RevMan: review – intervention; 6663210104160159 58 (version 1.5)

Status: UNPUBLISHED DRAFT

Colchicine for the primary prevention of cardiovascular events

Editors: Cochrane Heart Group

Contact Person: Arturo J Martí-Carvajal (arturo.marti.carvajal@gmail.com)

Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC)
Facultad de Ciencias de la Salud Eugenio Espejo
Universidad UTE
Quito
Carabobo
Ecuador

Arturo J Martí-Carvajal[1][2][3]Juan Bautista De Sanctis[4]Ricardo Hidalgo[5]

Cristina Elena Martí-Amarista[6]Eduardo Alegría[2]Andrea Correa-Pérez[2][7]

Diana Monge Martín[2]Ricardo J Riera Lizardo[8]

[1] Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo , Universidad UTE, Quito, Ecuador

[2] Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain

[3] Cátedra Rectoral de Médicina Basada en la Evidencia, Universidad de Carabobo, Valencia, Venezuela

[4] The Institute of Molecular and Translational Medicine, Palacky University Olomouc, Faculty of Medicine and Dentistry, Czech Republic, Czech Republic

[5] Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador

[6] Department of Family Medicine, Northwell Health Southside Hospital, Bay Shore, New York, USA

[7] Clinical Biostatistics Unit, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

[8] Medicine Department, Rheumatology Unit, Universidad de Carabobo, Valencia, Venezuela

Citation

Martí-Carvajal AJ, De Sanctis JB, Hidalgo R, Martí-Amarista CE, Alegría E, Correa-Pérez A, Monge Martín D, Riera Lizardo RJ. Colchicine for the primary prevention of cardiovascular events (Protocol). Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD015003. DOI: 10.1002/14651858.CD015003.

Dates

Revision published: Issue TBD, TBD (TBD)

Version published (citation changed): Issue TBD, TBD (TBD)

Review first published: N/A

Protocol first published: Issue TBD, TBD

Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

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

Background

Description of the condition

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

The main cause of CVDs is atherosclerosis which is the result of cellular-molecular interactions in the artery wall (Gotlieb 1991); therefore, it is a chronic inflammatory disease with autoimmune foundations (Anyfanti 2021; Barrett 2020; Cochain 2017; Eshghjoo 2021; Fazeli 2021; Frostegård 2013; Geovanini 2018; Gisterå 2017; Hansson 2006; Hussain 2020; Kobiyama 2018; Libby 2019; Liu 2019; Martinez 2018; Mizuno 2011; Oikonomou 2020; Ozen 2021; Patel 2021; Pant 2014; Rahman 2017; Shi 2010; Veronese 2018; Wolf 2019; Zhu 2018). Patients with autoimmune disorders, rheumatic arthritis, systemic lupus erythematosus, and osteoarthritis have a higher frequency of cardiovascular events as compared to the healthy population (Croca 2017; Hannawi 2021; Li 2021; Liu 2018; Semb 2017; Vicente 2021; Yalcinkaya 2021). The incidence of myocardial infarction in people with rheumatoid arthritis seems to be comparable or higher than in people with diabetes mellitus (Ali 2021; Wang 2021). Therefore, rheumatoid arthritis should be considered as a prominent risk factor for CVDs events (Ferraz-Amaro 2021), and a multidisciplinary team should be cardiologists ((Ali 2021).

Recently, it has been pointed out a potential relationship between a pro-protein convertase subtilisin/kexin type 9 (PCSK9) and an autoimmune disease (Ministrini 2021).

The interrelationship between immunity, inflammation, and atherosclerosis could explain the cardiovascular construct termed residual inflammatory risk (RIR) (Ridker 2018). The

RIR is defined by the level of high-sensitivity C-reactive protein (hs-CRP) higher than 2 mg/l (Ridker 2018), a well-known biomarker of cardiovascular disease (Liuzzo 1994). The RIR should not be confused with the residual cholesterol risk (low-density lipoprotein cholesterol -LDL-C- higher to 100 mg/dl), residual triglyceride risk (triglycerides higher to 200 mg/dl and high-density lipoprotein cholesterol -HDL- lower to 40 mg/dl), residual lipoprotein a risk (Lp(a)) higher to 50 mg/dl), and residual thrombotic risk without a predefined biomarker (Ridker 2018). It has been suggested that, in primary prevention, the evaluation of hs-CRP is a useful prognostic factor as much as other conventional measurements of cardiovascular risk, i.e., low-density lipoprotein cholesterol or high-density lipoprotein cholesterol (Ridker 2018). Subclinical inflammation can be better monitored with hs-CRP (Ridker 2018). Therefore, a decrease in inflammatory burden should decrease the risk of future cardiovascular disease (Whayne 2021).

