-analyses only where this was meaningful, i.e. if the treatments, participants and the underlying clinical questions were similar enough for pooling to make sense.

Unit of analysis issues

We included RCTs with a parallel-group design (unit of randomisation typically was the individual participant) and there were no major unit-of-analysis issues. We would have included pseudo-randomised controlled trials and cluster-randomised trials, but we did not find any eligible ones. From randomised cross-over trials, only data from the first phase were eligible for inclusion.Should such trials be included in future updates, we would assess potential bias by excluding them in sensitivity analyses. From studies with multiple intervention groups we did not include the same intervention group more than once in the meta-analyses. We decided at the individual-study level whether to combine study groups before using data in the meta-analysis or selecting study groups.

Dealing with missing data

We systematically contacted investigators where possible in order to verify key study characteristics and obtain missing numerical outcome data.

Where this was not possible, and the missing data would have introduced serious bias, we planned to use a sensitivity analysis to explore the impact of including such studies in the overall assessment of results. However, we did not identify any study where the amount of missing numerical data seemed to introduce such serious bias.

Assessment of heterogeneity

We used the I^2 statistic (Higgins 2003) to describe heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (e.g. 50% to 90%, depending on the specific situation; Higgins 2011), we reported it and explored possible causes. Given the wide perspective of the review with broad inclusion criteria and the highly diverse fields of application of the intervention in various settings, we did not expect the true effects of the intervention to be homogeneous.

Assessment of reporting biases

If we were able to pool at least 10 trials, we created and examined a funnel plot to explore possible small-study biases for the primary outcomes. We deemed the risk of selective outcome reporting to be high for studies published as abstract only. We did not consider any other sources of selective reporting bias and we deemed an unclear risk as the default when there was a complete study report, unless we identified a study protocol. In such cases we compared the reported results in the protocol and the study publication, and assessed the risk of selective reporting bias.

Data synthesis

We used a random-effects model (DerSimonian 1986; continuity correction of 0.5 (Higgins 2011)) to synthesise the identified treatment effects, because we anticipated that the true effects of colchicine treatment would be very variable across included studies, especially in the context of the broad inclusion criteria. We calculated risk ratios (RRs) with 95% confidence intervals (CIs) (Lau 1997). For outcomes with event rates below 1% across all study groups, we applied the Peto approach (Higgins 2011). We preferred intention-to-treat analyses involving all randomised participants.

We used Review Manager 5 (RevMan 2014) for all analyses, with the exception of sensitivity analyses using the Mantel-Haenszel method without zero-correction (not implemented in Review Manager), where we used Stata 13 (Stata Corp, College Station, TX, USA).

Summary of findings table

We created a 'Summary of findings' table using the following outcomes:

1. All-cause mortality
2. Cardiovascular mortality
3. Myocardial infarction (total)
4. Heart failure (total)
5. Stroke (total)
6. Adverse events (total, gastrointestinal, serious).

We separately show the results for all-cause and cardiovascular mortality and myocardial infarction for the subgroup of participants at high risk for cardiovascular events.

Two review authors (LGH, MB) used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software. We justified all decisions to down- or upgrade the quality of

studies using footnotes and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses (for all outcomes) according to:

1. Colchicine dose (≤ 1 mg/d vs > 1 mg/d)
2. High risk for cardiovascular events (secondary prevention of cardiovascular disease events, established coronary heart disease)

Since most trials were not conducted to evaluate cardiovascular research questions, effects in populations without a history of cardiovascular disease events or without established coronary heart disease were never explicitly reported as such, precluding any originally planned analyses, including participants without a history of cardiovascular disease events or without established coronary heart disease**.**

However, we were able to specifically describe effects reported for populations at high risk for cardiovascular events (secondary prevention of cardiovascular disease events, established coronary heart disease) and most of the reported cardiovascular events occurred in this population. We therefore focused more specifically on this clinically very relevant population.

We used the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We conducted the following sensitivity analyses (for all outcomes) when there were at least three trials per outcome to be combined:

1. For outcomes with event rates between 1% and 5%, we used the Peto approach and the Mantel-Haenszel method without zero-correction
2. Type of comparator (active vs placebo or other)
3. Increased risk for selection bias (adequate randomisation sequence generation and allocation concealment vs other)
4. Double-blinding (blinding of participants and personnel vs other)
5. Blinded outcome assessment (vs other)
6. Increased risk for attrition bias (incomplete vs complete outcome reporting)
7. Increased risk for selective outcome reporting (abstract publication vs other)

Reaching conclusions

We based our conclusions for this review only on findings from the quantitative or narrative synthesis of included studies. We avoided making recommendations for practice, and our implications for research suggest priorities for future research and outline the remaining uncertainties in the area.

RESULTS

Description of studies

Results of the search

We identified 2294 potentially relevant records in our literature searches (Figure 1). In study registries, we identified five ongoing trials that meet our inclusion criteria but have no published results, three of them specifically addressing cardiovascular disease.

Figure 1. Study Flow

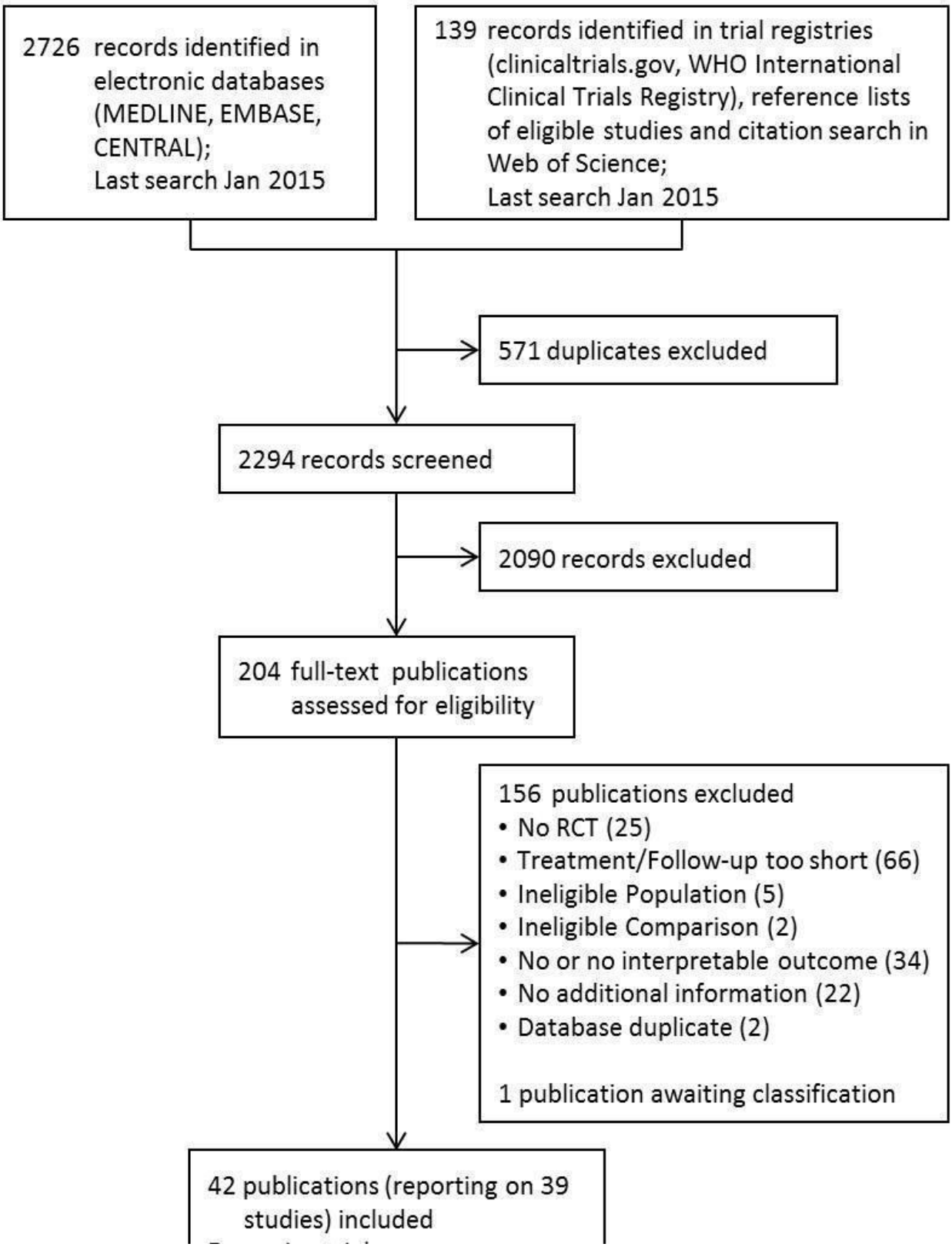
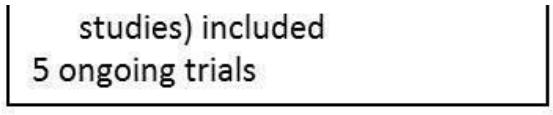


Figure 1. (Continued)



Included studies

We included 39 RCTs (reported in 42 publications) with 4992 participants for analysis (Table 1; Table 2). Study investigators provided unpublished outcome information for three trials (Deftereos 2013; Nidorf 2013; Yurdakul 2001), two of them in participants with cardiovascular disease (Deftereos 2013; Nidorf 2013). Most included RCTs were small, single-centre studies with a median of 84 randomised participants (interquartile range, IQR 54 - 129) and published before 2000.

Four RCTs including 1230 participants compared colchicine to placebo or usual care in a cardiovascular setting (Deftereos 2013; Deftereos 2014a; Nidorf 2013; O'Keefe 1992), i.e. in people with diabetes undergoing bare-metal-stent implantation (Deftereos 2013), in people with stable chronic heart failure (71% ischaemic) (Deftereos 2014a), in people with stable coronary disease (Nidorf 2013), and after elective angioplasty (O'Keefe 1992). Most other studies (n = 24) used colchicine as treatment for hepatobiliary (mainly cirrhotic) diseases.

Colchicine was administered in doses of 1 mg/day or less in 27 trials (69%), and most of the other studies used 1.2 mg/day. None of the included studies evaluated any of the cardiovascular endpoints in this systematic review as their primary outcome.

Excluded studies

We excluded 156 publications and could not retrieve the full-text for one publication which therefore still awaits classification (Figure 1). The excluded studies had in most cases ineligible treatment comparisons or too short follow-up (66 publications), did not report any useful outcome (34 publications), were not (pseudo)-randomized (25 publications) or provided no additional information to other publications (typically abstract publications, double publications, or abridged versions of complete papers; 22 publications). Details are shown in the Characteristics of excluded studies table.

Ongoing studies

In trial registries, we identified five ongoing RCTs of which three specifically looked at cardiovascular populations (NCT01906749; NCT02162303; ACTRN12614000093684). In a double-blinded design, they compare effects of low-dose colchicine (0.5 and 0.6 mg/day) versus placebo on cardiovascular outcomes. They aim to follow up about 100 participants over six months, 500 over two years, and more than 2000 over three to five years, and plan to be completed in December 2015 (NCT02162303), June 2016 (NCT01906749), and 2018 or 2019 (ACTRN12614000093684), respectively. Details are shown in Characteristics of ongoing studies.

Risk of bias in included studies

We provide an overview over the 'Risk of bias' assessment in Figure 2 and Figure 3. Reporting was frequently insufficient, but many of the studies were published long before there were any reporting guidelines. Overall, we deemed the risk of bias to be lower across the four cardiovascular trials.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

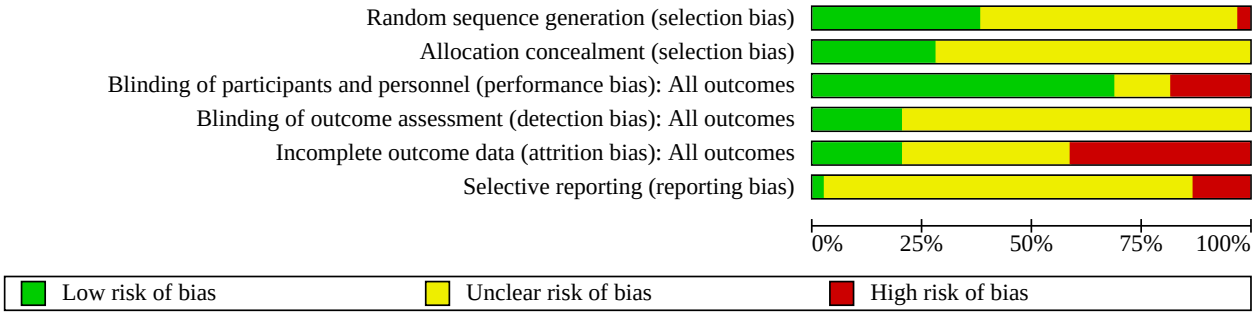


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

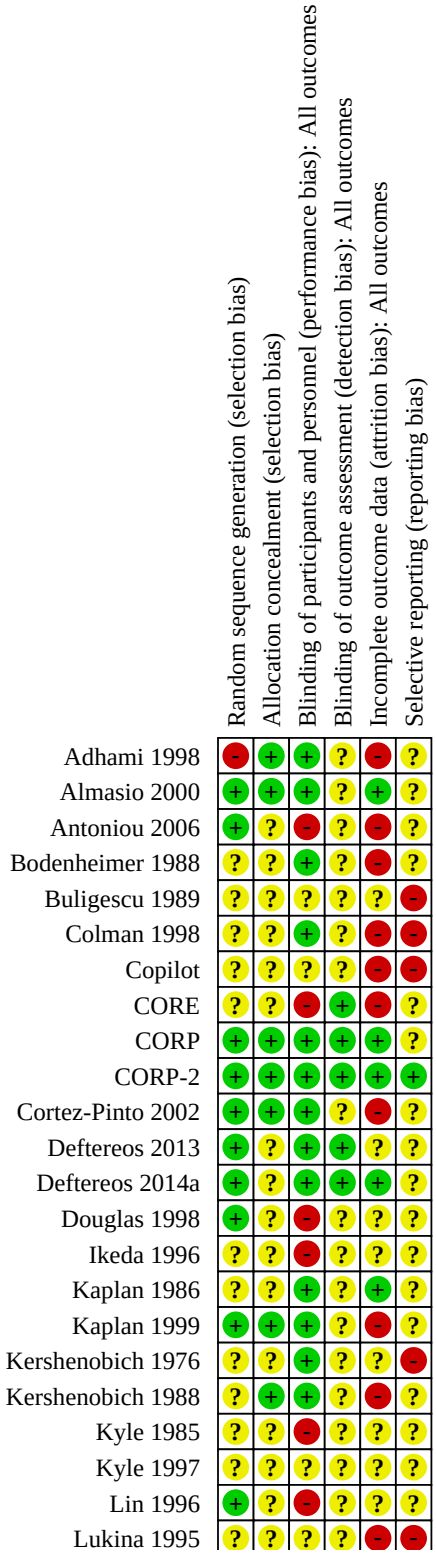
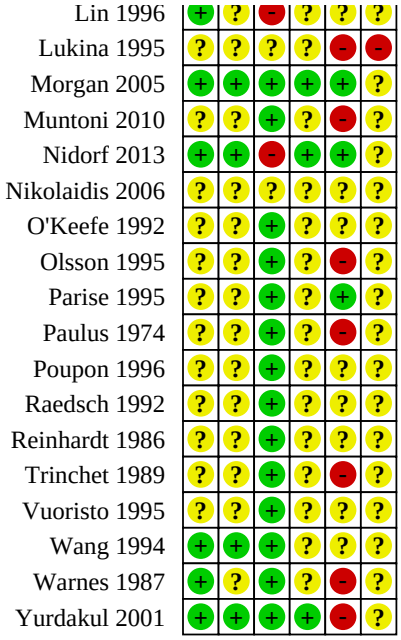


Figure 3. (Continued)



Allocation

We found no indication for relevant selection bias, but we could not determine whether the randomisation and allocation concealment was adequate in 29 of 39 studies, and one study had a high risk of selection bias (Adhami 1998).

Blinding

The overall risk for performance bias was low (27 studies were double-blinded, 25 used placebo controls) and we found no indication for high risk of detection bias, although blinded outcome assessment was frequently unclear and only eight studies had blinded outcome assessment.

Incomplete outcome data

The risk for bias due to incomplete outcome data was high for many trials (16 of 39), because results were missing for substantial proportions of randomised participants or incompleteness was unbalanced between study groups. We deemed the risk of bias to be lower across the four cardiovascular trials.

Selective reporting

Five studies were reported as abstract only and we judged them to be at high risk for selective outcome reporting (Buligescu 1989; Colman 1998; Copilot; Kershenobich 1976; Lukina 1995).

Funnel plots suggested no evidence of reporting bias for all-cause mortality but adverse events seem to be selectively reported (Figure 4; Figure 5; Figure 6).

Figure 4. Funnel plot: Mortality (all-cause)

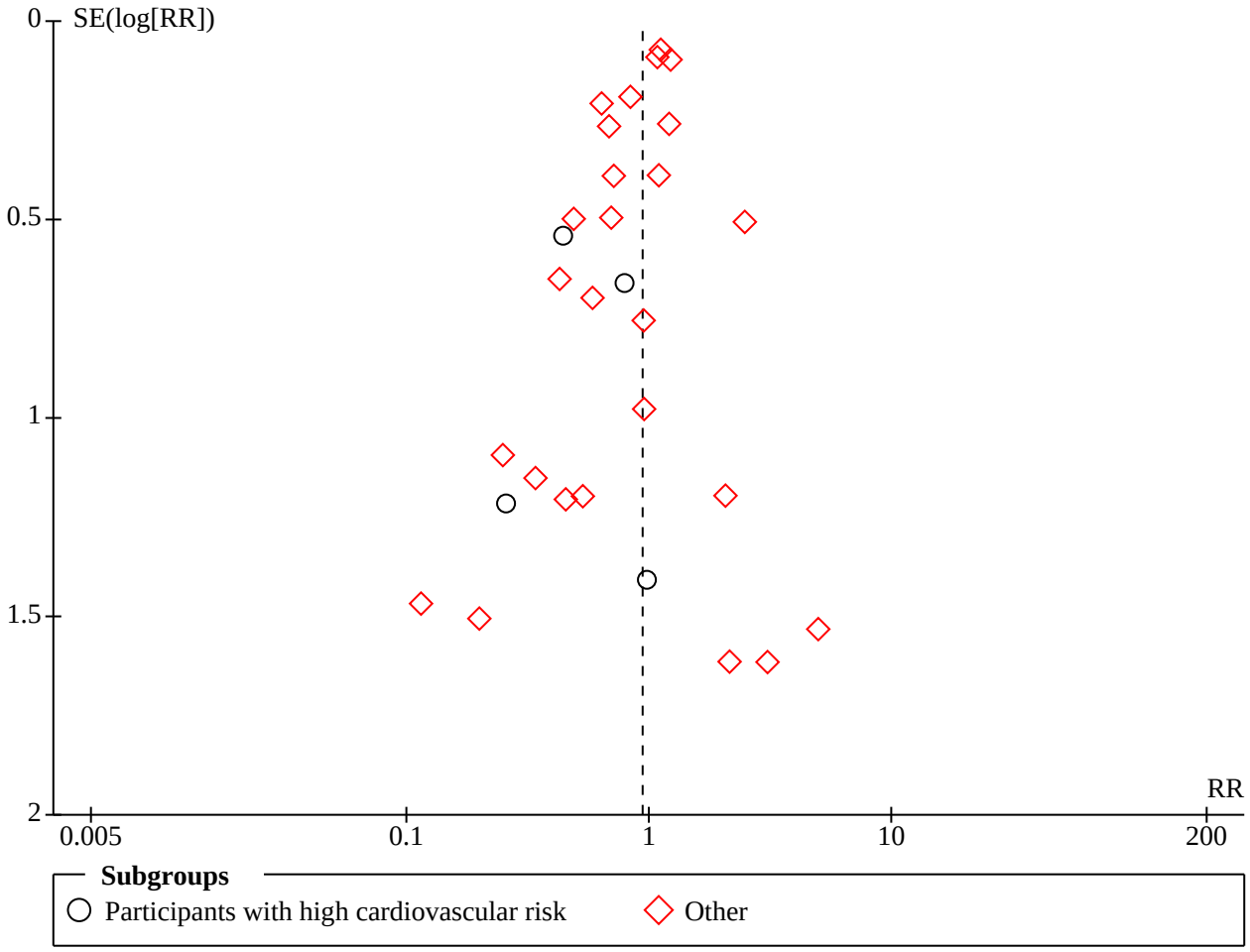


Figure 5. Funnel plot: Adverse event (total)

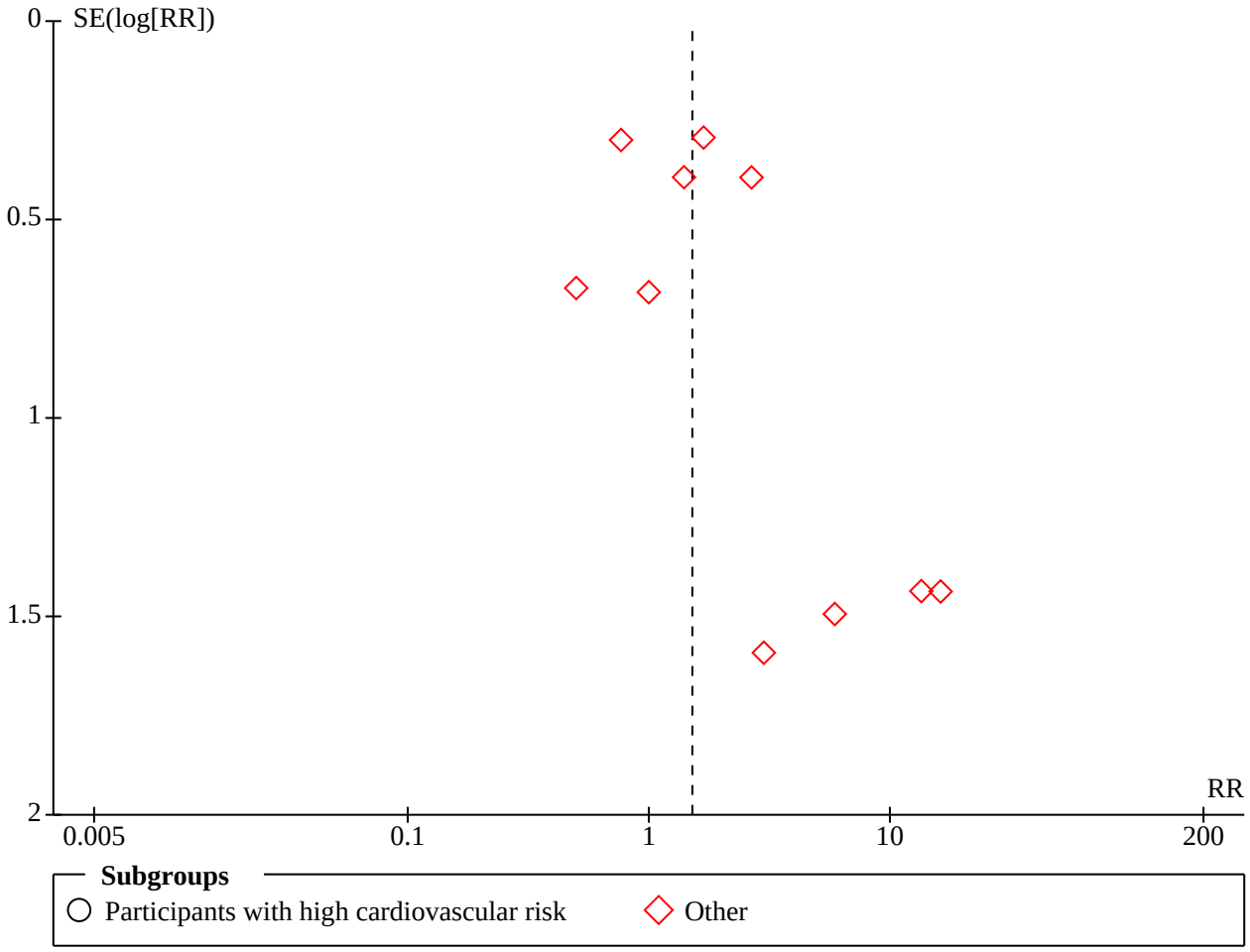
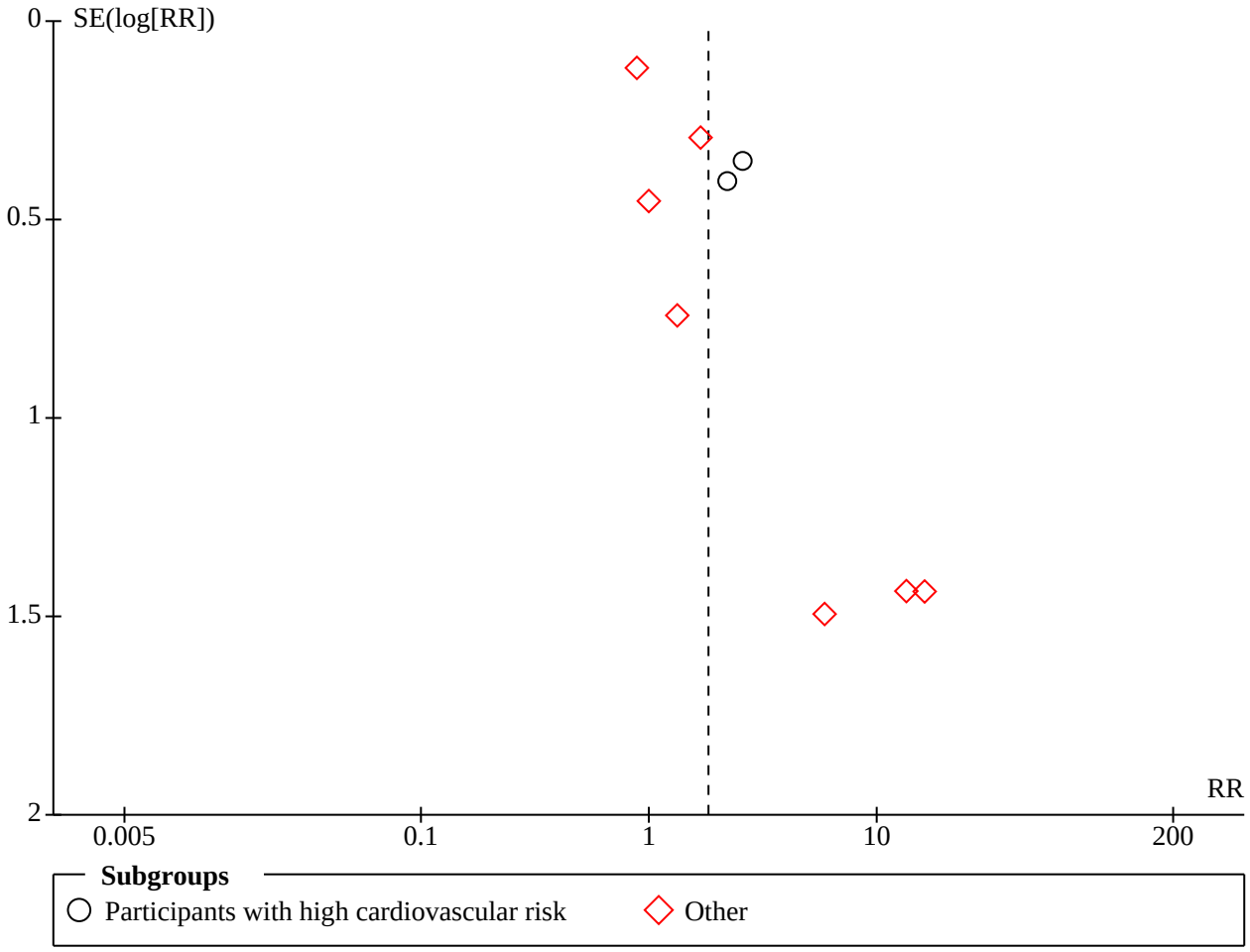


Figure 6. Funnel plot: Adverse event (gastrointestinal)



Other potential sources of bias

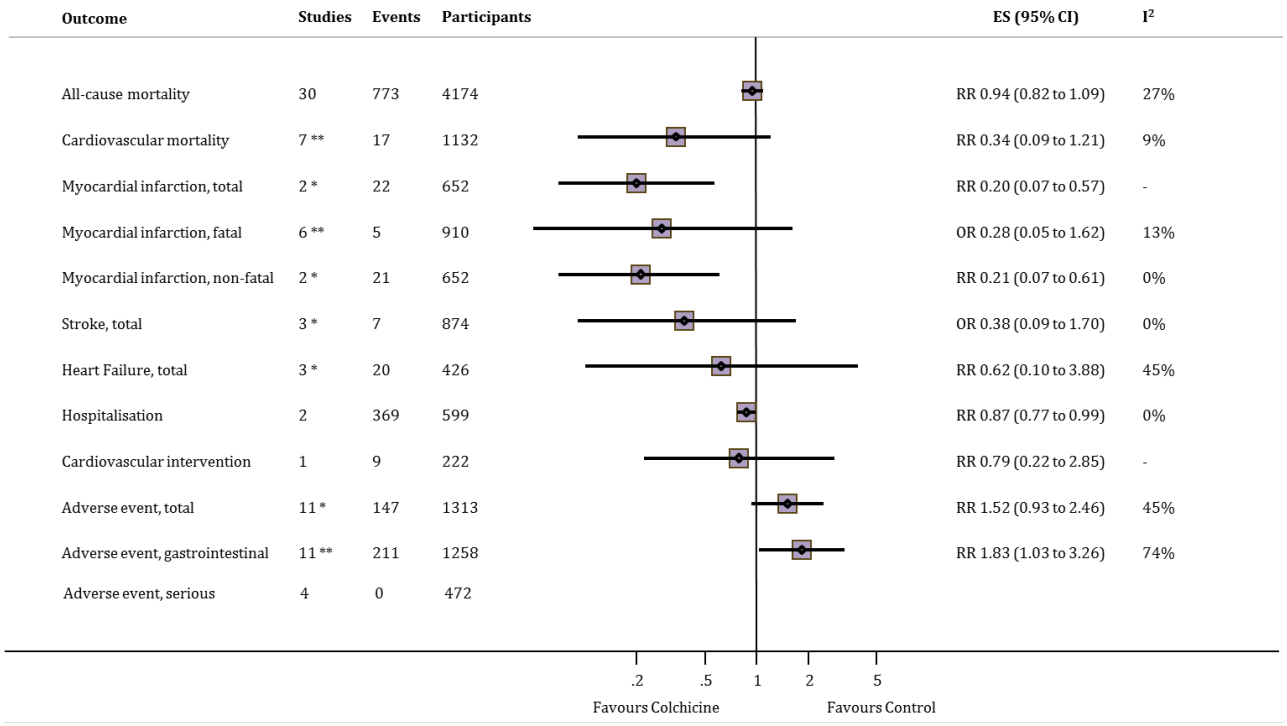
We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Colchicine compared to any control treatment for prevention of cardiovascular events

We deemed the quality of evidence (GRADE) moderate in most cases, due to imprecision. For adverse effects the quality of evidence was low or very low (Summary of findings 1). We provide a graphical overview of the effects in Figure 7.

Figure 7. Overview of results of meta-analyses for colchicine treatment vs. control ES: Effect Estimate; OR: Peto Odds Ratio; RR: risk ratio. * including one study without events ** including two studies without events. Effects for some outcomes were estimated using Peto Odds Ratios because this is a more appropriate method when event rates are very low.



