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Colchicine for pericarditis (Review)

Alabed S, Cabello JB, Irving GJ, Qintar M, Burls A

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[Intervention Review]

Colchicine for pericarditis

Samer Alabed[1], Juan B Cabello[2], Greg J Irving[3], Mohammed Qintar[4], Amanda Burls[5]

[1]Continuing Education, University of Oxford, Oxford, UK. [2]Department of Cardiology & CASP Spain, Hospital General Universitario de Alicante, Alicante, Spain. [3]Division of Primary Care, University of Liverpool, Liverpool, UK. [4]Internal Medicine Department, Cleveland Clinic Foundation, Cleveland, Ohio, USA. [5]School of Health Sciences, City University London, London, UK

Contact address: Samer Alabed, Continuing Education, University of Oxford, Oxford, UK. samer.alabed@conted.ox.ac.uk.

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ABSTRACT

Background

Pericarditis is the inflammation of the pericardium, the membranous sac surrounding the heart. Recurrent pericarditis is the most common complication of acute pericarditis, causing severe and disabling chest pains. Recurrent pericarditis affects one in three patients with acute pericarditis within the first 18 months. Colchicine has been suggested to be beneficial in preventing recurrent pericarditis.

Objectives

To review all randomised controlled trials (RCTs) that assess the effects of colchicine alone or combined, compared to any other intervention to prevent further recurrences of pericarditis, in people with acute or recurrent pericarditis.

Search methods

We searched the following bibliographic databases on 4 August 2014: Cochrane Central Register of Controlled Trials (CENTRAL, Issue 7 of 12, 2014 on *The Cochrane Library*), MEDLINE (OVID, 1946 to July week 4, 2014), EMBASE (OVID, 1947 to 2014 week 31), and the Conference Proceedings Citation Index - Science on Web of Science (Thomson Reuters) 1990 to 1 Aug 2014. We did not apply any language or time restrictions.

Selection criteria

RCTs of people with acute or recurrent pericarditis who are receiving colchicine compared to any other treatment, in order to prevent recurrences.

Data collection and analysis

Two review authors independently selected trials for inclusion, extracted data and assessed the risk of bias. The first primary outcome was the time to recurrence, measured by calculating the hazard ratios (HRs). The second primary outcome was the adverse effects of colchicine. Secondary outcomes were the rate of recurrences at 6, 12 and 18 months, and symptom relief.

Main results

We included four RCTs, involving 564 participants in this review. We compared the effects of colchicine in addition to a non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen, aspirin or indomethacin to the effects of the NSAID alone. Two comparable trials studied the effects of colchicine in 204 participants with recurrent pericarditis and two trials studied 360 people with acute

pericarditis. All trials had a moderate quality for the primary outcomes. We identified two on-going trials; one of these trials examines acute pericarditis and the other assesses recurrent pericarditis.

There was moderate quality evidence that colchicine reduces episodes of pericarditis in people with recurrent pericarditis over 18 months follow-up (HR 0.37; 95% confidence interval (CI) 0.24 to 0.58). It is expected that at 18 months, the number needed to treat (NNT) is 4. In people with acute pericarditis, there was moderate quality evidence that colchicine reduces recurrence (HR 0.40; 95% CI 0.27 to 0.61) at 18 months follow-up. Colchicine led to a greater chance of symptom relief at 72 hours (risk ratio (RR) 1.4; 95% CI 1.26 to 1.56; low quality evidence). Adverse effects were mainly gastrointestinal and included abdominal pain and diarrhoea. The pooled RR for adverse events was 1.26 (95% CI 0.75 to 2.12). While the number of people experiencing adverse effects was higher in the colchicine than the control groups (9% versus 7%), the quality of evidence was low owing to imprecision, and there was no statistically significant difference between the treatment groups (P = 0.42). There was moderate quality evidence that treatment with colchicine led to more people stopping treatment due to adverse events (RR 1.87; 95% CI 1.02 to 3.41).

Authors' conclusions

Colchicine, as adjunctive therapy to NSAIDs, is effective in reducing the number of pericarditis recurrences in patients with recurrent pericarditis or acute pericarditis. However, evidence is based on a limited number of small trials. Patients with multiple resistant recurrences were not represented in any published or on-going trials, and it is these patients that are in the most need for treatment.

PLAIN LANGUAGE SUMMARY

Systematic review of randomised controlled trials about the efficacy and safety of colchicine in people with pericarditis

Pericarditis is the inflammation and swelling of the tissue covering the outer layer of the heart. Pericarditis causes severe and disabling chest pain and fever, however the main issue is the repeated recurrence of pericarditis attacks. Colchicine is an ancient medication that has been used in the treatment of other inflammatory diseases such as gout.

We wanted to discover whether colchicine alone or added to other medications is better or worse than alternative therapies in preventing pericarditis. We have reviewed all randomised controlled trials about the effect of colchicine in preventing recurrence of pericarditis in people with pericarditis. We found four trials involving 564 participants, who were followed up for at least 18 months. Two studies examined the use of colchicine in people with recurrent pericarditis and two examined the use of colchicine in people with a first episode of pericarditis. The evidence is current to August 2014.

The trials showed that people taking colchicine have a lower risk of developing pericarditis recurrence and a higher proportion experience symptom relief. It is expected that at 18 months, one pericarditis recurrence can be avoided for every four people receiving colchicine with NSAIDs rather than NSAIDs alone. Adverse effects were reported in all trials and affected 15 people (9%) of the 162 taking colchicine. Adverse effects included abdominal pain, nausea and vomiting.

Two studies were designed so that participants knew the type of intervention they were taking and people in the comparison group had no dummy pill. The results of these studies could exaggerate the effects of the drug.

The evidence suggests beneficial effects of colchicine in preventing recurrence of pericarditis, however this is based on a limited number of small trials. More trials are currently being done and we await their results to see if the benefits of colchicine can be further confirmed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Time to recurrence of pericarditis			
Outcomes	**Relative effect (95% CI)**	**No. of Participants (studies)**	**Quality of the evidence (GRADE)**
Recurrent pericarditis Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Intervention: colchicine with NSAID; Comparison: NSAID alone Follow-up: median 18 months Setting: multicentre secondary care	**HR 0.37** (0.24 to 0.58)	204 (2 studies)	**moderate**[1]
Acute pericarditis Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Intervention: colchicine with NSAID; Comparison: NSAID alone Follow-up: median 18 months Setting: multicentre secondary care	**HR 0.40** (0.27 to 0.61)	360 (2 studies)	**moderate**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **ECG**: electrocardiography; **HR:** Hazard ratio; **NSAID**: non-steroidal anti-inflammatory drug

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] High risk of bias in blinding domain.

Description of the condition

BACKGROUND

Definitions

Pericarditis is the inflammation of the pericardium, the membranous sac surrounding the heart. Acute pericarditis is idiopathic without an obvious aetiology in 80% to 90% of cases but has a presumed viral origin (Dudzinski 2012). Other causes include tuberculosis, or bacterial and neoplastic diseases that are more common in low-income countries (Zayas 1995).

Recurrent pericarditis is both the most common and most troublesome complication of acute pericarditis and is mostly idiopathic. This is because the exact cause of the recurrence of pericarditis is not known, but appears to be autoimmune as indicated by the presence of autoantibodies and response to steroids (Cantarini 2013). There are two types of recurrent pericarditis, intermittent or incessant. In the incessant type, discontinuation of NSAIDs usually causes a relapse in less than six weeks. In the intermittent type, people have varying symptom-free intervals, usually longer than six weeks, without therapy (Soler-Soler 2004).

Incidence

The actual incidence of acute pericarditis in unknown, but it is estimated to be 28 cases per 100,000 population/year (Imazio 2008a). It is responsible for 4% of all causes of chest pain (Launbjerg 1996) and 0.1% of all hospitalisations (Pölzl 2011). Recurrent pericarditis can occur in up to 20% to 30% of people who have experienced acute pericarditis (Fowler 1990; Adler 1998); this figure increases to 50% after the first recurrence (Imazio 2005a). The rate of recurrence varies and can be a single episode in some people, however, other people can experience more frequent episodes over many years. Almost 45% of people experience two episodes, 40% have between three and five episodes, and 10% have more than five episodes (Soler-Soler 2004; Shabetai 2005).

Presentation and diagnosis

The manifestation of acute pericarditis is a pleuritic chest pain with a sign or symptom marking the activity of the disease, such as fever, a pericardial rub, electrocardiography (ECG) changes (a widespread ST-segment elevation or PR-segment depression), pericardial effusion and raised inflammatory markers (erythrocyte sedimentation rate or C-reactive protein (CRP)) (Spodick 2003; Troughton 2004). Acute pericarditis is diagnosed if at least two of these manifestations are met (Dudzinski 2012).

Recurrent pericarditis is a repeat episode of acute pericarditis and can have similar symptoms, although it tends to be milder (Soler-Soler 2004; Adler 2011). There are no uniform diagnostic criteria for recurrent pericarditis (Imazio 2007), however, observational studies identified pleuritic chest pain, increased CRP and ECG changes as the minimum criteria for diagnosing a recurrent episode of acute pericarditis (Brucato 2006a; Khandaker 2010).

Prognosis

The first relapse usually occurs within 18 months after the initial pericarditis episode (Imazio 2005a; Imazio 2005b). However, people can have many relapses that manifest as severe chest pain lasting from several hours to several days. These painful and disabling episodes impair quality of life and cause a severe clinical problem (Soler-Soler 2004).

Acute and recurrent pericarditis can be complicated by life-threatening consequences, such as pericardial effusion, tamponade or constriction, which may increase mortality (Soler-Soler 2004; Dudzinski 2012). These complications can occur in up to 3.5% of people in recurrent pericarditis and even more frequently in people with acute pericarditis (Imazio 2007). However, in the long term, complications are rare and the prognosis of recurrent pericarditis is good (Brucato 2006a).

Description of the intervention

Therapy of acute pericarditis should always be targeted as much as possible to the underlying aetiology. In idiopathic pericarditis, treatment aims to manage the symptoms of the acute episode and to then prevent subsequent recurrences. For a long time, high-dose steroids were the mainstay of treatment. Yet, high-dose steroids caused numerous serious adverse effects (Shabetai 2005), and their prolonged use has actually worsened the prognosis by increasing the recurrence rate of pericarditis and lengthening the course of the disease (Artom 2005; Imazio 2005b; Imazio 2008). Therefore, identifying interventions with a safer adverse effect profile was essential in order avoid worsening the natural course of recurrent pericarditis in other ways.

Episodes of pericarditis are currently treated with aspirin or other NSAIDs and with steroids for refractory cases (Maisch 2004; Soler-Soler 2004). Colchicine has been used for the prevention of recurrences (Brucato 2006).

Colchicine has anti-inflammatory actions and antiproliferative effects (Robert 2009). It inhibits many of the functions of neutrophils, such as the adhesion to endothelium and the release of a chemotactic factor from neutrophil lysosomes (Nuki 2008).

Colchicine is considered a safe treatment in the treatment dose (Imazio 2007), however, in high doses, it has many toxic effects and, in addition, it has a narrow therapeutic window (Robert 2009). The maximum therapeutic dose is 4 mg/24 hours, while a fatal dose can be as low as 7 mg/24 hours with a higher fatality rate if the dose exceeds 0.5 - 0.8 mg/kg (Niel 2006; Cocco 2010; Finkelstein 2010). The parenteral use increases the risk of mortality and is not used in clinical practice (Cocco 2010). Overdose is associated with gastrointestinal, hepatic, renal, neuromuscular and cerebral toxicity; bone marrow damage; and high mortality (Nuki 2008; Finkelstein 2010). Colchicine is excreted mainly by the liver after 20 to 40 hours (Niel 2006) and can accumulate in people with advanced liver disease (Rudi 1994).