Similarly, the concept of residual cardiovascular risk (RCR) has been proposed (Vanuzzo 2011). Hermans et al. 2010, defined it as the "residual risk of incident vascular events or progression of established vascular damage persisting in patients treated with current evidence-based recommended care. This risk includes established risk factors, such as dyslipidemia, high blood pressure, hyperglycemia, inflammation, unhealthy lifestyles, and the risk related to emerging or newer risk factors" (Hermans 2010). Both RIR and RCR are unique. The link between inflammation and atherosclerosis has been supported by the use of anti-inflammatory therapies, biological agents, or anti-inflammatory drugs used to treat non-atherosclerotic inflammatory diseases and hence reduce cardiovascular events (Arbel 2018; Bäck 2015; Kottoor 2018; Moriya 2019; Roman 2020). Colchicine belongs to the second group of medications (Chistiakov 2018; Dasgeb 2018; Imazio 2016; Thompson 2019; Whayne 2021). Colchicine's prescription in cardiovascular medicine is a new use for an ancient drug (Chen 2017; Tong 2016).

Colchicine has been used in gout, familial Mediterranean fever disorders, osteoarthritis (Akman 2018; Alarcón 1981; Aran 2011; Cronstein 2013; Das 2002; Halabe-Cherem 2009; Kiraz 1998; Lazaros 2018; Liantinioti 2018; Meneses 2015; Nuki 2008; Plotz 2021; Richette 2010; Vilardell 1978), dermatological disorders (Kaur 2020; Fujii 2021; Micheletti 2020; Zhao 2021), urological disorders (Sinanoglu 2018; Akman 2011; Ibrahim 2019), hepatology (Gong 2004; Rambaldi 2001), respiratory medicine (Gomer 2010), gastroenterology (Verne 2003; Rajapakse 2001; Verne 1997), and from secondary prevention of cardiovascular outcomes (Fiolet 2020; Imazio 2005; Imazio 2005a; Imazio 2011; Imazio 2014; Imazio 2014; Imazio 2014a; Maisch 2004; Nidorf 2013; Nidorf 2014; Roubille 2020; Siak 2021; Tardif 2019; Xia 2021). The effect of colchicine is unique since it binds to unpolymerized tubulin heterodimers, forming a stable complex that effectively inhibits microtubule dynamics, not affecting the glucocorticoid signaling pathway as well arachidonic acid metabolites production and signal transduction (Deftereos 2013). Reglero-Real 2021 et al have reported the importance of leukocyte trafficking and organ damage and have shown that endothelial cell autophagy remodels endothelial cell architecture, restraining neutrophils diapedesis in inflamed tissue. It follows then that colchicine could protect against damage in peripheral organs by a similar mechanism.

The Cochrane review's scope will be the colchicine use for primary prevention of cardiovascular outcomes in the general population.

Description of the intervention

Colchicine is a tricyclic alkaloid extracted from Colchicum autumnale and *Gloriosa superba* (Finkelstein 2010; Imazio 2021; Karamanou 2018).

This drug is administered in either solid or liquid oral dosage form (FDA 2021; FDA 2021a). It is rapidly absorbed from the gastrointestinal tract (Finkelstein 2010) and is mainly metabolized in the liver. Cytochrome P3A4 and P-glycoprotein metabolize colchicine; thus, any drug that binds these proteins influences the colchicine's pharmacokinetics (Borron 1996; Nuki 2008; Slobodnick 2015). The leukocytes are the main targets of colchicine (Chappey 1993). The drug's half-life is between 41 and 46 hours for leukocytes and 49 hours for plasma (Chappey 1993). Colchicine binds to albumin in ~40% (Sabouraud 1994), and it is excreted in unchanged form. As metabolites

in the faeces (about 80%) and 10-20% are excreted in the urine, the levels increase with liver disease. In patients with kidney impairment, colchicine's clearance is also reduced (Liantinioti 2018).