Data on ***all-cause mortality*** were available for 30 trials (4174 participants; Adhami 1998; Almasio 2000; Antoniou 2006; Bodenheimer 1988; Buligescu 1989; Colman 1998; Copilot; Cortez-Pinto 2002; Deftereos 2013; Deftereos 2014a; Douglas 1998; Kaplan 1986; Kaplan 1999; Kershenobich 1976; Kershenobich 1988; Kyle 1985; Kyle 1997; Lin 1996; Morgan 2005; Muntoni 2010; Nidorf 2013; O'Keefe 1992; Olsson 1995; Parise 1995; Poupon 1996; Reinhardt 1986; Trinchet 1989; Vuoristo 1995; Wang 1994; Warnes 1987). The RR for colchicine versus control was 0.94 (95% CI 0.82 to 1.09; Analysis 1.1.1). Between-study heterogeneity was low (I^2 = 27%). When we analysed only the four studies including participants with an increased risk of cardiovascular events (1230 participants; Deftereos 2013; Deftereos 2014a; Nidorf 2013; O'Keefe 1992), the RR for colchicine versus control was 0.54 (95% CI 0.26 to 1.14; Analysis 1.1.2). This was stable in sensitivity analyses using alternative meta-analytical models (due to event rates close to 1%; Table 3). There was no evidence for heterogeneity (I^2 = 0%).

Data on ***myocardial infarction*** were available for six studies (910 participants; Kaplan 1986; Kershenobich 1988; Nidorf 2013: Parise 1995; Vuoristo 1995; Yurdakul 2001). One trial, involving participants with high cardiovascular risk, reported the number of total, fatal, and non-fatal myocardial infarctions (Nidorf 2013). For four trials only data on fatal myocardial infarctions were available (Kaplan 1986; Kershenobich 1988; Parise 1995; Vuoristo 1995), and in one trial no cardiovascular events occurred (Yurdakul 2001). We found a statistically significant reduction in total myocardial infarctions (2 trials; 652 participants; RR 0.20, 95% CI 0.07 to 0.57; Analysis 1.2). Since almost all reported events were non-fatal, results for non-fatal myocardial infarctions were similar (Analysis 1.3). Across all studies, only five fatal myocardial infarctions were reported (in Kaplan 1986; Kershenobich 1988; Nidorf 2013; Vuoristo 1995) and we found no significant effect when we analysed fatal myocardial infarction separately (6 trials; 910 participants; Peto OR 0.28, 95% CI 0.05 to 1.62; Analysis 1.4; Table 3). There was little between-study heterogeneity across all analyses ($I^2 \leq 13\%$).

Data on ***adverse events*** were available for 13 trials; 11 reported the risk of any adverse event (1313 participants; Copilot; CORE; CORP; CORP-2; Cortez-Pinto 2002; Ikeda 1996; Kershenobich 1988; Lukina 1995; Nikolaidis 2006; Paulus 1974; Raedsch 1992) and 11 reported gastrointestinal side effects specifically (1258 participants; CORP; CORP-2; Cortez-Pinto 2002; Deftereos 2013; Deftereos 2014a; Ikeda 1996; Kershenobich 1988; Nikolaidis 2006; Paulus 1974; Raedsch 1992; Yurdakul 2001). In four trials, the number of serious adverse events (SAEs) per study group was reported (n = 472; CORE; CORP; CORP-2; Raedsch 1992), and there were no events over the whole 824 patient-years of follow-up (Analysis 1.5; Table 3). The RR for colchicine versus control on any adverse events was 1.52 (95% CI 0.93 to 2.46; participants = 1313; studies = 11; Analysis 1.6). We found an increased risk associated with colchicine for gastrointestinal side effects (RR 1.83, 95% CI 1.03 to 3.26; participants = 1258; studies = 11; I^2 = 74%; Analysis 1.7). Within the eight trials reporting both total and gastrointestinal adverse events, 66 of the 73 (90%) reported adverse events for gastrointestinal reasons. For participants with increased cardiovascular risk, only data on gastrointestinal side effects from two studies were available, but the findings were consistent (RR 2.41, 95% CI 1.43 to 4.06; participants = 501; Analysis 1.7).

Data on ***cardiovascular mortality*** were available for seven trials (1132 participants; Deftereos 2013; Kaplan 1986; Kershenobich 1988; Nidorf 2013; Parise 1995; Vuoristo 1995; Yurdakul 2001;). The RR was 0.34 (95% CI 0.09 to 1.21; Analysis 1.8) for colchicine compared with control. Between-study heterogeneity was low (I^2 = 9%). We found similar effects in sensitivity analyses with alternative meta-analytical models (Peto OR 0.24, 95% CI 0.09 to 0.64; Mantel-Haenszel fixed-effect RR 0.20, 95% CI 0.06 to 0.68; Table 3). We found similar effect estimates but with wide confidence intervals for the meta-analysis of two studies that focused on participants with increased cardiovascular risk (RR 0.25, 95% CI 0.02 to 2.66; participants = 754; studies = 2; I^2 = 49%; Table 3).

Few studies reported only few events on ***stroke, heart failure, non-scheduled hospitalisations, and unscheduled cardiovascular interventions*** (Table 3; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.16). Colchicine treatment compared with control reduced non-scheduled hospitalisations for any reason (RR 0.87, 95% CI 0.77 to 0.99; participants = 599; studies = 2). Data specifically related to non-scheduled hospitalisations for cardiovascular reasons were not available. For other outcomes we found no significant effects.

Impact of colchicine dose

We detected a statistically significant dose effect of colchicine on all-cause mortality in favour of lower-dose treatment (P = 0.03 for interaction; Table 3; Analysis 2.1). In studies using 0.5 to 1 mg colchicine per day (n = 21; 2420 participants), all-cause mortality was significantly reduced (RR 0.82, 95% CI 0.67 to 0.99) in contrast to studies using higher doses (n = 9; 1754 participants) (RR 1.08, 95% CI 0.93 to 1.25). The effect on adverse events was not modified (Table 3; Analysis 2.6). There were insufficient data to evaluate dose effects on other outcomes.

Impact of control treatment and risk of bias

We found no evidence for an interaction between colchicine effects and the type of control treatment (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5), potential selection bias (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5), double-blinding (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5), blinding of outcome assessment (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5), incomplete outcome data (Analysis 7.1; Analysis 7.2; Analysis 7.3; Analysis 7.4; Analysis 7.5), or whether studies were published as abstract or in full text (Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4; Analysis 8.5).

DISCUSSION

Summary of main results

This systematic review and meta-analysis includes 39 RCTs with follow-up to 14 years comparing colchicine with any control in 4992 participants with any condition or disease. Colchicine had no significant effect on all-cause mortality across all studies. Moderate quality evidence suggests an 80% risk ratio reduction for myocardial infarction, although most of the evidence was provided by a single study. We found similar large effects ranging between 0.2 and 0.34 (RR and OR, respectively), with uncertainty around the estimate of effects, for cardiovascular mortality, which was significantly reduced in some but not all meta-analytical models. The observed 13% RR reduction for non-scheduled hospitalisations is not clearly attributable to underlying cardiovascular effects.

As expected, colchicine treatment was associated with an increased RR of 83% for gastrointestinal side effects. These were typically described as mild and transient, including diarrhoea, nausea, abdominal pain, or vomiting. In contrast, we found no evidence indicating increased risks for serious adverse events over the whole 824 patient-years, although the quality of evidence was low.

Results for stroke, heart failure, and non-scheduled cardiovascular interventions were inconclusive, due to wide confidence intervals.

Overall completeness and applicability of evidence

Balancing potential benefits and harms based on the available evidence (Summary of findings 1), we estimate that treating 1000 people with high cardiovascular risk over one year with colchicine may protect 20 people (11 to 23) from experiencing a myocardial infarction at the cost of 110 (4 to 299) having mostly mild and transient gastrointestinal intolerance (Summary of findings 1). The potential clinical impact of three years of treatment on prevention of myocardial infarction can be estimated by a number needed to treat for an additional beneficial outcome (NNTB) of 17 (assuming a baseline risk of 72/1000 as in the control group of the trial providing most of the evidence for myocardial infarction (Nidorf 2013)).

There was no evidence that daily doses of over 1 mg improve survival; in contrast, lower doses may be associated with mortality benefits. This should inform further research on the optimal treatment dose, in particular for many indications where the available trial evidence is insufficient to address dosing questions, including gout, pericarditis, and familial Mediterranean fever (Alabed 2014; Hentgen 2013; Van Echteld 2014). However, although this analysis was specified a priori, we did not anticipate stronger effects with lower doses; it might be a chance finding, and this underlines that there is still much to be learned about the clinical use of colchicine.

Quality of the evidence

We deemed the quality of evidence (GRADE; Summary of findings 1) to be moderate for all-cause mortality, cardiovascular mortality, and myocardial infarction. Thus it is likely that further research will have an important impact on confidence in the effect estimates and may also change them. We downgraded the quality due to imprecision of the effect sizes (few events, wide confidence intervals, and compatible with participant-relevant benefit or harm). We deemed the quality for stroke and heart failure to be lower due to substantial imprecision with very few effects. For adverse effects, we rated the quality of evidence as low or very low, mainly because of potential bias (as discussed in detail below). Our grading reflects our opinion that it is very likely that the availability of further (randomised) evidence on adverse effects will have an important impact on our confidence in the effect estimates and that they may also change. For serious adverse events, we are very uncertain about the estimate.

There are some caveats that need to be discussed. First, as for all systematic reviews, the validity of our results depends on the methodological quality of the included studies. We evaluated RCTs which were mostly placebo-controlled, double-blinded, and some explicitly mentioning blinded outcome assessment (most of the

observed fatal cardiovascular events and myocardial infarctions were assessed by blinded outcome assessors). We could not rule out bias due to missing outcome data for many studies, although this was less of a problem for the cardiovascular trials. However, in sensitivity analyses we found no indication that such bias affected the results.

Secondly, the results depend on the reporting quality of the primary studies, and reporting of adverse events is known to be problematic (Pitrou 2009). Most trials were published long before reporting guidelines were established and some studies were published as abstracts only. Cardiovascular outcomes were often only casually reported as adverse events, typically among the causes of death. Some studies selectively described serious adverse events (SAEs) that the investigators deemed related to the study drug. Some studies reported that no SAEs occurred while there were events which would meet the definition of an SAE (such as deaths, myocardial infarctions or strokes). The funnel plots for adverse events showed asymmetry, suggesting reporting bias and thus the increased risk of adverse events might be overestimated. In addition, reporting of adverse events was frequently limited to the most common ones. However, cardiovascular events were uncommon in most eligible trials, which were not designed to evaluate such effects. Thus, reporting of non-fatal events, cardiovascular or not, was probably often neglected. Only studies focusing specifically on cardiovascular topics reported some cardiovascular outcomes. Yet, despite wide confidence intervals, the effect estimates for studies of non-cardiovascular topics were similar to those for studies systematically assessing cardiovascular effects, and we also found no substantial between-study heterogeneity (although heterogeneity tests are limited due to the low number of studies; Ioannidis 2007). Moreover, the study that contributed most of the evidence on myocardial infarction (Nidorf 2013) clearly reported the ascertainment of such events. We aimed to address the reporting problem and could obtain, for at least some trials, complete information on cardiovascular outcomes by contacting study authors.

Thirdly, there were few events in some meta-analyses and some outcome results were dominated by only a single study, which is a clear limitation. For example, effects on myocardial infarction are based on only a small proportion of all randomised participants. However, effect sizes showed a consistent pattern across various scenarios with respect to non-fatal myocardial infarction (RR 0.21; results are mainly driven by a large study specifically designed for cardiovascular effects), fatal myocardial infarction (OR 0.28; some small studies without systematic outcome assessment), cardiovascular mortality (RR 0.34; six studies in diverse clinical settings) and all-cause mortality (RR 0.54; four studies with participants at high cardiovascular risk).

Fourthly, we did not assess effects on inflammatory markers or surrogate outcomes because we focused on outcomes most important for patients and clinical decision making. Among the studies in cardiovascular disease, one trial reported changes in levels of high-sensitivity-CRP and interleukin-6 and demonstrated significant reductions for both biomarkers (Deftereos 2014a).

Fifthly, there was insufficient information on concomitant cardiovascular medication, e.g. aspirin, statins. However, in the study contributing most information on effects in participants with established cardiovascular disease (Nidorf 2013), almost all participants used statins and antiplatelet therapy. This suggests that colchicine effects are additional to concomitant standard treatments.

Finally, we found a dose effect when we dichotomised studies according to allowed dosage. Some studies used individualised dose regimens within a certain range and we had no information on the median dose actually used across all participants in such studies. This reduced the granularity of the data and thus we did not perform meta-regression to further analyse the dose effect. Individual patient data meta-analyses are needed to further elucidate the question on the optimal treatment dose.

Potential biases in the review process

One author (MN) was involved in one of the included studies. This author was not involved in the processes of risk of bias assessment of the included studies for this systematic review and meta-analysis.

Agreements and disagreements with other studies or reviews

Previous meta-analyses on colchicine addressed specific conditions, including familial Mediterranean fever (Wu 2015), gout (Van Echteld 2014), pericarditis (Alabed 2014; Imazio 2012c; Imazio 2014c; Raval 2015), atrial fibrillation (Trivedi 2014), liver fibrosis and cirrhosis (Rambaldi 2005) or primary biliary cirrhosis (Gong 2004) but evaluated safety only in relative narrow spectra of participants. We kept a broad perspective by applying wide eligibility criteria to include populations with any disease or clinical condition. This allowed us to evaluate colchicine effects, particularly safety, independently of the medical indication and using the entire clinical trial evidence (Ioannidis 2010). To our knowledge this is the first systematic review and meta-analysis on colchicine that evaluated cardiovascular outcomes in any patient population and the largest analysis of randomised evidence on colchicine safety. Our results are in keeping with the main findings of a recently-published systematic review which was limited to participants with cardiac disease (Verma 2015), which indicates potential cardiovascular benefits of colchicine but also highlights the need for further randomised evidence to reduce the uncertainty surrounding the merits of this drug.

AUTHORS' CONCLUSIONS

Implications for practice

There is much uncertainty surrounding the benefits and harms of colchicine treatment. Our findings indicate cardiovascular benefits, especially on myocardial infarction. These may be restricted to high-risk groups, and we need more evidence in these patients to confirm these effects. There is uncertainty about the size of the effect on mortality and other cardiovascular outcomes, especially in the general population from which most of the studies in our review were drawn. Given the limited quality of evidence, the beneficial effects need to be cautiously interpreted until more high-quality randomised trial evidence is available. Colchicine is associated with gastrointestinal side effects, based on low-quality evidence.

Implications for research

The potential benefits of this inexpensive treatment on patient-important clinical outcomes and mortality encourage funding and conduct of large-scale high-quality randomised trials to further explore the merits of colchicine in cardiovascular disease.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adhami 1998

Study characteristics	
Methods	**Design:** Pseudo-randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 11 years
Participants	**Number randomised:** Total 52. 29 colchicine. 23 control **Condition:** Ascitic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age mean (SD) in years:** colchicine 54.27 (14.27). control 54.21 (15.04) **Sex (women):** 13% **Inclusion criteria:** "The trial included 52 ascitic cirrhotic patients." **Exclusion criteria:** "According to Kershenobich the patients were excluded if they had evidence of gastrointestinal bleeding or of encephalopathy during a period of two weeks before the trial."
Interventions	**Colchicine:** • Dose: 1 mg/d 5d/week • Duration: "Colchicine treatment, according to need, was given from 4 to 84 months on average 27.63±20.54 months, while the Placebo was given 0.75 to 36.25 months, on average 11.63±11.42 months." **Control:** • Dose: placebo
Outcomes	**Primary outcome of the study:** • "the goal is to determine the role of colchicine in the survival of cirrhotic patients. This is thought to occur by decreasing hepatic fibrosis and decrease of portal hypertension." **Outcomes considered in this review:** • All-cause mortality
Notes	Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation according to odd/even age

Adhami 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Pharmacy supplied drugs and kept identity of drugs confidential
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"neither staff, nor the patients knew the drug used", double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis unclear; 13% missing data reported for control group - imbalance to colchicine group might cause bias
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Almasio 2000

Study characteristics	
Methods	**Design:** Randomised controlled trial, multicentre (6 centres, 2 centres in substudy) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 3 years
Participants	**Number randomised:** Total 90. 46 colchicine, 44 control. (Substudy: Total 44. colchicine 22, control 22) **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Italy **Age mean (SD) in years:** Colchicine 55.5 (10.9), control 53.3 (10.2). (Substudy: colchicine 55 (11), control 58 (10)) **Sex (women):** Colchicine 87%, control 93% (Substudy: colchicine 86, control 86) **Inclusion criteria:** "The criteria for entry into the trial were: an established diagnosis of primary biliary cirrhosis according to Taal et al.; symptomatic disease as defined by presence of pruritus (severe enough to necessitate therapy); and/or serum bilirubin higher than 2 mg/dl; and/or histological or clinical diagnosis of cirrhosis. Patients were included regardless of the duration of symptoms or the stage." **Exclusion criteria: "**Exclusion criteria were: advanced liver disease (ascites, encephalopathy, portal hypertensive bleeding, bilirubin >10 mg/dl); hepatocellular carcinoma; any concomitant immunosuppressive treatment; evidence of other major diseases unrelated to primary biliary cirrhosis; alcohol abuse; and low compliance. Treatment with cholestyramine, antihistamines, H_2-blockers or proton-pump inhibitors, calcium supplementation and liposoluble vitamins was allowed."
Interventions	**Colchicine:** • Dose: 1 mg/d • Plus 500 mg/d ursodeoxycholic acid

Almasio 2000 *(Continued)*

	• Duration: 3 years **Control:** • Placebo plus ursodeoxycholic acid 500 mg/d • Duration: 3 year
Outcomes	**Primary outcome of the study:** • "In order to evaluate the efficacy of the two therapeutic regimens, we analysed clinical, biochemical and histological end-points. We considered as 'treatment failure' the occurrence of any of the following events: death, liver transplantation, decompensation of cirrhosis, doubling of serum bilirubin" **Outcomes considered in this review:** • All-cause mortality
Notes	Substudy results are reported from 2 of 6 centres (with separate randomisation) with longer follow-up. We used the main study results for our analyses. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was performed by a central study unit using the same randomized blocks separately for each centre"
Allocation concealment (selection bias)	Low risk	Central randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT; ≤ 10% missing data per group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Antoniou 2006

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre (8 centres) **Blinding:** Open-label **Longest mean follow-up period for a review-relevant outcome:** 25 months
Participants	**Number randomised:** Total 50. 18 colchicine, 32 control.

Antoniou 2006 *(Continued)*

Condition: Idiopathic pulmonary fibrosis

Cardiovascular risk profile: Not reported

Setting: outpatient

Country: Greece

Age median (range) in years: Colchicine 69 (54 - 85), control 66 (42 - 82)

Sex (women): 16%

Inclusion criteria: "Eligible patients were aged 40–80 yrs, had shown clinical symptoms of IPF for ≥3 months, and had a forced vital capacity (FVC) of ≥55% and ≤90% of the predicted value, a transfer factor of the lung for carbon monoxide (TL,CO) of ≥35% pred and an arterial oxygen tension (Pa,O_2) of >7.3 kPa while breathing room air at rest."

Exclusion criteria: "Criteria for exclusion were a significant history of exposure to organic or inorganic dust or drugs known to cause pulmonary fibrosis and connective tissue disease or other chronic lung diseases causing pulmonary fibrosis, a ratio of the forced expiratory volume in one second to FVC of <0.6 after bronchodilator use, a residual volume of >120% pred, active infection within 1 week before enrolment, unstable cardiovascular or neurological disease, uncontrolled diabetes, pregnancy, lactation, any active malignancy likely to result in death or any condition other than IPF likely to result in death within 3 yrs."

Interventions

Colchicine:

- Dose: 1 mg/d
- Plus prednisolone 10 mg/d
- Duration: 15 months median duration (range 5 – 44 months), intended 24 months

Control:

- IFN-c 1b 200 mg 3 x / week subcutaneously plus prednisolone 10 mg/d
- Duration: 20 months median duration (range 2 – 44 months), intended 24 months

Outcomes

Primary outcome of the study:

- "The study was originally designed to investigate the molecular perspective after both treatment regimens. [...] The study did not have prespecified end-points. [...] The study objectives were to compare the clinical effects of the two treatment regimens after 6, 12 and 24 months of therapy using: pulmonary function tests (FVC, total lung capacity (TLC), TL,CO and Pa,O2 at rest), the extent of lung fibrosis on high-resolution computed tomography (HRCT), quality of life (St George's Respiratory Questionnaire (SGRQ)), treatment outcome (using the ATS/ERS criteria), and overall survival."

Outcomes considered in this review:

- All-cause mortality, non-scheduled hospitalisation

Notes

"supported by an unrestricted grant from Boehringer Ingelheim Hellas (Athens, Greece) and the Society for Pulmonary and Intensive Care Research in the district of East Macedonia and Thrace (Alexandrou´polis, Greece). The Greek National Health System supported both colchicine and interferon gamma-1b."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using a random number table."

Antoniou 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Two readers, blinded to the clinical functional data and type of treatment, examined the HRCT images"; however, we do not measure the outcomes related to the HRCT images; no other blinding reported
Incomplete outcome data (attrition bias) All outcomes	High risk	In total, 17 (11 in the IFN-c-1b group and 6 in the colchicine group) of the 50 participants discontinued treatment before 24 months. Of the 11 participants in the IFN-c-1b group, 8 stopped because of an adverse event and/or disease progression and 3 for social reasons. Of the colchicine group, 6 participants withdrew; 2 stopped because of disease progression and 4 for social reasons. In addition, median follow-up was longer (median 5 months) in control group than in colchicine group
Selective reporting (reporting bias)	Unclear risk	"The study was originally designed to investigate the molecular perspective after both treatment regimens. Owing to technical difficulties, this aim was only investigated in a subgroup of 10 patients (data not shown). The study did not have prespecified end-points."

Bodenheimer 1988

Study characteristics	
Methods	**Design:** Randomised controlled trial **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 26 months
Participants	**Number randomised:** Total 57. Colchicine 28 control 29 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age mean (SD) in years:** Colchicine 53 (not reported), control 51 (not reported) **Sex (women):** Colchicine 93%, control 90% **Inclusion criteria:** "History of chronic cholestatic liver disease and liver biopsy results compatible with PBC were entered into the study. Fifty-one of our patients were followed at Mount Sinai Medical." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: mean 33 months

Bodenheimer 1988 *(Continued)*

	Control: • Placebo • Duration: mean 33 months
Outcomes	**Primary outcome of the study:** • To test the safety of long-term colchicine administration **Outcomes considered in this review:** • All-cause mortality
Notes	Endpoint mortality (extracted from Bodenheimer 1985) reported only for 26 months. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The liver histology was reviewed without knowledge of the clinical status or the drug the patient was receiving." However, we did not look into liver outcomes, so the blinding remains unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced attrition and missing reporting: in the abstract from 1985, Bodenheimer et al report 39% attrition in colchicine group and 24% in the control group at 26 weeks follow-up. In their publication from 1988, they report 29% attrition in colchicine and 21% in the control group at a mean follow-up of 33 months.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Buligescu 1989

Study characteristics	
Methods	**Design:** Randomised controlled trial **Blinding:** Not reported **Longest mean follow-up period for a review-relevant outcome:** 36 months
Participants	**Number randomised:** Total 180. Colchicine 100, placebo 80 **Condition:** Liver cirrhosis

Buligescu 1989 *(Continued)*

	Cardiovascular risk profile: Not reported **Setting:** Outpatient **Country:** Not reported **Age:** Not reported **Sex (women):** Not reported **Inclusion criteria:** Liver cirrhosis **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 1.0 mg/d • Duration: 6 - 36 months. Mean 17.4 months **Control:** • "Conventional therapy" • Duration: 6 - 36 months. Mean 17.4 months
Outcomes	**Primary outcome of the study:** • Clinical improvement of liver cirrhosis markers **Outcomes considered in this review:** • All-cause mortality
Notes	This study is reported only as an abstract. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear, no withdrawal reported
Selective reporting (reporting bias)	High risk	Only abstract, objectives unclear

Colman 1998

Study characteristics	
Methods	**Design:** Randomised controlled trial **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** mean 45 months
Participants	**Number randomised:** Total 129. Colchicine 63, control 66 **Condition:** Alcoholic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age:** Not reported **Sex (women):** Not reported **Inclusion criteria:** People with alcoholic cirrhosis **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: mean follow-up 45.3 months (range 1 - 106) **Control:** • Placebo • Duration: mean follow-up 45.3 months (range 1 - 106)
Outcomes	**Primary outcome of the study:** • Overall survival and liver-related death • Effect on the natural history of chronic alcoholic liver disease or liver-related complications **Outcomes considered in this review:** • All-cause mortality
Notes	This study is only reported as an abstract. Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)

Colman 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	From initially 129 participants: 41 died, another 41 were withdrawn (26 did not comply, 10 had adverse events, 5 for geographic reasons)
Selective reporting (reporting bias)	High risk	Abstract only; no protocol reported

Copilot

Study characteristics	
Methods	**Design:** Randomised controlled trial **Blinding:** Unclear **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 555. Colchicine 269, control 286 **Condition:** HCV with advanced liver disease **Cardiovascular risk profile:** Not reported **Setting:** Not reported **Country:** Unclear **Age mean (SD) in years:** mean 51 (not reported) **Sex (women):** 30% **Inclusion criteria:** "IFN failures with Ishak stage 3–6" and "Study patients had no evidence of liver decompensation or HCV (liver cancer); Ishak Fibrosis stage 3 or more; HIV & HbeAg negative." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: 4 years ("49% of patients discontinued medication over 4 years") **Control:** • Peg-Interferon-alpha 0.5 µg/kg/w • Duration: 4 years ("49% of patients discontinued medication over 4 years")
Outcomes	**Primary outcome of the study:** • All-cause mortality, liver failure, transplant, variceal bleeding and HCC **Outcomes considered in this review:**

Copilot *(Continued)*

	• All-cause mortality, adverse events (any) at 2 years follow-up
Notes	This study was reported as an abstract only. Outcomes from Afdhal 2008 not included in analysis because group assignment unclear. Funding not reported but 1 or more of the authors with pharmaceutical industry affiliation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT; dropouts were censored; unclear how many dropouts
Selective reporting (reporting bias)	High risk	Abstract only; results from secondary endpoints not described

CORE

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Open-label **Longest mean follow-up period for a review-relevant outcome:** 20 months
Participants	**Number randomised:** Total 84. Colchicine 42, control 42 **Condition:** Recurrent pericarditis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Italy **Age mean (SD) in years:** Colchicine 56.4 ± 16.9 control 51.2 ± 16.3 **Sex (women):** Colchicine 62%, control 69% **Inclusion criteria:** "Inclusion criteria were a diagnosis of recurrent pericarditis (first episode); previous idiopathic, viral, and autoimmune etiologies (including postpericardiotomy syndromes and connective tissue diseases) of the first episode of acute pericarditis; 18 years or older; and informed consent."

CORE *(Continued)*

	Exclusion criteria: "Exclusion criteria were tuberculous, neoplastic, or purulent etiologies of the first episode; known severe liver disease or current transaminase levels greater than 1.5 times the upper limit of normal; a current serum creatinine level greater than 2.5 mg/dL (221 µmol/L); known myopathy or a current serum creatine kinase level greater than the upper limit of normal; known blood dyscrasias or gastrointestinal disease; pregnant and lactating women or women of child bearing potential not protected by a contraception method; known hypersensitivity to colchicine; and current treatment with colchicine for any indication."
Interventions	**Colchicine:** • Dose: 1 - 2 mg the first day, maintenance dose of 0.5 - 1.0 mg/d • < 70 kg or intolerant to higher dose: 1 x 1.0 mg then maintenance dose 1 x 0.5 mg/d; ≥ 70 kg: 2 x 1.0 mg then maintenance dose 2 x 0.5 mg/d • Plus Aspirin, 800 mg every 6 or 8 hours for 7 - 10 days, with gradual tapering for 3 - 4 weeks • Duration: 6 months **Control:** • Aspirin, 800 mg every 6 or 8 hours for 7 - 10 days, with gradual tapering for 3 - 4 weeks • Duration: 6 months
Outcomes	**Primary outcome of the study:** • "to verify the safety and efficacy of colchicine therapy as an adjunct to conventional therapy for the first episode of recurrence of pericarditis and to verify whether the natural history of the disease may change because of the early use of colchicine" **Outcomes considered in this review:** • Adverse events (any), serious adverse events
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified ("Randomization was based on permuted blocks, with a block size of 4.")
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The validation of clinical events was ensured by an ad hoc committee of expert cardiologists blinded to patient treatment assignment", "data analyses were performed by an external data analysis committee masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT, but "clinical follow-up data were available in all patients for a mean of 20 months (range, 8-44 months)"
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

CORP

Study characteristics	
Methods	**Design:** Randomised controlled trial, multicentre (4 centres) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 120. Colchicine 60, control 60 **Condition:** Recurrent pericarditis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Italy **Age mean (SD) in years:** Colchicine 47.3 (14.4), control 47.9 (15.4) **Sex (women):** Colchicine 57%, control 52% **Inclusion criteria:** "Inclusion criteria were a definite diagnosis of recurrent pericarditis (first recurrence), age 18 years or older, and provision of informed consent. The relevant institutional review boards and ethics committees approved our research protocol, and all participants gave written informed consent" **Exclusion criteria:** "Patients were excluded if they were having their first episode of acute pericarditis or their second or subsequent recurrence or had pericarditis with tuberculous, purulent, or neoplastic causes; known severe liver disease; current aminotransferase levels greater than 1.5 times the upper limit of normal, current serum creatinine level greater than 221 mol/L(2.5mg/dL); known myopathy; serum creatine kinase level above the upper limit of normal; known blood dyscrasias; gastrointestinal disease; or known hypersensitivity to colchicine. Also excluded were pregnant or lactating women (because of the contraindication to colchicine) and women in their childbearing years who were not using contraception. Finally, we excluded persons who were receiving or had previously received colchicine for any indication."
Interventions	**Colchicine:** • Dose: colchicine 1 - 2 mg on the first day, followed by maintenance dose of 0.5 - 1.0 mg/d • < 70 kg or intolerant to higher dose: 0.5 mg/12h, then maintenance dose 0.5 mg/d; ≥ 70 kg: 2 mg/d, then maintenance dose 1 mg/d • Plus conventional treatment of 800 to 1000 mg aspirin (or ibuprofen, 600 mg) every 8 hours for 7 - 10 days, with gradual tapering over 3 - 4 weeks • Duration: 6 months **Control:** • Placebo plus conventional treatment of 800 to 1000 mg Aspirin (or ibuprofen, 600 mg) per os every 8 hours for 7-10 days, with gradual tapering over 3-4 weeks • Duration: 6 months
Outcomes	**Primary outcome of the study:** • Pericarditis recurrence rate at 18 months **Outcomes considered in this review:** • Gastrointestinal adverse event, adverse event (any), serious adverse events

CORP *(Continued)*

Notes	"Primary Funding Source: Maria Vittoria Hospital, Torino, Italy."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"central computer– based automated sequence Randomization was based on permuted blocks, with a block size of 4. The random allocation sequence was implemented by using sequentially numbered containers."
Allocation concealment (selection bias)	Low risk	"central computer–based automated sequence"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"participants and trial investigators were blinded to randomized treatment"; double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data were collected by using case report and clinical events adjudication forms and were managed by investigators who were blinded to treatment assignments. A blinded clinical end point committee adjudicated all events."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT, 7% in the control and 8% in the colchicine group discontinued intervention
Selective reporting (reporting bias)	Unclear risk	"Study protocol: Available from Dr. Imazio (e-mail, massimo_imazio@yahoo.it). Statistical code and data set: available from Dr. Imazio (e-mail, massimo_imazio@yahoo.it) for personal use, with approval from the Steering Committee"

CORP-2

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 20 months
Participants	**Number randomised:** Total 240. Colchicine 120, control 120 **Condition:** Recurrent pericarditis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Italy **Age mean (SD) in years:** Colchicine 48.6 (13.6), placebo 48.9 (15.5) **Sex (women):** Colchicine 45%, control 55% **Inclusion criteria: "**Consecutive patients aged 18 years or older with two or more recurrences of pericarditis (idiopathic, viral, post-cardiac injury, or caused by connective tissue disease) were eligible for enrolment."