The recommended dose of colchicine used in gout and in recurrent pericarditis is 1 mg/day by oral administration (Adolph 1990;

Adler 1998; Cocco 2010). Analgesia with colchicine is evident within 12 to 14 hours of oral administration (Imazio 2009). The most common adverse effects of the therapeutic dose are nausea, vomiting, diarrhoea and abdominal pain (Niel 2006).

How the intervention might work

Colchicine is used in treating several inflammatory diseases such as gout and familial Mediterranean fever (FMF) (Famaey 1988; Niel 2006). Considering the possible autoimmune inflammatory pathophysiology of recurrent pericarditis (Caforio 2010; Cantarini 2013), and its response to immunosuppressive and anti-inflammatory treatment (Marcolongo 1995), it is deemed acceptable and logical to determine the effects of colchicine in the management of recurrent pericarditis.

Why it is important to do this review

People with recurrent pericarditis can have a number of relapses over many years, causing severe chest pain. These episodes of pain limit both the functionality of patients and their quality of life, causing both a social and psychological burden for the patients and an economic burden on the hospitals taking care of them (Soler-Soler 2004). The high incidence of recurrent pericarditis in almost one-third of patients with acute pericarditis increases this burden. Therefore, there is a need to find and examine therapies that decrease the number of recurrences.

Observational studies have shown that colchicine might be effective in treating recurrent pericarditis (Rodríguez de la Serna 1987; Guindo 1990; Millaire 1994; Soler-Soler 2004; Imazio 2005b; Brucato 2006). However, RCTs have only recently studied the effect of colchicine on pericarditis. Therefore, there is a need to systematically assess and critically appraise these trials in order to obtain a more definite clinical answer for both patients and clinicians dealing with recurrent pericarditis.

A similar review has been published in the *Heart* journal (Imazio 2012). The main differences in our review are that we did not include postcardiac injury syndromes due to the different aetiology and pathophysiology from acute or recurrent pericarditis. In addition, we analysed trials of acute pericarditis separately from trials of recurrent pericarditis. We mention any differences between our review and the *Heart* journal review explicitly in the section 'Agreements and disagreements with other studies or reviews'.

OBJECTIVES

To review all randomised controlled trials (RCTs) that assess the effects of colchicine alone or combined, compared to any other intervention to prevent further recurrences of pericarditis, in people with acute or recurrent pericarditis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs with any length of follow-up, and we will not impose any limitations on language or publication status.

Types of participants

1. People with acute idiopathic pericarditis treated to prevent recurrences.
2. People with recurrent idiopathic pericarditis who have had a documented episode of acute pericarditis, defined by any clinically valid diagnostic criteria such as described in the 'Description of the condition' section and who have evidence of recurrent pericarditis.

We included participants regardless of the number of pericarditis recurrences, gender, age or ethnicity. We excluded acute or recurrent pericarditis that has bacterial or neoplastic causes, as in these cases the known cause has to be treated and managed. We excluded pericarditis as a result of postcardiac injury such as postmyocardial infarction pericarditis (Dressler's syndrome), postpericardiotomy syndrome and post-traumatic pericarditis.

Types of interventions

1. Colchicine: in any dose, duration, intensity or means of administration and alongside any additional therapy, on the condition that the additional therapy was also used at the same or similar dose in the control group.
2. Controls: any inactive control intervention (e.g. placebo or no treatment) or any active control intervention (e.g. aspirin, NSAIDs or steroids).

Types of outcome measures

We considered study eligibility regardless of the outcomes investigated or presented.

Primary outcomes

1. Time to first recurrence expressed using hazard ratios (HRs).
2. Adverse effects of colchicine: general and specific during treatment and on withdrawal of treatment.

Secondary outcomes

1. Rate of first recurrence of pericarditis as expressed by the risk ratio (RR) at the following periods: short term (six months), medium term (12 months) and long term (splitting > 12 months into categories e.g. 18 months, 24 months).
2. Symptom relief during pericarditis episode.

Search methods for identification of studies

Electronic searches

SA and the Trials Search Co-ordinator (TSC) of the Cochrane Heart Group (CHG) searched the following databases on 4 August 2014.

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 7 of 12, 2014 on *The Cochrane Library*).
- MEDLINE (Ovid, 1946 to July week 4, 2014).
- EMBASE Classic and EMBASE (Ovid, 1947 to 2014 week 31).
- Conference Proceedings Citation Index- Science (CPCI-S) on Web of Science (Thomson Reuters, 1990 to 5 August 2014).

The search did not include any language or time restriction. The "not" Boolean was not used. The search strategies used can be found in Appendix 1.

The RCT filter for MEDLINE is the Cochrane sensitivity-maximising RCT filter, and for EMBASE, terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* have been applied (Lefebvre 2011).

Searching other resources

We searched the following three databases of on-going trials on 5 August 2013.

- International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- European Union Clinical Trials Register (www.clinicaltrialsregister.eu).

We examined the references of all identified studies to look for more studies. We contacted the first author of each included study for information about trials that had not been published.

Data collection and analysis

Selection of studies

Two review authors (SA, MQ) independently reviewed the titles and abstracts identified from the searches done by SA and the TSC. SA and MQ obtained full-text publications when necessary, and determined eligibility independently. The opinion of a third author (JBC) was sought when encountered with one of the unpublished trials and dealing with studies of postcardiac injury syndrome. We did not need to contact study authors for further information.

Data extraction and management

Two authors (SA, GJI) independently assessed the methodological quality and extracted data from the studies fulfilling the inclusion criteria. The data were extracted using an agreed data extraction form. We included essential items mentioned in the *Cochrane Handbook for Systematic Reviews of Interventions* table 7.3a (Higgins 2011a) regarding methods, participants, intervention, outcomes and results. The data extraction form was piloted by (SA) on one of the included studies.

'Summary of findings' table

We used the GRADE approach, adopted by The Cochrane Collaboration, to interpret findings (Schünemann 2011). We used the GRADE profiler (GRADEpro) (GRADEpro 2008) programme to import data from Review Manager 5 (RevMan 2012), to create the 'Summary of findings' tables. The GRADE system involves an assessment of the quality of a body of evidence for each individual outcome. In GRADEpro the quality of evidence for each outcome is separately rated as high, moderate, low and very low quality. The rate of the outcomes of all randomised trials were regarded as high and downgraded depending on: limitations in the design of the selected studies, high risk of bias, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high probability of publication bias. The outcome-specific ratings were produced in tables by GRADEpro and give information about the overall quality of evidence from each included study. We selected all primary outcomes for inclusion in the 'Summary of findings' table.

Assessment of risk of bias in included studies

Two review authors (SA, GJI) independently assessed the risk of bias in each study using the 'Risk of bias' tool of The Cochrane Collaboration. A third author (JBC) was consulted about differences in opinion about grading the risk of bias in the blinding domain.

Risk of bias for an outcome within a study (across domains)

The specific characteristics assessed included random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other sources of bias.

Risk of bias for an outcome across studies (e.g. for a meta-analysis)

We summarised the risk of bias of the outcomes for each domain included in the meta-analyses and incorporated judgements into the 'Summary of findings' tables. We expressed the risk of bias in each domain using the following judgements: 'low risk', 'high risk' or 'unclear risk' of bias, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* table 8.5.d (Higgins 2011b).

Measures of treatment effect

We followed recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* sections 9.2 and 9.4 (Higgins 2011c) for measuring the effects of different data types.

Time-to-recurrence

We used hazard ratios (HRs) with 95% confidence intervals (CIs) to express events such as time until the first recurrence of pericarditis. We used the methods described in Tierney 2007 to calculate approximate hazard ratios.

Dichotomous data

We calculated the risk ratio (RR) with 95% CI for binary data (i.e. recurrence rates, adverse effects). We calculated the number needed to treat (NNT) from the absolute risk reduction (ARR) if available.

Continuous data

We did not encounter any continuous data.

Counts and rates

We expressed count data (i.e. recurrence rate of pericarditis) as rate ratios.

Unit of analysis issues

Our primary outcome was any recurrence of pericarditis and our unit of analysis was the patient. We did not encounter any cluster trials, studies with multiple treatment groups or cross-over trials.

Dealing with missing data

There was no issues with missing data in the included studies.

Assessment of heterogeneity

Clinical heterogeneity

Clinical heterogeneity might be due to differences in the population i.e. age or ethnicity, or differences in interventions i.e. different doses, duration, intensity or delivery method, or due to differences in the way outcomes are measured, such as different criteria for pericarditis recurrence. All studies with outlying situations will be fully discussed. A subgroup analysis of different causes of clinical heterogeneity is planned.

People with acute pericarditis and recurrent pericarditis have a different baseline risk for recurrence, as patients who already have experienced recurrent episodes of pericarditis are more susceptible to recurrence (Soler-Soler 2004; Shabetai 2005). Therefore, we analysed the two patient groups separately for any outcome comparing recurrence rates, as specified in the protocol. We combined outcomes of adverse effects and symptom relief for people with acute and recurrent pericarditis as they are not affected by the risk for recurrence.

Methodological heterogeneity

We investigated all included trials for unpredicted outlying methods. All included studies were methodologically comparable.

Statistical heterogeneity

We investigated statistical heterogeneity by visual inspection and carrying out both the Chi^2 test and the I^2 test. The Chi^2 test with a small P value provides evidence of heterogeneity. However, because of the low power of the Chi^2 test we used a P value of 0.1 to determine statistical significance. We used the I^2 statistic to quantify statistical inconsistency and assess the impact of heterogeneity on the meta-analysis. An I^2 > 50% was set to demonstrate high heterogeneity.

Assessment of reporting biases

As the number of included studies was less than ten studies we did not attempt to use the funnel plot test, because it would have too low a power to distinguish chance from real asymmetry (Sterne 2011).

Data synthesis

We pooled data in meta-analyses where they were available and it was clinically acceptable to do so. We used Review Manager software for meta-analyses (RevMan 2012). For the statistical analyses, we used the fixed-effect model with 95% CI as the main analysis. In addition, we undertook a sensitivity analysis using the random-effects model as per protocol.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We intended to do a subgroup meta-analyses for:

1. dosage of colchicine used; and
2. age of patient (children and adults).

However, there was not enough data to perform any of the subgroup analyses.

2. Investigation of heterogeneity

We did not encounter high levels of heterogeneity.

Sensitivity analysis

1. We performed a sensitivity analyses of fixed-effect versus random-effects, as per protocol.
2. It was not possible to perform a sensitivity analyses of studies judged to be at high risk of bias.