Colchicine has a narrow therapeutic index (Essame 2020; Finkelstein 2010; Ghawanmeh 2020), and its toxicity is associated with a poor prognosis (Essame 2020; Finkelstein 2010). Several drugs inhibit colchicine metabolism; either cytochrome P450 or P-glycoprotein: macrolides (mainly clarithromycin), antiretroviral therapy, broad-spectrum oral antifungal agent (ketoconazole, etc.), grapefruit juice, histamine H2-antagonists (cimetidine), steroids (hydrocortisone, dexamethasone), selective serotonin reuptake inhibitors (fluoxetine, paroxetine), calcium-channel blocker (verapamil, diltiazem), and immunosuppressors (cyclosporine A and tacrolimus are potent inhibitors). Colchicine's dosage must be reduced and closely monitored in patients with relevant hepatic and/or renal dysfunction (Cocco 2010; Curiel 2012; Hung 2005; Imai 2020). Thus, the patients receiving colchicine must be monitored closely, especially in elderly patients with kidney failure (Anonymous 2008; Ho 2019). Colchicine prescribers must know the drug interaction between colchicine and several drugs to reduce the likelihood of fatal and non-fatal colchicine-related side effects (Amanova 2014; Borron 1996; Dahan 2009; Davis 2013; Imai 2020; Magro 2021; Rollot 2004; Slobodnick 2015; Stewart 2020; Villa Zapata 2020). Colchicine increases the rate of diarrhoea and gastrointestinal adverse events that precedes liver, sensory, muscle, infectious, hematologic adverse events, or death (Stewart 2020). Recently, Dubé et al. described two genomic regions associated with gastrointestinal events in patients treated with colchicine. It may benefit some patients with genetic predispositions to lower tolerability of treatment with colchicine (Dubé 2021).

As mentioned above, the colchicine effect, despite its narrow therapeutic window, is to protect the damage of organs by impeding the recruitment of neutrophils and hence decrease the inflammatory burden.

How the intervention might work

Colchicine binds to the following three proteins: tubulin, cytochrome P450, and P-glycoprotein (Slobodnick 2015). The first protein, tubulin, is the main one to explain the drug's clinical benefits and harms. The other two are essential to explain that the colchicine's pharmacokinetic properties as it was described.

Colchicine acts blocking the microtubules' functions (Wilson 1976). Microtubules are the main component of the eukaryotic cytoskeleton (Bershadsky 1988) which possess essential roles in cell division, shaping, motility, and intracellular transport (Forkosh 2020; Janke 2020; Morton 1999; Roll-Mecak 2020, Taylor 1965). The colchicine target is tubulin; a protein made up of two subunits called alpha and beta (Janke 2020; Roll-Mecak 2020). The union colchicine-tubulin yields a microtubule-disassembling (Chaldakov 2018) which explains the anti-inflammatory benefits of colchicine (Forkosh 2020; Terkeltaub 2009). The inhibitory action may explain the benefits due to the colchicine effects over macrophages, platelets, endothelial cells, and leukocytes, especially neutrophils (Cerquaglia 2005; Cronstein 1995; Imazio 2016; Hu 2021; Leung 2015; Paschke 2013; Perico 1996; Pircher 2019; Liang 2019; Rudolph 1977). Leung et al. have reported diverse molecular mechanisms induced by the inhibitory action of colchicine (Leung 2015). These cells play a central role in the inflammatory process by several pathways and, thus, in the previous steps of the atheroma plaque (d'Alessandro 2020; Ma 2019; Nording 2020; Schrottmaier 2020). Therefore, colchicine could prevent cardiovascular events in a primary prevention setting (Tsivgoulis 2018).

Why it is important to do this review

This review is critical for the following reasons. First, according to a Cochrane review, there is uncertainty about the benefits and risks of colchicine in the general population (Hemkens 2016). Of the 39 randomised controlled trials (RCTs) included in Hemkens 2016, 82% (32/39) come from populations with chronic liver diseases, renal and primary

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

Second, numerous non-Cochrane systematic reviews emphasize the prevention of atrial fibrillation (AF) after a post-cardiac procedure. Some included both levels of prevention (Lennerz 2017; Papageorgiou 2017; Salih 2017; Verma 2015; Trivedi 2014; Wang 2016). However, these meta-analyses show inconsistencies: in the measure of evaluation of the effect of the intervention, i.e., odds ratio or risk ratio; reported funnel-plots with less than ten RCTs, lack of assessment of the risk of bias in the included trials or that used out-of-date assessment scales, and without information about the certainty of the evidence. Therefore, it is mandatory to specify the role of colchicine in the primary prevention of cardiovascular events with Cochrane's methodology.

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

Objectives

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

Methods

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) irrespective of publication status. We will only include RCTs with a parallel design and a minimum follow-up of 1 year. The 1-year minimum follow-up is based on the premise that cardiovascular events require enough time to develop. The exception will be for studies including people with post-cardiac procedure atrial fibrillation, in which case there will not be a minimum follow-up requirement.