CORP-2 *(Continued)*

	Exclusion criteria: "Patients with any of the following were ineligible: tuberculous, neoplastic, or purulent pericarditis; severe liver disease or current aminotransferase concentrations more than 1.5 times the upper limit of the normal; serum creatinine concentration more than 221.00 µmol/L; skeletal myopathy or serum creatine kinase concentration more than the upper limit of the normal; blood dyscrasia; inflammatory bowel disease; hypersensitivity to colchicine or other contraindication to colchicine; current treatment with colchicine; and life expectancy of 18 months or less. Pregnant or lactating women or women of childbearing potential not using contraception were also ineligible, as were patients with evidence of myopericarditis as indicated by any increase of serum troponin concentration."
Interventions	**Colchicine:** • Dose: 0.5 or 1.0 mg daily • < 70 kg or intolerant to higher dose: 0.5 mg/d; ≥ 70 kg: 2 x 0.5 mg/d • Duration: 6 months **Control:** • Placebo • "Colchicine and placebo tablets were identical" • Duration: 6 months
Outcomes	**Primary outcome of the study:** • Recurrent pericarditis **Outcomes considered in this review:** • Gastrointestinal adverse events, adverse events (any), serious adverse events
Notes	"supported by the former Azienda Sanitaria 3 of Torino (now ASLTO2) within the Italian National Health service. Acarpia (Madeira, Portugal) provided the study drug and placebo as an unrestricted grant."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned to receive colchicine or placebo (1:1) with a central computer-based automated sequence."
Allocation concealment (selection bias)	Low risk	"The random allocation sequence was implemented with sequentially numbered study drug containers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled, "All patients and investigators were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All patients and investigators were masked to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT, 6% in the control and 7% in the colchicine group discontinued intervention
Selective reporting (reporting bias)	Low risk	Protocol available.

Cortez-Pinto 2002

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 41 months
Participants	**Number randomised:** Total 62. Colchicine 31, control 31 **Condition:** Alcoholic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age mean (SD) in years:** Colchicine 53.2 (8.5), control 54.4 (9.1) **Sex (women):** Colchicine 7%, control 15% **Inclusion criteria:** "Ambulatory subjects aged 18-65 years, with biopsy proven liver cirrhosis and a 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, in whom other causes of liver disease were excluded, were eligible for inclusion." **Exclusion criteria:** "Exclusion criteria included the presence of other liver diseases, namely haemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, autoimmune hepatitis, primary biliary cirrhosis, or viral hepatitis, as evaluated by the latter tests. Child-Pugh class C, serum bilirubin >10 mg/dl, gastrointestinal bleeding in the previous 15 days, refractory ascites, or serious illness, e.g. renal failure (creatinine >2.5 mg/dl), cardiac failure or neoplasia were also exclusion criteria."
Interventions	**Colchicine:** • Dose: 1 mg/d, 5 d/week • Duration: median 40.6 months (range 1.4 - 126.3) **Control:** • Placebo • Duration: median 42.4 months (range 5.7 - 118.2)
Outcomes	**Primary outcome of the study:** • "Clinical endpoints were death from any cause, episodes of gastrointestinal bleeding, ascites, encephalopathy or jaundice." **Outcomes considered in this review:** • All-cause mortality, gastrointestinal adverse events, adverse events (any)
Notes	Maximum follow-up 10 years. "supported in part by a grant from the Center of Nutrition and Metabolism (RUN 437)."

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Cortez-Pinto 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated randomization list (blocks of four)"
Allocation concealment (selection bias)	Low risk	"either 1 mg 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, according to a computer-generated randomization list (blocks of four)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, "At no time were the treatment codes disclosed for any patient, attending physicians or investigators."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, although "investigators" are blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two (6%) patients in the colchicine group and five (16%) in the placebo, who did not return for the first follow-up visit, were not included in the analysis of data." ITT mentioned but not all randomised participants were analysed; "Patient dropouts were as follows: nine patients (16%) before 3 years, 14 patients (25%) before 5 years, and 33 patients (60%) before 10 years."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Deftereos 2013

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 months
Participants	**Number randomised:** Total 222. Colchicine 112, control 110 **Condition:** PCI **Cardiovascular risk profile:** Secondary prevention **Setting:** Outpatient **Country:** Not reported **Age mean (SD) in years:** Colchicine 63.7 (6.9), control 63.5 (7.2) **Sex (women):** Colchicine 37%, control 32% **Inclusion Criteria:** "Eligible patients were diabetic, 40 to 80 years of age, undergoing PCI in a coronary artery with a diameter of at least 2.5 mm with a BMS. Acceptable reasons for not implanting a drug-eluting stent were: contraindication to long-term dual antiplatelet treatment, need for triple antithrombotic therapy, planned or high probability of necessary surgery in the following 12 months, or the patient's expressed wish in the context of the PCI informed consent procedure. Only 1 lesion per patient was included in the study. (If PCI was performed in >1 coronary site in a patient, the site with the greater artery diameter was in-

Deftereos 2013 *(Continued)*

	cluded.) Diabetes mellitus had to be previously diagnosed by a specialist, with the patient treated with either oral medication or insulin." **Exclusion Criteria:** "Exclusion criteria were left main artery disease (>30% in angiography); PCI performed as primary treatment for ST-segment elevation myocardial infarction, hepatic impairment (Child-Pugh class B or C); target vessel segment presenting particular technical challenges for intravascular ultrasound (IVUS) (e.g., marked tortuosity, vessel with steep take-off angle); severe or end-stage renal failure (estimated glomerular filtration rate ≤20 ml/min/1.73 m^2 or requiring dialysis); history of intolerance to colchicine, myopathy, and statin hepatotoxicity or myotoxicity; women with child-bearing potential; and inability or unwillingness to adhere to standard treatment or to provide consent."
Interventions	**Colchicine:** • Dose: 2 x 0.5 mg/d • Duration: 6 months **Control:** • Placebo • Duration: 6 months
Outcomes	**Primary Outcome of the Study:** • "The main outcome measures were angio-ISR and IVUS-ISR." **Outcomes considered in this review:** • Gastrointestinal adverse events, cardiovascular intervention, all-cause mortality, stroke fatal; from author request: heart failure fatal and non-fatal, stroke non-fatal, cardiovascular mortality
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation not specified in publication; author reply: “This is not reported in the paper, but randomization was computer-based, with the random number sequence being produced by a short script in R language.”
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported in the publication; author reply: “Outcome assessment was completely blinded. It is stated in the published paper that 'Captured IVUS data, identified only by a serial number, were analyzed offline.' That means that assessors of IVUS-defined restenosis were not in knowledge of the images-patient correspondence (even if they had been they would not know the treatment allocation of each patient). The same was true for the QCA measurements (for angiographic restenosis).”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified ITT: "All patients who received at least 1 dose of study treatment were included in the analysis"; "Of 222 eligible patients who consented to take part in the study, 26 (12%) were not available for follow-up catheterization. As

Deftereos 2013 *(Continued)*

		a result, 196 (100 in the colchicine and 96 in the placebo group) completed the study procedures and were available for analysis"; according to author reply, all randomised participants were analysed for outcomes pertinent to this review.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Deftereos 2014a

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 months
Participants	**Number randomised:** Total 279. Colchicine 140, control 139 **Condition:** Chronic heart failure **Cardiovascular risk profile:** Secondary prevention **Setting:** Outpatient **Country:** Not reported **Age mean (SD) in years:** Colchicine 66.9 (5.8), control 66.4 (5.7) **Sex (women):** Colchicine 33%, control 33% **Inclusion criteria:** "Patients with stable symptomatic heart failure and systolic left ventricular dysfunction (ejection fraction ≤40%) were included." **Exclusion criteria:** "Recently hospitalized patients (hospital stay for heart failure in the previous 3 months) were excluded. Other exclusion criteria were New York Heart Association (NYHA) class IV, recent (in the previous 6 months) implantation of a cardiac resynchronization treatment device, active inflammatory/infectious disease or malignancy, known autoimmune diseases, corticosteroid or other immunosuppressive or immunomodulatory therapy, moderate or severe hepatic impairment (Child-Pugh class B or C), severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2), current participation in another research protocol, and inability or unwillingness to adhere to standard treatment or to provide consent."
Interventions	**Colchicine:** • Dose: 0.5 mg/d if body weight < 60 kg. 2 x 0.5 mg/d if body weight ≥ 60 kg • Duration: 6 months **Control:** • Placebo daily • Duration: 6 months
Outcomes	**Primary outcome of the study:** • "The primary endpoint was the proportion of patients achieving at least one-grade improvement in New York Heart Association class for heart failure." **Outcomes considered in this review:**

Deftereos 2014a *(Continued)*

	• All-cause mortality, gastrointestinal adverse events
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported specifically enough (sequential numbers); from author: "Randomization was computer-based. Random numbers were produced by a short script written in R language."
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT and PP; 3 participants excluded from analysis (1%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Douglas 1998

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Open-label **Longest mean follow-up period for a review-relevant outcome:** 30 months
Participants	**Number randomised:** Total 26. Colchicine 14, control 12 **Condition:** Idiopathic pulmonary fibrosis **Cardiovascular risk profile:** Not reported **Setting:** Not reported **Country:** USA **Age mean (SD) in years:** Colchicine 65.9 (12.3), control 69.9 (4.0) **Sex (women):** Colchicine 17%, control 29% **Inclusion criteria:** "Conforms to clinical plus either high-resolution computed tomography (HRCT) or histopathologic criteria for the diagnosis of idiopathic UIP; baseline tests performed, including pulmonary function, chest radiograph, serum creatinine, liver function tests, and complete blood count;

Douglas 1998 *(Continued)*

	willing to return for follow-up examination at 3 month intervals for 1 year; age 18 years or older; written informed consent given." **Exclusion criteria:** "Exclusion criteria were as follows: history of allergy, intolerance, or unwillingness to take either study drug; pregnancy, lactation, or women capable of becoming pregnant who were without adequate birth control; history of chronic asthma and/or treated for asthma within the previous year; diabetes treated (including dietary therapy) within the previous year; active tuberculosis treated within the previous year; use of either study drug within the previous 2 months."
Interventions	**Colchicine:** • Dose: 0.6 - 1.2 mg/day as tolerated • Duration: 12 months **Control:** • "The minimum dose of prednisone used was 60 mg/d for 1 mo, tapered to 40 mg/d over the second month, tapered to 40 mg every other day during the third month, with subsequent doses adjusted as clinically indicated" • Duration: 12 months
Outcomes	**Primary outcome of the study:** • "Death, significant deterioration of pulmonary function, intolerance or adverse event due to the study drug requiring cessation of therapy, addition of a second drug for treatment of UIP, and study dropout for any other reason." **Outcomes considered in this review:** • All-cause mortality
Notes	"Funding was provided by Mayo Institute funds."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation not specified, but was done by biostatistician: "Randomization was accomplished by the Section of Biostatistics at Mayo Rochester." and "Within each stratum defined by the three stratification factors described previously, the randomization was done in blocks of four, ensuring that after every fourth subject was entered in a given stratum the number of subjects in the stratum assigned to prednisone was the same as the number of subjects in the strata assigned to colchicine."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear; missing data reported for baseline and various outcomes (e.g. baseline symptoms 7.1% vs 16.7% missing data)

Douglas 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Ikeda 1996

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Not reported **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 22. Colchicine 10, control 12 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age mean (SE) in years:** Colchicine 57 (3), control 64 (3) **Sex (women):** Colchicine 90%, control 83% **Inclusion criteria:** "The diagnosis of PBC was made based on the following observations: 1) elevation of alkaline phosphatase (ALP) over the upper limit of normal, 2) presence of antimitochondrial antibody in the serum, 3) compatible histological appearance of liver biopsy specimens, and 4) radiological or ultrasonographic evidence that the bile ducts were patent. Anti-mitochondrial antibody titers were measured by the immunofluorescence technique. Histological staging of liver biopsy specimens was carried out as previously described." **Exclusion criteria: "**None of them had a history of blood transfusion, ethanol addiction, or drug abuse, and none had anti-HCV antibodies (second-generation RIA assay), HBs antigen, or anti-HBc antibody in the serum" and "No patients had taken any medicines known to be hepatotoxic nor had been treated with corticosteroids, immunosuppressive agents, colchicine, penicillamine, or UDCA in the previous 6 months."
Interventions	**Colchicine:** • Dose: 1 mg/d • Plus ursodeoxycholic acid 600 mg/d • Duration: 2 years **Control:** • Ursodeoxycholic acid 600 mg/d • Duration: 2 years
Outcomes	**Primary outcome of the study:** • "The major pre-defined parameters for the evaluation of UDCA treatment were serum levels of total bilirubin, ALP, y-glutamyltranspeptidase (y-GTP), aspartate aminotransferase (AST), and IgM. To evaluate the effectiveness of UDCA treatment in each patient, indices were calculated as weighted means of changes in these values (expressed as the ratio to baseline values) according to Battezzati et al. with slight modifications as follows" **Outcomes considered in this review:**

Ikeda 1996 *(Continued)*

	• Gastrointestinal adverse events, adverse events (any)
Notes	Previous treatment with 600 mg/d ursodeoxycholic acid during 30 months before randomisation in 2 different groups, and continued for 2 years after randomisation. "supported by a grant from the Intractable Liver Diseases Research Committee, the Ministry of Health and Welfare, Japan."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, no placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear; missing data unclear
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kaplan 1986

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 60. Colchicine 30, control 30 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age:** 6 participants ≤ 50 years in colchicine group and 6 participants ≤ 50 years in control group (no further information provided in paper) **Sex (women):** Colchicine 93%, control 97% **Inclusion criteria:** "The criteria for entry into the trial included a clinical history and biochemical profile consistent with primary biliary cirrhosis, a positive test for antimitochondrial antibody, liv-

Kaplan 1986 *(Continued)*

	er-biopsy results consistent with or diagnostic of primary biliary cirrhosis, and radiologic or ultrasonographic evidence that the bile ducts were patent." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: 2 years **Control:** • Placebo • Duration: 2 years
Outcomes	**Primary outcome of the study:** • "Each patient remained in the double-blind phase of the study for 24 months unless clear evidence of progression of the disease was found, at which time treatment was considered to have failed in that patient. Treatment failure was defined as (1) doubling of both serum alkaline phospatase and bilirubin levels on at least two consecutive measurements at two-month intervals, (2) tripling of either level - also at two consecutive two-months intervals appearance, or (3) the appearance of a serious complications such as hepatic encephalopathy, intractable ascites, hemorrhage from esophageal varices." **Outcomes considered in this review:** • Fatal myocardial infarction, cardiovascular mortality, all-cause mortality
Notes	Control group received colchicine after 2 years. "Supported by a Research Grant (AM-28490), a Training Grant (AM-07024). and a General Research Center Grant (M01-RR00054) from the National institutes of Health."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not sufficiently specified ("randomization scheme in which the numbers […] tended to be kept equal")
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind until 24 months; placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 of 60 participants (5%) dropped out and were excluded from the analysis; the rest were included in analyses. 2 of them had early disease and did no tolerate medication, 1 had Stage 4 disease.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kaplan 1999

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 10 years
Participants	**Number randomised:** 87. Colchicine 43, control 42; (2 never received any drug, allocation not reported) **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age mean (SD) in years:** Colchicine 51 (1.4), control 51 (1.5) **Sex (women):** 94% **Inclusion criteria:** "15 Patients were included provided they had (1) a medical history and blood test results consistent with chronic cholestatic liver disease; (2) a serum alkaline phosphatase that was at least twice that of the upper limit of normal; (3) a serum bilirubin that was not greater than 10 mg/dL; (4) a liver biopsy performed within 12 months of entry that was consistent with primary biliary cirrhosis, and (5) imaging tests that demonstrated that bile ducts were patent." **Exclusion criteria:** "Patients were excluded if they had end-stage liver disease, which was defined as: (1) a serum bilirubin level greater than 10 mg/dL or a serum albumin level less than 3.0 g/dL on two examinations two months apart; (2) hepatic encephalopathy; (3) hemorrhage from esophageal varices and/or portal gastropathy; (4) refractory ascites; or (5) signs of hypersplenism (i.e. a hematocrit less than 30, white blood cell count less than 2,500, and platelet count less than 100,000). Other reasons for exclusion were history of alcohol abuse, administration of drugs associated with chronic liver disease, contemplation of pregnancy, or any serious medical illness that might in itself cause liver dysfunction or shorten life expectancy."
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: 2 - 10 years **Control:** • Methotrexate 15 mg/week • Duration: 2 - 10 years
Outcomes	**Primary outcome of the study:** • "Initially, the study was designed such that each patient would remain in the double-blind phase of the study for 6 years or until clear evidence of progression of disease or drug toxicity was detected and the patient was judged a treatment failure. Evidence of progression included: (1) an increase in serum bilirubin of 3 mg/dL or more to a level exceeding 4 mg/dL that was maintained for at least 3 months; (2) a decrease in serum albumin of 0.8 g/dL or more to a level below 3 g/dL that was maintained for at least 3 months; and 3) appearance of a serious complication, such as hepatic encephalopathy, intractable ascites, or hemorrhage from esophageal varices. Patients who developed toxicity attributable to a drug were also classified as treatment failures. Drug toxicity attributable to methotrexate included interstitial pneumonitis and persistent cytopenias that were not due to hypersplenism (determined after patients had undergone bone marrow biopsy). Drug toxicity attributable to colchicine included intractable diarrhea and cytopenias not due to hypersplenism. Patients classified as treat-

Kaplan 1999 *(Continued)*

	ment failures were censored and then referred for liver transplantation if clinically indicated or followed outside of the study." **Outcomes considered in this review:** • All-cause mortality
Notes	Ursodeoxycholic acid was administered to all participants after 2 years. "Supported in part by National Institutes of Health Center for Research Resources, General Clinical Research Center, grant RR 00054; by GRASP (Gastroenterologic Research in Absorptive and Secretory Processes) Digestive Disease Center grant NIH-NIDDK P30 DK34928; and by a grant from Lederle Laboratories (Pearl River, New York)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned, using a computer generated list in blocks of four"
Allocation concealment (selection bias)	Low risk	Active drug and placebo were kept in the hospital pharmacy and dispensed by a research pharmacist who was the only caregiver with access to the randomisation code.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT; high rate of withdrawals: 14% in both study groups at 2-year follow-up, 51% in colchicine group and 67% in control at 10-year follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kershenobich 1976

Study characteristics

Methods	**Design:** Randomised controlled trial **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 24 months
Participants	**Number randomised:** Total 28. Colchicine 14, control 14 **Condition:** Liver fibrosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported

Kershenobich 1976 *(Continued)*

	Age: Not reported **Sex (women):** Not reported **Inclusion criteria:** "Each patient had bilirubin below 1 mg%, prothrombin below 16/12 and pre-trial histologic evidence of cirrhosis." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 1 mg/d, 5 d/week • Duration: 24 months **Control:** • Placebo • Duration: 24 months
Outcomes	**Primary outcome of the study:** • Liver biopsy, histological changes **Outcomes considered in this review:** • All-cause mortality
Notes	This study was reported as an abstract only. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data reported, 2 participants in group B (placebo) died
Selective reporting (reporting bias)	High risk	Abstract only

Kershenobich 1988

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 14 years
Participants	**Number randomised:** Total 100.Colchicine 54, control 46 **Condition:** Liver fibrosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Mexico **Age mean (SE) in years:** Colchicine 49.7 (1.5), control 50.8 (1.7) **Sex (women):** Colchicine 55%, control 46% **Inclusion criteria:** "They had to have a definitive diagnosis of liver cirrhosis, as established by history, physical examination, and biochemical tests, histologic studies of the liver, or both. Second, they had to be at least 18 years of age." **Exclusion criteria:** "Patients were excluded if they had an episode of gastrointestinal bleeding or encephalopathy within two weeks before entry into the trial, if they had a total serum bilirubin level above 171 µmol per liter (10 mg per deciliter) or a serum albumin level below 220 µmol per liter (1.5 g per deciliter), if they had a severe concomitant disease, or if they were unable to attend the clinic regularly for geographic or other reasons."
Interventions	**Colchicine:** • Dose: 1 mg/d, 5 d/week • Duration: up to 14 years, mean 4.7 years **Control:** • Placebo • Duration: up to 14 years, mean 4.7 years
Outcomes	**Primary outcome of the study:** • "Patients' survival and histologic manifestations of cirrhosis" **Outcomes considered in this review:** • Fatal myocardial infarction, all-cause mortality, cardiovascular mortality, gastrointestinal adverse events, adverse events (any)
Notes	Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not sufficiently specified ("Randomization was carried out by one of us […]")

Kershenobich 1988 *(Continued)*

Allocation concealment (selection bias)	Low risk	"At no time […] disclose the treatment code for any patients to the attending physicians"; person who conducted randomisation was in another institution
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT; all randomised participants analysed, 19 participants lost to follow-up (number of participants balanced between groups, but considerably unbalanced median follow-up: colchicine 42 months vs control 12 months)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kyle 1985

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Not reported **Longest mean follow-up period for a review-relevant outcome:** 5 years
Participants	**Number randomised:** Total 101. Colchicine 52, control 49 **Condition:** Primary systemic amyloidosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age median (SD) in years:** Colchicine 62 (not reported), control 64 (not reported) **Sex (women):** Colchicine 43%, control 40**%** **Inclusion criteria:** "All patients had clinical or laboratory evidence of systemic amyloidosis." **Exclusion criteria:** "Excluded from the study were patients with secondary, familial, or localized amyloidosis; patients with overt symptomatic multiple myeloma or diarrhea; patients who had received alkylating agents or colchicine; and patients with brittle diabetes, severe hypertension, or an active peptic ulcer that would prevent the use of prednisone as indicated in the protocol."
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg at beginning, then increased by 0.6 mg/d each week until abdominal cramps or diarrhoea developed. The use of colchicine was then discontinued and was resumed in the highest dose that did not produce side effects. Median dose was 1.5 mg. • Duration: median 12 months (range 1 - 56 months) **Control:**

Kyle 1985 *(Continued)*

	• "Dose: melphalan 0.15 mg/kg daily and prednisone 0.8 mg/kg daily for a 7-day period. Melphalan/prednisone therapy was repeated every 6 weeks. The dose of melphalan was increased by 2 mg daily for each 6-week course until mid-cycle leukopenia or thrombocytopenia occurred. If severe leukopenia or thrombocytopenia occurred, the dose of melphalan was reduced accordingly." • Duration: median 12 months (range 1 - 30 months)
Outcomes	**Primary outcome of the study:** • Time of death, or progression of disease **Outcomes considered in this review:** • Heart failure, all-cause mortality
Notes	"Forty-nine patients initially received melphalan/prednisone and eight subsequently had colchicine added to their regimen. Fifty-two patients lnitially received colchicine and 35 subsequently required melphalan/prednisone because of progressive disease." "supported in part by Research Grant CA-16835 from the National Institutes of Health, Public Health Service, Bethesda, Maryland, and by the Toor Myeloma Research Fund, West Palm Beach, Florida."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not specified, but authors report that colchicine dosage was weekly increased until side effects occurred, thus no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear; it seems all randomised participants were analysed
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kyle 1997

Study characteristics

Methods	**Design:** Randomised controlled trial **Blinding:** Unclear **Longest mean follow-up period for a review-relevant outcome:** 9 years
Participants	**Number randomised:** Total 148. Colchicine, melphalan and prednisone 71 (MPC), melphalan and prednisone 77 (MP)

Kyle 1997 *(Continued)*

	Condition: Primary amyloidosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age median (SD) in years:** Colchicine 65 (not reported), control 63 (not reported) **Sex (women):** Not reported **Inclusion criteria:** "Amyloidosis was confirmed by biopsy in every patient." **Exclusion criteria:** "Patients with secondary, familial, senile, or localized amyloidosis were not admitted to the study. Patients with overt symptomatic multiple myeloma or diarrhea were ineligible, as were patients who had previously received alkylating drugs or colchicine."
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Plus melphalan (0.15 mg per kilogram) and prednisone (0.8 mg per kilogram) daily for 7 d once every 6 weeks • Duration: Not reported **Control:** • Melphalan (0.15 mg per kilogram) and prednisone (0.8 mg per kilogram) daily for 7 d once every 6 weeks
Outcomes	**Primary outcome of the study:** • Survival **Outcomes considered in this review:** • All-cause mortality
Notes	One-third treatment group (colchicine without melphalan or prednisone, 72 participants) was not considered for analysis. "Supported in part by grants from the National Institutes of Health (CA62242) and the Quade Amyloidosis Research Fund."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Kyle 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear; missing data unclear (14 participants "were removed from the study" = 6.4%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Lin 1996

Study characteristics	
Methods	**Design:** Randomised trial, single-centre **Blinding:** Open-label **Longest mean follow-up period for a review-relevant outcome:** 4 years
Participants	**Number randomised:** Total 66. Colchicine 38, control 27. Exclusion of 1 participant after randomisation, assignment unclear **Condition:** Chronic hepatitis B cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Taiwan **Age mean (SD) in years:** Cochicine 40 (9), control 40 (13) **Sex (women):** Colchicine 13%, control 11% **Inclusion criteria:** "Patients with hepatic decompensation, bridging necrosis or an alpha-fetoprotein level greater than 100 ng/ml during an exacerbation of hepatitis have a high risk of developing cirrhosis" **Exclusion criteria:** "Patients under age 25, pregnant, with renal insufficiency (serum creatinine > 2.5mg/ml (normal < 1.0 mg/ml)), a history of idiosyncrasy or who refused the trial after careful explanation were excluded. (...)Those with clinical suspicions of cirrhosis, including spider angioma, palmar erythaema, an albumin <1.5 g m % (normal > 3.5 g m %), and endoscopy documented esophageal varices were also excluded."
Interventions	**Colchicine:** • Dose: 1.0 mg/d, 5 d/week • Duration: 4 years **Control:** • No treatment (no steroids, no antiviral agents)
Outcomes	**Primary outcome of the study:** • Developing cirrhosis, episodes of acute exacerbation **Outcomes considered in this review:** • All-cause mortality

Lin 1996 *(Continued)*

Notes	"supported by grants from the National Science Council of the Republic of China: NSC-79-0419-B18209, NSC-80-0412-B-182A-32 and NSC-82-0412-B-182-029."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random table sequence"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12% participants were lost, unclear group allocation
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Lukina 1995

Study characteristics

Methods	**Design:** Randomised controlled trial **Blinding:** Not reported **Longest mean follow-up period for a review-relevant outcome:** Colchicine up to 2 years, control up to 7 years
Participants	**Number randomised:** Total 54. Colchicine 27, control 27 **Condition:** Renal amyloidosis **Cardiovascular risk profile:** Not reported **Setting:** Not reported **Country:** Not reported **Age:** Not reported **Sex:** Not reported **Inclusion criteria:** People with renal amyloidosis secondary to rheumatic diseases **Exclusion criteria:** Not reported

Lukina 1995 *(Continued)*

Interventions	**Colchicine:** • Dose: 1 - 2 mg/d • Duration: up to 2 years **Control:** • Dimethyl sulfoxide, 1 - 2 g/d • Duration: up to 7 years
Outcomes	**Primary outcome of the study:** • "changes in glomerular filtration rate, serum creatinine level and fluid retention, in physician and patient global assessment and tolerability." **Outcomes considered in this review:** • Adverse events (any)
Notes	This study was reported as an abstract only. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up in the control group was 5 years longer
Selective reporting (reporting bias)	High risk	Abstract only

Morgan 2005

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre (13 centres) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 years

Morgan 2005 *(Continued)*

Participants	**Number randomised:** Total 549. Colchicine 274, control 275 **Condition:** Alcoholic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age mean (SD) in years:** Colchicine 55.2 (8.0), control 55.9 (7.6) **Sex (women):** Colchicine 2.5%, control 1.4% **Inclusion criteria:** "Outpatients were eligible for the study if they had a clinical diagnosis of alcoholic cirrhosis (based on a long history of alcohol use and the exclusion of other causes of liver disease and a modified Pugh 27 score of 7 or greater. Liver biopsy demonstrating cirrhosis was required unless contraindications to biopsy were present (eg. ascites, coagulopathy)." **Exclusion criteria:** "Patients were excluded for the following reasons: gastrointestinal bleeding within the prior 28 days requiring transfusion; explicit drug use in the prior 12 months, human immunodeficiency virus infection; cancer in the prior 10 years; serum creatinine greater than 1.5 mg/dL; total white blood cell (WBC) count less than 3500/mL; age 70 years or greater; serious chronic disease interfering with adherence to the protocol follow-up schedule; no home telephone; and refusal."
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: all participants at least 24 months, some up to 72 months **Control:** • Placebo • Duration: all participants at least 24 months, some up to 72 months
Outcomes	**Primary outcome of the study:** • All-cause mortality **Outcomes (time points) considered in this review:** • All-cause mortality, non-scheduled hospitalisation
Notes	"Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation scheme based on permuted bocks of random length separately for each study centre
Allocation concealment (selection bias)	Low risk	"Patient enrollment and random assignment to treatment was by telephone call to the data-coordinating center" and matched placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither participants nor study personnel were aware of treatment group assignment

Morgan 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"physicians assessing the outcomes were aware of the treatment group assignment until all data analysis was complete."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT, no losses to follow-up for survival analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Muntoni 2010

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 4 years
Participants	**Number randomised:** Total 74. Colchicine 37, control 37 **Condition:** Chronic liver disease **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Not reported **Age mean (SD) in years:** 53 (13) **Sex (women):** 38% **Inclusion criteria:** Not reported. Diverse chronic liver diseases **Exclusion criteria:** "Exclusion criteria were: age < 20 years or a known hypersensitivity to colchicine. Patients were recruited by referral from general practitioner or by self choice and gave informed consent to be assigned to intervention (colchicine) or control by using random allocation."
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: 4.4 years **Control:** • Standard treatment (diuretics, beta-blockers, ursodeoxycholic acid, withdrawal of alcohol) • Duration: 4.4 years
Outcomes	**Primary outcome of the study:** • "To test whether colchicine would be an effective antifibrotic agent for treatment of chronic liver diseases in patients who could not be treated with α-interferon." **Outcomes (time-points) considered in this review:** • All-cause mortality

Muntoni 2010 *(Continued)*

Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified ("using random allocation. Randomization was performed by giving 74 consecutive numbers to all patients coming to our clinic")
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blind in the abstract, not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis unclear; odd mentioning of ITT ("Inclusion criteria were on an intention-to-treat basis."); 12 (colchicine 9 and control 3; 16%) participants withdrew due to personal reasons, another 10 (colchicine 3 and control 7; 14%) died
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Nidorf 2013

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Open trial, observer-blinded endpoint **Longest mean follow-up period for a review-relevant outcome:** 3 years
Participants	**Number randomised:** Total 532. Colchicine 282, control 250 **Condition:** Stable coronary disease **Cardiovascular risk profile:** Secondary prevention **Setting:** Outpatient **Country:** Australia **Age mean (SD) in years:** Colchicine 66 (9.6), control 67 (9.2) **Sex (women):** Colchicine 11%, control 11% **Inclusion criteria:** "Patients were eligible for inclusion if they met each of the following criteria: 1) angiographically proven coronary disease; 2) age 35 to 85 years; 3) clinically stable for at least 6 months; 4) no major competing comorbidities or contraindication to colchicine therapy; 5) considered to be compliant with therapy and attending routine cardiology follow-up appointments; and 6) willing to

Nidorf 2013 *(Continued)*

	provide consent and be randomized into the study. Patients with a history of bypass surgery were only eligible if they had undergone bypass surgery more than 10 years before, had angiographic evidence of graft failure, or had undergone stenting since their bypass surgery." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 0.5 mg/d • Duration: 3 years **Control:** • No placebo • Duration: 3 years
Outcomes	**Primary outcome of the study:** • Composite incidence of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischaemic stroke **Outcomes considered in this review:** • Fatal and non-fatal myocardial infarction, cardiovascular mortality, fatal and non-fatal stroke, all-cause mortality
Notes	93% of the participants continued with aspirin and/or clopidogrel and 95% continued with statins; "Patients (N=32) who were intolerant of therapy remained in the study, were followed in the usual manner, and were included in the primary ITT analysis"; Trial "conducted under the auspices of the Heart Research Institute of Western Australia." "There was no external funding source."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was computer-generated
Allocation concealment (selection bias)	Low risk	Concealed from the investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observer-blinded outcome trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT: "All patients who received at least 1 dose of study treatment were included in the analysis"; ≤ 10% missing data per group that were excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Nikolaidis 2006