RESULTS

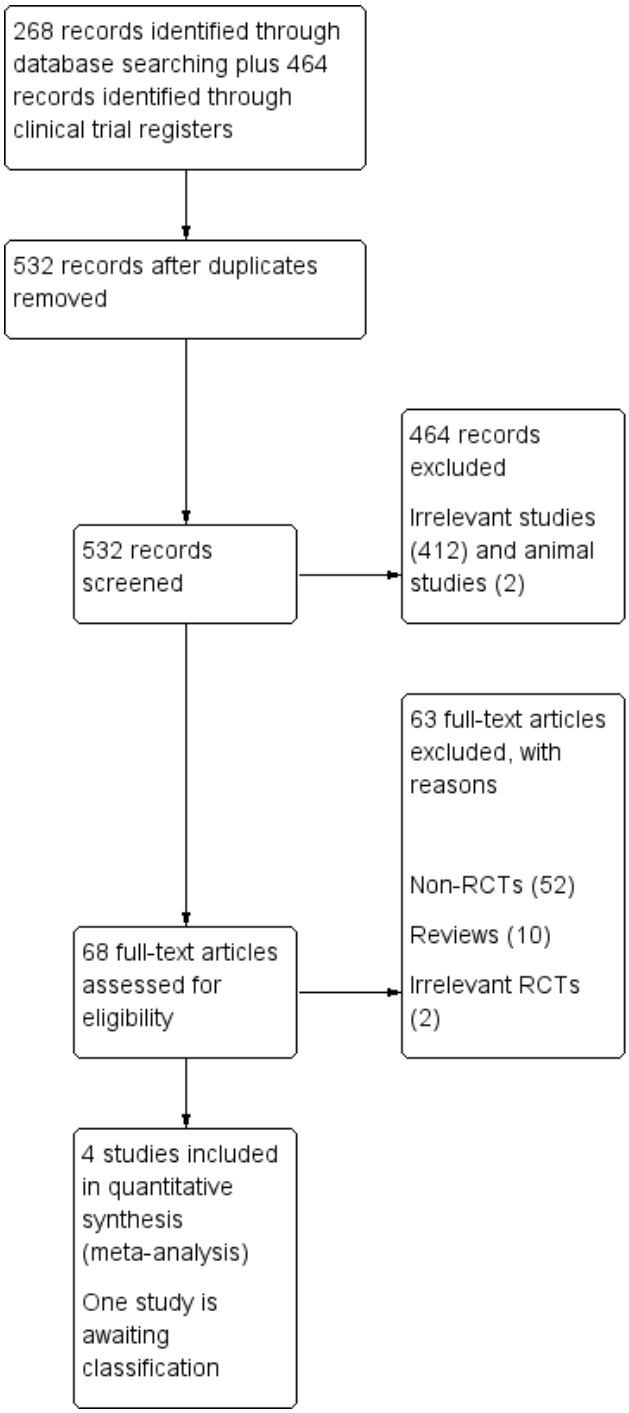
Description of studies

Results of the search

We identified a total of 732 articles from the search of CENTRAL, MEDLINE, EMBASE, Web of Science and clinical trial registers. Removal of duplicates left 481 articles for screening, including 68 abstracts of conferences. From the 532 screened articles we excluded 464 and retrieved 68 full papers. A further 63 were not RCTs or were RCTs not related to our review. This left four trials that met the inclusion criteria (Imazio 2005; Imazio 2005a; Imazio 2011; Imazio 2013) and one study awaiting classification (Imazio 2014). We did not identify any additional eligible trials after scanning the reference lists of full-text papers.

The process with reasons for exclusions is described in Figure 1 and a list of excluded trials is given in the table 'Characteristics of excluded studies'.

Figure 1. Study flow diagram.



Additionally, we identified one on-going RCT registered on the European Union Clinical Trials Register EUCTR2009-011258-16-ES.

Included studies

The four included trials were conducted between 2005 and 2013. The trials, Imazio 2005 and Imazio 2005a were done by the same research group and some members of this research group were also involved in Imazio 2011 and Imazio 2013. All four studies were parallel design, RCTs. Two studies were double-blind (Imazio 2011; Imazio 2013) and the other two (Imazio 2005; Imazio 2005a) were open-label. Two studies addressed people with recurrent pericarditis (Imazio 2005a; Imazio 2011), whereas (Imazio 2005; Imazio 2013) addressed patients with acute pericarditis.
The mean follow-up of all included studies was from 20 to 24 months. All studies were conducted in secondary care settings in Italy. Imazio 2011 and Imazio 2013 are multicentre studies, Imazio 2005 was conducted in two health centres and Imazio 2005a was conducted in one hospital. All trials were done by the same research group. All studies were published in English.

Population

We included a total of 564 participants in this review. Of these, 204 participants were recruited in the trials for recurrent pericarditis and 360 for acute pericarditis. Only patients with a first recurrence of pericarditis were recruited in Imazio 2005a and Imazio 2011. Diagnosed pericarditis was either idiopathic (80% to 85%) or autoimmune (15% to 20%) in Imazio 2005, Imazio 2005a and Imazio 2011). In Imazio 2013, 77% of included participants had idiopathic pericarditis, 3% autoimmune pericarditis and 20% had postcardiac injury syndrome. Although we initially decided to exclude patients with postcardiac injury syndrome, it was not possible in Imazio 2013 to analyse data of patients with idiopathic pericarditis only.

All included participants had chest pain as the main symptom. The main signs were ECG changes (70% to 85%), pericardial effusion (60% to 68%) and pericardial rub (20% to 35%). The number of female participants was slightly higher in Imazio 2005, Imazio 2005a and Imazio 2011, making up 52% to 57% in Imazio 2005 and Imazio 2011 and 62% to 69% in Imazio 2005a. In Imazio 2013, female participants made up 40%.
The mean ages in years (standard errors are given in brackets) of the included patients in each group are as follows.

- Imazio 2005: control 57.2 (19.6), colchicine 56.5 (18.2).
- Imazio 2005a: control 51.2 (16.3), colchicine 56.4 (16.9).
- Imazio 2011: control 47.3 (14.4), colchicine 47.9 (15.4).
- Imazio 2013: control 50.7 (17.5), colchicine 53.5 (16.2).

No study included children, elderly people, pregnant or lactating women or women of childbearing age who were not using contraception. People with severe liver disease, serum creatinine levels greater than 221 µmol/L (2.5 mg/dL), gastrointestinal disease; or known hypersensitivity to colchicine were also excluded.

Baseline characteristics of participants in the trials are shown in Table 1.

Intervention

The intervention was oral colchicine tablets in all included trials. Colchicine was given at a loading dose of 1 mg every 12 hours for the first day of treatment, except Imazio 2013 which did not have a loading dose. A maintenance dose of 0.5 mg twice daily was then continued for six months in Imazio 2005a and Imazio 2011 and three months in Imazio 2005 and Imazio 2013. People who weighed less than 70 kg, had the loading dose changed to 0.5 mg every 12 hours, followed by a maintenance dose of 0.5 mg once daily.
Participants in both the intervention and control group in all included studies received oral aspirin at a dose of 800 mg every six to eight hours for seven to 10 days. The dosage of aspirin was then gradually tapered down over a period of three to four weeks. In Imazio 2011 and Imazio 2013, ibuprofen 600 mg was additionally offered as an alternative to aspirin. People who had contraindications to aspirin received prednisone for four weeks with gradual tapering down. The dose of prednisone given was 1 to 1.5 mg/kg in Imazio 2005 and Imazio 2005a, and 0.2 to 0.5 mg/kg in Imazio 2011 and Imazio 2013.
Participants in both the intervention and control group also received a proton-pump inhibitor (PPI) while they were on aspirin or another NSAID. The dose of the PPI was not mentioned in the studies.
The control group in Imazio 2011 and Imazio 2013 also received placebo tablets that were identical in colour, shape, and taste to the colchicine tablets and were provided in identical packs. The control group in Imazio 2005 and Imazio 2005a did not receive a placebo.

Outcomes

The recurrence of pericarditis was reported in all studies using survival analysis with Kaplan-Meier event-free curves. The endpoint chosen in the studies was the rate of pericarditis recurrence at 18 months. Recurrences were defined in all studies by chest pain with at least one other objective outcome measure such as pericardial friction rub, widespread ST-segment elevation or PR-segment depression on ECG, new or worsening pericardial effusion on echocardiography and raised inflammatory markers such

as white blood cell count, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

All studies reported on the type and number of adverse events.

Relief from the symptoms of pericarditis at 72 hours was a reported secondary outcome in all included studies. Additonally, Imazio 2011 and Imazio 2013 reported remission rate at one week, number of recurrences, time to first recurrence, disease-related hospitalisation, cardiac tamponade, and rates of constrictive pericarditis as other secondary outcomes.

The main characteristics of the included studies are summarised in the table Characteristics of included studies.

All trials stated that outcomes were assessed and measured by blinded expert cardiologists.

Excluded studies

The main reason for excluding studies was if they were not RCTs and if they were literature reviews. We excluded two RCTs (Finkelstein 2002; Imazio 2007b) as they were of postpericardectomy syndrome which is not relevant to this systematic review. The main characteristics of the excluded studies are in the table 'Characteristics of excluded studies'.

Risk of bias in included studies

In summary, Imazio 2011 and Imazio 2013 have been rated to have a low risk of bias and Imazio 2005 and Imazio 2005a have a moderate risk of bias. For details on the risk of bias in included studies see 'Risk of bias' table (Characteristics of included studies). The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3.

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

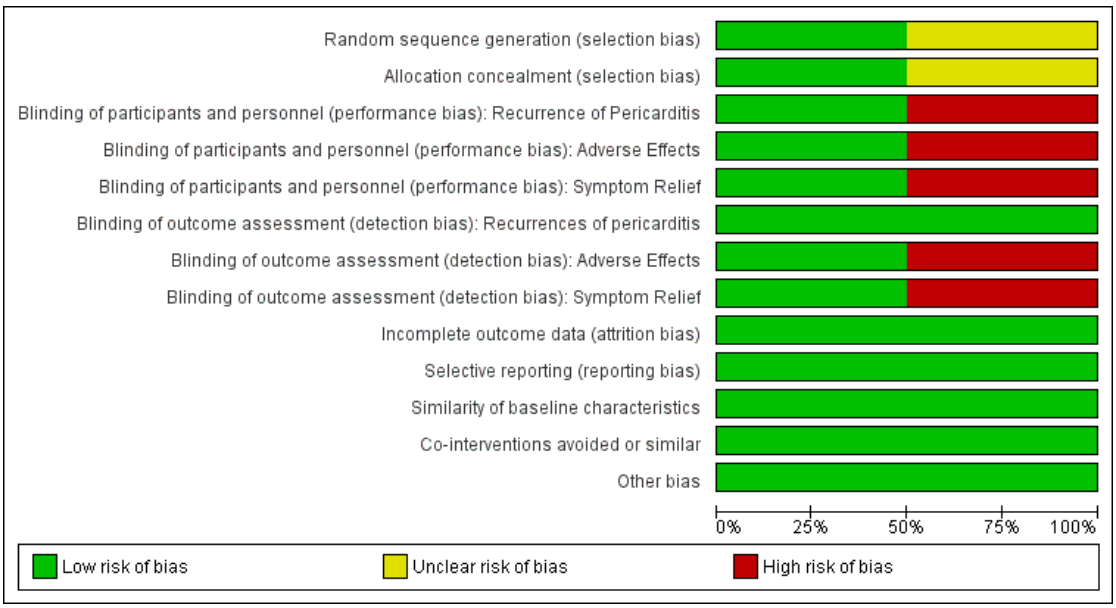
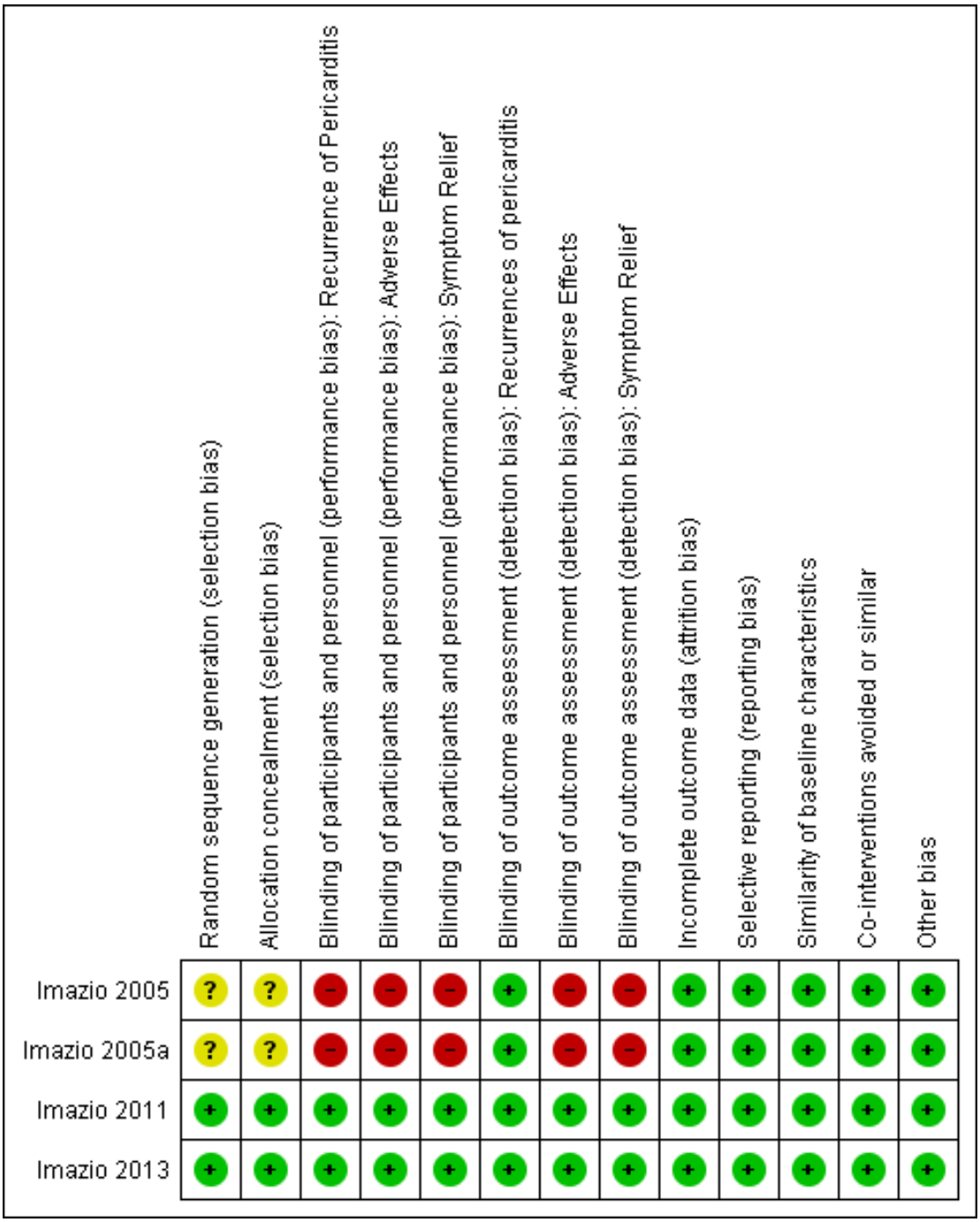