We will exclude non-randomized clinical trials. Furthermore, we will not apply any limitation by language, and country. We will include studies reported as full-text, those published as abstract only, and unpublished data. Cross-over and cluster-randomized trials are not suitable due to the nature of the clinical conditions where colchicine is prescribed and its intervention's pharmacodynamic properties, especially the very long elimination half-life of the colchicine.

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

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

Types of participants

We will only include adults (aged 18 years or more), regardless of gender, without a known history of cardiovascular outcomes (myocardial infarction, unstable angina, heart failure, stroke, pericardial effusion, atrial fibrillation, and peripheral arterial disease). We will include participants with any risk factor of cardiovascular outcomes (i.e., blood hypertension, obesity, dyslipidemia, diabetes mellitus, and chronic kidney diseases).

We will also include pregnant women. However, we will no report pregnancy or childbirth outcomes. It means that we will only report cardiovascular outcomes and harms if available.

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

Types of interventions

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

1. Intervention:

Colchicine is only administered by the oral route. We will only consider colchicine given alone (monotherapy), regardless of colchicine dosage.

2. Control:

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

We plan to conduct the following comparisons:

- Colchicine versus placebo
- Colchicine versus non-steroidal anti-inflammatory drugs
- Colchicine versus corticosteroids
- Colchicine versus immunomodulating drugs
- Colchicine versus usual care

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

Types of outcome measures

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

For all outcomes that could happen more than once in a trial participant, we will report the number of people with at least one event.

All outcomes will be assessed at maximum follow-up.

Primary outcomes

1. All-cause mortality
2. Non-fatal myocardial infarction
3. Stroke. We will include either acute ischemic stroke or acute cerebral hemorrhage. However, the clinical diagnosis with imaging will be an eligibility criterion.
4. Adverse events: we will prioritize on:
    a. Gastrointestinal (diarrhea)
    b. Liver (jaundice)
    c. Kidney (acute renal failure)
    d. Neurological (seizure, confusion)
    e. Multiorgan failure

Secondary outcomes

1. Cardiovascular mortality
2. Post-cardiac procedure atrial fibrillation
3. Pericardial effusion
4. Symptoms or intervention related to peripheral artery disease
5. Heart failure
6. Unstable angina

We will exclude economic costs as an outcome of this Cochrane Review. However, we will state that economic costs will be discussed in the discussion section in a narrative form if data are available.

Search methods for identification of studies

Electronic searches

We will identify relevant trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library
- MEDLINE (Ovid, from 1946 onwards)
- Embase (Ovid, from 1980 onwards)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Bireme, from 1982 onwards).

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

We will search all databases from their inception to the present, and we will impose no restriction on the language of publication or publication status.

We will not perform a separate search for adverse events of colchicine used for the treatment of any disease. We will consider the adverse events described in included studies only.

Searching other resources

We will also search in Web of Science CPCI-S (Conference Proceedings citation index-science to include conference abstracts.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) for ongoing or unpublished trials.

We will search the following regulatory data websites:

- European Medicines Agency (EMA) (www.ema.europa.eu/en)
- Food and Drugs Administration (FDA) (www.fda.gov/Drugs)

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

We will also examine any relevant retraction statements and errata for included studies. We will exclude the retraction RCTs.

Data collection and analysis

We will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019).

Selection of studies

Two review authors [AMC, ACP] will independently screen titles and abstracts for the inclusion of all the potential studies. We will identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (RH). We will retrieve the full-text study reports/publication and three review authors [DM, CMA, RR] will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult to third-person [JBS]. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Three review authors (AMC, RR, DM) will extract study characteristics from included studies. AC and CMA will check all this information. We will extract the following study characteristics.

1. Methods: study design, the total duration of the study, follow-up period, details of any 'run in' period, number of study centers and location, and study setting.
2. Participants: N randomized, N lost to follow-up/withdrawn, N analyzed, age (as reported by trialist), sex, body mass index (BMI) (it is relevant to determine obesity diagnosis), high-sensitivity C-reactive protein level, relevant details for co-morbidities, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications. Appendix 2 shows details of the intervention description (Hoffmann 2014; Hoffmann 2017). We will collect adverse events information according to Li 2019. Appendix 3 shows details to recollect adverse events information with an Excel spreadsheet (Li 2019).
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: number registration trial, trial conduction dates, a priori sample estimation, financial disclosures, other disclosures, and funding/support. Published in a predatory journal.

Two review authors (AMC, RR) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving two authors (RH, EA). One review author (AMC) will transfer data into the Review Manager (RevMan Web 2019). One review author (RR) will do the double-check that data is entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (DM) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (AMC, DM, and RR) will independently assess the risk of bias for each study using version two of the Cochrane 'Risk of bias' tool (RoB 2), outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Boutron 2019; Higgins 2019a). We will resolve any disagreements by discussion or by involving another author (CMA). We will assess the risk of bias for the outcomes of the included trials that will be included in our Summary of Findings table (Schünemann 2019).