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Not reported **Longest mean follow-up period for a review-relevant outcome:** 12 months
Participants	**Number randomised:** Total 38. Colchicine 21, control 17 **Condition:** Liver cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Greece **Age median (SD) in years:** Colchicine 49 (not reported), control 53 (not reported) **Sex (women):** Colchicine 43%, control 35% **Inclusion criteria:** Chronic liver disease **Exclusion criteria:** "Patients were excluded from the study if they had: age <20 and >70 years, evidence of pregnancy, malignancies or renal, cardiopulmonary, hematological, neurological and collagen diseases, diabetes mellitus, hyper/hypothyroidism or Child C liver function."
Interventions	**Colchicine:** • Dose: 1.0 mg/d, 5d/week • Duration: at least 12 months **Control:** • No antifibrotic treatment • Duration: at least 12 months
Outcomes	**Primary outcome of the study:** • Biochemical parameters; PIIINP, IgA, IgG, IgM, CD4, CD 8, CD 4 **Outcomes considered in this review:** • Adverse events (any), gastrointestinal adverse events
Notes	Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Method of concealment not specified
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Nikolaidis 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Liver tissue samples were evaluated by two pathologists (K.P., M.L.) who were blinded to the treatment groups and to response to treatment." However, we did not look into liver outcomes, so the blinding remains unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear, no dropouts reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

O'Keefe 1992

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 months
Participants	**Number randomised:** Total 197. Colchicine 130, control 67 **Condition:** Coronary angioplasty **Cardiovascular risk profile:** Secondary prevention **Setting:** Outpatient **Country:** USA **Age mean (SD) in years:** Colchicine 59 (not reported), control 62 (not reported) **Sex (women):** Colchicine 15%, control 13% **Inclusion criteria:** "Elegibility criteria for entry into the trial were 1) successful elective coronary angioplasty; 2) single or multivessel angioplasty; 3) bypass graft angioplasty; 4) angioplasty of previously undiluted (new) and restenosed lesions; 5) angioplasty performed for silent ischemia and stable or unstable angina pectoris" **Exclusion criteria:** "Exclusion criteria were 1) direct angioplasty for acute myocardial infarction; 2) unsuccessful coronary angioplasty; 3) premenopausal women; 4) baseline leukopenia; 5) active peptic ulcer disease; 6) active diarrhea; 7) creatinine ≥2.5 mg/dl at baseline; 8) known colchicine intolerance. Successful angioplasty was defined as the reduction of the dilated lesion to ≤50% lumen diameter stenosis without documented acute reocclusion during the hospital stay."
Interventions	**Colchicine:** • Dose: 2 x 0.6 mg/d • Duration: 6 months **Control:** • Placebo • Duration: 6 months
Outcomes	**Primary outcome of the study:**

O'Keefe 1992 *(Continued)*

	• Restenosis after coronary angioplasty **Outcomes considered in this review:** • All-cause mortality
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT analysis reported, incomplete outcome measures (angiographic follow-up rate 74%) mainly due to refusal of catheterisation, reported dropout rate due to adverse events, Colchicine 6.9% vs control 1.5%
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Olsson 1995

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre (7 centres) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 3 years
Participants	**Number randomised:** Total 84. Colchicine 44, control 40 **Condition:** Primary sclerosing cholangitis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Sweden **Age mean (95% CI) in years:** Colchicine 39.5 (36.2 to 42.7), control 43.7 (40.1 to 47.3) **Sex (women):** Colchicine 39%, control 28% **Inclusion criteria:** Diagnosis of PSC based on typical cholangiographic appearance

Olsson 1995 *(Continued)*

	Exclusion criteria: Not reported
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: 3 years **Control:** • Placebo • Duration: 3 years
Outcomes	**Primary outcome of the study:** • All-cause mortality or liver transplantation **Outcomes considered in this review:** • All-cause mortality
Notes	"Supported by G. D. Searle Ltd."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not sufficiently specified ("randomization procedure was performed for each center using the sealed envelope technique")
Allocation concealment (selection bias)	Unclear risk	Not sufficiently specified ("sealed envelope technique")
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT; dropout colchicine 18% vs control 5%, overall 12%
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Parise 1995

Study characteristics

Methods	**Design:** Randomised controlled trial, single centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 1 year

Parise 1995 *(Continued)*

Participants	**Number randomised:** Total 41. Colchicine 21, control 20 **Condition:** Alcoholic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Brazil **Age mean (SD) in years:** Colchicine 49.2 (9.9), control 47.8 (9.8) **Sex (women):** Colchicine 10%, control 14% **Inclusion criteria:** Chronic liver disease (confirmed by biopsy and/or ultrasound, endoscopy and clinical findings) due to alcohol abuse (alcoholic cirrhosis) **Exclusion criteria:** Hepatitis B confirmed by laboratory exams; any previous history of post-transfusion hepatitis; alcoholic hepatitis; heart failure; renal failure; schistosomiasis (bilharzia); gastric bleeding during the last 30 days before the study start; advanced hepatic encephalopathy; refractory ascites; hepatorenal syndrome; type-II diabetes; use of corticosteroids or sexual hormones
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: 1 year **Control:** • Placebo • Duration: 1 year
Outcomes	**Primary outcome of the study:** • Improvement in serum albumin, pre-albumin, prothrombin and transferrin levels **Outcomes considered in this review:** • All-cause mortality, cardiovascular mortality, myocardial infarction (fatal), stroke (fatal), heart failure (fatal)
Notes	Study published in Portuguese. The study was funded by Smith-Kline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information is given. The authors state that the a stratified randomisation was “applied”, but no detail is provided on how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias)	Unclear risk	No information given

Parise 1995 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 3 participants lost during the 12-month follow-up (table 2, “perdas deseguimento”/ translation: “loss of follow-up“): 1 from the colchicine group and 2 from the placebo group. Those participants were included in the final assessment regarding alcohol relapse, all-cause mortality and hepatic decompensation. Those losses are unlikely to have significant effects on the results.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Paulus 1974

Study characteristics	
Methods	**Design:** Randomised controlled trial, multicentre (2 centres) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 months
Participants	**Number randomised:** Total 52. Colchicine 29, control 23 **Condition:** Gout **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** USA **Age mean (SD) in years:** Colchicine 53 (not reported), control 52 (not reported) **Sex (women):** 0% **Inclusion criteria:** "Diagnosis of gout in presence of hyperuricaemia. Patients were selected from the Gout Clinics of the Veterans Administration Hospitals in West Los Angeles and Kansas City, and the UCLA and University of Kansas Medical Center Hospitals." **Exclusion criteria:** "Patients were excluded if they were known to be uncooperative during treatment or if significant renal disease was present as reflected in a serum creatinine greater than 1.2 mg/100ml."
Interventions	**Colchicine:** • Dose: 3 x 0.5 mg/d • Plus probenecid 1500 mg/d • Duration: 6 months **Control:** • Placebo plus probenecid 1500 mg/d • Duration: 6 months
Outcomes	**Primary outcome of the study:** • Episodes of acute recurrent gout **Outcomes considered in this review:**

Paulus 1974 *(Continued)*

	• Adverse events (any), gastrointestinal adverse events
Notes	Mean therapy duration < 6 months: colchicine 5.5 months and control 5.2 months. "Supported by the Veterans Administration, Southern California Arthritis Foundation, Merck Sharpe and Dohme and USPHS Grant GM 15759."; "Merck Sharpe and Dohme Research Laboratories, West Point, Pennsylvania, who kindly provided the colchicine used in this study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout: colchicine 31% and control 22%; per protocol analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Poupon 1996

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre (10 centres) **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 74. Colchicine 37, control 37 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** France **Age mean (SE) in years:** Colchicine 55 (2), control 52 (2) **Sex (women):** Colchicine 89%, control 81% **Inclusion criteria:** "Criteria for entry to the trial were persistent abnormalities in liver function tests, in particular serum alkaline phosphatase activity of >1.5N (N is the upper limit of normal values), in

Poupon 1996 *(Continued)*

	patients with PBC who have been previously treated with UDCA (13-15 mg/kg^{-1}/d^{-1}) for at least 8 months. All patients had biopsy-proven PBC. They were admitted to the trial regardless of the duration of symptoms or the histological stage." **Exclusion criteria:** "drug therapy (except UDCA) for PBC during the previous 6 months (colchicine, azathioprine, chlorambucil, corticosteroids, D-penicillamine, and cyclosporine); serum bilirubin concentration of >100 µmol/L; a serum albumin concentration of >25 g/L; past or active bleeding from esophageal varices; ascites; other identified causes of liver or biliary diseases; excessive alcohol consumption (>50 g/d); severe intercurrent disease; and aged older than 75 years."
Interventions	**Colchicine:** • Dose: 1 mg/d, 5 d/week • Plus 13 - 15 mg/kilo/d of ursodeoxycholic acid in 2 doses • Duration: 2 years **Control:** • Dose: Placebo, 5 d/week plus 13 - 15 mg/kilo/d of ursodeoxycholic acid in 2 doses • Duration: 2 years
Outcomes	**Primary outcome of the study:** • Efficacy of UDCA and colchicine in participants with non-advanced primary biliary cirrhosis **Outcomes considered in this review:** • All-cause mortality
Notes	"Supported in part by Laboratoires Houde´ (France) and Jouveinal (Canada)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, for liver biopsy "assessed by two pathologists unaware of the [...] treatment", no other blindings of assessment specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT; missing data not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Raedsch 1992

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 24 months
Participants	**Number randomised:** Total 28. Colchicine 14, control 14 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Not reported **Country:** Germany **Age mean (range) in years:** Colchicine + control 54 years (37 - 71) **Sex (women):** 100% **Inclusion criteria: Women** with primary biliary cirrhosis. "Initially all patients received monotherapy with UDCA in a dose of 10-12 mg/kg per day for 12 months." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 1 mg/d • Plus ursodeoxycholic acid 10 - 12 mg/kg/d • Duration: 24 months **Control:** • Placebo and ursodeoxycholic acid 10 - 12 mg/kg/d • Duration: 24 months
Outcomes	**Primary outcome of the study:** • "Haematology, aminotransferases, alkaline phosphatase, bilirubin, IgM,antimitochondrial antibodies, cholesterol, procollagen-type III-peptide(P-III-P) and clinical symptoms were monitored every 3 months." **Outcomes considered in this review:** • Adverse events (any), serious adverse events, gastrointestinal adverse events
Notes	Initially all participants received monotherapy with UDCA in a dose of 10 - 12 mg/kg/d for 12 months. After this period the treatment was continued in a randomised fashion with UDCA plus placebo or UCDA plus colchicine. Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not specified

Raedsch 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blinded; placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear; 2 participants were excluded (7%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Reinhardt 1986

Study characteristics	
Methods	**Design:** Randomised controlled trial, single centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 3 years
Participants	**Number randomised:** Total 74. Colchicine 37, control 37 **Condition:** Liver fibrosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Germany **Age:** Not reported **Sex (women):** Not reported **Inclusion criteria:** Liver fibrosis or cirrhosis. **Exclusion criteria:** Participants were excluded if they had episodes of gastrointestinal bleedings, hepatic encephalopathy in the last two 2 weeks, bilirubin-levels > 2 mg %, 34 µmol/l respectively, because of noncompliance, non-hepatic diseases which change the biochemical parameters of the metabolism of the connective tissue, and the inability to asses the histological process
Interventions	**Colchicine:** • Dose: 4 x 0.25 mg/d, 5d/week • Duration: 3 years **Control:** • Placebo • Duration: 3 years
Outcomes	**Primary outcome of the study:**

Reinhardt 1986 *(Continued)*

	• Clinical results, paraclinical data, concerning hepatological diagnostic and connective tissue metabolism and morphologic data **Outcomes considered in this review:** • All-cause mortality
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 of 74 individuals lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Trinchet 1989

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 6 months
Participants	**Number randomised:** Total 67. Colchicine 33, control 34 **Condition:** Alcoholic cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Belgium **Age mean (SD) in years:** Colchicine 52 (8), control 52 (9) **Sex (women):** Colchicine 36%, control 50%

Trinchet 1989 *(Continued)*

	Inclusion criteria: "Alcoholic patients with histologically proven Alcoholic cirrhosis assessed by percutaneous liver biopsy, with or without cirrhosis, were consecutively included in the study." **Exclusion criteria:** "Patients were not included in case of hepatic encephalopathy, presence of ascites, prothrombin activity below 50 per cent or platelet count below 100.10^9/l, hepatocellular carcinoma, evident lack of compliance or refusal to participate in the trial."
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: 6 months **Control:** • Placebo • Duration: 6 months
Outcomes	**Primary outcome of the study:** • Change in alcoholic hepatitis score **Outcomes considered in this review:** • All-cause mortality
Notes	Houdé Pharmaceutical Laboratories, Paris, France, supplied colchicine and placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified (sealed envelopes, but not opaque)
Allocation concealment (selection bias)	Unclear risk	Details of concealment not sufficiently specified ("sealed envelopes")
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis unclear; dropouts 48.5% vs 52.9% at 6 months
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Vuoristo 1995

Study characteristics

Methods	**Design:** Randomised controlled trial, multicentre

Vuoristo 1995 *(Continued)*

	Blinding: Double-blind **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 90. Colchicine 29, placebo 31 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Finland **Age mean in years:** Colchicine 56, placebo 57 **Sex: (women):** Colchicine 86%, placebo 87% **Inclusion criteria:** "Criteria for entry into the trial were elevated serum alkaline phosphatase activity, liver biopsy findings diagnostic of or compatible with PBC, and a positive result for serum mitochondrial antibodies. In patients fulfilling the above criteria but negative for antimitochondrial antibodies, other potential causes of liver disease were excluded, and the patency of the bile ducts was evaluated by endoscopic retrograde cholangiography. All patients tested negative for hepatitis B surface antigen and for hepatitis C antibodies." **Exclusion criteria:** "Patients with endstage PBC and those who used drugs that might affect the course of PBC were excluded from the study. Thus, patients whose serum bilirubin level was >150 btmol/L, serum albumin level was <25 g/L, or TT-SPA (thrombotest) was <50% in two successive determinations were excluded, as were patients with drug-resistant ascites and those in whom liver transplantation was indicated. None of the patients had used colchicine, UDCA, D-penicillamine, or immunosuppressive drugs (corticosteroids, azathioprine, cyclosporin A, methotrexate) for 6 months before the trial. "
Interventions	**Colchicine:** • Dose: 2 x 0.5 mg/d • Duration: 2 years **Control:** • Placebo • Duration: 2 years
Outcomes	**Primary outcome of the study:** • "Deaths; the absence or presence (intermittent or continuous) of pruritus, fatigue, or anorexia; and adverse effects of the drugs were evaluated." **Outcomes considered in this review:** • All-cause mortality, cardiovascular mortality, myocardial infarction
Notes	Third study group receiving UDCA (n = 30) not relevant for this review and thus not extracted. "Supported by grants from the Finnish Foundation for Gastroenterological Research and the Mary and Georg C. Ehrnrooth Foundation. Leiras Oy, Finland, supplied the drugs for this study and financial support."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified, "using consecutive case numbers"

Vuoristo 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported specifically enough (sequential numbers)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT mentioned, data analysis unclear. Dropouts: colchicine 17%, control 26%, UDCA 0%
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Wang 1994

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** median 26 months
Participants	**Number randomised:** Total 100. Colchicine 50, control 50 **Condition:** Chronic hepatitis B **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Taiwan **Age mean (SD) in years:** Colchicine 60 (not reported), control 59 (not reported) **Sex (women):** Colchicine 6%, control 6% **Inclusion criteria:** People with HBsAg-positive cirrhosis **Exclusion criteria:** "Patients were excluded if they had end-stage liver cirrhosis (serum albumin level below 25 g/l or total bilirubin level above 171 µmol/l), episodes of variceal bleeding, or hepatic encephalopathy within 2 weeks before recruitment into this trial, a concomitant debilitating illness, or if they were unable to attend the clinic regularly."
Interventions	**Colchicine:** • Dose: 1 mg/d • Duration: median: 26 months (range 15 - 51 months) **Control:** • Placebo • Duration: median: 26 months (range 15 - 51 months)

Wang 1994 *(Continued)*

Outcomes	**Primary outcome of the study:** • Mortality **Outcomes considered in this review:** • All-cause mortality
Notes	"supported by grant NSC No. 82-0412-B075-027 from the National Science Council, Republic of China."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random numbers were computer generated and arranged in numerical order and divided in two."
Allocation concealment (selection bias)	Low risk	"a nurse [...] prepared coded supplies of colchicine or placebo according to the random numbers for the staff physicians and each patient at entry and every follow-up"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled. "Neither the patients nor the physicians knew which treatment was given."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis unclear; missing data 9%, but unclear how allocated to the groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Warnes 1987

Study characteristics

Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 18 months
Participants	**Number randomised:** Total 64. Colchicine 34, placebo 30 **Condition:** Primary biliary cirrhosis **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** UK **Age:** Not reported

Warnes 1987 *(Continued)*

	Sex (women): Not reported **Inclusion criteria:** "All patients gave their informed consent and the study was approved by the hospital ethical committee. At entry, 48% of patients had 'classical PBC' with pruritus followed by jaundice, whilst the other 52% had few, if any, symptoms directly referrable to the disease. All patients in the study had a raised serum alkaline phosphatase, a positive anti-mitochondrial antibody test, and liver histology compatible with, or diagnostic of, PBC." **Exclusion criteria:** Not reported
Interventions	**Colchicine:** • Dose: 2 x 0.5 mg/d • Duration: 23 months (range 0.6 - 49.6) **Control:** • Placebo • Duration: 15 months (range 0.9 - 51.5)
Outcomes	**Primary outcome of the study:** • All-cause mortality **Outcomes considered in this review:** • All-cause mortality
Notes	Survival data is reported for 12 and 18 months. Dropouts reported until 12 months. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The first patient in any pair was allocated by the staff pharmacist to the treatment or placebo group by reference to random tables."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT for survival data. 16% participants dropped out within 12 months (colchicine 24%, control 7%), but were available for survival analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Yurdakul 2001

Study characteristics	
Methods	**Design:** Randomised controlled trial, single-centre **Blinding:** Double-blind **Longest mean follow-up period for a review-relevant outcome:** 2 years
Participants	**Number randomised:** Total 116. Colchicine 58. Control 58. **Condition:** Behçet's syndrome **Cardiovascular risk profile:** Not reported **Setting:** Outpatient **Country:** Turkey **Age mean (SD) in years:** Women:cColchicine 26.7 (4.8), control 27.2 (5.5). Men: colchicine 27.0 (5.5), control 27.3 (5.3) **Sex (women):** Colchicine 47%, control 47% **Inclusion criteria:** "All patients were required to meet the inclusion criteria, which meant that they had to 1) be consecutive patients (male or female), 2) be 18–35 years of age, 3) have active disease, 4) have a disease duration of ≤2 years, and 5) live at a reasonable traveling distance from our center. Active disease was defined as the minimum presence of oral or genital ulceration or erythema nodosum occurring at least 3 times within the preceding 6 months. The disease duration was defined as the time that had elapsed since the diagnostic criteria had been fulfilled." **Exclusion criteria:** "We excluded patients who 1) had received immunosuppressive agents, steroids, or colchicine within the preceding 6 months, 2) had organ involvement requiring immunosuppression, or 3) had eye disease, especially with retinal involvement, during the recruitment period. However, patients who had only a few cells in vitreous body were included if their visual acuity was >9/10 (assessed on a 10-line scale, with a best vision of 10/10). Patients were to be withdrawn from the study in the event of a major systemic or life-threatening manifestation such as severe eye, major vein, or central nervous system involvement."
Interventions	**Colchicine:** • Dose: colchicine 1 - 2 mg/d daily, adjusted to body weight • Duration: 2 years **Control:** • Dose: placebo daily, adjusted to body weight • Duration: 2 years
Outcomes	**Primary outcome of the study:** • Sustained absence of any lesions during treatment **Outcomes considered in this review:** • Gastrointestinal adverse events; from author request: mortality cardiovascular, stroke fatal/non-fatal, myocardial infarction fatal/non-fatal, heart failure fatal/non-fatal
Notes	"Supported by TUBITAK (Turkish Scientific and Technical Research Council; TAG 0754) and, in part, by the Research Fund of the University of Istanbul."
Risk of bias	

Yurdakul 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was done separately for each sex. In each sex group, equal numbers of cards that were assigned to either the active drug or the placebo arm were mixed, drawn, and placed sequentially on a list by a secretary not involved in running the trial."
Allocation concealment (selection bias)	Low risk	Sealed envelopes were not stated as opaque in the publication; from author request: "The sealed envelop was really opaque but was forgotten to mention in the paper."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported in publication; from author request: "Here all patients and physicians were blinded and as well as the outcome assessment."
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT; 27% did not complete month 24, but "There were no differences in the number of dropouts or reasons for withdrawal (Figure 1) between the 2 treatment arms."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

HCC: hepatocellular carcinoma
HCV: hepatitis C virus
ITT: intention-to-treat
PCI: Percutaneous coronary intervention
PP: per protocol
PSC: Primary Sclerosing Cholangitis
UDCA: ursodeoxycholic acid

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

Study	Reason for exclusion
Afdhal 2002	Other publications of this study available; this publication provides no additional information
Afdhal 2004	Other publications of this study available; this publication provides no additional information
Ahern 1986	Duration of follow-up or treatment was too short
Ahern 1987	Duration of follow-up or treatment was too short
Ahmad 2011	Duration of follow-up or treatment was too short
Ahmadieh 2014	Duration of follow-up or treatment was too short
Akriviadis 1988	Duration of follow-up or treatment was too short
Aktulga 1980	No pertinent outcome reported at all

Study	Reason for exclusion
Albillos 2013	No pertinent outcome reported at all
Alsahaf 2010	No pertinent outcome reported at all
Angelico 1998	Duration of follow-up or treatment was too short
Angelico 2000	There are outcomes but reported in an uninterpretable way
Anonymous 2014	Not an RCT
Antoniou 2003	Other publications of this study available; this publication provides no additional information
Antoniou 2004	No pertinent outcome reported at all
Aran 2011	Duration of follow-up or treatment was too short
Basak 1993	Duration of follow-up or treatment was too short
Bhuiyan 2010	Duration of follow-up or treatment was too short
Bodenheimer 1986	Other publications of this study available; this publication provides no additional information
Brucato 2011	Other publications of this study available; this publication provides no additional information
Buligescu 1990	Other publications of this study available; this publication provides no additional information
Cacciatore 2014	Duration of follow-up or treatment was too short
Campollo 2001	No pertinent outcome reported at all
Cetin 2013	Study was not an RCT
Coatney 1949	Duration of follow-up or treatment was too short
Cohen 1991	Duration of follow-up or treatment was too short
Collins 1991	Study was not conducted in adults
Cortez Pinto 1992	No pertinent outcome reported at all
Cortez Pinto 1994	Other publications of this study available; this publication provides no additional information
Cortez Pinto 2000	Other publications of this study available; this publication provides no additional information
Cumetti 2012	Other publications of this study available; this publication provides no additional information
Davatchi 2009	Duration of follow-up or treatment was too short
De Abreu 2009	There are outcomes but reported in an uninterpretable way
De Maria 1996	There are outcomes but reported in an uninterpretable way
Deftereos 2014b	Duration of follow-up or treatment was too short
Dinarello 1974	Duration of follow-up or treatment was too short

Study	Reason for exclusion
Dinarello 1976	Study was not an RCT
Ediz 2012	No pertinent outcome reported at all
El-Sherif 1999	Duration of follow-up or treatment was too short
El-Zahaar 1995	Duration of follow-up or treatment was too short
English 1983	Duration of follow-up or treatment was too short
Erden 2011	No pertinent outcome reported at all
Filipowicz-Sosnowska 1990	There are outcomes but reported in an uninterpretable way
Fish 1997	Duration of follow-up or treatment was too short
Floreani 2001	No pertinent outcome reported at all
Frayha 1979	No pertinent outcome reported at all
Gianni 2012	Study was not an RCT
Giudice 1988	Study was not an RCT
Goddard 1995	No pertinent outcome reported at all
Goldfinger 2014	Study was not an RCT
Goldstein 1974	Duration of follow-up or treatment was too short
Goulet 2001	Duration of follow-up or treatment was too short
Grimaitre 1999	Duration of follow-up or treatment was too short
Gultepe 1994	No pertinent outcome reported at all
Hadzic 2005	Study was not conducted in adults
Hamuryudan 2010a	Study was not an RCT
Hamuryudan 2010b	Study was not an RCT
Hamuryudan 2011	No pertinent outcome reported at all
Hamuryudan 2014	No pertinent outcome reported at all
Hatziioannidou 1992	Study was not conducted in adults
Huet 1996a	No pertinent outcome reported at all
Huet 1996b	No pertinent outcome reported at all
Imazio 2003	Duration of follow-up or treatment was too short
Imazio 2005	Duration of follow-up or treatment was too short

Study	Reason for exclusion
Imazio 2010	Duration of follow-up or treatment was too short
Imazio 2011a	Duration of follow-up or treatment was too short
Imazio 2011b	Duration of follow-up or treatment was too short
Imazio 2011c	Duration of follow-up or treatment was too short
Imazio 2011d	Duration of follow-up or treatment was too short
Imazio 2011e	Duration of follow-up or treatment was too short
Imazio 2012a	Duration of follow-up or treatment was too short
Imazio 2012b	Other publications of this study available; this publication provides no additional information
Imazio 2013	Duration of follow-up or treatment was too short
Imazio 2014a	Database duplicate
Imazio 2014b	Duration of follow-up or treatment was too short
Iona 2014	Other publications of this study available; this publication provides no additional information
Jones 2000	Study was not an RCT
Judkins 2011	Duration of follow-up or treatment was too short
Kaplan 1985	Other publications of this study available; this publication provides no additional information
Kaplan 1987	Other publications of this study available; this publication provides no additional information
Kaplan 1993	Other publications of this study available; this publication provides no additional information
Kar 1988	Colchicine not part of the treatment
Karaaslan 2014	Study was not an RCT
Kelly 1995	Duration of follow-up or treatment was too short
Kershenobich 1979	Duration of follow-up or treatment was too short
Kershenobich 1980	No pertinent outcome reported at all
Kisand 1996	Duration of follow-up or treatment was too short
Koyuncu 2009	Duration of follow-up or treatment was too short
Kulkarni 2014	Study was not an RCT
Kyle 1990	Duration of follow-up or treatment was too short
Lenior 2001	Study was not conducted in adults
Leung 2010	Study was not an RCT

Study	Reason for exclusion
Leung 2011	Study was not an RCT
Liu 2002	Duration of follow-up or treatment was too short
Lu 2014	Study was not an RCT
Luo 2001	Duration of follow-up or treatment was too short
Maestroni 2011	No pertinent outcome reported at all
Maestroni 2013	Duration of follow-up or treatment was too short
Maestroni 2014	Other publications of this study available; this publication provides no additional information
Mann 2014	Study was not an RCT
Masuda 1989	Duration of follow-up or treatment was too short
Meek 1984	Duration of follow-up or treatment was too short
Meek 1985	Duration of follow-up or treatment was too short
Meek 1990	Duration of follow-up or treatment was too short
Miettinen 1993	No pertinent outcome reported at all
Miettinen 1995	No pertinent outcome reported at all
Mimura 2009	Study was not an RCT
Mingxing 1983	Study was not an RCT
Moon 2011	Duration of follow-up or treatment was too short
NCT00004748	No pertinent outcome reported at all
Nidorf 2012	There are outcomes but reported in an uninterpretable way
Ozcelik 2014	Study was not an RCT
Podda 1993	Other publications of this study available; this publication provides no additional information
Poupon 1994	Other publications of this study available; this publication provides no additional information
Prieto 2003	No pertinent outcome reported at all
Raedsch 1991a	No pertinent outcome reported at all
Raedsch 1991b	No pertinent outcome reported at all
Raedsch 1992b	No pertinent outcome reported at all
Rask 1989	Study was not an RCT
Roche 1995	Duration of follow-up or treatment was too short

Study	Reason for exclusion
Rockey 2006	Study was not an RCT
Rubinow 1981	Study was not an RCT
Ruhe 1949	Duration of follow-up or treatment was too short
Rutecki 2006	Duration of follow-up or treatment was too short
Sainz 1992	No pertinent outcome reported at all
Sais 1995a	Duration of follow-up or treatment was too short
Schlesinger 2010a	Duration of follow-up or treatment was too short
Schlesinger 2010b	Duration of follow-up or treatment was too short
Schlesinger 2011a	Duration of follow-up or treatment was too short
Schlesinger 2011b	Duration of follow-up or treatment was too short
Schlesinger 2011c	Duration of follow-up or treatment was too short
Schwarz 1990	Duration of follow-up or treatment was too short
Sernet-Gaudelus 2001	Study was not conducted in adults
Simmons 1990	Duration of follow-up or treatment was too short
So 2010	Duration of follow-up or treatment was too short
Srivastava 2013	No pertinent outcome reported at all
Stamato 2006	Duration of follow-up or treatment was too short
Trande 1996	No pertinent outcome reported at all
Trinchet 1983	Duration of follow-up or treatment was too short
Trinchet 1985	Other publications of this study available; this publication provides no additional information
Tzvetkova 1990	Study was not an RCT
Vetter 2014	Other publications of this study available; this publication provides no additional information
Wallace 1967	Study was not an RCT
Wang 1992	Other publications of this study available; this publication provides no additional information
Wang 2014	Duration of follow-up or treatment was too short
Warnes 1984	Other publications of this study available; this publication provides no additional information
Warnes 1985	Other publications of this study available; this publication provides no additional information
Wolff 1974	Duration of follow-up or treatment was too short

Study	Reason for exclusion
Wright 1975	Duration of follow-up or treatment was too short
Wu 1995	Study was not an RCT
Wu 2014	No pertinent outcome at all
Xu 1999	Duration of follow-up or treatment was too short
Yang 2010	Study was not an RCT
Zemer 1974	Duration of follow-up or treatment was too short
Zifroni 1991	All participants receive colchicine

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

Sais 1995b

Methods	N/A
Participants	N/A
Interventions	N/A
Outcomes	N/A
Notes	There is neither abstract nor full-text available for this reference.