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Risk of bias across studies

We assessed the risk of bias for the reported outcomes using the GRADE approach. We created 'Summary of findings' tables using the Gradepro software. The quality of evidence was moderate for outcomes of pericarditis recurrence and low quality for total adverse events and symptom relief. Details of the risk of bias across studies can be found in: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; and Summary of findings 5.

Allocation

Randomisation

There was no description of how randomisation had been achieved in Imazio 2005 and Imazio 2005a. In Imazio 2011 and Imazio 2013 participants were assigned to treatment groups by a central computer-based automated sequence. In all studies, the sequence for allocation was based on permuted blocks with a block size of four.

Overall, the baseline characteristics of participants in all studies in the intervention and control groups appeared similar after randomisation, as shown in Table 1.

Allocation concealment

Allocation concealment was not reported in Imazio 2005 or Imazio 2005a. In Imazio 2011 and Imazio 2013 allocation concealment was implemented by using sequentially numbered containers. Imazio 2013 mentions that allocation was concealed from patients and investigators.

Blinding

Blinding of participants and personnel

Both Imazio 2005 and Imazio 2005a had an open-label design. Imazio 2011 and Imazio 2013 were double-blinded RCTs for both participants and trial investigators. Additionally, the intervention and control tablets were reported to be identical in colour, shape and taste.

The control intervention was given for only four to five weeks in all studies, whereas colchicine was given for six months (Imazio 2005a; Imazio 2011) or three months (Imazio 2005; Imazio 2013). The study authors did not clarify if anything was given to the control group after the control intervention was stopped in order to maintain blinding. The unequal duration of intervention between the therapeutic and control group might have introduced blinding bias for the participants.

Blinding of outcome assessors and data analysers

Clinical events were validated by an ad-hoc committee of expert cardiologists who were blinded to participants' allocation. Even for Imazio 2005 and Imazio 2005a that had open-label designs, recurrences of pericarditis were assessed by blinded outcome assessors and required the presence of objective outcome measures (raised inflammatory markers or ECG changes). Therefore, we considered the risk of bias to be low. Data analyses were performed by an external committee blinded to treatment allocation.

Incomplete outcome data

The risk of attrition bias seemed low. Intention-to-treat (ITT) analysis was reported in all trials and all randomised participants were included in the final analyses and results. Colchicine therapy was discontinued due to adverse effects (mainly gastrointestinal symptoms) in five patients (8.3%) in Imazio 2005, three patients (7%) in Imazio 2005a, five patients (8%) in Imazio 2011 and fourteen patients (11.7%) in Imazio 2013. In the control group, four (6%) people in Imazio 2011 discontinued therapy due to adverse effects and ten people (8.3%) in Imazio 2013. Whereas in Imazio 2005 and Imazio 2005a no one in the control group withdrew from treatment. All patients who discontinued therapy were followed up for recurrences and were included in all analyses.

Selective reporting

All reported outcomes were clinically relevant.

All studies were done to assess the rate of recurrence of pericarditis with colchicine therapy and this has been reported as the main outcome in all studies.

The secondary outcome of symptom persistence at 72 hours was subjectively chosen by the researchers. Symptoms were not reported at any point in time before or after the studied 72 hours. It was not possible to ensure that this time point was decided on before the trials were done or because it showed the most favourable results. Therefore, we considered the outcome of symptom relief to be of high risk of bias for selective reporting.

Other potential sources of bias

No potential threats to validity had been detected, such as early trial termination or any imbalance in the baseline characteristics of the colchicine or control groups.

No declarations of conflict of interest were made by the trial authors. The funding source had been reported in Imazio 2011 to

be the Italian National Healthcare System. Imazio 2005, Imazio 2005a and Imazio 2013 did not declare the funding source.

Effects of interventions

See: **Summary of findings for the main comparison** Time to recurrence of pericarditis; **Summary of findings 2** Adverse effects of colchicine; **Summary of findings 3** Recurrences in patients with recurrent pericarditis; **Summary of findings 4** Recurrence rate in patients with acute pericarditis; **Summary of findings 5** Symptom relief for pericarditis

Time-to-recurrence

The time-to-recurrence has been expressed in HRs. The log HRs and their standard error have been obtained using the log-rank analysis from a method provided by Trivella 2012 [pers comm]. We calculated the HRs using the generic inverse variance methods in Review Manager (RevMan 2012). We included two trials (Imazio 2005a; Imazio 2011) with 204 participants in the meta-analysis for participants with recurrent pericarditis over 18 months of follow-up: HR 0.37; 95% CI (0.24 to 0.58); I^2= 0%, fixed-effect model (Analysis 1.1).

We included two trials (Imazio 2005; Imazio 2013) with 360 participants in the meta-analysis participants with acute pericarditis over 18 months of follow-up: HR 0.40; 95% CI (0.27 to 0.61); I^2= 0%, fixed-effect model (Analysis 1.2).

Adverse effects of colchicine

All included studies reported on adverse events and their type. All adverse effects of colchicine were due to gastrointestinal intolerance, mainly consisting of diarrhoea but also other effects such as nausea, vomiting or abdominal pain. Two people in Imazio 2013 experienced hepatotoxicity (an elevation of aminotransferase levels) and one person got alopecia.
Similarly most adverse events in the control group were of gastrointestinal origin and one person in each Imazio 2011 and Imazio 2013 experienced hepatotoxicity. No serious adverse effects have been reported.
In Imazio 2011 all adverse effects were recorded in the first week of treatment. No comment on the time of adverse events was made in Imazio 2005, Imazio 2005a or Imazio 2013.
We pooled the results of 564 participants in all four included studies as they had similar baseline characteristics and the interventions were given in similar doses.

Total adverse event

A total of 29 people (10%) in the colchicine group and 23 people (8%) in the control group had adverse effects (RR 1.26; 95% CI (0.75 to 2.12) (P = 0.38); I^2 = 0%, fixed-effect model (Analysis 2.1)). The absolute risk difference (ARD) for adverse effects between colchicine and NSAIDs was 2%.

Adverse effects causing withdrawal of therapy

A total of 27 people out of 282 (9.6%) in the colchicine group had to stop therapy due to adverse effects. Almost everyone who had adverse effects with colchicine decided to stop therapy (27 out of 29). In the control group, 14 participants (5%) decided to stop therapy.
The RR of adverse effects necessitating the stop of therapy was 1.87; 95% CI (1.02 to 3.41), (P = 0.04); I^2 = 5%, fixed-effect model (Analysis 2.2), the ARD was 4.6%.

Recurrence rate

The recurrence rates have been reported by all included studies in a Kaplan-Meier survival curve. Ideally, the recurrence rate should have been calculated using the individual patient data, however as these were not available, the data for recurrence rate has been extracted from the survival curves using the DigitizeIt software (DigitizeIt 2012). The shortcomings of data from Kaplan-Meier curves is that it ignores the censored observations as it is not known whether the outcome event occurred after follow-up ended. The Kaplan-Meier curves do not show how many patients had the recurrence with each drop in the survival-curve. Additionally, it does not take into account the time for the event to happen as participants may have joint the trial at different times (Altman 1991). This might result in some inaccuracies in the results.
The RR was calculated for the recurrence rates at time points of 6 months, 12 months and 18 months.

Recurrence rate in people with recurrent pericarditis

The recurrence rate for participants with recurrent pericarditis was reported in Imazio 2005a and Imazio 2011. We combined the data of 204 participants of both trials to calculate the RR.
Meta-analysis for recurrences in participants with recurrent pericarditis at 6 months: RR 0.28; 95% CI (0.17 to 0.47); I^2= 0%, fixed-effect model (Analysis 3.1).
Meta-analysis for recurrences in participants with recurrent pericarditis at 12 months: RR 0.36; 95% CI (0.23 to 0.56); I^2= 56%, fixed-effect model (Analysis 3.2).
Meta-analysis for recurrences in participants with recurrent pericarditis at 18 months: RR 0.38; 95% CI (0.25 to 0.58); I^2= 0%, fixed-effect model (Analysis 3.3).
The total number of people who had one further recurrence at 18 months in the colchicine group was 21 of 102 (21%) and 55 of 102 (54%) in the NSAIDs group. The ARD was 23%. The number needed to treat (NNT) to prevent one recurrence was 4.4.

Recurrence rate in people with acute pericarditis

The recurrence rate for participants with acute pericarditis was reported in Imazio 2005 and Imazio 2013. We combined the data of 360 participants of both trials to calculate the RR.

At 6 months the RR was 0.36; 95% CI (0.23 to 0.58) (Analysis 4.1). At 6 months, 20 patients (11%) in the colchicine group and 55 patients (31%) in the control group had a first recurrence. The ARD was 20%.

At 12 months the RR was 0.40; 95% CI (0.26 to 0.61) (Analysis 4.2). At 12 months, 24 patients (13%) in the colchicine group and 60 patients (33%) in the control group had a first recurrence. The ARD was 20%.

At 18 months the RR was 0.41; 95% CI (0.28 to 0.61) (Analysis 4.3). At 18 months, 27 patients (15%) In the colchicine group and 66 patients (37%) in the control group had a first recurrence. The ARD was 22% and NNT to prevent one recurrence was 4.5.

Symptom relief

All included trials assessed the effect of colchicine on patients' symptoms. Only symptom relief at 72 hours had been reported. The pooled RR for symptom relief at 72 hours was 1.40; 95% CI (1.26 to 1.56); I^2= 0%, fixed-effect model (Analysis 5.1).

Assessment of heterogeneity

All the studies were clinically homogenous and had patients with similar baseline characteristics. All pooled estimates were statistically homogenous (I^2= 0%). The only exception was the pooled effect of symptom relief which had an I^2 = 89%. However, as there is no clinical heterogeneity this might be due to the low number of events in the control group in Imazio 2011.