None

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

ACTRN12614000093684

Study name	LoDoCo2
Methods	Double-blind, randomised trial
Participants	Coronary heart disease
Interventions	Colchicine (0.5 mg/d) vs placebo Treatment duration (colchicine): 3 - 4 years
Outcomes	Primary outcome: Time to first occurrence of either non-fatal myocardial infarction, unstable angina, non-cardio-embolic ischaemic stroke or fatal or non-fatal out-of-hospital cardiac arrest; minimum of 3 years follow-up for each individual, estimated median follow-up of 4 years and a maximum follow-up of 4 to 5 years (information through personal communication with the principal investigator who is also author of this review (MN)). Secondary outcome: Time to first occurrence of either non-fatal myocardial infarction or episode of unstable angina, unrelated to stent disease; other cardiovascular endpoints including new onset atrial fibrillation, deep vein thrombosis, pulmonary embolism as evidenced from the participant record; safety measures including rate of intolerance or serious adverse events including rhab-

ACTRN12614000093684 *(Continued)*

	domyolysis as evidenced by the participant records. Rhabdomyolysis determined by acute onset of severe myonecrosis evident by marked elevation in serum creatinine kinase
Starting date	February 2014
Contact information	Mark Nidorf, MD, +61 413145410, smnidorf@gmail.com
Notes	ACTRN12614000093684

IRCT138807112539N1

Study name	IRCT138807112539N1
Methods	Double-blind, randomised trial
Participants	Chronic hepatitis B
Interventions	Lamivudine + colchicine (0.5 mg/d) vs lamivudine + placebo Treatment duration (colchicine): 6 months
Outcomes	Treatment of chronic hepatitis B. time point: 1 month before intervention and 1 month after intervention. Method of measurement: laboratory measurement of serum ALT- Albumin-bilirubin and PT
Starting date	July 2009
Contact information	Amir Hassanpour, MD, +988614173608, +989166134349, +988614173630, drhassanpor@arak-mu.ac.ir
Notes	IRCT138807112539N1

NCT01906749

Study name	COACS
Methods	Multicentre, double-blind, randomised trial
Participants	Acute coronary syndrome
Interventions	Colchicine (0.5 mg/d) vs placebo Treatment duration (colchicine): 24 months
Outcomes	Primary outcome: Combined endpoint (all-cause mortality, new acute coronary syndrome, and ischaemic stroke); at 24 months Secondary outcomes: Each of the combined outcome separately at 24 months
Starting date	June 2013
Contact information	Massimo Imazio, MD +39011439 ext 3391 massimo_imazio@yahoo.it
Notes	NCT01906749

NCT02035891

Study name	CQMU-2013-QLi
Methods	Double-blind, randomised trial
Participants	Type 2 diabetes mellitus and microalbuminuria
Interventions	Colchicine (0.5 mg/d) vs placebo Treatment duration (colchicine): unclear
Outcomes	Primary outcome: changes in UACR from baseline to the 6th month; changes in CIMT from baseline to the 18th month; incidence of overt nephropathy;composite cardiovascular events Secondary outcome: Changes in 24 h urinary albumin; proportion of participants achieving at least a 15% reduction in UACR; changes in estimated glomerular filtration rate (eGFR); new or worsening diabetic neuropathy; new or worsening diabetic retinopathy; death from any cause; each component of primary outcomes of phase 4; overt nephropathy; new or worsening diabetic neuropathy; new or worsening diabetic retinopathy
Starting date	December 2013
Contact information	Qifu Li, First Affiliated Hospital of Chongqing Medical University
Notes	NCT02035891

NCT02162303

Study name	COLPET
Methods	Double-blind, randomised trial
Participants	Atherosclerotic vascular disease
Interventions	Colchicine (0.6 mg/d) vs placebo Treatment duration (colchicine): 6 months
Outcomes	Primary outcome: Change in the average of maximum target-to-background (TBR) values (mean MAX TBR) of the ascending aorta; participants will be followed over a period of 6 months Secondary outcome: Change in the mean maximum target-to-background (Mean MAX TBR) of carotid arteries; change in the average of the mean TBR values; change in the most diseased segment TBR values (MDS TBR) in the carotid arteries and ascending aorta; change in soluble biomarkers of inflammation
Starting date	May 2014
Contact information	Jean-Claude Tardif, MD Montreal Heart Institute
Notes	NCT02162303

DATA AND ANALYSES

Comparison 1. Colchicine vs control

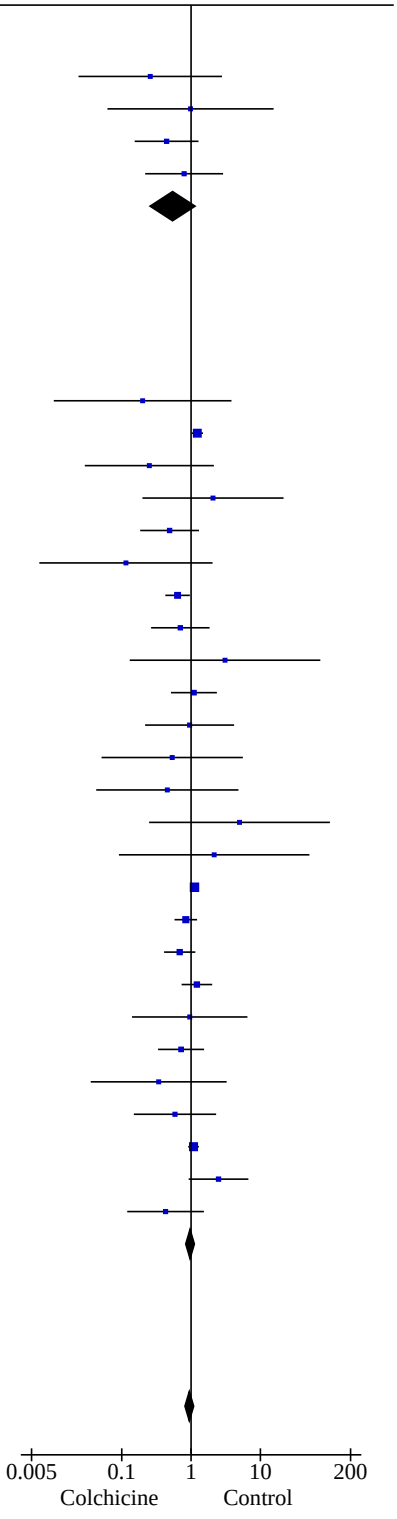
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
1.1.1 Participants with high cardiovascular risk	4	1230	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.26, 1.14]
1.1.2 Other	26	2944	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.12]
1.2 Myocardial infarction (total)	2	652	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.57]
1.2.1 Participants with high cardiovascular risk	1	532	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.57]
1.2.2 Other	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Myocardial infarction (non-fatal)	2	652	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.07, 0.61]
1.3.1 Participants with high cardiovascular risk	1	532	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.07, 0.61]
1.3.2 Other	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Myocardial Infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
1.4.1 Participants with high cardiovascular risk	1	532	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 6.04]
1.4.2 Other	5	378	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.47]
1.5 Adverse event (serious)	4	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5.1 Participants with high cardiovascular risk	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5.2 Other	4	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.6 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
1.6.1 Participants with high cardiovascular risk	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6.2 Other	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
1.7 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Participants with high cardiovascular risk	2	501	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.43, 4.06]
1.7.2 Other	9	757	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.82, 3.02]
1.8 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
1.8.1 Participants with high cardiovascular risk	2	754	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.02, 2.66]
1.8.2 Other	5	378	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.09, 3.32]
1.9 Stroke (total)	3	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.09, 1.70]
1.9.1 Participants with high cardiovascular risk	2	754	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.09, 1.70]
1.9.2 Other	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.10 Stroke (fatal)	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.10.1 Participants with high cardiovascular risk	2	754	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.85]
1.10.2 Other	2	161	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.11 Stroke (non-fatal)	3	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.17]
1.11.1 Participants with high cardiovascular risk	2	754	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.17]
1.11.2 Other	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.12 Heart failure (total)	3	426	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.10, 3.88]
1.12.1 Participants with high cardiovascular risk	1	222	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.69]
1.12.2 Other	2	204	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.46, 2.51]
1.13 Heart failure (fatal)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.13.1 Participants with high cardiovascular risk	1	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
1.13.2 Other	2	161	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Heart failure (non-fatal)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.14.1 Participants with high cardiovascular risk	1	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.12]
1.14.2 Other	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.15 Non-scheduled hospitalisation (total)	2	599	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
1.15.1 Participants with high cardiovascular risk	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.15.2 Other	2	599	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
1.16 Non-scheduled cardiovascular interventions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.16.1 Participants with high cardiovascular risk	1	222	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.85]
1.16.2 Other	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

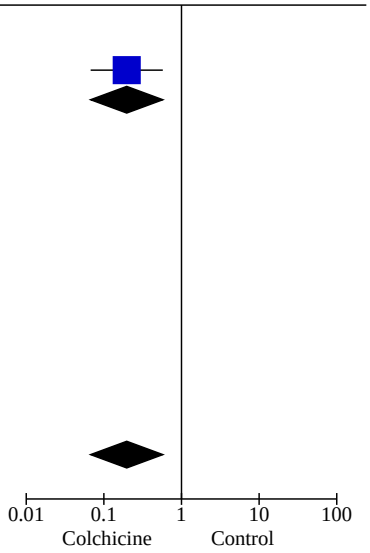
Analysis 1.1. Comparison 1: Colchicine vs control, Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Participants with high cardiovascular risk						
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**664**		**566**	**3.5%**	**0.54 [0.26 , 1.14]**
Total events:	11		18			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 3 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.1.2 Other						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Subtotal (95% CI)		**1487**		**1457**	**96.5%**	**0.97 [0.84 , 1.12]**
Total events:	372		372			
Heterogeneity: Tau² = 0.02; Chi² = 34.52, df = 25 (P = 0.10); I² = 28%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 2.24, df = 1 (P = 0.13), I² = 55.4%						



Analysis 1.2. Comparison 1: Colchicine vs control, Outcome 2: Myocardial infarction (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Participants with high cardiovascular risk						
Nidorf 2013	4	282	18	250	100.0%	0.20 [0.07 , 0.57]
Subtotal (95% CI)		**282**		**250**	**100.0%**	**0.20 [0.07 , 0.57]**
Total events:	4		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.98 (P = 0.003)						
1.2.2 Other						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**342**		**310**	**100.0%**	**0.20 [0.07 , 0.57]**
Total events:	4		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.98 (P = 0.003)						
Test for subgroup differences: Not applicable						

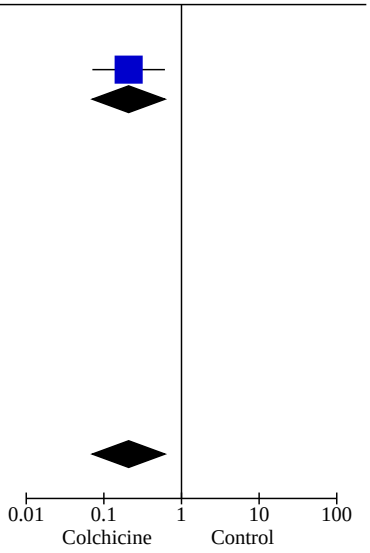


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.3. Comparison 1: Colchicine vs control, Outcome 3: Myocardial infarction (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Participants with high cardiovascular risk						
Nidorf 2013	4	282	17	250	100.0%	0.21 [0.07 , 0.61]
Subtotal (95% CI)		**282**		**250**	**100.0%**	**0.21 [0.07 , 0.61]**
Total events:	4		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
1.3.2 Other						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**342**		**310**	**100.0%**	**0.21 [0.07 , 0.61]**
Total events:	4		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
Test for subgroup differences: Not applicable						

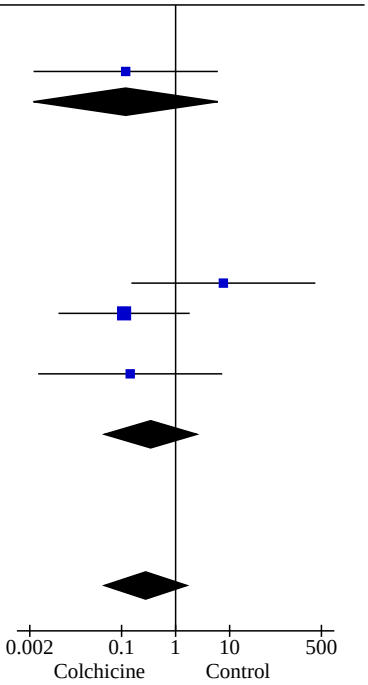


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.4. Comparison 1: Colchicine vs control, Outcome 4: Myocardial Infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 Participants with high cardiovascular risk						
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**282**		**250**	**20.1%**	**0.12 [0.00 , 6.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.4.2 Other						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Parise 1995	0	21	0	20		Not estimable
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**192**		**186**	**79.9%**	**0.35 [0.05 , 2.47]**
Total events:	1		3			
Heterogeneity: Chi² = 3.22, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

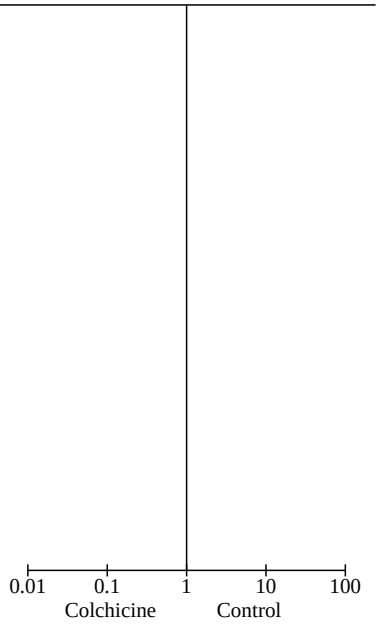


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

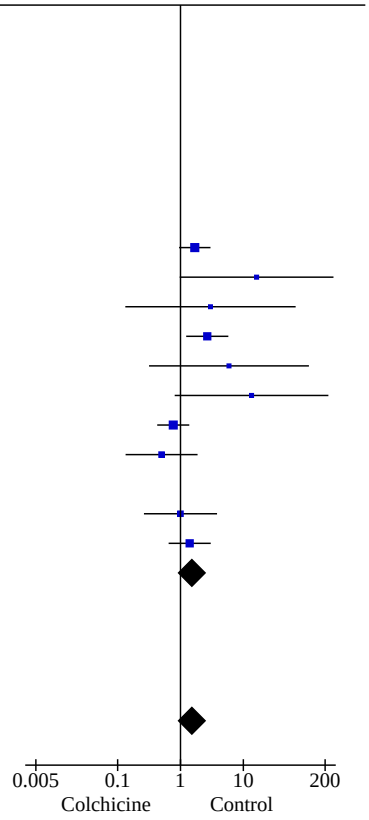
Analysis 1.5. Comparison 1: Colchicine vs control, Outcome 5: Adverse event (serious)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.5.1 Participants with high cardiovascular risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.2 Other						
Raedsch 1992	0	14	0	14		Not estimable
CORE	0	42	0	42		Not estimable
CORP	0	60	0	60		Not estimable
CORP-2	0	120	0	120		Not estimable
Subtotal (95% CI)		**236**		**236**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**236**		**236**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



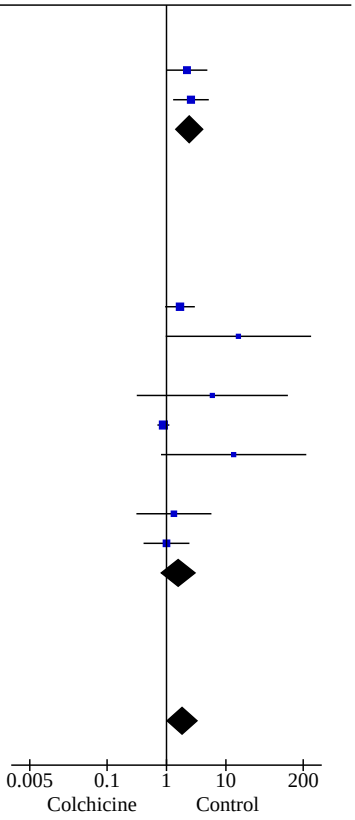
Analysis 1.6. Comparison 1: Colchicine vs control, Outcome 6: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Participants with high cardiovascular risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.2 Other						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 16.43$, df = 9 (P = 0.06); $I^2 = 45\%$						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 16.43$, df = 9 (P = 0.06); $I^2 = 45\%$						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Not applicable						



Analysis 1.7. Comparison 1: Colchicine vs control, Outcome 7: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Participants with high cardiovascular risk						
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
Subtotal (95% CI)		**252**		**249**	**30.5%**	**2.41 [1.43 , 4.06]**
Total events:	44		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
1.7.2 Other						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Subtotal (95% CI)		**386**		**371**	**69.5%**	**1.57 [0.82 , 3.02]**
Total events:	85		64			
Heterogeneity: Tau² = 0.36; Chi² = 17.96, df = 6 (P = 0.006); I² = 67%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² = 1.6%						

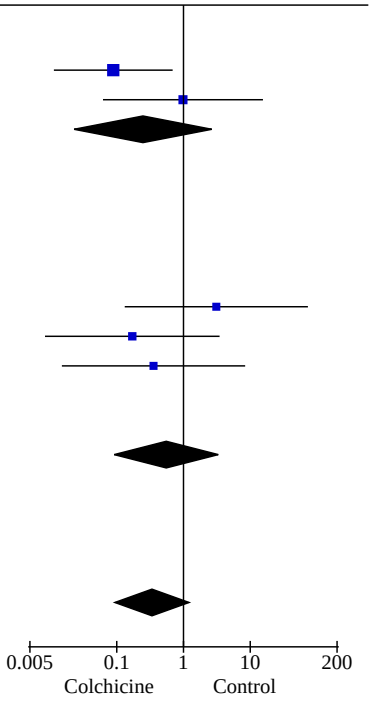


Footnotes

(1) From author request

Analysis 1.8. Comparison 1: Colchicine vs control, Outcome 8: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Participants with high cardiovascular risk						
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**394**		**360**	**52.8%**	**0.25 [0.02 , 2.66]**
Total events:	2		11			
Heterogeneity: Tau² = 1.47; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.8.2 Other						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**192**		**186**	**47.2%**	**0.55 [0.09 , 3.32]**
Total events:	1		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						

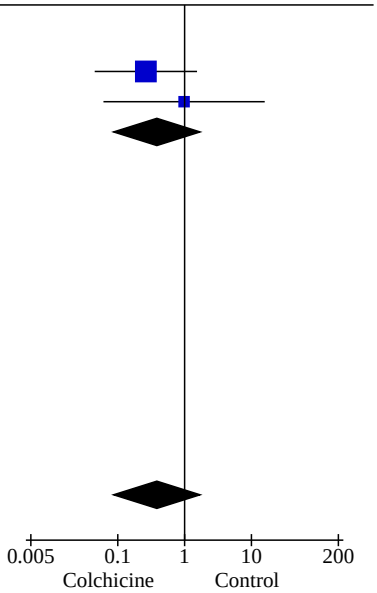


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.9. Comparison 1: Colchicine vs control, Outcome 9: Stroke (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.9.1 Participants with high cardiovascular risk						
Nidorf 2013	1	282	4	250	71.3%	0.26 [0.05 , 1.53]
Deftereos 2013	1	112	1	110	28.7%	0.98 [0.06 , 15.80]
Subtotal (95% CI)		**394**		**360**	**100.0%**	**0.38 [0.09 , 1.70]**
Total events:	2		5			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
1.9.2 Other						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**454**		**420**	**100.0%**	**0.38 [0.09 , 1.70]**
Total events:	2		5			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Not applicable						

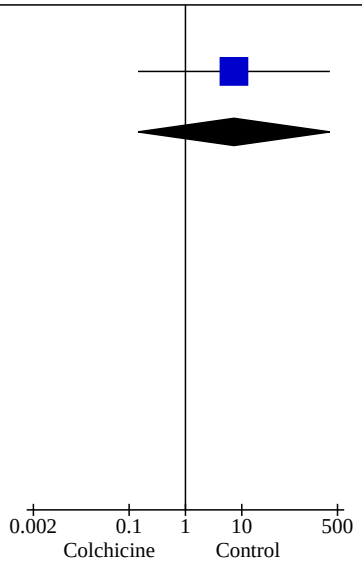


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.10. Comparison 1: Colchicine vs control, Outcome 10: Stroke (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 Participants with high cardiovascular risk						
Deftereos 2013	1	112	0	110	100.0%	7.26 [0.14 , 365.85]
Nidorf 2013	0	282	0	250		Not estimable
Subtotal (95% CI)		**394**		**360**	**100.0%**	**7.26 [0.14 , 365.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.10.2 Other						
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**81**		**80**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

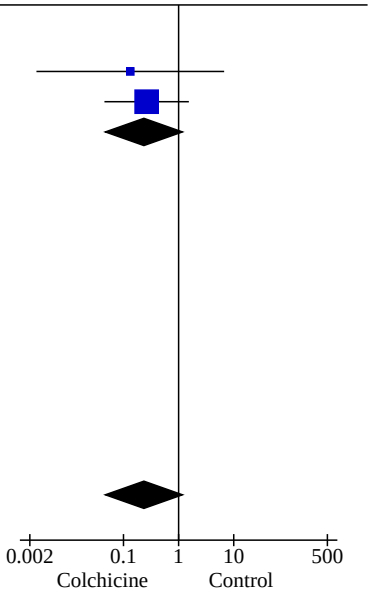


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.11. Comparison 1: Colchicine vs control, Outcome 11: Stroke (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.11.1 Participants with high cardiovascular risk						
Deftereos 2013 (1)	0	112	1	110	16.8%	0.13 [0.00 , 6.70]
Nidorf 2013	1	282	4	250	83.2%	0.26 [0.05 , 1.53]
Subtotal (95% CI)		**394**		**360**	**100.0%**	**0.23 [0.05 , 1.17]**
Total events:	1		5			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.11.2 Other						
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**454**		**420**	**100.0%**	**0.23 [0.05 , 1.17]**
Total events:	1		5			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
Test for subgroup differences: Not applicable						



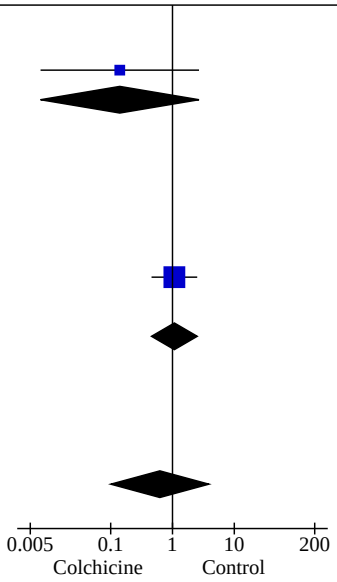
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.12. Comparison 1: Colchicine vs control, Outcome 12: Heart failure (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Participants with high cardiovascular risk						
Deftereos 2013 (1)	0	112	3	110	26.6%	0.14 [0.01 , 2.69]
Subtotal (95% CI)		**112**		**110**	**26.6%**	**0.14 [0.01 , 2.69]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
1.12.2 Other						
Kyle 1985	9	43	8	41	73.4%	1.07 [0.46 , 2.51]
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**103**		**101**	**73.4%**	**1.07 [0.46 , 2.51]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**215**		**211**	**100.0%**	**0.62 [0.10 , 3.88]**
Total events:	9		11			
Heterogeneity: $Tau^2 = 0.99$; $Chi^2 = 1.81$, df = 1 (P = 0.18); $I^2 = 45\%$						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: $Chi^2 = 1.68$, df = 1 (P = 0.19), $I^2 = 40.6\%$						



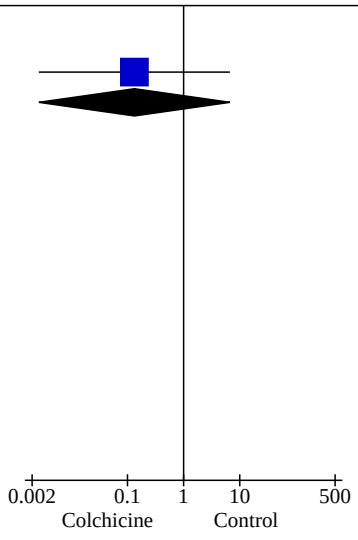
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.13. Comparison 1: Colchicine vs control, Outcome 13: Heart failure (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.13.1 Participants with high cardiovascular risk						
Deftereos 2013 (1)	0	112	1	110	100.0%	0.13 [0.00 , 6.70]
Subtotal (95% CI)		**112**		**110**	**100.0%**	**0.13 [0.00 , 6.70]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.13.2 Other						
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**81**		**80**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



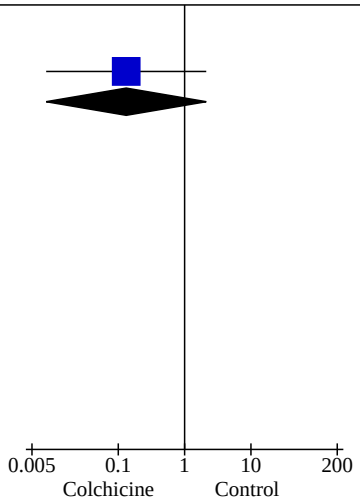
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.14. Comparison 1: Colchicine vs control, Outcome 14: Heart failure (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.14.1 Participants with high cardiovascular risk						
Deftereos 2013 (1)	0	112	2	110	100.0%	0.13 [0.01 , 2.12]
Subtotal (95% CI)		**112**		**110**	**100.0%**	**0.13 [0.01 , 2.12]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.14.2 Other						
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



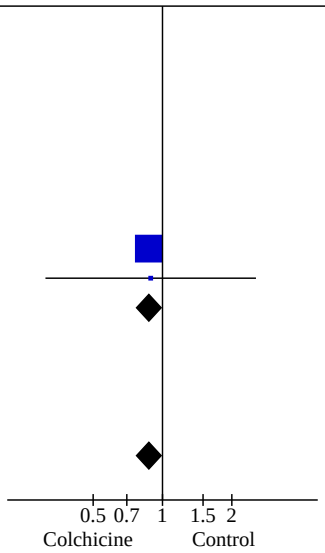
Footnotes

(1) From author request

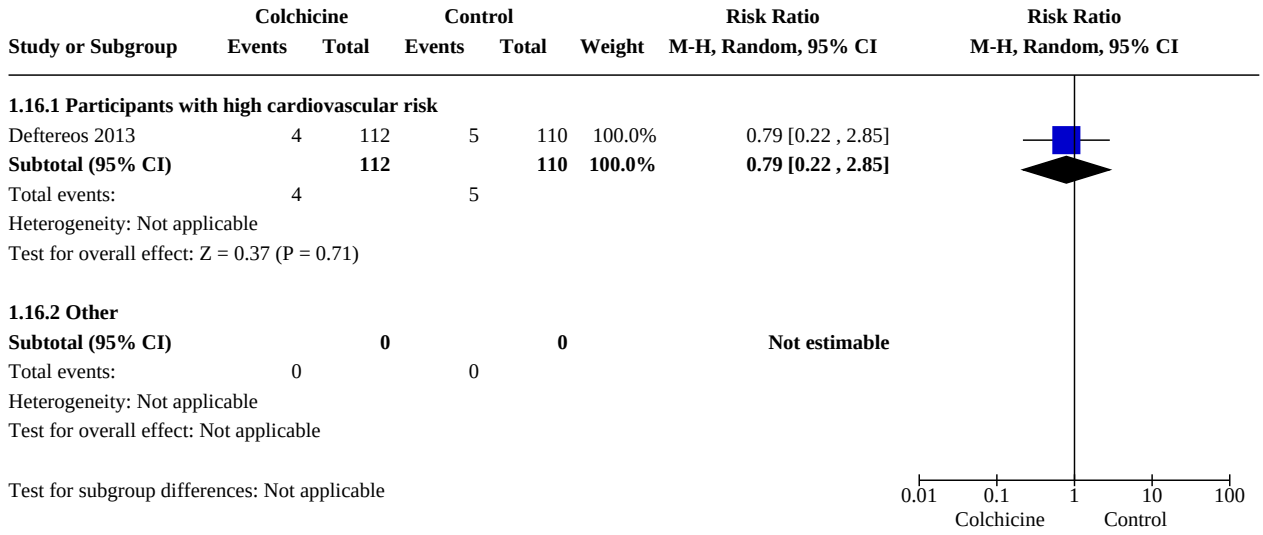
(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 1.15. Comparison 1: Colchicine vs control, Outcome 15: Non-scheduled hospitalisation (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Participants with high cardiovascular risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.15.2 Other						
Morgan 2005	166	274	191	275	98.6%	0.87 [0.77 , 0.99]
Antoniou 2006	4	18	8	32	1.4%	0.89 [0.31 , 2.55]
Subtotal (95% CI)		**292**		**307**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	170		199			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						
Total (95% CI)		**292**		**307**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	170		199			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: Not applicable						



Analysis 1.16. Comparison 1: Colchicine vs control, Outcome 16: Non-scheduled cardiovascular interventions



Comparison 2. Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d

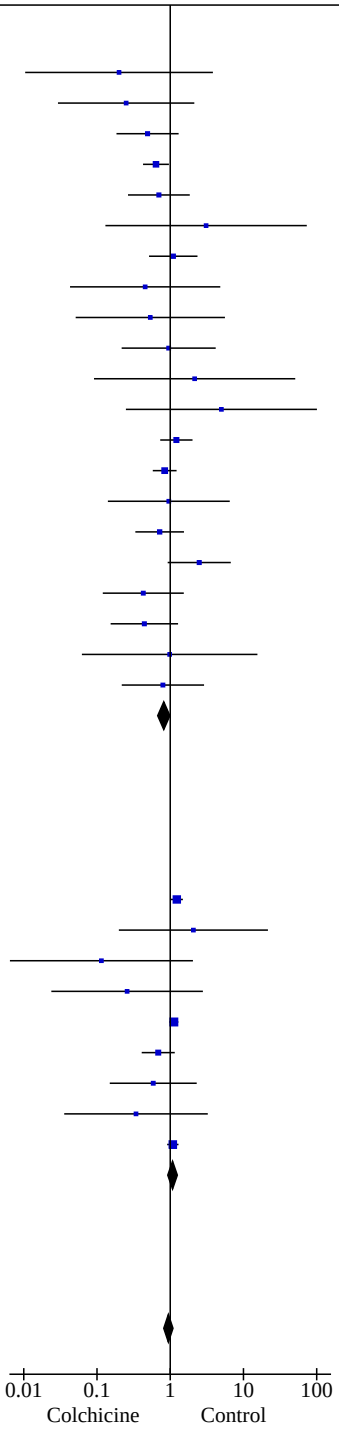
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
2.1.1 ≤ 1 mg/d	21	2420	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 0.99]
2.1.2 > 1 mg/d	9	1754	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.25]
2.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
2.2.1 ≤ 1 mg/d	5	955	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.82]
2.2.2 > 1 mg/d	2	177	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.13, 73.12]
2.3 Myocardial infarction (total)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 ≤ 1 mg/d	1	532	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.57]
2.3.2 > 1 mg/d	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
2.4.1 ≤ 1 mg/d	4	733	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.02, 0.87]
2.4.2 > 1 mg/d	2	177	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.66 [0.15, 386.16]
2.5 Myocardial infarction (non-fatal)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 ≤ 1 mg/d	1	532	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.07, 0.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.2 > 1 mg/d	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.6 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
2.6.1 ≤ 1 mg/d	8	687	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.74, 4.14]
2.6.2 > 1 mg/d	3	626	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.72, 2.97]
2.7 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
2.7.1 ≤ 1 mg/d	9	1104	Risk Ratio (M-H, Random, 95% CI)	2.15 [1.26, 3.66]
2.7.2 > 1 mg/d	2	154	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.61, 2.19]
2.8 Adverse event (serious)	4	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.8.1 ≤ 1 mg/d	4	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.8.2 > 1 mg/d	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.9 Stroke (total)	3	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.09, 1.70]
2.9.1 ≤ 1 mg/d	2	754	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.09, 1.70]
2.9.2 > 1 mg/d	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.10 Stroke (fatal)	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.10.1 ≤ 1 mg/d	3	795	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.85]
2.10.2 > 1 mg/d	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.11 Stroke (non-fatal)	3	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.17]
2.11.1 ≤ 1 mg/d	2	754	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.17]
2.11.2 > 1 mg/d	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.12 Heart failure (total)	3	426	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.10, 3.88]
2.12.1 ≤ 1 mg/d	1	222	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.69]
2.12.2 > 1 mg/d	2	204	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.46, 2.51]
2.13 Heart failure (fatal)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.13.1 ≤ 1 mg/d	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
2.13.2 > 1 mg/d	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.14 Heart failure (non-fatal)	2	342	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.14.1 ≤ 1 mg/d	1	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.12]
2.14.2 > 1 mg/d	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.15 Non-scheduled hospitalisation (total)	2	599	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
2.15.1 ≤ 1 mg/d	1	50	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.31, 2.55]
2.15.2 > 1 mg/d	1	549	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
2.16 Non-scheduled cardiovascular interventions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.16.1 ≤ 1 mg/d	1	222	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.85]
2.16.2 > 1 mg/d	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 2.1. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 # 1 mg/d						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**1247**		**1173**	**42.4%**	**0.82 [0.67 , 0.99]**
Total events:	124		144			
Heterogeneity: Tau² = 0.00; Chi² = 17.65, df = 20 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.09 (P = 0.04)						
2.1.2 > 1 mg/d						
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Douglas 1998 (1)	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Subtotal (95% CI)		**904**		**850**	**57.6%**	**1.08 [0.93 , 1.25]**
Total events:	259		246			
Heterogeneity: Tau² = 0.01; Chi² = 11.51, df = 8 (P = 0.17); I² = 31%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 4.99, df = 1 (P = 0.03), I² = 79.9%						