Subgroup analysis

We have not performed any subgroup analysis. See the 'Differences between protocol and review'.

We had intended to analyse any paediatric population as a subgroup. However, no trial included people younger than 18 years. A review of all non-randomised trials identified in the systematic review search (Table 2) showed that colchicine has been tried in children in 10 cases. In six children (Adler 1998; Yazigi 1998; Jurko 2002) colchicine was effective in preventing further recurrences, however, it failed to show any effect in four other children Raatikka 2003.

It was not possible to perform a subgroup analysis on the dose used as all trials used the same dose of colchicine (1 mg/day). A review of observational studies (Table 2) showed that the most frequent dose used is 1 mg/d (10 of 15 studies). The rest of the reports used doses varying from 0.25 to 2 mg/d with or without a loading dose.

Sensitivity analysis

Due to the limited number of studies, it was not possible to conduct a sensitivity analysis for studies that we judged to be at high risk of bias across at least one domain.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Adverse effects of colchicine for pericarditis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Colchicine			
Total adverse effects Patient reported Follow-up: median 18 months	**Study population**		**RR 1.26** (0.75 to 2.12)	564 (4 studies)	⊕⊕ **low**[1,2]
	82 per 1000	**103 per 1000** (61 to 173)			
	Moderate				
	69 per 1000	**87 per 1000** (52 to 146)			
Adverse effects necessitating stop of therapy Patient reported Follow-up: median 18 months	**Study population**		**RR 1.87** (1.02 to 3.41)	564 (4 studies)	⊕⊕⊕ **moderate**[2]
	50 per 1000	**93 per 1000** (51 to 169)			
	Moderate				
	33 per 1000	**62 per 1000** (34 to 113)			

[1] P value > 0.05 (imprecise).
[2] High risk of bias in blinding domain.

Recurrences in patients with recurrent pericarditis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Colchicine			
6 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: mean 6 months Intervention: colchicine with NSAID Comparison: NSAID alone Setting: multicentre secondary care	**Study population**		**RR 0.28** (0.17 to 0.47)	204 (2 studies)	⊕⊕⊕ **moderate**[1,2]
	490 per 1000	**137 per 1000** (83 to 230)			
	Moderate				
	481 per 1000	**135 per 1000** (82 to 226)			
12 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: median 12 months	**Study population**		**RR 0.36** (0.23 to 0.56)	204 (2 studies)	⊕⊕⊕ **moderate**[1,2]
	520 per 1000	**187 per 1000** (120 to 291)			
	Moderate				
	510 per 1000	**184 per 1000** (117 to 286)			
18 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: median 18 months	**Study population**		**RR 0.38** (0.25 to 0.58)	204 (2 studies)	⊕⊕⊕ **moderate**[1,2]

	539 per 1000	**205 per 1000** (135 to 313)		
	Moderate			
	533 per 1000	**203 per 1000** (133 to 309)		

[1] High risk of bias in blinding domain.

[2] Low precision (small sample size and small number of events).

Recurrence rate in patients with acute pericarditis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Colchcine			
6 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: mean 6 months Intervention: colchicine with NSAID Comparison: NSAID alone Setting: multicentre secondary care	**Study population**		**RR 0.36** (0.23 to 0.58)	360 (2 studies)	⊕⊕⊕ **moderate**[1]
	306 per 1000	**110 per 1000** (70 to 177)			
	Moderate				
	292 per 1000	**105 per 1000** (67 to 169)			
12 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: median 12 months	**Study population**		**RR 0.4** (0.26 to 0.61)	360 (2 studies)	⊕⊕⊕ **moderate**[1]
	333 per 1000	**133 per 1000** (87 to 203)			
	Moderate				
	321 per 1000	**128 per 1000** (83 to 196)			
18 months Chest pain + (ECG changes +/- echocardiographic changes +/- raised inflammatory markers) Follow-up: median 18 months	**Study population**		**RR 0.41** (0.28 to 0.61)	360 (2 studies)	⊕⊕⊕ **moderate**[1]

	367 per 1000	**150 per 1000** (103 to 224)		
	Moderate			
	358 per 1000	**147 per 1000** (100 to 218)		

[1] High risk of bias in blinding domain.

Symptom relief for pericarditis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Colchcine			
Symptom relief at 72 hours Patient reported Follow-up: median 7 days Intervention: colchicine with NSAID Comparison: NSAID alone Setting: multi centre secondary care	**Study population**		**RR 1.40** (1.26 to 1.56)	564 (4 studies)	⊕⊕ **low** [1,2]
	592 per 1000	**829 per 1000** (746 to 924)			
	Moderate				
	617 per 1000	**864 per 1000** (777 to 963)			

[1] Two open-label studies.
[2] High risk of bias in selective reporting domain.

DISCUSSION

Summary of main results

The main results of the review compare the recurrence of pericarditis in people taking colchicine in addition to a NSAID such as ibuprofen, aspirin or indomethacin to the recurrence of pericarditis in people taking a NSAID alone. We included four trials with a total of 564 adult participants in this review. Two studies (Imazio 2005a; Imazio 2011) included 204 participants with recurrent pericarditis and showed that colchicine is effective in preventing further recurrences. The evidence shows that, the risk of pericarditis recurrence in people with recurrent pericarditis, who are taking colchicine, is 37% of the risk of recurrence in people not taking colchicine over a period of 18 months. Thus, the average reduction in recurrence of pericarditis with colchicine compared to NSAIDs alone is 63% over a period of 18 months. The risk of having a recurrent episode of pericarditis at 6, 12 and 18 months is reduced by 72%, 64% and 63% respectively. It is expected that at 18 months, one pericarditis recurrence can be avoided for every four people receiving colchicine with NSAIDs rather than NSAIDs alone.

Two studies (Imazio 2005; Imazio 2013) included 360 people with acute pericarditis and assessed the recurrence of pericarditis. The evidence shows that the average reduction in recurrence of pericarditis with colchicine compared to NSAIDs alone is 60% over a period of 18 months. The risk of having a recurrent episode of pericarditis at 6, 12 or 18 months is reduced by 64%, 60% and 59% respectively.

The primary outcomes are summarised in the following table.

	Risk of relapse without colchicine	Risk of relapse with colchicine over 18 months	No. patients with adverse effects for 100 treated
Acute pericarditis	20% to 30% (Fowler 1990; Adler 1998)	8% to 15% (Analysis 1.2, Analysis 4.3)	10
Recurrent pericarditis	40% to 50% (Soler-Soler 2004)	15% to 20% (Analysis 1.1, Analysis 3.3)	10

Adverse events were reported in all studies. Combining the results of all 564 participants showed a similar adverse events rate in both the intervention and control group. All adverse events were related to the gastrointestinal system. The adverse effects in the colchicine group were almost twice more likely to be the cause of stopping treatment than in the control group.

The review showed that colchicine is effective in reducing the symptoms of pericarditis. The combined data of all studies shows that symptoms of the pericarditis episode are reduced by up to 60% in the colchicine group compared to the control group.

We used GradePro to create a summary of the findings and quality of the evidence (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

Overall completeness and applicability of evidence

The two combined studies for acute pericarditis (Imazio 2005; Imazio 2013) and for recurrent pericarditis (Imazio 2005a; Imazio 2011) were homogenous in methodology, patients baseline characteristics, intervention duration and dose and outcomes. This makes the combined result a robust estimate of effect, however it might be limited as to how it can be generalised to different populations (Berman 2002).

All participants in the included trials were Italians with a mean age of 47 to 57 years. Consequently, the evidence has limited applicability to children, elderly adults or people from an ethnicity other than European.

Patients with several recurrences were not studied. Consequently, it is possible that the studies represent a population with a lower risk of recurrence and better response to therapy. The results of this review, therefore might not apply to patients with resistant multiple recurrences. Pregnant and lactating women or fertile women not protected by a contraceptive method are also not represented by the studies. In addition, people were excluded from the trials if they were receiving or had previously received colchicine for any indication. Therefore, results might not be applicable to patients taking colchicine for any other medical condition such as gout. People with abnormal liver function were also excluded, although this might have been because of acute infections or medications (Adler 2006).

The colchicine therapy duration of three months for acute peri-

carditis and six months for recurrent pericarditis is debatable. It was not possible to do a subgroup analysis for different doses or therapy durations. In order to identify different regimes of duration and dose of treatment, we systematically identified and reviewed non-RCT publications. This search retrieved 15 reports (Table 2). The duration of therapy ranged from one or two months to 18 months. The suggested duration of therapy in this review might not apply to all patients in a clinical setting and different durations might be needed for different patients.

The review of all non-randomised trials (Table 2) shows that a loading dose has not always been used and that there is no universal agreement on the dosage of the loading dose which ranged from 1 mg to 3 mg. This review could not assess the importance of the loading dose, as a subgroup analysis or comparison with a trial that has not used a loading dose was not possible.

Quality of the evidence

All included studies are RCTs. We judged the outcomes, studying time to recurrence and recurrence rates, to be of a moderate methodological quality using the GRADE approach (GRADEpro 2008).

All three included studies stated that they were randomised trials but only Imazio 2011 adequately reported the randomising method and the allocation sequence generation.

The Imazio 2011 trial had a double-blind design. Although duration of therapies in the intervention and control group varied largely, which might have undermined the blinding of participants, outcomes were determined by blinded assessors and objective outcome measures. Two studies, Imazio 2005 and Imazio 2005a, were open-label design without blinding of the participants or researchers, however both had blinded outcome assessors and an external data analysis committee masked to intervention allocation.

The comparator in all trials was either aspirin (800 mg) or prednisolone in Imazio 2005 and Imazio 2005a or as an additional alternative, ibuprofen in Imazio 2011. However in clinical practice, stronger NSAIDs such as ibuprofen, indomethacin or higher aspirin doses (1000 to 2000 mg/d) tend to be used. This might have positively affected the apparent benefit of colchicine.

All included studies followed an intention-to-treat (ITT) approach and every randomised participant was followed up and analysed.

The quality of evidence for symptom relief during the pericarditis episode is of low quality. The time point chosen to assess the symptoms was subjectively chosen and symptoms were not reported over a range of time, suggesting a high risk of selective reporting. Additionaly, it is not clear which symptoms were relieved or to what extend the symptoms were reduced. No description was made on how the symptoms were assessed or measured. Complete study protocols were not available to make judgements regarding the risk of selective reporting.

Potential biases in the review process

The review was conducted according to the previously published protocol. Attempts have been made to minimise review bias by having two authors independently perform the literature search, study selection, data extraction and risk of bias assessment. Unfortunately, we were unable to obtain study protocols of the included studies from the study authors. We were also unable to use funnel plots to determine if there was any publication bias as we only found four studies. It is unlikely that there are any published randomised trials that have been overlooked in this review.

Agreements and disagreements with other studies or reviews

The authors of the included trials (Imazio 2005; Imazio 2005a; Imazio 2011) performed a systematic review of their studies, published in the *Heart* journal (Imazio 2012). The main contrast with this review is that they analysed all pericardial disease (acute pericarditis, recurrent pericarditis and postpericardial syndrome) in one meta-analysis. Our approach was to exclude postpericardial syndrome due to the different aetiology and pathophysiology than that of acute or recurrent pericarditis. In addition, we decided not to pool the trials of acute and recurrent pericarditis together as there are significant differences in the baseline risk for further recurrence of pericarditis. In addition, our review included an independent risk of bias assessment involving authors not participating in the initial trial. This review includes the results of an additional study (Imazio 2013) not included in the *Heart* journal review Imazio 2012.

AUTHORS' CONCLUSIONS

Implications for practice

Colchicine as adjunctive therapy to NSAIDs is effective in reducing the number of further recurrences in patients with recurrent pericarditis or acute pericarditis. However, data is limited and may not be sufficient to recommend routine use of colchicine for the general pericarditis population. It has also been found that patients with multiple resistant recurrences have not been represented in any trials, and it is these patients that are in most need of a treatment.