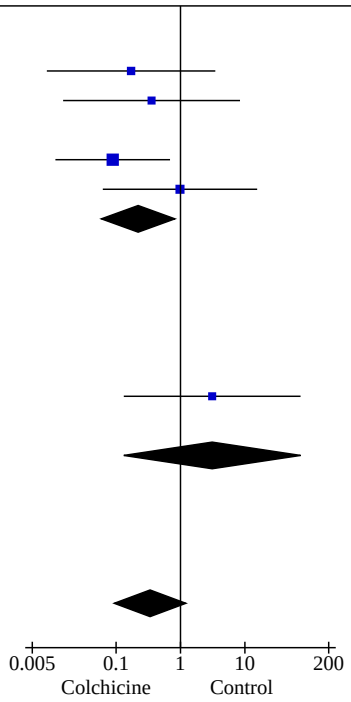


Footnotes

(1) Dose 0.6-1.2 - as high as tolerated

Analysis 2.2. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 # 1 mg/d						
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**498**		**457**	**84.7%**	**0.22 [0.06 , 0.82]**
Total events:	2		14			
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
2.2.2 > 1 mg/d						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**88**		**89**	**15.3%**	**3.10 [0.13 , 73.12]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 2.30, df = 1 (P = 0.13), I² = 56.5%						

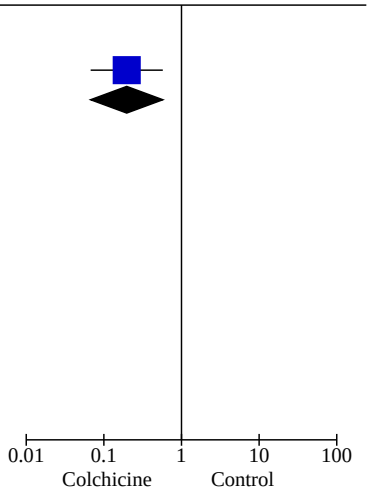


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.3. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 3: Myocardial infarction (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 # 1 mg/d						
Nidorf 2013	4	282	18	250	100.0%	0.20 [0.07 , 0.57]
Subtotal (95% CI)		**282**		**250**	**100.0%**	**0.20 [0.07 , 0.57]**
Total events:	4		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.98 (P = 0.003)						
2.3.2 > 1 mg/d						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

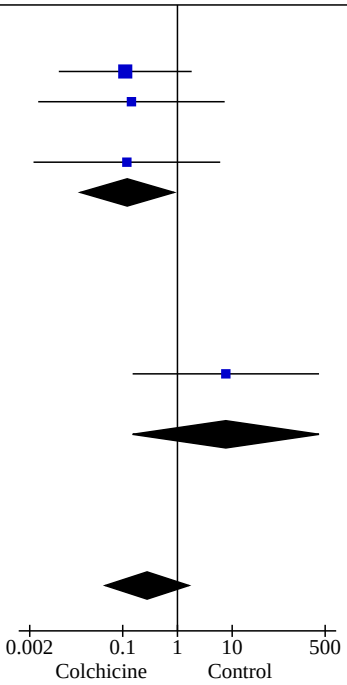


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."; Dose: 2-4x 0.5 mg/d

Analysis 2.4. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 4: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.4.1 # 1 mg/d						
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Parise 1995	0	21	0	20		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**386**		**347**	**79.9%**	**0.12 [0.02 , 0.87]**
Total events:	0		4			
Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
2.4.2 > 1 mg/d						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**88**		**89**	**20.1%**	**7.66 [0.15 , 386.16]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 3.44, df = 1 (P = 0.06), I² = 70.9%						

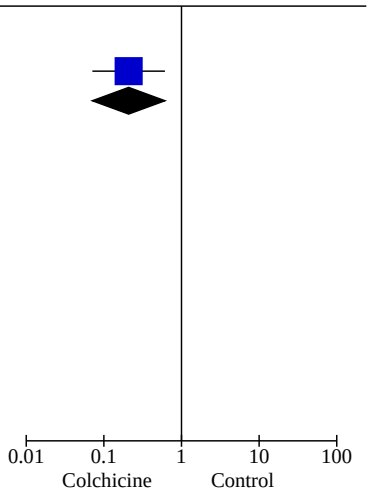


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.5. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 5: Myocardial infarction (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 # 1 mg/d						
Nidorf 2013	4	282	17	250	100.0%	0.21 [0.07 , 0.61]
Subtotal (95% CI)		**282**		**250**	**100.0%**	**0.21 [0.07 , 0.61]**
Total events:	4		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
2.5.2 > 1 mg/d						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

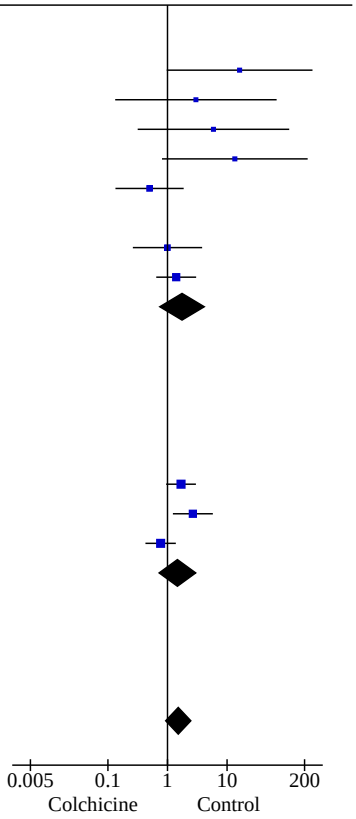


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

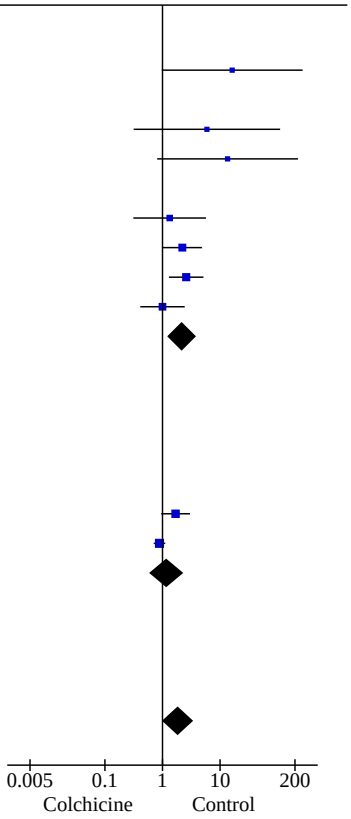
Analysis 2.6. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 6: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 # 1 mg/d						
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**350**		**337**	**44.3%**	**1.75 [0.74 , 4.14]**
Total events:	40		20			
Heterogeneity: Tau² = 0.48; Chi² = 10.04, df = 6 (P = 0.12); I² = 40%						
Test for overall effect: Z = 1.28 (P = 0.20)						
2.6.2 > 1 mg/d						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
Subtotal (95% CI)		**311**		**315**	**55.7%**	**1.47 [0.72 , 2.97]**
Total events:	49		38			
Heterogeneity: Tau² = 0.28; Chi² = 7.32, df = 2 (P = 0.03); I² = 73%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



Analysis 2.7. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 7: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 # 1 mg/d						
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Subtotal (95% CI)		**560**		**544**	**63.4%**	**2.15 [1.26 , 3.66]**
Total events:	75		30			
Heterogeneity: Tau² = 0.12; Chi² = 7.97, df = 6 (P = 0.24); I² = 25%						
Test for overall effect: Z = 2.81 (P = 0.005)						
2.7.2 > 1 mg/d						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Subtotal (95% CI)		**78**		**76**	**36.6%**	**1.16 [0.61 , 2.19]**
Total events:	54		52			
Heterogeneity: Tau² = 0.17; Chi² = 4.32, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.15), I² = 52.9%						

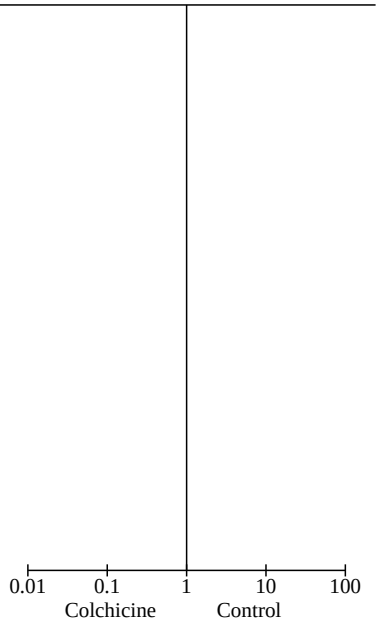


Footnotes

(1) From author request

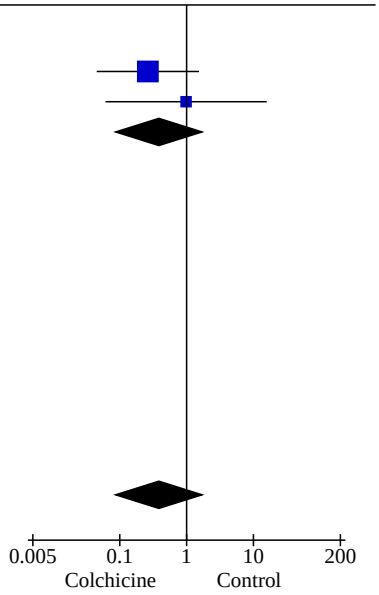
Analysis 2.8. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 8: Adverse event (serious)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.8.1 # 1 mg/d						
Raedsch 1992	0	14	0	14		Not estimable
CORE	0	42	0	42		Not estimable
CORP	0	60	0	60		Not estimable
CORP-2	0	120	0	120		Not estimable
Subtotal (95% CI)		**236**		**236**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.8.2 > 1 mg/d						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**236**		**236**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 2.9. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 9: Stroke (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.9.1 # 1 mg/d						
Nidorf 2013	1	282	4	250	71.3%	0.26 [0.05 , 1.53]
Deftereos 2013	1	112	1	110	28.7%	0.98 [0.06 , 15.80]
Subtotal (95% CI)		**394**		**360**	**100.0%**	**0.38 [0.09 , 1.70]**
Total events:	2		5			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
2.9.2 > 1 mg/d						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**454**		**420**	**100.0%**	**0.38 [0.09 , 1.70]**
Total events:	2		5			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Not applicable						

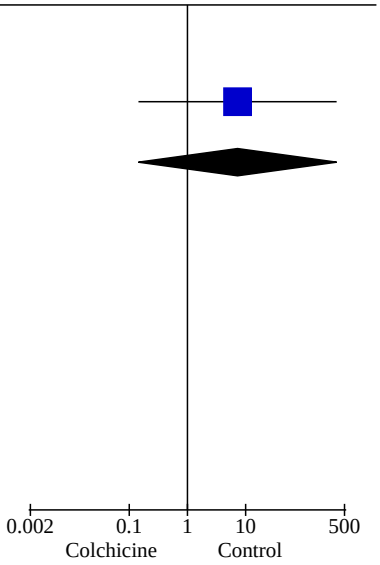


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.10. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 10: Stroke (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.10.1 # 1 mg/d						
Parise 1995	0	21	0	20		Not estimable
Deftereos 2013	1	112	0	110	100.0%	7.26 [0.14 , 365.85]
Nidorf 2013	0	282	0	250		Not estimable
Subtotal (95% CI)		**415**		**380**	**100.0%**	**7.26 [0.14 , 365.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.10.2 > 1 mg/d						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

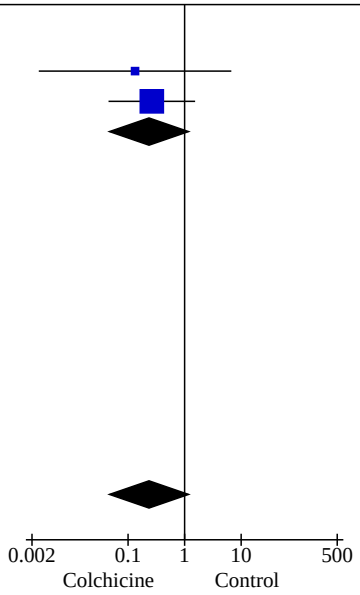


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.11. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 11: Stroke (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.11.1 # 1 mg/d						
Deftereos 2013 (1)	0	112	1	110	16.8%	0.13 [0.00 , 6.70]
Nidorf 2013	1	282	4	250	83.2%	0.26 [0.05 , 1.53]
Subtotal (95% CI)		**394**		**360**	**100.0%**	**0.23 [0.05 , 1.17]**
Total events:	1		5			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
2.11.2 > 1 mg/d						
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**454**		**420**	**100.0%**	**0.23 [0.05 , 1.17]**
Total events:	1		5			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
Test for subgroup differences: Not applicable						



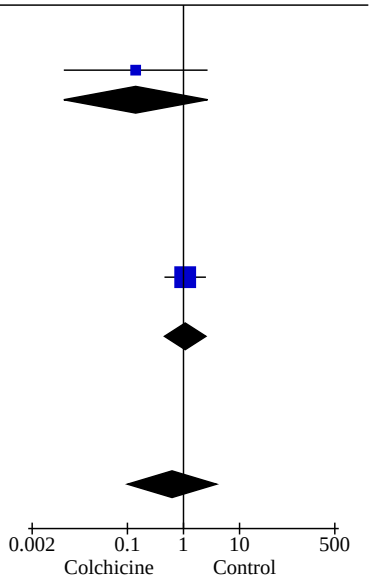
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.12. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 12: Heart failure (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 # 1 mg/d						
Deftereos 2013 (1)	0	112	3	110	26.6%	0.14 [0.01 , 2.69]
Subtotal (95% CI)		**112**		**110**	**26.6%**	**0.14 [0.01 , 2.69]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
2.12.2 > 1 mg/d						
Kyle 1985	9	43	8	41	73.4%	1.07 [0.46 , 2.51]
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**103**		**101**	**73.4%**	**1.07 [0.46 , 2.51]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**215**		**211**	**100.0%**	**0.62 [0.10 , 3.88]**
Total events:	9		11			
Heterogeneity: Tau² = 0.99; Chi² = 1.81, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.6%						



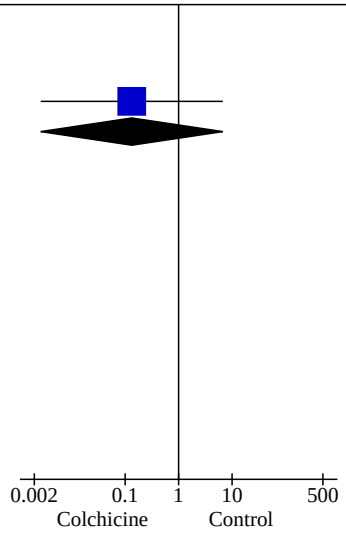
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.13. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 13: Heart failure (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.13.1 # 1 mg/d						
Parise 1995	0	21	0	20		Not estimable
Deftereos 2013 (1)	0	112	1	110	100.0%	0.13 [0.00 , 6.70]
Subtotal (95% CI)		**133**		**130**	**100.0%**	**0.13 [0.00 , 6.70]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
2.13.2 > 1 mg/d						
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



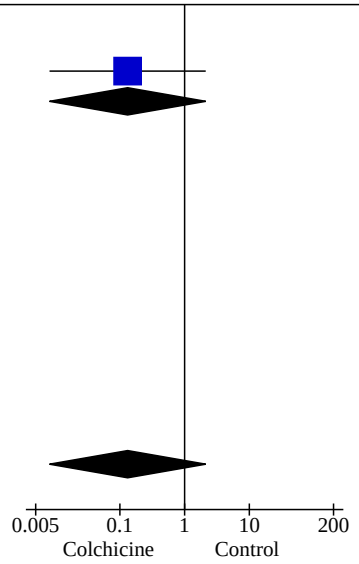
Footnotes

(1) From author request

(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.14. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 14: Heart failure (non-fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.14.1 # 1 mg/d						
Deftereos 2013 (1)	0	112	2	110	100.0%	0.13 [0.01 , 2.12]
Subtotal (95% CI)		**112**		**110**	**100.0%**	**0.13 [0.01 , 2.12]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
2.14.2 > 1 mg/d						
Yurdakul 2001 (2)	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**172**		**170**	**100.0%**	**0.13 [0.01 , 2.12]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Not applicable						



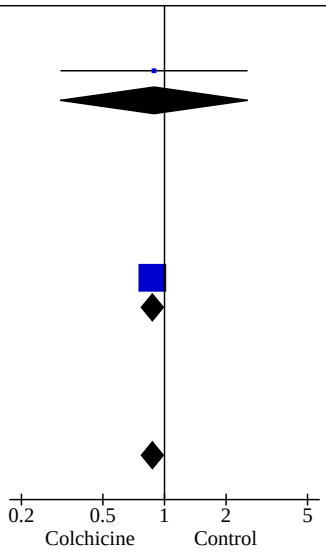
Footnotes

(1) From author request

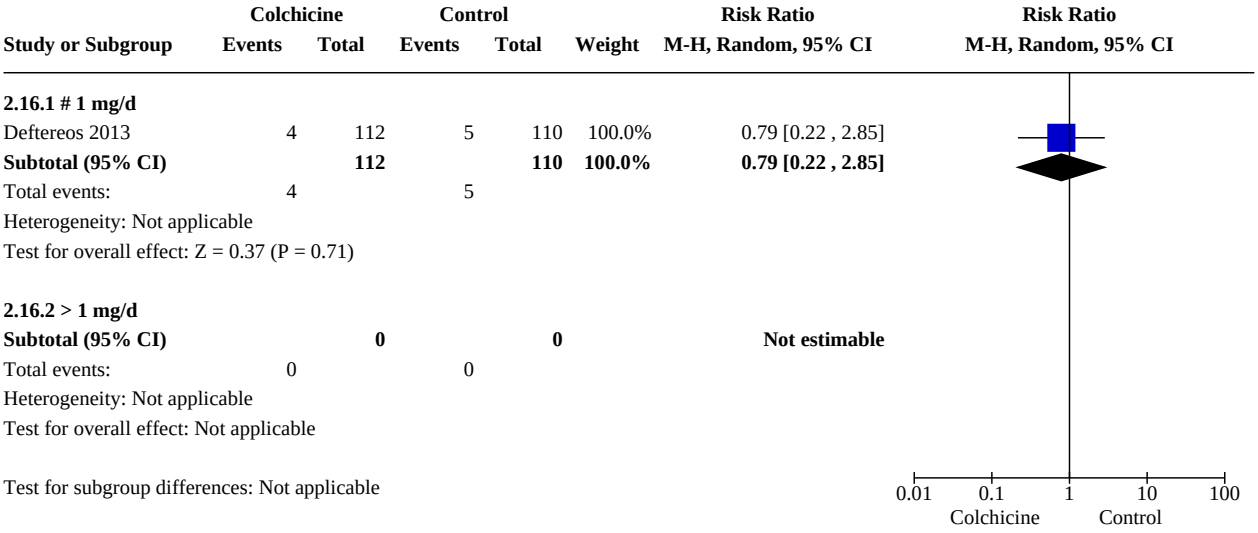
(2) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 2.15. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 15: Non-scheduled hospitalisation (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 # 1 mg/d						
Antoniou 2006	4	18	8	32	1.4%	0.89 [0.31 , 2.55]
Subtotal (95% CI)		**18**		**32**	**1.4%**	**0.89 [0.31 , 2.55]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
2.15.2 > 1 mg/d						
Morgan 2005	166	274	191	275	98.6%	0.87 [0.77 , 0.99]
Subtotal (95% CI)		**274**		**275**	**98.6%**	**0.87 [0.77 , 0.99]**
Total events:	166		191			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
Total (95% CI)		**292**		**307**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	170		199			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						



Analysis 2.16. Comparison 2: Colchicine vs control: subgroup analysis - colchicine dose fixed ≤ 1 mg/d, Outcome 16: Non-scheduled cardiovascular interventions



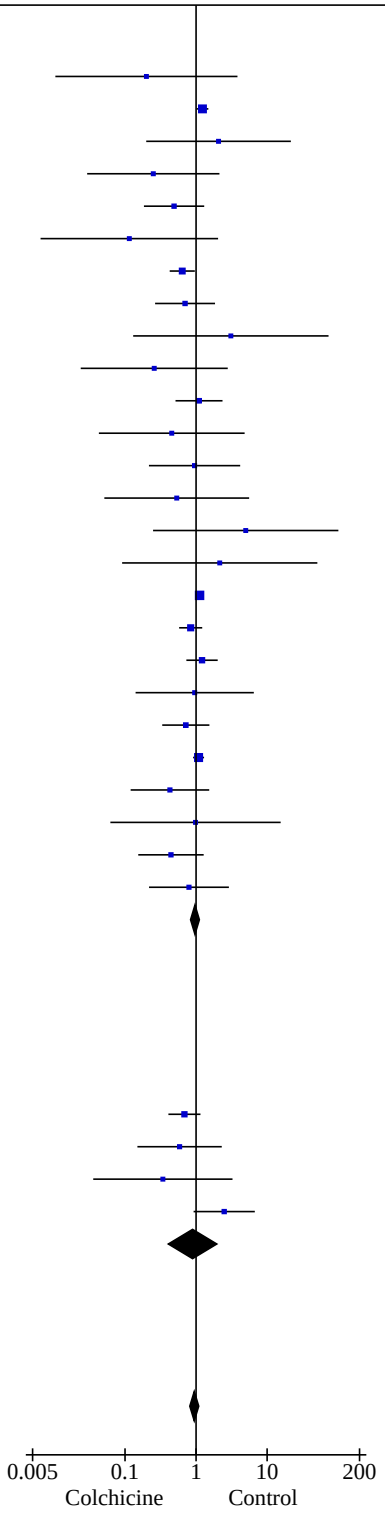
Comparison 3. Colchicine vs control: sensitivity analysis - placebo or other inactive control

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
3.1.1 Placebo, inactive control	26	3479	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.11]
3.1.2 Active control	4	695	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.41, 1.95]
3.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
3.2.1 Placebo, inactive control	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
3.2.2 Active control	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
3.3.1 Placebo, inactive control	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
3.3.2 Active control	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
3.4.1 Placebo, inactive control	9	725	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.90, 2.84]
3.4.2 Active control	2	588	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.41, 4.74]
3.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.5.1 Placebo, inactive control	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
3.5.2 Active control	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

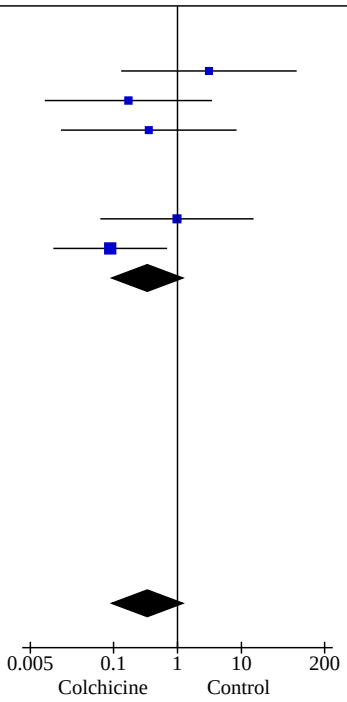
Analysis 3.1. Comparison 3: Colchicine vs control: sensitivity analysis - placebo or other inactive control, Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Placebo, inactive control						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**1812**		**1667**	**91.0%**	**0.96 [0.84 , 1.11]**
Total events:	364		367			
Heterogeneity: Tau² = 0.02; Chi² = 32.92, df = 25 (P = 0.13); I² = 24%						
Test for overall effect: Z = 0.49 (P = 0.62)						
3.1.2 Active control						
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Subtotal (95% CI)		**339**		**356**	**9.0%**	**0.89 [0.41 , 1.95]**
Total events:	19		23			
Heterogeneity: Tau² = 0.31; Chi² = 6.21, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%						



Analysis 3.2. Comparison 3: Colchicine vs control: sensitivity analysis - placebo or other inactive control, Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Placebo, inactive control						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Subtotal (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
3.2.2 Active control						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Not applicable						

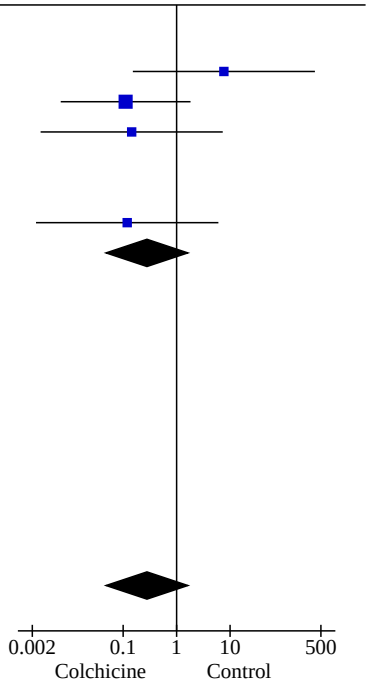


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 3.3. Comparison 3: Colchicine vs control: sensitivity analysis - placebo or other inactive control, Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.3.1 Placebo, inactive control						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
3.3.2 Active control						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Not applicable						

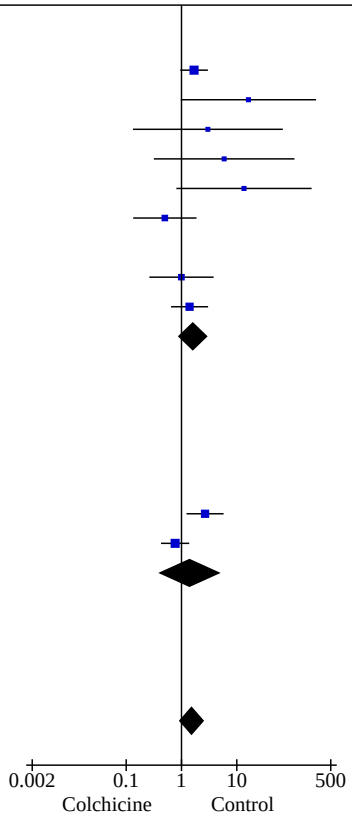


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

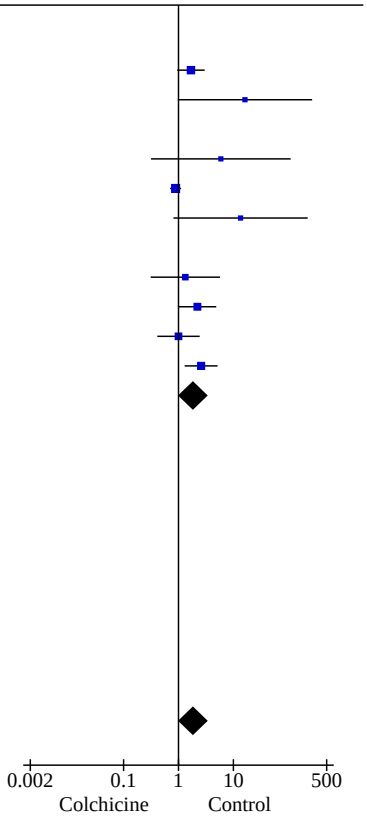
Analysis 3.4. Comparison 3: Colchicine vs control: sensitivity analysis - placebo or other inactive control, Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Placebo, inactive control						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**370**		**355**	**64.1%**	**1.60 [0.90 , 2.84]**
Total events:	55		28			
Heterogeneity: Tau² = 0.18; Chi² = 9.94, df = 7 (P = 0.19); I² = 30%						
Test for overall effect: Z = 1.60 (P = 0.11)						
3.4.2 Active control						
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
Subtotal (95% CI)		**291**		**297**	**35.9%**	**1.39 [0.41 , 4.74]**
Total events:	34		30			
Heterogeneity: Tau² = 0.66; Chi² = 6.39, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



Analysis 3.5. Comparison 3: Colchicine vs control: sensitivity analysis - placebo or other inactive control, Outcome 5: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Placebo, inactive control						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
Subtotal (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
3.5.2 Active control						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						



Footnotes

(1) From author request

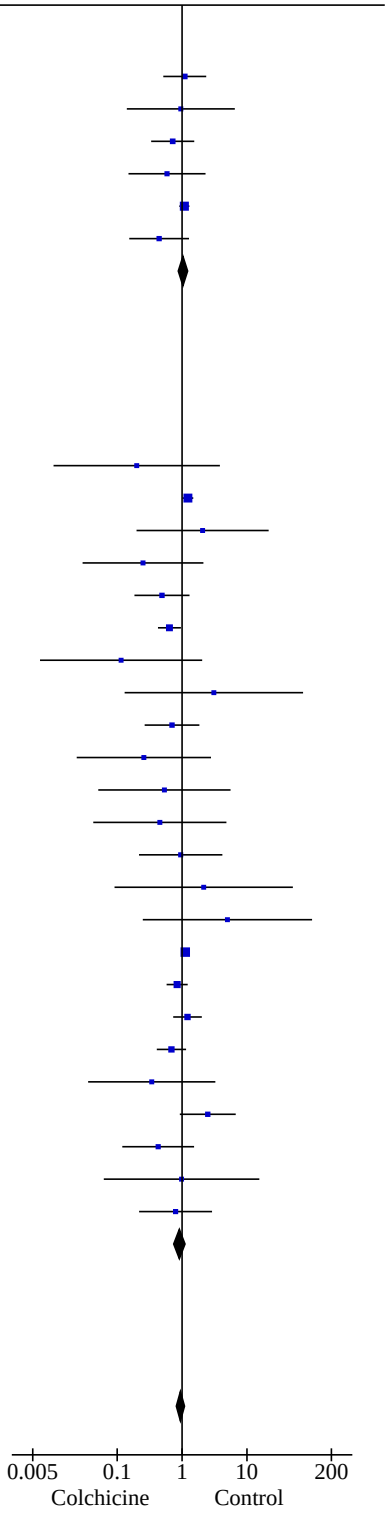
Comparison 4. Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
4.1.1 Low risk	6	1411	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.87, 1.22]
4.1.2 High or unclear risk	24	2763	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
4.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
4.2.1 Low risk	2	652	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.69]
4.2.2 High or unclear risk	5	480	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.95]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
4.3.1 Low risk	2	652	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 6.04]
4.3.2 High or unclear risk	4	258	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.47]
4.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
4.4.1 Low risk	3	415	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.61, 4.04]
4.4.2 High or unclear risk	8	898	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.81, 2.91]
4.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
4.5.1 Low risk	4	531	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.59, 2.04]
4.5.2 High or unclear risk	7	727	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.49, 3.17]

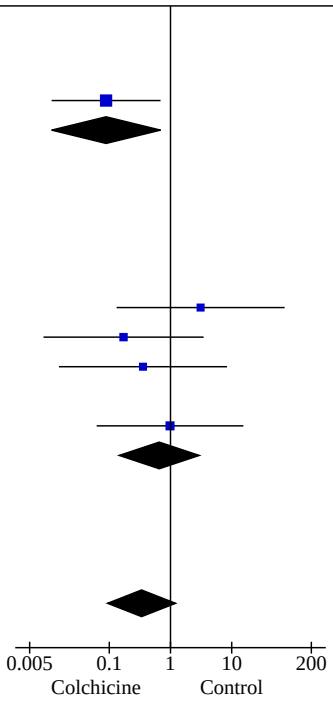
Analysis 4.1. Comparison 4: Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment), Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Low risk						
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Subtotal (95% CI)		**724**		**687**	**25.6%**	**1.03 [0.87 , 1.22]**
Total events:	163		161			
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.1.2 High or unclear risk						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**1427**		**1336**	**74.4%**	**0.91 [0.74 , 1.11]**
Total events:	220		229			
Heterogeneity: Tau² = 0.05; Chi² = 37.08, df = 23 (P = 0.03); I² = 38%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%						



Analysis 4.2. Comparison 4: Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment), Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Low risk						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Subtotal (95% CI)		**342**		**310**	**33.2%**	**0.09 [0.01 , 0.69]**
Total events:	1		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
4.2.2 High or unclear risk						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**244**		**236**	**66.8%**	**0.65 [0.15 , 2.95]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.12), I² = 57.9%						