No severe adverse effects were reported and all adverse effects were related to gastrointestinal sensitivity such as abdominal pain, diarrhoea and nausea or vomiting. Although we do not have definitive evidence that colchicine increases the risk of adverse events overall, it was associated with higher therapy withdrawal rates than the control group.

Implications for research

Pericarditis is a relatively common disease which can relapse and recur despite treatment. This can cause frustration for both patients and healthcare providers. Current research of the use of colchicine includes two RCTs in people with acute pericarditis and two in people with recurrent pericarditis. Another two on-going RCTs are awaited.

New research should study participants not covered in the current trials, such as people with multiple resistant pericarditis recurrences, elderly people and children. About 2 to 3 in 1000 hospitalised children experience episodes of pericarditis (Yazigi 1998). It is therefore important to assess the efficacy and safety of colchicine in paediatric populations. In addition, trials looking at different populations such as from a non-European background are necessary. Other questions that need to be addressed are the optimal therapy durations, loading and maintenance doses.

All existing trials of colchicine in pericarditis have been conducted by similar research groups. Although this is not a risk of bias itself, it is beneficial to have trials undertaken by different researchers.

We know of one ongoing RCTs (EUCTR2009-011258-16-ES) registered on ClinicalTrials.gov and the EU Clinical Trials Register seeking to address the use of colchicine in pericarditis. We hope that with the results of the ongoing research, a more definite conclusion can be given.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Imazio 2005

Methods	Randomised controlled trial with an open-label design
Participants	A sample of 120 people with a first episode of acute pericarditis
Interventions	Colchicine (1 to 2 mg on the first day then 0.5 to 1.0 mg daily for 3 months) + Aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d Comparator: Aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d
Outcomes	Recurrence rate Secondary end point was the rate of symptom persistence at 72 hours from treatment onset
Notes	Clinical setting: 2 Italian centres Follow-up: mean of 24 months (range 8 to 39 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned in detail. Randomisation was based on permuted blocks, with a block size of 4
Allocation concealment (selection bias)	Unclear risk	Not mentioned. However, permuted-block randomisation might lead to selection bias
Blinding of participants and personnel (performance bias) Recurrence of Pericarditis	High risk	Open-label design and the duration of treatment in the colchicine group was longer than the duration of treatment in the non-steroidal anti-inflammatory drug group. However, the outcome assessors were blinded to treatment assignment and the objective outcome measures limit the effect of the participants knowing their intervention regime and reduces the risk of bias
Blinding of participants and personnel (performance bias) Adverse Effects	High risk	Open-label design. There is a high risk of bias as part of participants and personnel were not blinded to the treatment and adverse effects were reported subjectively by the participants

Blinding of participants and personnel (performance bias) Symptom Relief	High risk	Open-label design. There is a high risk of bias as part of participants and personnel were not blinded to the treatment and symptom relief was reported subjectively by the participants
Blinding of outcome assessment (detection bias) Recurrences of pericarditis	Low risk	The outcome assessors for pericarditis recurrences were blinded to treatment assignment
Blinding of outcome assessment (detection bias) Adverse Effects	High risk	Open-label design. Adverse effects were reported subjectively by participants not blinded to the intervention
Blinding of outcome assessment (detection bias) Symptom Relief	High risk	Open-label design. Symptom relief was reported subjectively by the participants not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were performed by intention-to-treat No patient was lost to follow-up, and all participants were analysed for outcomes according to their original assigned groups
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome have been reported The secondary end point "symptom persistence at 72 hours" is chosen subjectively A protocol with a prespecified statistical analysis was not available
Similarity of baseline characteristics	Low risk	Participants in both the intervention and control group were similar in demographic and clinical characteristics
Co-interventions avoided or similar	Low risk	The cointervention used in the treatment group was aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d. This intervention was similar in the control group
Other bias	Low risk	Not found

Imazio 2005a

Methods	Randomised Controlled Trial with an open-label design
Participants	A sample of 84 people with a first episode of recurrent pericarditis
Interventions	Colchicine (1 to 2 mg on the first day then 0.5 to 1.0 mg daily for 6 months) + Aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d Comparator: Aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d
Outcomes	Recurrence rate of pericarditis Secondary end point was the rate of symptom persistence at 72 hours from treatment onset
Notes	Clinical setting: Cardiology Department, Maria Vittoria Hospital, Torino Follow-up: mean of 20 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned in detail. Randomisation was based on permuted blocks, with a block size of 4
Allocation concealment (selection bias)	Unclear risk	Not mentioned. However, permuted-block randomisation might lead to selection bias
Blinding of participants and personnel (performance bias) Recurrence of Pericarditis	High risk	Open-label design and the duration of treatment in the colchicine group was longer than the duration of treatment in the non-steroidal anti-inflammatory drug group. However, the outcome assessors were blinded to treatment assignment which limits the effect of the participants knowing their intervention regime and reduces the risk of bias
Blinding of participants and personnel (performance bias) Adverse Effects	High risk	Open-label design. Open-label design. There is a high risk of bias as part of participants and personnel were not blinded to the treatment and adverse effects were reported subjectively by the participants
Blinding of participants and personnel (performance bias) Symptom Relief	High risk	Open-label design. There is a high risk of bias as part of participants and personnel were not blinded to the treatment and symptom relief was reported subjectively by the participants

Imazio 2005a (*Continued*)

Blinding of outcome assessment (detection bias) Recurrences of pericarditis	Low risk	The outcome assessors for pericarditis recurrences were blinded to treatment assignment
Blinding of outcome assessment (detection bias) Adverse Effects	High risk	Open-label design. Adverse effects were reported subjectively by participants not blinded to the intervention
Blinding of outcome assessment (detection bias) Symptom Relief	High risk	Open-label design. Symptom relief was reported subjectively by the participants not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis. All participants analysed in the group they were randomised to. No missing data
Selective reporting (reporting bias)	Low risk	The primary and secondary outcome has been reported The secondary end point "symptom persistence at 72 hours" is chosen subjectively A protocol with a prespecified statistical analysis was not available
Similarity of baseline characteristics	Low risk	Participants in both the intervention and control group were similar in demographic and clinical characteristics
Co-interventions avoided or similar	Low risk	The cointervention used in the treatment group was aspirin 800 mg or prednisolone 1.0 to 1.5 mg/kg/d. This intervention was similar in the control group
Other bias	Low risk	No

Imazio 2011

Methods	Multicentre double-blind randomised controlled trial
Participants	A sample of 120 people with a first recurrence of pericarditis
Interventions	Colchicine (1 to 2 mg on the first day then 0.5 to 1.0 mg/d for 6 months) + Aspirin 800 mg to 1000 mg or ibuprofen 600 mg or prednisolone 0.2 to 0.5 mg/kg/d Comparator: Aspirin 800 mg or ibuprofen 600 mg or prednisolone 0.2 to 0.5 mg/kg/d
Outcomes	Recurrence rate at 18 months follow-up The secondary end points were symptom persistence at 72 hours, remission rate at 1 week, number of recurrences, time to first recurrence, disease-related hospitalisation, cardiac tamponade, and rates of constrictive pericarditis

Notes	Clinical setting: 4 general hospitals in Italy (Maria Vittoria Hospital, Torino; Ospedali Riuniti, Bergamo; San Maurizio Regional Hospital, Bolzano; and Ospedale SS Annunziata, Savigliano) Follow-up: mean of 20 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to treatment groups by a central computer-based automated sequence. Randomisation was based on permuted blocks, with a block size of 4
Allocation concealment (selection bias)	Low risk	The random allocation sequence was implemented by using sequentially numbered containers
Blinding of participants and personnel (performance bias) Recurrence of Pericarditis	Low risk	All participants and trial investigators were blinded to randomised treatment Placebo tablets were identical to colchicine in colour, shape, and taste; premarked to allow splitting into 2 equal parts; and provided in blister packs. However, intervention was given for 6 months whereas the control was given for 4 to 5 weeks only
Blinding of participants and personnel (performance bias) Adverse Effects	Low risk	All adverse effects happened in the first week of the trial. At that time the intervention and control were given under double-blind conditions
Blinding of participants and personnel (performance bias) Symptom Relief	Low risk	Symptom relief was assessed after 72 hours of the trial under double-blind conditions
Blinding of outcome assessment (detection bias) Recurrences of pericarditis	Low risk	All trial investigators were blinded to randomised treatment. Data were collected by using case report and clinical events adjudication forms
Blinding of outcome assessment (detection bias) Adverse Effects	Low risk	Adverse effects were reported by patients blinded to intervention and blinded trial investigators assessed data by using case report and clinical events adjudication forms
Blinding of outcome assessment (detection bias) Symptom Relief	Low risk	Symptom relief was reported by patients blinded to intervention and blinded trial

Imazio 2011 (*Continued*)

		investigators assessed data by using case report and clinical events adjudication forms
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were performed by intention-to-treat No patient was lost to follow-up, and all participants were analysed for outcomes according to their original assigned groups
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome have been reported Some secondary end points are chosen subjectively such as symptom persistence at 72 hours and remission rate at 1 week. There was no rationale explained for choosing those end points nor were outcomes around the chosen end points reported. A protocol with a prespecified statistical analysis was not available
Similarity of baseline characteristics	Low risk	Participants in both the intervention and control group were similar in demographic and clinical characteristics
Co-interventions avoided or similar	Low risk	The cointervention used in the treatment group was aspirin 800 mg or ibuprofen 600 mg or prednisolone 0.2 to 0.5 mg/kg/d. This has been similarly used in the control group
Other bias	Low risk	Not found

Imazio 2013

Methods	Multicentre double-blind randomised controlled trial
Participants	A sample of 120 people with a first recurrence of pericarditis
Interventions	Colchicine was administered at a dose of 0.5 to 1.0 mg daily for 3 months + (800 mg of aspirin or 600 mg of ibuprofen or prednisolone 0.2 to 0.5 mg/kg/d) Comparator: 800 mg of aspirin or 600 mg of ibuprofen given orally every 8 hours for 7 to 10 days, followed by tapering during a period of 3 to 4 weeks or prednisolone 0.2 to 0.5 mg/kg/d for 2 weeks with gradual tapering)
Outcomes	Recurrence rate at 18 months follow-up Secondary end points were symptom persistence at 72 hours, remission within 1 week, number of recurrences, the time to the first recurrence, disease-related hospitalisation, cardiac tamponade, and constrictive pericarditis

Notes	Settings: Five general hospitals in Northern Italy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to treatment groups by a central computer-based automated sequence
Allocation concealment (selection bias)	Low risk	The random-assignment sequence was implemented with the use of sequentially numbered study-drug containers. All patients and investigators were unaware of study-group assignments
Blinding of participants and personnel (performance bias) Recurrence of Pericarditis	Low risk	All participants and trial investigators were blinded to randomised treatment Placebo tablets were identical to colchicine in colour, shape, and taste; premarked to allow splitting into 2 equal parts; and provided in blister packs. However, intervention was given for 3 months whereas the control was given for 4 to 5 weeks only
Blinding of participants and personnel (performance bias) Adverse Effects	Low risk	All participants and trial investigators were blinded to randomised treatment
Blinding of participants and personnel (performance bias) Symptom Relief	Low risk	Symptom relief was assessed after 72 hours of the trial under double-blind conditions
Blinding of outcome assessment (detection bias) Recurrences of pericarditis	Low risk	All trial investigators were blinded to randomised treatment. Data were collected by using case report and clinical events adjudication forms
Blinding of outcome assessment (detection bias) Adverse Effects	Low risk	All trial investigators were blinded to randomised treatment. Data were collected by using case report and clinical events adjudication forms
Blinding of outcome assessment (detection bias) Symptom Relief	Low risk	Symptom relief was reported by patients blinded to intervention and blinded trial investigators assessed data by using case report and clinical events adjudication forms

Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were performed by intention-to-treat No patient was lost to follow-up, and all participants were analysed for outcomes according to their original assigned groups
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome have been reported Some secondary end points are chosen subjectively such as symptom persistence at 72 hours and remission rate at 1 week. There was no rationale explained for choosing those end points nor were outcomes around the chosen end points reported. A protocol with a prespecified statistical analysis was not available
Similarity of baseline characteristics	Low risk	Participants in both the intervention and control group were similar in demographic and clinical characteristics
Co-interventions avoided or similar	Low risk	The cointervention used in the treatment group was aspirin 800 mg or ibuprofen 600 mg or prednisolone 0.2 to 0.5 mg/kg/d. This has been similarly used in the control group
Other bias	Low risk	Not found

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

Study	Reason for exclusion
Adler 1994	Not RCT
Adler 1998	Not RCT (case series)
Adler 1998a	Not RCT (case series)
Artom 2005	Not RCT (case series)
Brucato 2006	Not RCT (case series)
Cacoub 2000	Not RCT (case series)
Finkelstein 2002	Outcome studied is prevention of postpericardiotomy syndrome not pericarditis

(*Continued*)

Grande 1995	Not RCT (case series)
Guindo 1990	Not RCT (case series)
Imazio 2005b	Not RCT
Imazio 2007b	Outcome studied is prevention of postpericardiotomy syndrome not pericarditis
la Serna 1987	Not RCT (case series)
Millaire 1994	Not RCT (case series)
Raatikka 2003	Not RCT (case series)
Yazigi 1998	Not RCT (case series)

RCT - randomised controlled trial

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

Imazio 2014

Methods	Multicentre, double-blind, placebo-controlled, randomised trial
Participants	Recurrent pericarditis
Interventions	Colchicine with NSAIDs compared to NSAIDs alone
Outcomes	Recurrence rate and symptom relief
Notes	

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

EUCTR2009-011258-16-ES

Trial name or title	EUCTR2009-011258-16-ES
Methods	Open-label randomised controlled trial
Participants	Patients with first episode of acute pericarditis
Interventions	Colchicine

EUCTR2009-011258-16-ES (*Continued*)

Outcomes	Incidence of recurrences
Starting date	18/05/2010
Contact information	Dr. Jaime Sagrista Sauleda jsagrist@gmail.com
Notes	http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2009-011258-16-ES https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract˙number:2009-011258-16

DATA AND ANALYSES

Comparison 1. Time to recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to recurrence in people with recurrent pericarditis	2	204	Hazard Ratio (Fixed, 95% CI)	0.37 [0.24, 0.58]
2 Time to recurrence in people with acute pericarditis	2	360	Hazard Ratio (Fixed, 95% CI)	0.40 [0.27, 0.61]

Comparison 2. Adverse effects of colchicine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total adverse effects	4	564	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.75, 2.12]
2 Adverse effects necessitating stop of therapy	4	564	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.02, 3.41]

Comparison 3. Recurrence rate in people with recurrent pericarditis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 6 months	2	204	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.17, 0.47]
2 12 months	2	204	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.56]
3 18 months	2	204	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.25, 0.58]

Comparison 4. Recurrence rate in people with acute pericarditis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 6 months	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.58]
2 12 months	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.26, 0.61]
3 18 months	2	360	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.28, 0.61]

Comparison 5. Symptom relief

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom relief at 72 hours	4	564	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.26, 1.56]

Analysis 1.1. Comparison 1 Time to recurrence, Outcome 1 Time to recurrence in people with recurrent pericarditis.

Review: Colchicine for pericarditis

Comparison: 1 Time to recurrence

Outcome: 1 Time to recurrence in people with recurrent pericarditis

Study or subgroup	Colchicine N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Imazio 2005a	42	-1.0083163 (0.3592106)	42		40.8 %	0.36 [0.18, 0.74]
Imazio 2011	60	-0.98104553 (0.2981424)	60		59.2 %	0.37 [0.21, 0.67]
Total (95% CI)	**102**	**102**			**100.0 %**	**0.37 [0.24, 0.58]**

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 4.32 (P = 0.000015)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Time to recurrence, Outcome 2 Time to recurrence in people with acute pericarditis.

Review: Colchicine for pericarditis

Comparison: 1 Time to recurrence

Outcome: 2 Time to recurrence in people with acute pericarditis

Study or subgroup	Colchicine N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Imazio 2005	60	60	-1.1512647 (0.4)		27.8 %	0.32 [0.14, 0.69]
Imazio 2013	120	-0.81627922 (0.24806947)	120		72.2 %	0.44 [0.27, 0.72]
Total (95% CI)	**180**	**180**			**100.0 %**	**0.40 [0.27, 0.61]**

Heterogeneity: Chi^2 = 0.51, df = 1 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 4.31 (P = 0.000016)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Adverse effects of colchicine, Outcome 1 Total adverse effects.

Review: Colchicine for pericarditis

Comparison: 2 Adverse effects of colchicine

Outcome: 1 Total adverse effects

Study or subgroup	Colchicine n/N	Control group n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005	6/42	3/42		13.0 %	2.00 [0.54, 7.47]
Imazio 2005a	5/60	4/60		17.4 %	1.25 [0.35, 4.43]
Imazio 2011	4/60	4/60		17.4 %	1.00 [0.26, 3.81]
Imazio 2013	14/120	12/120		52.2 %	1.17 [0.56, 2.42]
Total (95% CI)	**282**	**282**		**100.0 %**	**1.26 [0.75, 2.12]**

Total events: 29 (Colchicine), 23 (Control group)

Heterogeneity: Chi^2 = 0.63, df = 3 (P = 0.89); I^2 =0.0%

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Adverse effects of colchicine, Outcome 2 Adverse effects necessitating stop of therapy.

Review: Colchicine for pericarditis

Comparison: 2 Adverse effects of colchicine

Outcome: 2 Adverse effects necessitating stop of therapy

Study or subgroup	Colchicine n/N	Control group n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005	5/60	0/60		3.3 %	11.00 [0.62, 194.63]
Imazio 2005a	3/42	0/42		3.3 %	7.00 [0.37, 131.47]
Imazio 2011	5/60	4/60		26.7 %	1.25 [0.35, 4.43]
Imazio 2013	14/120	10/120		66.7 %	1.40 [0.65, 3.03]
Total (95% CI)	**282**	**282**		**100.0 %**	**1.87 [1.02, 3.41]**

Total events: 27 (Colchicine), 14 (Control group)

Heterogeneity: $Chi^2 = 3.16$, df = 3 (P = 0.37); $I^2 = 5\%$

Test for overall effect: Z = 2.03 (P = 0.043)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Recurrence rate in people with recurrent pericarditis, Outcome 1 6 months.

Review: Colchicine for pericarditis

Comparison: 3 Recurrence rate in people with recurrent pericarditis

Outcome: 1 6 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005a	6/42	18/42		36.0 %	0.33 [0.15, 0.76]
Imazio 2011	8/60	32/60		64.0 %	0.25 [0.13, 0.50]
Total (95% CI)	**102**	**102**		**100.0 %**	**0.28 [0.17, 0.47]**

Total events: 14 (Colchicine), 50 (Control)

Heterogeneity: Chi^2 = 0.28, df = 1 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 4.75 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Recurrence rate in people with recurrent pericarditis, Outcome 2 12 months.

Review: Colchicine for pericarditis

Comparison: 3 Recurrence rate in people with recurrent pericarditis

Outcome: 2 12 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005a	10/42	19/42		35.8 %	0.53 [0.28, 0.99]
Imazio 2011	9/60	34/60		64.2 %	0.26 [0.14, 0.50]
Total (95% CI)	**102**	**102**		**100.0 %**	**0.36 [0.23, 0.56]**

Total events: 19 (Colchicine), 53 (Control)

Heterogeneity: Chi^2 = 2.26, df = 1 (P = 0.13); I^2 =56%

Test for overall effect: Z = 4.48 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Recurrence rate in people with recurrent pericarditis, Outcome 3 18 months.

Review: Colchicine for pericarditis

Comparison: 3 Recurrence rate in people with recurrent pericarditis

Outcome: 3 18 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005a	10/42	21/42		38.2 %	0.48 [0.26, 0.89]
Imazio 2011	11/60	34/60		61.8 %	0.32 [0.18, 0.58]
Total (95% CI)	**102**	**102**		**100.0 %**	**0.38 [0.25, 0.58]**

Total events: 21 (Colchicine), 55 (Control)

Heterogeneity: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 4.47 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Recurrence rate in people with acute pericarditis, Outcome 1 6 months.

Review: Colchicine for pericarditis

Comparison: 4 Recurrence rate in people with acute pericarditis

Outcome: 1 6 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005	4/60	15/60		27.3 %	0.27 [0.09, 0.76]
Imazio 2013	16/120	40/120		72.7 %	0.40 [0.24, 0.67]
Total (95% CI)	**180**	**180**		**100.0 %**	**0.36 [0.23, 0.58]**

Total events: 20 (Colchicine), 55 (Control)

Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 4.25 (P = 0.000021)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Recurrence rate in people with acute pericarditis, Outcome 2 12 months.

Review: Colchicine for pericarditis

Comparison: 4 Recurrence rate in people with acute pericarditis

Outcome: 2 12 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005	5/60	17/60		28.3 %	0.29 [0.12, 0.75]
Imazio 2013	19/120	43/120		71.7 %	0.44 [0.27, 0.71]
Total (95% CI)	**180**	**180**		**100.0 %**	**0.40 [0.26, 0.61]**

Total events: 24 (Colchicine), 60 (Control)

Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 4.23 (P = 0.000023)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Recurrence rate in people with acute pericarditis, Outcome 3 18 months.

Review: Colchicine for pericarditis

Comparison: 4 Recurrence rate in people with acute pericarditis

Outcome: 3 18 months

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Imazio 2005	5/60	20/60		30.3 %	0.25 [0.10, 0.62]
Imazio 2013	22/120	46/120		69.7 %	0.48 [0.31, 0.74]
Total (95% CI)	**180**	**180**		**100.0 %**	**0.41 [0.28, 0.61]**

Total events: 27 (Colchicine), 66 (Control)

Heterogeneity: $Chi^2 = 1.60$, df = 1 (P = 0.21); $I^2 = 38\%$

Test for overall effect: Z = 4.42 (P < 0.00001)

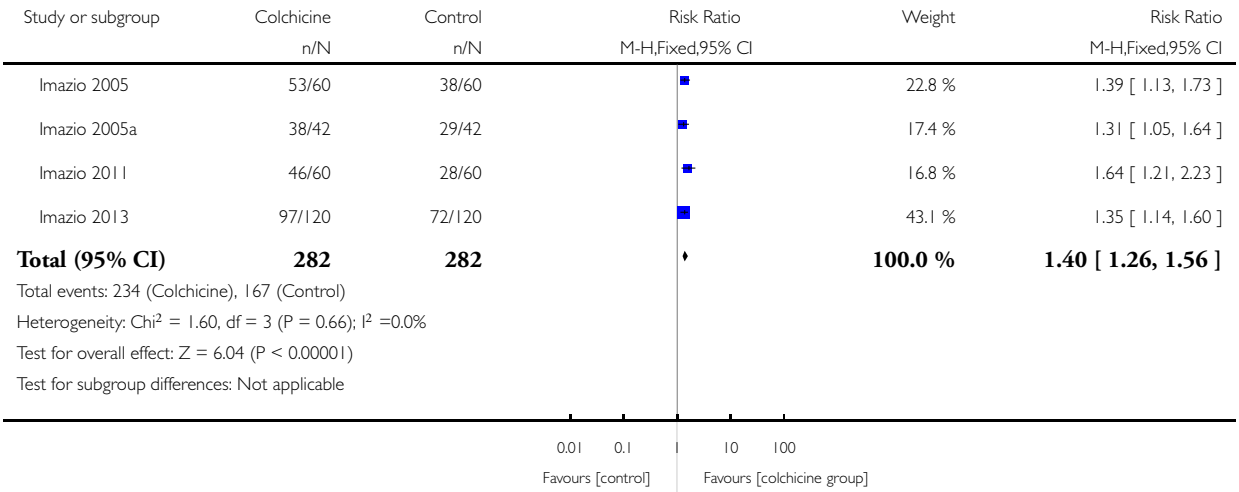
Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Symptom relief, Outcome 1 Symptom relief at 72 hours.