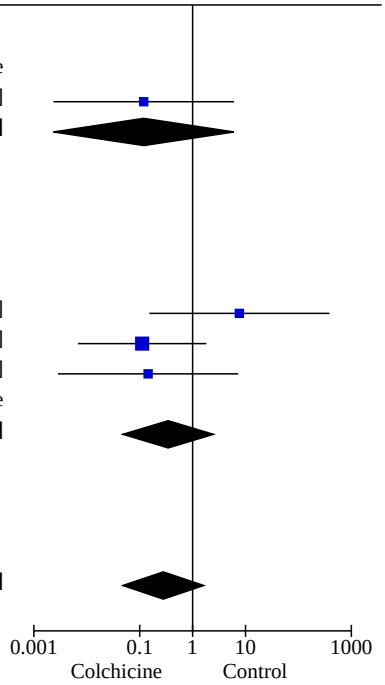


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 4.3. Comparison 4: Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment), Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.3.1 Low risk						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**342**		**310**	**20.1%**	**0.12 [0.00 , 6.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
4.3.2 High or unclear risk						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Parise 1995	0	21	0	20		Not estimable
Subtotal (95% CI)		**132**		**126**	**79.9%**	**0.35 [0.05 , 2.47]**
Total events:	1		3			
Heterogeneity: Chi² = 3.22, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

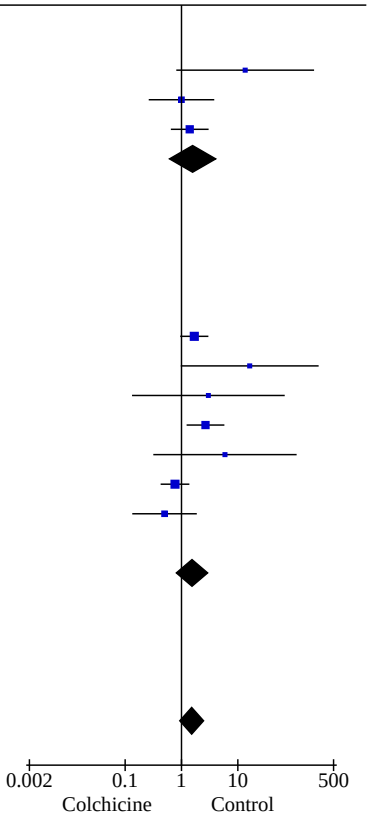


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

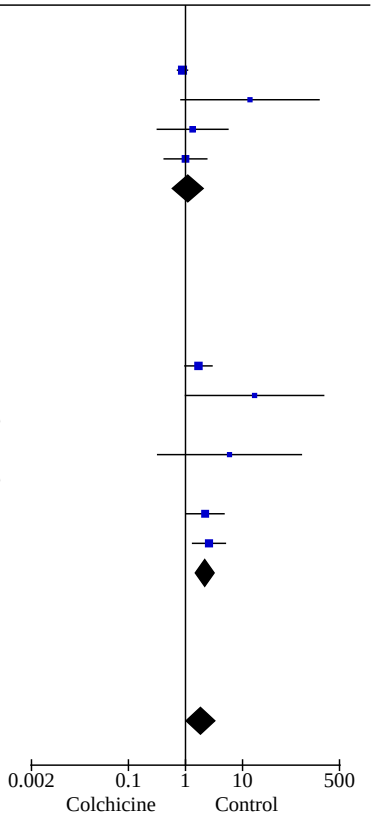
Analysis 4.4. Comparison 4: Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment), Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Low risk						
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**209**		**206**	**27.8%**	**1.57 [0.61 , 4.04]**
Total events:	25		14			
Heterogeneity: Tau² = 0.25; Chi² = 2.98, df = 2 (P = 0.23); I² = 33%						
Test for overall effect: Z = 0.94 (P = 0.34)						
4.4.2 High or unclear risk						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**452**		**446**	**72.2%**	**1.54 [0.81 , 2.91]**
Total events:	64		44			
Heterogeneity: Tau² = 0.32; Chi² = 13.54, df = 6 (P = 0.04); I² = 56%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						



Analysis 4.5. Comparison 4: Colchicine vs control: sensitivity analysis - selection bias (random sequence generation and allocation concealment), Outcome 5: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Low risk						
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Subtotal (95% CI)		**267**		**264**	**45.8%**	**1.10 [0.59 , 2.04]**
Total events:	59		56			
Heterogeneity: Tau² = 0.17; Chi² = 5.26, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 0.29 (P = 0.77)						
4.5.2 High or unclear risk						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Nikolaidis 2006	0	21	0	17		Not estimable
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
Subtotal (95% CI)		**371**		**356**	**54.2%**	**2.17 [1.49 , 3.17]**
Total events:	70		26			
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 4.01 (P < 0.0001)						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%						



Footnotes
(1) From author request

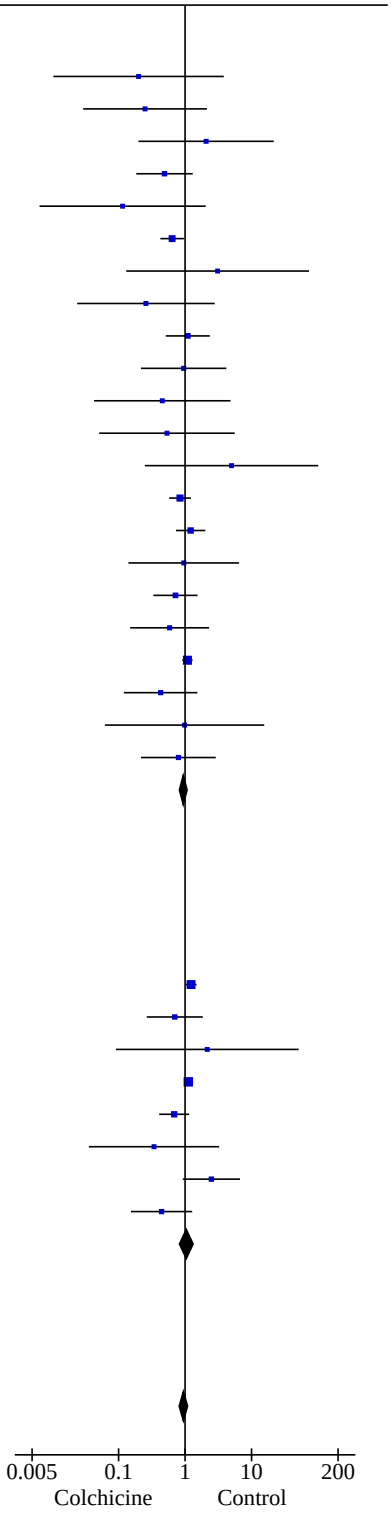
Comparison 5. Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
5.1.1 Double-blind	22	2538	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
5.1.2 Not clearly double-blind	8	1636	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.82, 1.32]
5.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
5.2.1 Double-blind	6	600	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.95]
5.2.2 Not clearly double-blind	1	532	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.69]
5.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.3.1 Double-blind	5	378	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.47]
5.3.2 Not clearly double-blind	1	532	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 6.04]
5.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
5.4.1 Double-blind	6	581	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.01, 3.12]
5.4.2 Not clearly double-blind	5	732	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.49, 3.11]
5.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
5.5.1 Double-blind	9	1198	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.98, 3.14]
5.5.2 Not clearly double-blind	2	60	Risk Ratio (M-H, Random, 95% CI)	5.91 [0.32, 110.47]

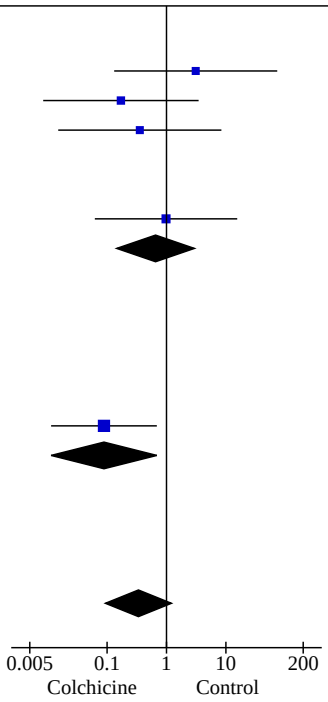
Analysis 5.1. Comparison 5: Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies), Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Double-blind						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**1312**		**1226**	**54.7%**	**0.94 [0.82 , 1.07]**
Total events:	244		257			
Heterogeneity: Tau² = 0.00; Chi² = 20.22, df = 21 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
5.1.2 Not clearly double-blind						
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Subtotal (95% CI)		**839**		**797**	**45.3%**	**1.04 [0.82 , 1.32]**
Total events:	139		133			
Heterogeneity: Tau² = 0.03; Chi² = 13.03, df = 7 (P = 0.07); I² = 46%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.45), I² = 0%						



Analysis 5.2. Comparison 5: Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies), Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Double-blind						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**304**		**296**	**66.8%**	**0.65 [0.15 , 2.95]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
5.2.2 Not clearly double-blind						
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Subtotal (95% CI)		**282**		**250**	**33.2%**	**0.09 [0.01 , 0.69]**
Total events:	1		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.12), I² = 57.9%						

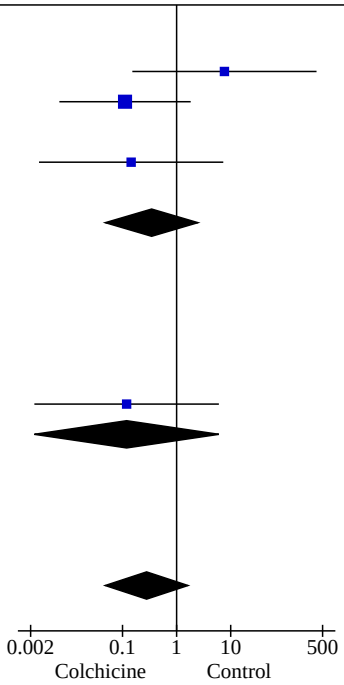


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 5.3. Comparison 5: Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies), Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.3.1 Double-blind						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Parise 1995	0	21	0	20		Not estimable
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**192**		**186**	**79.9%**	**0.35 [0.05 , 2.47]**
Total events:	1		3			
Heterogeneity: Chi² = 3.22, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 1.06 (P = 0.29)						
5.3.2 Not clearly double-blind						
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**282**		**250**	**20.1%**	**0.12 [0.00 , 6.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

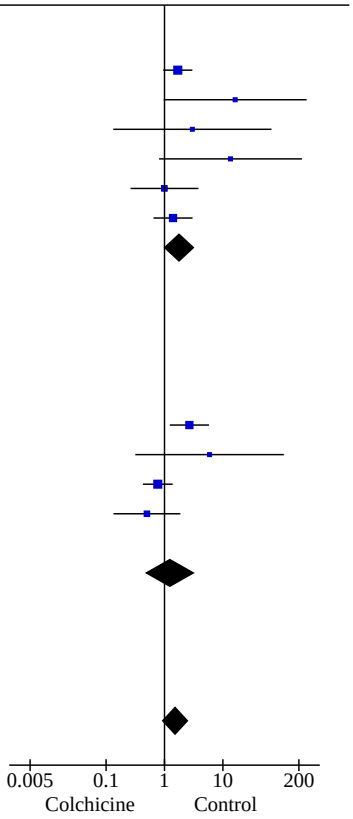


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

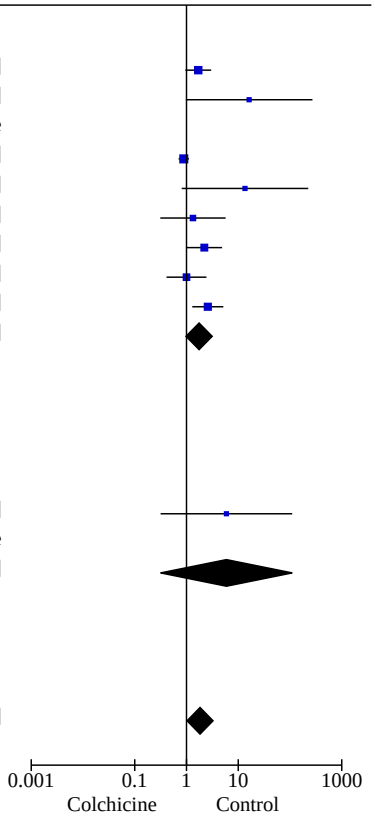
Analysis 5.4. Comparison 5: Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies), Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 Double-blind						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**297**		**284**	**52.6%**	**1.77 [1.01 , 3.12]**
Total events:	50		22			
Heterogeneity: Tau² = 0.11; Chi² = 6.41, df = 5 (P = 0.27); I² = 22%						
Test for overall effect: Z = 1.99 (P = 0.05)						
5.4.2 Not clearly double-blind						
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**364**		**368**	**47.4%**	**1.23 [0.49 , 3.11]**
Total events:	39		36			
Heterogeneity: Tau² = 0.52; Chi² = 9.14, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



Analysis 5.5. Comparison 5: Colchicine vs control: sensitivity analysis - performance bias (double-blinded studies), Outcome 5: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 Double-blind						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
Subtotal (95% CI)		**607**		**591**	**96.7%**	**1.75 [0.98 , 3.14]**
Total events:	127		82			
Heterogeneity: Tau² = 0.42; Chi² = 29.50, df = 7 (P = 0.0001); I² = 76%						
Test for overall effect: Z = 1.89 (P = 0.06)						
5.5.2 Not clearly double-blind						
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**31**		**29**	**3.3%**	**5.91 [0.32 , 110.47]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.23)						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%						



Footnotes

(1) From author request

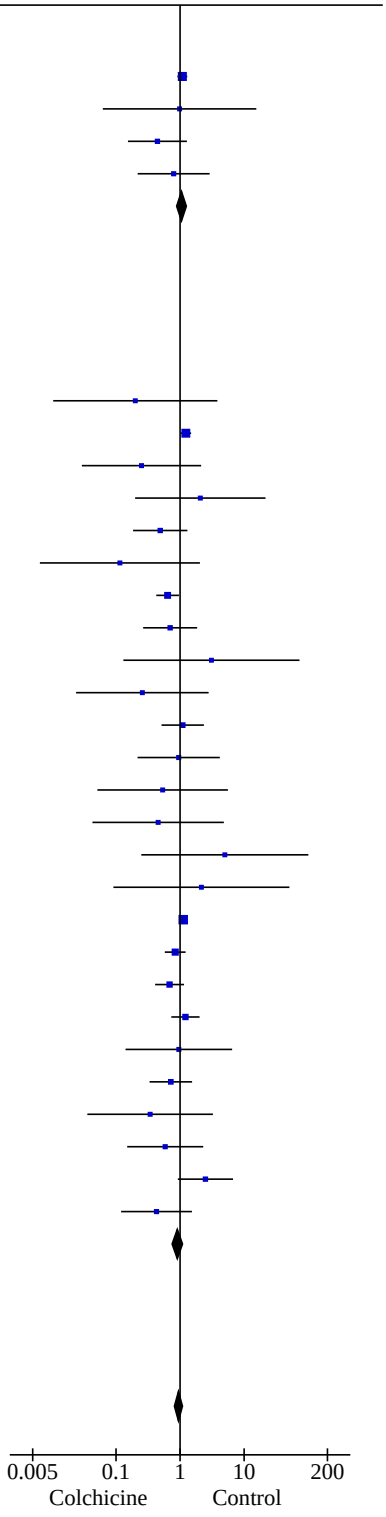
Comparison 6. Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
6.1.1 Outcome assessment blinded	4	1582	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.25]
6.1.2 Not clearly blinded	26	2592	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.09]
6.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
6.2.1 Outcome assessment blinded	3	874	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.02, 2.66]
6.2.2 Not clearly blinded	4	258	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.09, 3.32]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
6.3.1 Outcome assessment blinded	2	652	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 6.04]
6.3.2 Not clearly blinded	4	258	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.47]
6.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
6.4.1 Outcome assessment blinded	3	444	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.58, 1.93]
6.4.2 Not clearly blinded	8	869	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.03, 4.16]
6.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
6.5.1 Outcome assessment blinded	5	977	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.77, 2.68]
6.5.2 Not clearly blinded	6	281	Risk Ratio (M-H, Random, 95% CI)	5.06 [0.92, 27.72]

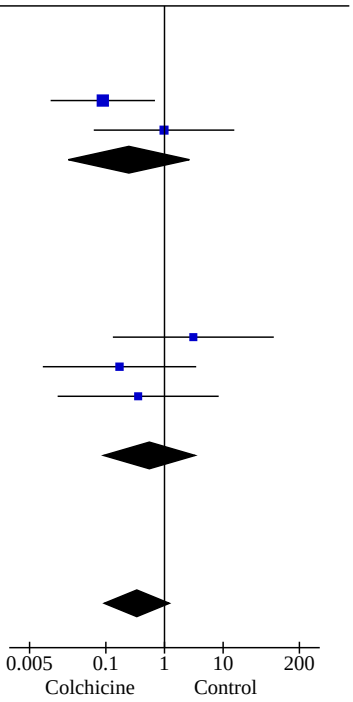
Analysis 6.1. Comparison 6: Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment), Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Outcome assessment blinded						
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**808**		**774**	**19.3%**	**1.05 [0.88 , 1.25]**
Total events:	144		140			
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
6.1.2 Not clearly blinded						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Subtotal (95% CI)		**1343**		**1249**	**80.7%**	**0.91 [0.75 , 1.09]**
Total events:	239		250			
Heterogeneity: Tau² = 0.05; Chi² = 38.77, df = 25 (P = 0.04); I² = 36%						
Test for overall effect: Z = 1.05 (P = 0.30)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.6%						



Analysis 6.2. Comparison 6: Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment), Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Outcome assessment blinded						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**454**		**420**	**52.8%**	**0.25 [0.02 , 2.66]**
Total events:	2		11			
Heterogeneity: Tau² = 1.47; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 1.15 (P = 0.25)						
6.2.2 Not clearly blinded						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Parise 1995	0	21	0	20		Not estimable
Subtotal (95% CI)		**132**		**126**	**47.2%**	**0.55 [0.09 , 3.32]**
Total events:	1		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						

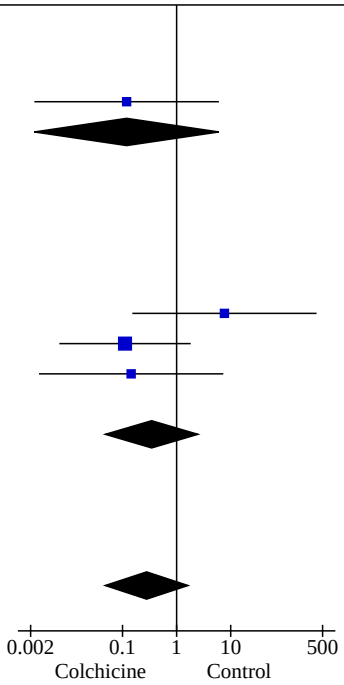


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 6.3. Comparison 6: Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment), Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.3.1 Outcome assessment blinded						
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**342**		**310**	**20.1%**	**0.12 [0.00 , 6.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
6.3.2 Not clearly blinded						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Parise 1995	0	21	0	20		Not estimable
Subtotal (95% CI)		**132**		**126**	**79.9%**	**0.35 [0.05 , 2.47]**
Total events:	1		3			
Heterogeneity: Chi² = 3.22, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

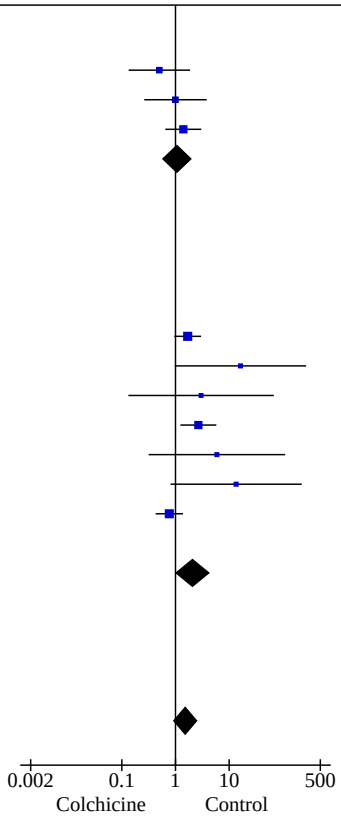


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

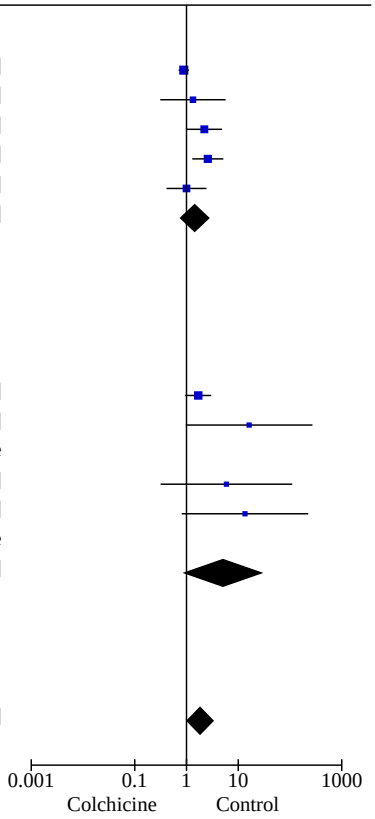
Analysis 6.4. Comparison 6: Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment), Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 Outcome assessment blinded						
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**222**		**222**	**34.2%**	**1.06 [0.58 , 1.93]**
Total events:	21		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.85)						
6.4.2 Not clearly blinded						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**439**		**430**	**65.8%**	**2.07 [1.03 , 4.16]**
Total events:	68		38			
Heterogeneity: Tau² = 0.36; Chi² = 13.75, df = 6 (P = 0.03); I² = 56%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 2.04, df = 1 (P = 0.15), I² = 50.9%						



Analysis 6.5. Comparison 6: Colchicine vs control: sensitivity analysis - detection bias (blinding of outcome assessment), Outcome 5: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Outcome assessment blinded						
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Subtotal (95% CI)		**490**		**487**	**72.8%**	**1.44 [0.77 , 2.68]**
Total events:	96		74			
Heterogeneity: Tau² = 0.34; Chi² = 16.18, df = 4 (P = 0.003); I² = 75%						
Test for overall effect: Z = 1.14 (P = 0.25)						
6.5.2 Not clearly blinded						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**148**		**133**	**27.2%**	**5.06 [0.92 , 27.72]**
Total events:	33		8			
Heterogeneity: Tau² = 1.73; Chi² = 7.55, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 1.86, df = 1 (P = 0.17), I² = 46.1%						



Footnotes
(1) From author request

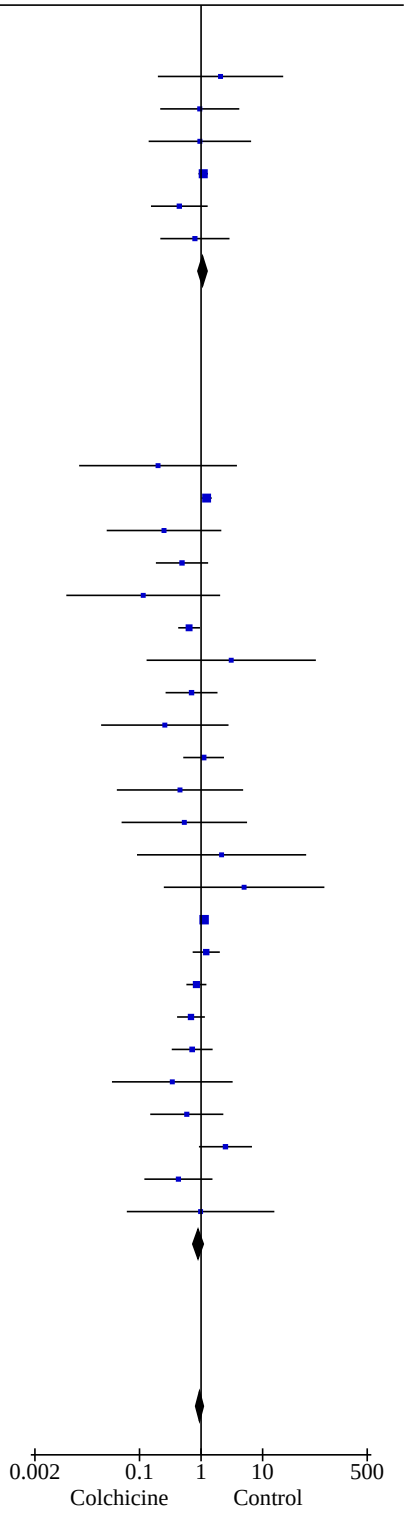
Comparison 7. Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
7.1.1 Low risk	6	1548	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.25]
7.1.2 High or unclear risk	24	2626	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.09]
7.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
7.2.1 Low risk	3	630	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.01, 13.68]
7.2.2 High or unclear risk	4	502	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.07, 2.30]
7.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.3.1 Low risk	3	630	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.36]
7.3.2 High or unclear risk	3	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.01, 1.18]
7.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
7.4.1 Low risk	2	360	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.66, 2.51]
7.4.2 High or unclear risk	9	953	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.89, 3.33]
7.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
7.5.1 Low risk	3	639	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.87, 3.16]
7.5.2 High or unclear risk	8	619	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.94, 5.04]

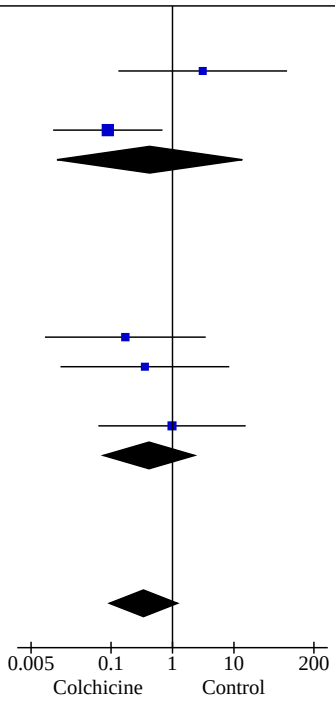
Analysis 7.1. Comparison 7: Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data), Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Low risk						
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**791**		**757**	**20.9%**	**1.05 [0.89 , 1.25]**
Total events:	150		145			
Heterogeneity: Tau² = 0.00; Chi² = 3.27, df = 5 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
7.1.2 High or unclear risk						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**1360**		**1266**	**79.1%**	**0.89 [0.73 , 1.09]**
Total events:	233		245			
Heterogeneity: Tau² = 0.05; Chi² = 38.82, df = 23 (P = 0.02); I² = 41%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.3%						



Analysis 7.2. Comparison 7: Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data), Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Low risk						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Parise 1995	0	21	0	20		Not estimable
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Subtotal (95% CI)		**331**		**299**	**48.5%**	**0.42 [0.01 , 13.68]**
Total events:	2		10			
Heterogeneity: Tau² = 4.52; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 0.48 (P = 0.63)						
7.2.2 High or unclear risk						
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**255**		**247**	**51.5%**	**0.41 [0.07 , 2.30]**
Total events:	1		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

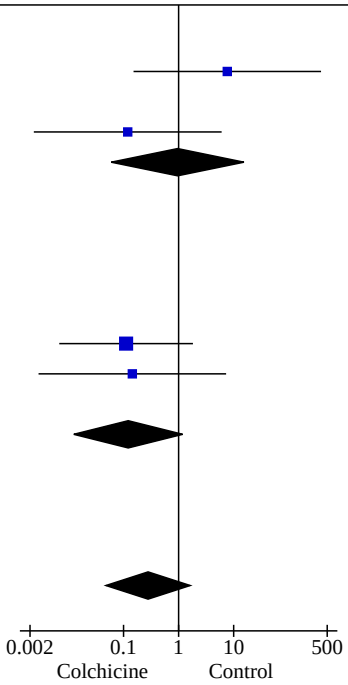


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 7.3. Comparison 7: Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data), Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.3.1 Low risk						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Parise 1995	0	21	0	20		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**331**		**299**	**40.2%**	**0.96 [0.06 , 15.36]**
Total events:	1		1			
Heterogeneity: Chi² = 2.16, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 0.03 (P = 0.98)						
7.3.2 High or unclear risk						
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Subtotal (95% CI)		**143**		**137**	**59.8%**	**0.12 [0.01 , 1.18]**
Total events:	0		3			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.4%						

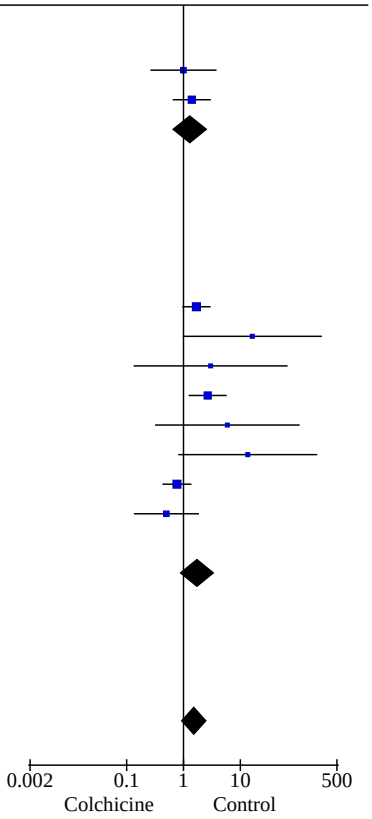


Footnotes

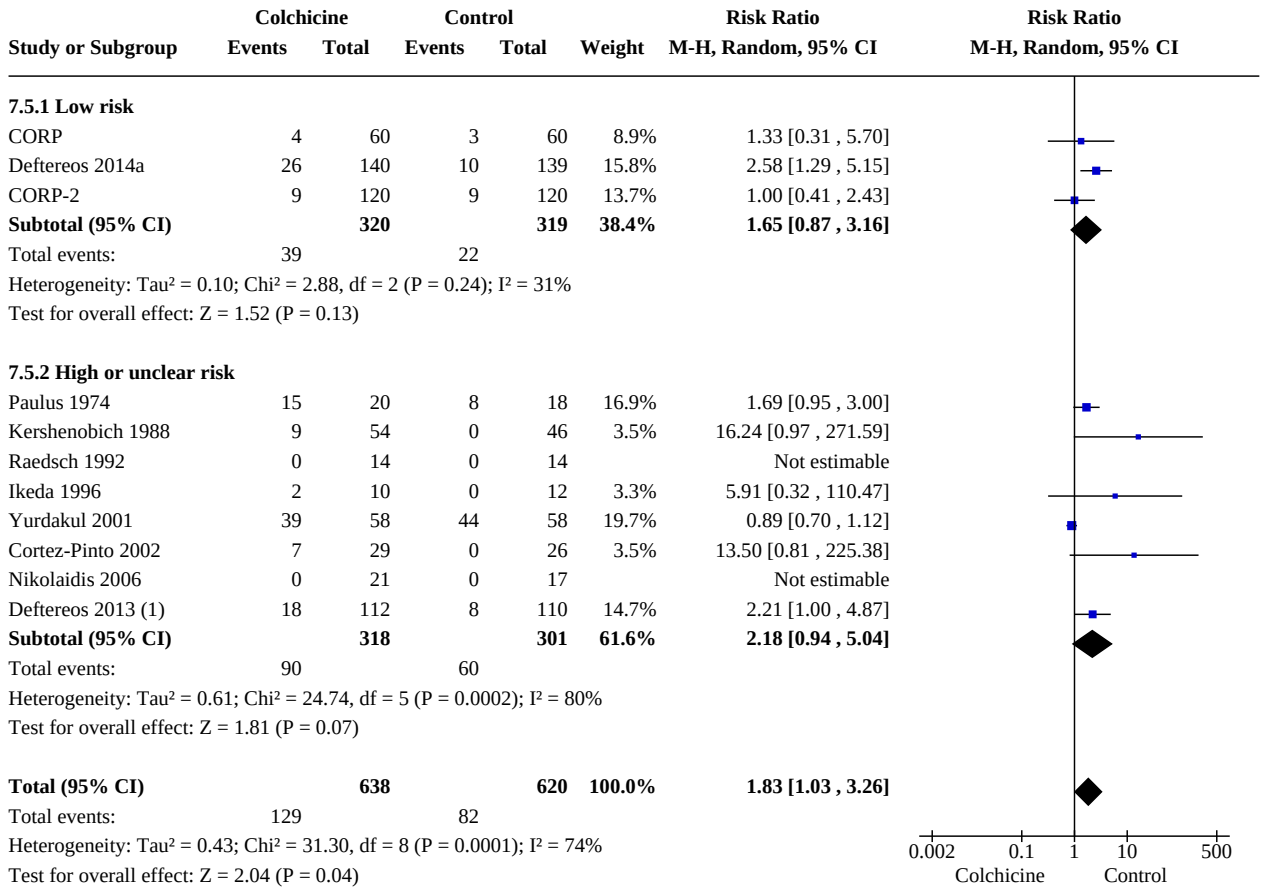
(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 7.4. Comparison 7: Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data), Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.4.1 Low risk						
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**180**		**180**	**25.1%**	**1.29 [0.66 , 2.51]**
Total events:	18		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
7.4.2 High or unclear risk						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
Subtotal (95% CI)		**481**		**472**	**74.9%**	**1.72 [0.89 , 3.33]**
Total events:	71		44			
Heterogeneity: Tau² = 0.38; Chi² = 16.24, df = 7 (P = 0.02); I² = 57%						
Test for overall effect: Z = 1.62 (P = 0.11)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



Analysis 7.5. Comparison 7: Colchicine vs control: sensitivity analysis - attrition bias (incomplete outcome data), Outcome 5: Adverse event (gastrointestinal)



Footnotes

(1) From author request

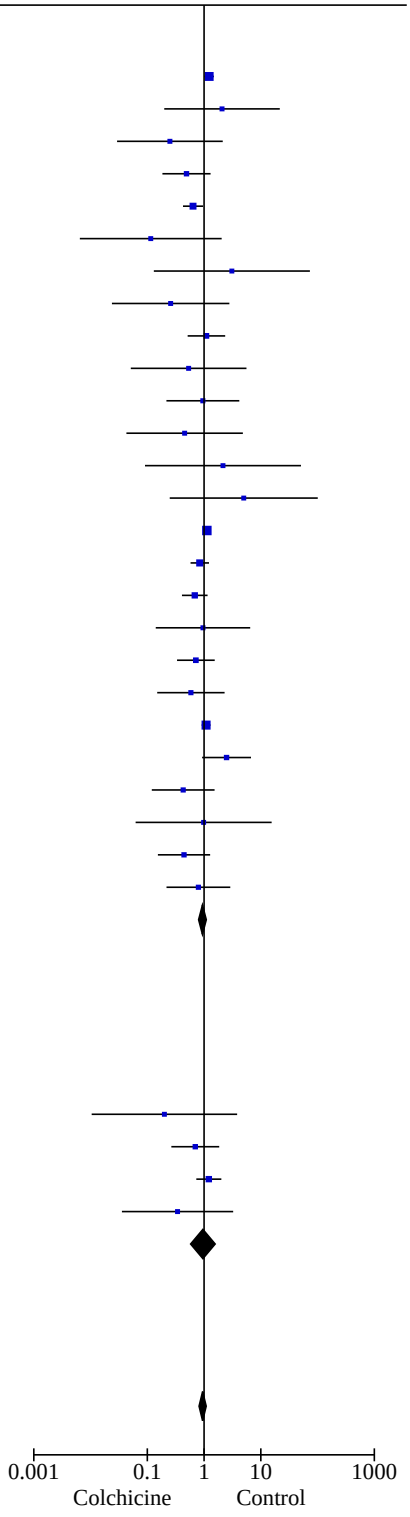
Comparison 8. Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Mortality (all-cause)	30	4174	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
8.1.1 Full journal publication	26	3303	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.09]
8.1.2 Abstract only	4	871	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.58, 1.57]
8.2 Mortality (cardiovascular)	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
8.2.1 Full journal publication	7	1132	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.21]
8.2.2 Abstract only	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.3 Myocardial infarction (fatal)	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
8.3.1 Full journal publication	6	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.05, 1.62]
8.3.2 Abstract only	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
8.4 Adverse event (total)	11	1313	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.93, 2.46]
8.4.1 Full journal publication	9	725	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.90, 2.84]
8.4.2 Abstract only	2	588	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.41, 4.74]
8.5 Adverse event (gastrointestinal)	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
8.5.1 Full journal publication	11	1258	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.03, 3.26]
8.5.2 Abstract only	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

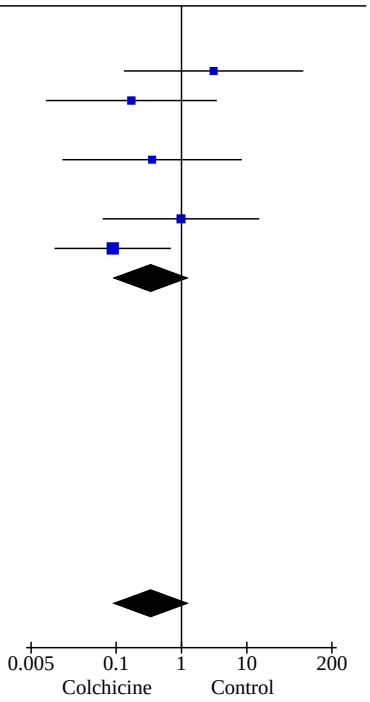
Analysis 8.1. Comparison 8: Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only), Outcome 1: Mortality (all-cause)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Full journal publication						
Kyle 1985	47	52	36	49	15.6%	1.23 [1.02 , 1.49]
Kaplan 1986	2	28	1	29	0.4%	2.07 [0.20 , 21.58]
Reinhardt 1986	1	37	4	37	0.4%	0.25 [0.03 , 2.13]
Warnes 1987	5	34	9	30	2.0%	0.49 [0.18 , 1.30]
Kershenobich 1988	21	54	28	46	7.9%	0.64 [0.43 , 0.96]
Bodenheimer 1988	0	28	4	29	0.2%	0.11 [0.01 , 2.04]
Trinchet 1989	1	33	0	34	0.2%	3.09 [0.13 , 73.20]
O'Keefe 1992	1	130	2	67	0.4%	0.26 [0.02 , 2.79]
Wang 1994	11	50	10	50	3.1%	1.10 [0.51 , 2.36]
Vuoristo 1995	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Parise 1995	3	21	3	20	0.9%	0.95 [0.22 , 4.18]
Olsson 1995	1	44	2	40	0.4%	0.45 [0.04 , 4.82]
Lin 1996	1	38	0	27	0.2%	2.15 [0.09 , 50.95]
Poupon 1996	2	37	0	37	0.2%	5.00 [0.25 , 100.72]
Kyle 1997	63	71	61	77	17.8%	1.12 [0.97 , 1.29]
Adhami 1998	18	29	17	23	8.8%	0.84 [0.58 , 1.22]
Douglas 1998	8	14	10	12	5.7%	0.69 [0.41 , 1.15]
Almasio 2000	2	46	2	44	0.6%	0.96 [0.14 , 6.50]
Cortez-Pinto 2002	8	29	10	26	3.0%	0.72 [0.33 , 1.54]
Kaplan 1999	3	43	5	42	1.1%	0.59 [0.15 , 2.30]
Morgan 2005	134	274	124	275	16.2%	1.08 [0.91 , 1.30]
Antoniou 2006	7	18	5	32	1.9%	2.49 [0.92 , 6.71]
Muntoni 2010	3	37	7	37	1.2%	0.43 [0.12 , 1.53]
Deftereos 2013	1	112	1	110	0.3%	0.98 [0.06 , 15.51]
Nidorf 2013	5	282	10	250	1.7%	0.44 [0.15 , 1.28]
Deftereos 2014a	4	140	5	139	1.2%	0.79 [0.22 , 2.90]
Subtotal (95% CI)		**1710**		**1593**	**91.5%**	**0.94 [0.80 , 1.09]**
Total events:	353		358			
Heterogeneity: Tau² = 0.03; Chi² = 36.26, df = 25 (P = 0.07); I² = 31%						
Test for overall effect: Z = 0.83 (P = 0.41)						
8.1.2 Abstract only						
Kershenobich 1976	0	14	2	14	0.2%	0.20 [0.01 , 3.82]
Buligescu 1989	7	100	8	80	2.0%	0.70 [0.27 , 1.85]
Colman 1998	22	63	19	66	5.9%	1.21 [0.73 , 2.02]
Copilot	1	264	3	270	0.4%	0.34 [0.04 , 3.26]
Subtotal (95% CI)		**441**		**430**	**8.5%**	**0.95 [0.58 , 1.57]**
Total events:	30		32			
Heterogeneity: Tau² = 0.03; Chi² = 3.22, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**2151**		**2023**	**100.0%**	**0.94 [0.82 , 1.09]**
Total events:	383		390			
Heterogeneity: Tau² = 0.03; Chi² = 39.72, df = 29 (P = 0.09); I² = 27%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Analysis 8.2. Comparison 8: Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only), Outcome 2: Mortality (cardiovascular)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Full journal publication						
Kaplan 1986	1	28	0	29	15.3%	3.10 [0.13 , 73.12]
Kershenobich 1988	0	54	2	46	16.7%	0.17 [0.01 , 3.47]
Parise 1995	0	21	0	20		Not estimable
Vuoristo 1995	0	29	1	31	15.2%	0.36 [0.02 , 8.39]
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Deftereos 2013	1	112	1	110	19.6%	0.98 [0.06 , 15.51]
Nidorf 2013	1	282	10	250	33.2%	0.09 [0.01 , 0.69]
Subtotal (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
8.2.2 Abstract only						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**586**		**546**	**100.0%**	**0.34 [0.09 , 1.21]**
Total events:	3		14			
Heterogeneity: Tau² = 0.19; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Not applicable						

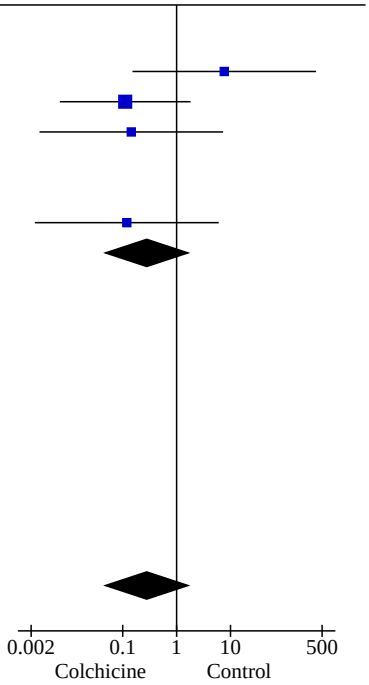


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

Analysis 8.3. Comparison 8: Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only), Outcome 3: Myocardial infarction (fatal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
8.3.1 Full journal publication						
Kaplan 1986	1	28	0	29	20.1%	7.66 [0.15 , 386.16]
Kershenobich 1988	0	54	2	46	39.6%	0.11 [0.01 , 1.82]
Vuoristo 1995	0	29	1	31	20.1%	0.14 [0.00 , 7.29]
Parise 1995	0	21	0	20		Not estimable
Yurdakul 2001 (1)	0	60	0	60		Not estimable
Nidorf 2013	0	282	1	250	20.1%	0.12 [0.00 , 6.04]
Subtotal (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
8.3.2 Abstract only						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**474**		**436**	**100.0%**	**0.28 [0.05 , 1.62]**
Total events:	1		4			
Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Not applicable						

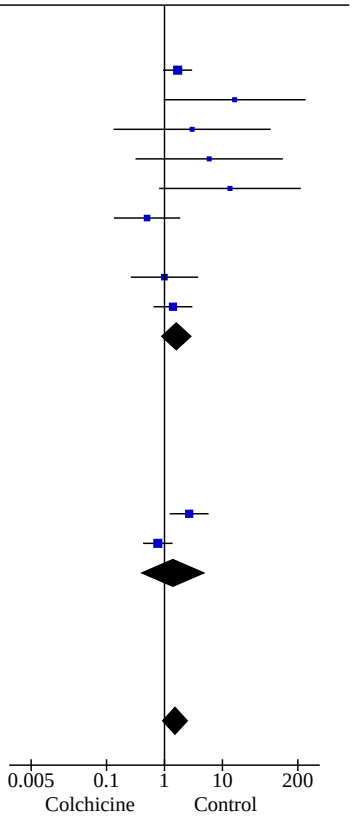


Footnotes

(1) From author request: "We have not seen any cardiovascular events during the trial or later."

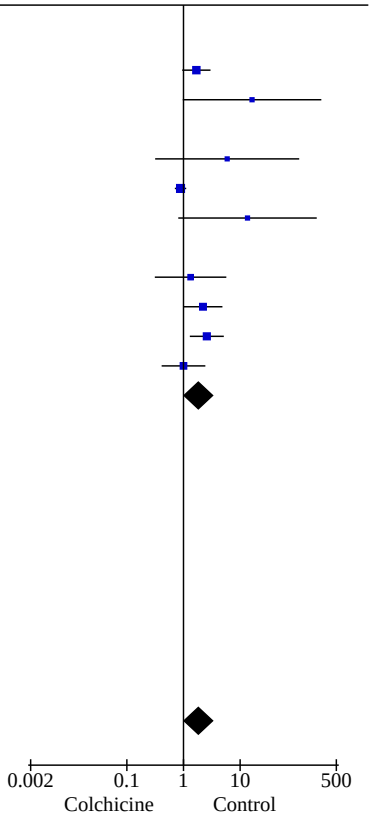
Analysis 8.4. Comparison 8: Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only), Outcome 4: Adverse event (total)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.4.1 Full journal publication						
Paulus 1974	15	20	8	18	19.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	2.7%	16.24 [0.97 , 271.59]
Raedsch 1992	1	14	0	14	2.2%	3.00 [0.13 , 67.91]
Ikeda 1996	2	10	0	12	2.5%	5.91 [0.32 , 110.47]
Cortez-Pinto 2002	7	29	0	26	2.7%	13.50 [0.81 , 225.38]
CORE	3	42	6	42	9.1%	0.50 [0.13 , 1.87]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	4	60	8.9%	1.00 [0.26 , 3.81]
CORP-2	14	120	10	120	16.2%	1.40 [0.65 , 3.03]
Subtotal (95% CI)		**370**		**355**	**64.1%**	**1.60 [0.90 , 2.84]**
Total events:	55		28			
Heterogeneity: Tau² = 0.18; Chi² = 9.94, df = 7 (P = 0.19); I² = 30%						
Test for overall effect: Z = 1.60 (P = 0.11)						
8.4.2 Abstract only						
Lukina 1995	16	27	6	27	16.2%	2.67 [1.23 , 5.77]
Copilot	18	264	24	270	19.6%	0.77 [0.43 , 1.38]
Subtotal (95% CI)		**291**		**297**	**35.9%**	**1.39 [0.41 , 4.74]**
Total events:	34		30			
Heterogeneity: Tau² = 0.66; Chi² = 6.39, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**661**		**652**	**100.0%**	**1.52 [0.93 , 2.46]**
Total events:	89		58			
Heterogeneity: Tau² = 0.22; Chi² = 16.43, df = 9 (P = 0.06); I² = 45%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



Analysis 8.5. Comparison 8: Colchicine vs control: sensitivity analysis - reporting bias (selective reporting, i.e. abstract publication only), Outcome 5: Adverse event (gastrointestinal)

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 Full journal publication						
Paulus 1974	15	20	8	18	16.9%	1.69 [0.95 , 3.00]
Kershenobich 1988	9	54	0	46	3.5%	16.24 [0.97 , 271.59]
Raedsch 1992	0	14	0	14		Not estimable
Ikeda 1996	2	10	0	12	3.3%	5.91 [0.32 , 110.47]
Yurdakul 2001	39	58	44	58	19.7%	0.89 [0.70 , 1.12]
Cortez-Pinto 2002	7	29	0	26	3.5%	13.50 [0.81 , 225.38]
Nikolaidis 2006	0	21	0	17		Not estimable
CORP	4	60	3	60	8.9%	1.33 [0.31 , 5.70]
Deftereos 2013 (1)	18	112	8	110	14.7%	2.21 [1.00 , 4.87]
Deftereos 2014a	26	140	10	139	15.8%	2.58 [1.29 , 5.15]
CORP-2	9	120	9	120	13.7%	1.00 [0.41 , 2.43]
Subtotal (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
8.5.2 Abstract only						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**638**		**620**	**100.0%**	**1.83 [1.03 , 3.26]**
Total events:	129		82			
Heterogeneity: Tau² = 0.43; Chi² = 31.30, df = 8 (P = 0.0001); I² = 74%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						



Footnotes
(1) From author request

ADDITIONAL TABLES

Table 1. Characteristics of included studies: Summary

	All Studies	Studies in participants with high cardiovascular risk
Total number of studies	39 (100%)	4 (100%)
No. of participants in all studies	4992	1230
Publication year, median (range)	1996 (1974 - 2014)	2013 (1992 - 2014)
Publication year < 2000	24 (62%)	1 (25%)
Multicentre studies	9 (23%)	0 (0%)
Study size, median (IQR)	84 (54 - 129)	251 (210 - 406)

Table 1. Characteristics of included studies: Summary *(Continued)*

Participant age, median (IQR)	54 (51 - 61)	66 (63 - 67)
Men, median (IQR)	62 (25 - 87)	77 (66 - 88)
***Follow-up*[1]**		
0.5 to 1 year	6 (15%)	3 (75%)
1 to 3 years	17 (44%)	0 (0%)
> 3 years	15 (38%)	1 (25%)
Colchicine treatment		
≤ 1 mg/d	27 (69%)	3 (75%)
> 1 mg/d	12 (31%)	1 (25%)
***Control treatment*, n (%)**		
Active treatment	8 (21%)	0 (0%)
Inactive, placebo	31 (79%)	4 (100%)
Clinical setting		
CVD, arteriosclerotic	3 (8%)	3 (75%)
CVD, other	1 (3%)	1 (25%)
Hepatobiliary disease	25 (64%)	0 (0%)
Other	10 (26%)	0 (0%)
Cardiovascular risk profile		
Primary prevention	0 (0%)	0 (0%)
Secondary prevention	4 (10%)	4 (100%)
Not specified	34 (87%)	0 (0%)

Number of studies (% of column total) if not stated otherwise.
IQR: Interquartile range
[1]Longest follow-up period for an outcome that was used in this systematic review.

Table 2. Characteristics of included studies: Overview

Study (Reference)	Partici-pants (n)	Centres	Clinical setting	Age* (y)	Men (%)	Colchicine dose (mg/d)	Control	Follow-up (yrs)e
Studies in patients with high cardiovascular risk								
Deftereos 2013	222	Single	PCI/CVD	64	65	2 x 0.5	Placebo	0.5
Deftereos 2014a	279	Single	Heart failure	67	67	1 - 2 x 0.5[2]	Placebo	0.5
Nidorf 2013	532	Single	PCI/CVD	67	89	0.5	Usual care[3]	3
O'Keefe 1992	197	Single	PCI/CVD	61	86	2 x 0.6	Placebo	0.5
Other studies								
Adhami 1998	52	Single	Liver disease	54	87	1[4]	Placebo	11
Almasio 2000	90	Multi	PBC	55	10	1	Placebo[5]	3
Antoniou 2006	50	Multi	Other	68	84	1	IFN-gamma[6]	2.1
Bodenheimer 1988	57	N/R	PBC	52	9	2 x 0.6	Placebo	2.2
Buligescu 1989	180	N/R.	Liver disease	N/R	N/R	1	“Conventional therapy”	3
Colman 1998	129	N/R	Liver disease	N/R	N/R	1	Placebo	3.8
Copilot	555	N/R	Liver disease	51	70	2 x 0.6	Peg-IFN-alpha	2
CORE	84	Single	Other	54	35	1 - 2 x 0.5[2]	Usual care[3,7]	1.7
CORP	120	Multi	Other	48	46	0.5 - 1[2]	Placebo[8]	2
CORP-2	240	Multi	Other	49	50	1 - 2 x 0.5[2]	Placebo	1.7
Cortez-Pinto 2002	62	Single	Liver disease	54	89	1[4]	Placebo	3.4
Douglas 1998	26	Single	Other	68	77	0.6 - 1.2[9]	Prednisone	2.5
Ikeda 1996	22	Single	PBC	61	14	1	Usual care [3,5]	2

Table 2. Characteristics of included studies: Overview *(Continued)*

Kaplan 1986	60	Single	PBC	N/R[e,0]	5	2 x 0.6	Placebo	2
Kaplan 1999	87	Single	PBC	51	6	2 x 0.6	Methotrexate[ee]	10
Kershenobich 1976	28	N/R	Liver disease	N/R	N/R	1[4]	Placebo	2
Kershenobich 1988	100	Single	Liver disease	51	50	1[4]	Placebo	14
Kyle 1985	101	Single	Other	63	58	2 x 0.6[e,2]	Melphalan/prednisone	5
Kyle 1997	148	N/R	Other	64	N/R	2 x 0.6	Usual care [3,e,3]	9
Lin 1996	66	Single	Liver disease	40	88	1[4]	Usual care[3]	4
Lukina 1995	54	N/R	Other	N/R	N/R	1 - 2	Dimethyl sulfoxide	2 or 7[e,4]
Morgan 2005	549	Multi	Liver disease	56	98	2 x 0.6	Placebo	6
Muntoni 2010	74	Single	Liver disease	53	62	1	"usual treatment for cirrhosis"	4
Nikolaidis 2006	38	Single	Liver disease	51	61	1[d]	Usual care[3]	1
Olsson 1995	84	Multi	PSC	42	67	1	Placebo	3
Parise 1995	41	Single	Liver disease	49	88	1	Placebo	1
Paulus 1974	52	Multi	Other	53	100	3 x 0.5	Placebo[e,5]	0.5
Poupon 1996	74	Multi	PBC	54	15	1[4]	Placebo[5]	2
Raedsch 1992	28	Single	PBC	54	0	1	Placebo[5]	2
Reinhardt 1986	74	Single	Liver disease	N/R	N/R	4 x 0.25[d]	Placebo	3
Trinchet 1989	67	Single	Liver disease	52	57	1	Placebo	0.5
Vuoristo 1995	90	Multi	Liver disease	57	14	2x 0.5	Placebo	2
Wang 1994	100	Single	Liver disease	60	94	1	Placebo	2.2
Warnes 1987	64	Single	PBC	N/R	N/R	2x 0.5	Placebo	1.5

Table 2. Characteristics of included studies: Overview *(Continued)*

Yurdakul 2001	116	Single	Other	27	53	2 - 4 x 0.5[2]	Placebo	2

*Age is reported as mean in all studies but three: Antoniou 2006; Kyle 1985; Nikolaidis 2006 reported median age.

[1]Longest mean follow-up-period for a review-relevant outcome.
[2]Weight adjusted maintenance dose.
[3]We assume usual care, but this was not explicitly reported.
[4]Five days per week.
[5]Ursodeoxycholic acid in both groups.
[6]Prednisolone in both groups.
[7]Aspirin in both groups.
[8]Aspirin or Ibuprofen in both groups.
[9]As tolerated.
[10]80% > 50 years.
[11]Ursodeoxycholic acid in both groups after 2 years.
[12]Increased in 0.6 mg steps (as tolerated). Median dose 1.5 mg/d.
[13]Melphalan and prednisone in both groups.
[14]Two years in colchicine group, 7 years in control group.
[15]Probenecid in both groups.

Table 3. Results of subgroup and sensitivity analyses

Outcome	Studies (n)	Events (n)	Participants (n)	Summary effect (95% CI)	Heterogeneity (I^2), %	Subgroup effect (P value)
Participants with high cardiovascular risk						
All-cause mortality	4	29	1230	RR 0.54 (0.26 to 1.14)	0%	0.13
Cardiovascular mortality	2	13	754	RR 0.25 (0.02 to 2.66)	49%	N/C
Myocardial infarction						
• fatal or non-fatal	1	22	532	RR 0.20 (0.07 to 0.57)	-	N/C
• fatal	1	1	532	RR 0.30 (0.01 to 7.22)	-	N/C
• non-fatal	1	21	532	RR 0.21 (0.07 to 0.61)	-	N/C
Stroke						
• fatal or non-fatal	2	7	754	OR 0.38 (0.09 to 1.70)	0%	N/C
• fatal	2	1	754	OR 7.26 (0.14 to 365.85)	-	N/C
• non-fatal	2	6	754	OR 0.23 (0.05 to 1.17)	0%	N/C
Heart failure						
• fatal or non-fatal	1	3	222	RR 0.14 (0.01 to 2.69)	-	N/C
• fatal	1	1	222	RR 0.33 (0.01 to 7.95)	-	N/C
• non-fatal	1	2	222	RR 0.20 (0.01 to 4.05)	-	N/C
Hospitalisation	0	-	-	-	-	-
Cardiovascular intervention	1	9	222	RR 0.79 (0.22 to 2.85)	-	N/C
Adverse event, any	0	-	-	-	-	N/C
Adverse event, gastrointestinal	2	62	501	RR 2.41 (1.43 to 4.06)	0%	N/C
Colchicine dose						
All-cause mortality	-	-	-	-	-	-
≤ 1mg/d	21	268	2420	RR 0.82 (0.67 to 0.99)	0%	0.03
> 1mg/d	9	505	1754	RR 1.08 (0.93 to 1.25)	31%	-
Adverse event, any						
≤ 1mg/d	7	60	687	RR 1.75 (0.74 to 4.14)	40%	0.75

Table 3. Results of subgroup and sensitivity analyses *(Continued)*

> 1mg/d	3	87	626	RR 1.47 (0.72 to 2.97)	73%	-
Peto odds ratio for outcomes with event rates between 1% and 5%						
All-cause mortality in participants with high cardiovascular risk	4	29	1230	OR 0.53 (0.25 to 1.11)	0%	-
Cardiovascular mortality	7	17	1132	OR 0.24 (0.09 to 0.64)	15%	-
Mantel-Haenszel risk ratio without zero correction for outcomes with event rates between 1% and 5%						
All-cause mortality in participants with high cardiovascular risk	4	29	1230	RR 0.54 (0.26 to 1.12)	0%	-
Cardiovascular mortality	7	17	1132	RR 0.20 (0.06 to 0.68)	0%	-

N/C: not calculated
OR: Peto odds ratio
RR: risk ratio

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Colchicine] explode all trees
#2 colcemid*
#3 demecolcine
#4 colchamine
#5 lumicolchicine*
#6 gamma-lumicolchicine*
#7 beta-lumicolchicine
#8 colchicin*
#9 colchichine
#10 aqua next colchin
#11 colchicum
#12 colchily
#13 colchimedio
#14 colchiquim
#15 colchisol
#16 colchysat
#17 colcine
#18 colcrys
#19 colgout
#20 goutichine
#21 goutnil
#22 kolkicin
#23 nsc next 757
#24 tolchicine
#25 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID)

1. exp Colchicine/
2. colcemid*.tw.
3. demecolcine.tw.

4. colchamine.tw.
5. lumicolchicine*.tw.
6. gamma-lumicolchicine*.tw.
7. beta-lumicolchicine.tw.
8. colchicin*.tw.
9. colchichine.tw.
10. aqua colchin.tw.
11. colchicum.tw.
12. colchily.tw.
13. colchimedio.tw.
14. colchiquim.tw.
15. colchisol.tw.
16. colchysat.tw.
17. colcine.tw.
18. colcrys.tw.
19. colgout.tw.
20. goutichine.tw.
21. goutnil.tw.
22. kolkicin.tw.
23. nsc 757.tw.
24. tolchicine.tw.
25. or/1-24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti.
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. exp animals/ not humans.sh.
35. 33 not 34
36. 25 and 35
37. (trial* or random*).tw.
38. 33 or 37
39. 38 not 34
40. 25 and 39

EMBASE.com

'colchicine'/de OR colcemid*:ab,ti OR demecolcine:ab,ti OR colchamine:ab,ti OR lumicolchicine*:ab,ti OR ((beta OR gamma) NEXT/1 lumicolchicine*):ab,ti OR colchicin*:ab,ti OR colchichine:ab,ti OR 'aqua colchin':ab,ti OR colchicum:ab,ti OR colchily:ab,ti OR colchimedio:ab,ti OR colchiquim:ab,ti OR colchisol:ab,ti OR colchysat:ab,ti OR colcine:ab,ti OR colcrys:ab,ti OR colgout:ab,ti OR goutichine:ab,ti OR goutnil:ab,ti OR kolkicin:ab,ti OR 'nsc 757':ab,ti OR tolchicine:ab,ti AND (random*:ab,ti OR placebo* OR (double NEXT/1 blind*):ab,ti)

EMBASE (OVID)

1. colchicine/
2. colcemid*.tw.
3. demecolcine.tw.
4. colchamine.tw.
5. lumicolchicine*.tw.
6. gamma-lumicolchicine*.tw.
7. beta-lumicolchicine.tw.
8. colchicin*.tw.
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16. colchysat.tw.
17. colcine.tw.
18. colcrys.tw.
19. colgout.tw.
20. goutichine.tw.
21. goutnil.tw.
22. kolkicin.tw.
23. nsc 757.tw.
24. tolchicine.tw.
25. or/1-24
26. random$.tw.
27. factorial$.tw.
28. crossover$.tw.
29. cross over$.tw.
30. cross-over$.tw.
31. placebo$.tw.
32. (doubl$ adj blind$).tw.
33. (singl$ adj blind$).tw.
34. assign$.tw.
35. allocat$.tw.
36. volunteer$.tw.
37. crossover procedure/
38. double blind procedure/
39. randomized controlled trial/
40. single blind procedure/
41. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. (animal/ or nonhuman/) not human/
43. 41 not 42
44. 25 and 43
45. limit 44 to embase

WHAT'S NEW

Date	Event	Description
29 May 2020	Review declared as stable	This Cochrane Review has been superseded because it has been split into two reviews, one for primary prevention and one for secondary prevention.

HISTORY

Protocol first published: Issue 3, 2014
Review first published: Issue 1, 2016

CONTRIBUTIONS OF AUTHORS

Design of the study: LGH, MB
Data extraction: LGH, HE, VLG, AA, KKO, DG, AJN, MB
Data analysis: LGH, HE
Interpreation of results:LGH, HE, AJN, MN, MB
Writing the first draft: LGH, HE
Critical revision of the manuscript: All authors
Reading and approval of the final version of the paper: All Authors
Guarantor: LGH

DECLARATIONS OF INTEREST

All authors declare no financial relationships with any organisation that might have an interest in the submitted work in the previous three years.

Mark Nidorf was involved in one of the included studies, which was investigator-initiated and conducted without external financial support. All other authors declare no other relationships or activities that could appear to have influenced the submitted work.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no relevant study protocol deviations.

We prespecified all analyses, with the exception of sensitivity analyses using alternative meta-analytical models, which we deemed useful when we observed event rates close to 1% (Bradburn 2007). In addition, we analysed the risk of bias in more detail.

Since there were no data specifically for populations without a history of cardiovascular disease events or without established coronary heart disease, but data specifically for participants at high risk for cardiovascular events (secondary prevention of cardiovascular disease events or established coronary heart disease), we focused more specifically on this clinically very relevant population and described the findings for this population in more detail. To be consistent, we also report the subgroup analyses on colchicine dose for all outcomes. The prespecified approach and the analyses remained unchanged.

To reduce the overall number of subanalyses, we dropped the analysis on the type of condition (other than CVD) for which colchicine was given and the analysis including only studies reporting on both a primary outcome indicating potential benefit and adverse events, and we did not evaluate the impact of funding of the primary studies. We conducted sensitivity analyses only when there were at least three studies to be combined.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [adverse effects] [*therapeutic use]; Cardiovascular Diseases [mortality] [*prevention & control]; Cause of Death; Colchicine [adverse effects] [*therapeutic use]; Heart Failure [prevention & control]; Myocardial Infarction [mortality] [prevention & control]; Randomized Controlled Trials as Topic; Risk; Stroke [mortality] [prevention & control]

MeSH check words

Humans