Review: Colchicine for pericarditis

Comparison: 5 Symptom relief

Outcome: 1 Symptom relief at 72 hours



ADDITIONAL TABLES

Table 1. Baseline characteristics

Characteristics	Imazio 2005		Imazio 2005a		Imazio 2011		Imazio 2013	
	Colchicine	Control	Colchicine	Control	Colchicine	Control	Colchicine	Control
Age	56.5 ± 18.2	57.2 ± 19.6	56.4 ± 16.9	51.2 ±16.3	47.9 ± 15.4	47.3 ± 14.4	53.5 ± 16.2	50.7 ± 17.5
Male Female	46.7% 53.3%	43.3% 56.7%	38% 62%	31% 69%	43% 57%	48% 52%	59.2% 40.8%	61.7% 38.3%
Region	Italy	Italy	Italy	Italy	Italy	Italy	Italy	Italy
Pericarditic chest pain	100%	100%	100%	100%	100%	100%	100%	99.2%
Pericardial rub	35%	31.7%	36%	33%	20%	22%	36.7%	31.7%

Table 1. Baseline characteristics (*Continued*)

ECG changes	86.7%	88.3%	74%	69%	n.a	n.a	29.2%	21.7%
Pericardial effusion	68.3%	63.3%	62%	64%	60%	58%	63.3%	68.3%
Cardiac tamponade	1.6%	1.6%	2%	0	n.a	n.a	1.7%	1.7%
Idiopathic pericarditis	83.3%	85%	86%	81%	83%	80%	76.7%	77.5%
Autoimmune pericarditis	16.7%	15%	14%	19%	17%	20%	2.5%	3.3%
Steroid use on index attack	15%	16.6%	33%	38%	8%	10%	n.a	n.a

Table 2. Review of observational studies

Author and date	Study type	Participants	Interventions	Results	Conclusion
Adler 1998	Case series	51 patients (36 men and 15 women; mean ± SD age, 40.8 ± 18.7 years) with recurrent pericarditis followed up for < or = 10 years	Colchicine (1 mg/day)	31 patients (60.7%) remained recurrence-free. Drug withdrawal in 39 (76%) patients	Colchicine is effective in the treatment of recurrent pericarditis
Adler 1998a	Two case reports	a 26-year-old male and a 2-year-old girl with idiopathic pericarditis and pericardial effusion	Colchicine (1 mg/day) for 1 month in the man and 6 months in the child	No recurrences in 24 months follow-up in the man and 6 months follow-up in the girl	Colchicine is effective in the treatment of recurrent pericarditis
Adler 1994	Case series	8 patients with recurrent pericarditis	Colchicine (1 mg/d)	No recurrences were noted during the 18 to 34 months of follow-up. Drug withdrawal was 50%	Colchicine is effective in the treatment of recurrent pericarditis
Brucato 2006	Controlled trial	58 patients with recurrent pericarditis (34 men	Colchicine (1 mg/day) for 18 months	No further recurrence in 29/44 colchicine pa-	Colchicine is effective in the treatment of recurrent

Table 2. Review of observational studies (*Continued*)

		and 24 women) were followed up for an average of 8.1 years		tients (65.9%). Drug withdrawal was 16%	pericarditis
Cacoub 2000	Case series	13 patients (7 women and 6 men) with recurrent pericarditis	Colchicine (1 to 2 mg/d) for 17 months	No further recurrence in 10 (77%) patients	Colchicine is effective in the treatment of recurrent pericarditis
Grande 1995	Case series	5 patients (age 24 to 64 years) with recurrent pericarditis. Followed up for 24 months	Colchicine (1 mg/d) for 18 months	There were no further recurrences of pericarditis during the follow-up	Colchicine is effective in the treatment of recurrent pericarditis
Guindo 1990	Case series	9 patients (7 men and 2 women; age, 18 to 64 years) with recurrent pericarditis followed up for a mean of 24.3 months (10 to 54 month)	Colchicine (1 mg/d)	No recurrences of pericarditis were noted within the follow-up	Colchicine is effective in the treatment of recurrent pericarditis
Guindo 2002	Controlled trial	51 patients with recurrent pericarditis (36 men, 14 women; mean age 40. 8 ± 18.7 years). Followed up for a median of 36 months	Colchicine (1 to 2 mg/day) (29 patients received steroids before colchicine)	6 of 22 (27%) patients who received colchicine but no steroids had recurrences 14 of 29 (48%) patients who were treated with steroids before colchicine had recurrences	Colchicine is effective in the treatment of recurrent pericarditis
Imazio 2002	Case series	55 patients with recurrent pericarditis. 10 patients treated with colchicine. The rest were treated with aspirin, or steroids, or both. Followed up for a mean of 36 months	Colchicine (loading dose of 2 mg then maintenance 1 mg/d)	Remission in 9 of 10 patients (90%) treated with colchicine compared to 33 of 48 (69%) with aspirin and 18 of 27 (67%) with steroids	Colchicine is effective in the treatment of recurrent pericarditis
Imazio 2005b	Controlled trial	35 patients with recurrent pericarditis. Followed up for a mean of 72 months	Colchicine (loading dose of 2 mg then 1 mg/d maintenance) for 6 months	Remission rate 32 of 35 patients (91.4%)	Colchicine is effective in the treatment of recurrent pericarditis

Table 2. Review of observational studies (*Continued*)

Millaire 1994	Case series	19 patients (10 men, nine women, age 46 ± 7 years) who had recurrent pericarditis. Followed up for 32 to 44 months	Colchicine (loading dose of 3 mg then maintenance 1 mg/d)	14 (74%) patients had no recurrences during a follow-up period	Colchicine is effective in the treatment of recurrent pericarditis
la Serna 1987	Case series	3 patients with recurrent pericarditis. Followed up for 15 to 35 months	Colchicine (1 mg/d) for 2 months	No relapses throughout the follow-up period	Colchicine is useful in the prevention of recurrence of acute pericarditis
Seferovic 2002	Controlled trial	17 into two groups. Group 1 had 7 patients with idiopathic chronic non-recurring pericarditis. Group 2 had 10 patients with idiopathic recurring pericarditis	Colchicine (loading dose of 2 mg for one week then a maintenance dose of 1.5 mg/d) for 5 months	Disappearance of the pericardial effusion in 60% of patients from group 2 compared to 14% in group 1. Relief of symptoms in 80% of group 1 and 28% of group 2	Colchicine is useful in treating the symptoms of recurrent pericarditis. However, recurrences were not reported
Raatikka 2003	Case series	4 children (aged 7 to 17 years) with recurrent pericarditis. Followed up for 4 to 16 years (mean 8 years)	Colchicine (0.5 to 2 mg/d)	All patients had further recurrences of pericarditis	Colchicine did not prevent pericarditis relapses in children
Jurko 2002	Two case reports	2 children with a severe form of idiopathic recurrent pericarditis	Colchicine	No further relapses occurred during a period of 12 months in the first case and 9 months in the second case	Colchicine is useful in the prevention of recurrence of pericarditis in children
Yazigi 1998	Case series	3 children with recurrent pericarditis. Followed up for 17 to 24 months	Colchicine (0.5 to 1.5 mg loading dose then 0.25 to 0.5 mg/d maintenance) for 6 months	No relapses throughout the follow-up period	Colchicine is useful in the prevention of recurrence of pericarditis in children

APPENDICES

Appendix 1. Search Strategies

CENTRAL (No. of results 23)

#1 MeSH descriptor: [Pericarditis] explode all trees

#2 MeSH descriptor: [Pericardium] this term only

#3 pericard*

#4 #1 or #2 or #3

#5 MeSH descriptor: [Colchicine] explode all trees

#6 colchi*

#7 colchysat or colcine or colcrys or colgout or goutichine or goutnil or kolkicin or "nsc 757" or

tolchicine

#8 #5 or #6 or #7

#9 #4 and #8

MEDLINE OVID (No. of results 153)

1. exp Pericarditis/

2. Pericardium/

3. pericard*.tw.

4. or/1-3

5. exp Colchicine/

6. colchicin*.tw.

7. colchin.tw.

8. colchicum*.tw.

9. colchily.tw.

10. colchimedio.tw.

11. colchiquim.tw.

12. colchisol.tw.

13. colchysat.tw.

14. colcine.tw.

15. colcrys.tw.

16. colgout.tw.

17. goutichine.tw.

18. goutnil.tw.

19. kolkicin.tw.

20. nsc 757.tw.

21. tolchicine.tw.

22. colchichin*.tw.

23. or/5-22

24. 4 and 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized.ab.

28. placebo.ab.

29. drug therapy.fs.

30. randomly.ab.

31. trial.ab.

32. groups.ab.

33. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34. exp animals/ not humans.sh.

35. 33 not 34

36. 24 and 35

EMBASE OVID (No. of results 74)

1. exp pericarditis/

2. pericardium/

3. pericard*.tw.

4. or/1-3

5. colchicine/

6. colchicin*.tw.

7. colchin.tw.

8. colchicum*.tw.

9. colchily.tw.

10. colchimedio.tw.

11. colchiquim.tw.

12. colchisol.tw.

13. colchysat.tw.

14. colcine.tw.

15. colcrys.tw.

16. colgout.tw.

17. goutichine.tw.

18. goutnil.tw.

19. kolkicin.tw.

20. nsc 757.tw.

21. tolchicine.tw.

22. colchichin*.tw.

23. or/5-22

24. 4 and 23

25. random$.tw.

26. factorial$.tw.

27. crossover$.tw.

28. cross over$.tw.

29. cross-over$.tw.

30. placebo$.tw.

31. (doubl$ adj blind$).tw.

32. (singl$ adj blind$).tw.

33. assign$.tw.

34. allocat$.tw.

35. volunteer$.tw.

36. crossover procedure/

37. double blind procedure/

38. randomized controlled trial/

39. single blind procedure/

40. 25 or 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

41. (animal/ or nonhuman/) not human/

42. 40 not 41

43. 24 and 42

Web of Science (No. of results 18)

3 #2 AND #1

2 TS=(colchi* or colchysat or colcine or colcrys or colgout or goutichine or goutnil or kolkicin or "nsc

757" or tolchicine)

1 TS= pericard*

Ongoing trials in (International Clinical Trials Registry Platform Search / ClinicalTrials.gov / www.clinicaltrialsregister.eu)

Search term: colchicine pericarditis

CONTRIBUTIONS OF AUTHORS

S Alabed: Conceived the review, designed and wrote the protocol, searched for studies, screened search results for included studies, data extraction and risk of bias assessment, co-ordinated the review, entered data into RevMan and wrote the review results.

JB Cabello: Conceived the review, co-ordinated the protocol and review, content and methodological expert.

GJ Irving: Data extraction and risk of bias assessment.

M Qintar: Screened search results for included studies.

A Burls: Contributed to the development of the review protocol and registration on *The Cochrane Library*, and reviewed and edited the draft report.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Continuing Education - University of Oxford, UK.

Providing access to journals and books

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We could not perform any subgroup analysis as available data were limited. We intended to assess the effect of high risk of bias in a sensitivity analysis and publication bias in a funnel plot, however, there were not enough included trials to do so.

Our exclusion criteria was to exclude studies of postcardiac injury syndrome, however, we included Imazio 2013 which involved patients with postcardiac injury syndrome. As Imazio 2013 included mainly idiopathic pericarditis (80%) we found it inappropriate to exclude this study from our review.