We will perform analysis based on the intention-to-treat principle which includes all randomized participants, irrespective of the interventions that participants actually received. We will use the following domains to assess the risk of bias in the individually randomized trials:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in the measurement of the outcome;
- and bias in the selection of the reported result (Higgins 2019a; Higgins 2019b).

We will use the signaling questions in the RoB 2 tool and rate each domain as 'low risk of bias', 'some concerns', or 'high risk of bias'. The following response options will answers the signaling questions for these domains:

- Yes
- Probably yes
- Probably no
- No
- No information

We will use algorithms to map our answers to the signaling questions per outcome and will propose a 'Risk of bias' for each domain (Higgins 2019b).

When we judge a result to be at a particular level of risk of bias for an individual domain, it implies that the overall result has a risk of bias that is at least this severe. Therefore, a judgment of ‘High’ risk of bias within any domain will have a similar implication for the result as a whole, irrespective of which domain is being assessed. ‘Some concerns’ in multiple domains may lead the review authors to decide on an overall judgment of ‘High’ risk of bias for that outcome or group of outcomes (Higgins 2019a).

The overall risk of bias for the result is the least favorable assessment across the domains of bias:

1. Low risk of bias will denote that the study will be judged to be at low risk of bias for all domains for this result.
2. Some concerns will denote that the study will be judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

3. High risk of bias will denote that study will be judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result (Higgins 2019a; Higgins 2019b).

We will store the data in an Excel tool to implement RoB 2 to show it to the audience (Higgins 2019b).

Measures of treatment effect

Due to all outcomes of this Cochrane review being dichotomous data, we will analyses them with the risk ratio (RR) with 95% confidence intervals (CIs).

Unit of analysis issues

The unit of analysis in this Cochrane Review will be the participant. The time of the analysis will be the longest established in each trial. In the case of multiple-armed trials, we plan to combine the groups to yield a single pairwise comparison (Higgins 2019c).

Dealing with missing data

We will assess the percentage of dropouts for each included trial, and for each intervention group, and will evaluate whether an intention-to-treat (ITT) analysis had been performed or could have been performed from the available published information. We will try to contact the study authors to resolve any questions arising from this issue.

In order to undertake an ITT analysis, we will seek data from the trial authors about the number of participants in treatment groups, irrespective of their compliance and whether or not they were later thought to be ineligible, otherwise excluded from treatment, or lost to follow-up.

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

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

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

Assessment of heterogeneity

The presence of heterogeneity will initially be detected from the visual assessment of the forest plots.

We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We will assume a range of 50% to 90% may represent substantial heterogeneity (Deeks 2019). For a proper interpretation of the I^2, we will follow the relevant Cochrane Handbook's recommendations: "The importance of the observed value of I^2 depends on (1) magnitude and direction of effects, and (2) strength of evidence for heterogeneity (e.g. P-value from the Chi2 test, or a confidence interval for I^2: uncertainty in the value of I^2 is substantial when the number of studies is small)." (Deeks 2019). However, we will consider statistical heterogeneity to be present if I^2 is greater than 70% (Deeks 2019).

Assessment of reporting biases

If there are 10 or more randomized clinical trials by the outcome, we will use the contour enhanced funnel plot to differentiate asymmetry that is due to publication bias from that due to other factors (Sterne 2011). We will assess the likelihood of publication bias with Harbord's test (Sterne 2011). We will use Stata statistical software to produce conventional and contour funnel plots.

Data synthesis

We will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions to summarize study characteristics and prepare for synthesis (McKenzie 2019). If data pooling is not feasible, we will show the information as a narrative summary of the evidence presented in either text or tabular form. However, if there is evidence that an effect exists in at least one study, we plan to use an albatross plot with combines P values (Harrison 2017; McKenzie 2019). Albatross plot requires a two-sided P value, sample size, and direction of effect (or equivalently, a one-sided P value and sample size) for each result (Harrison 2017; McKenzie 2019).

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

Regardless of the overall risk of bias, all RCTs will contribute to the primary analyses. We will conduct the meta-analyses with Review Manager Web (RevMan Web 2019).

Subgroup analysis and investigation of heterogeneity

If there are ten or more RCTs by the outcome and I^2 is greater than 70%, we will conduct a meta-regression with Stata statistical software. We hypothesize that the following covariates could explain the potential statistical heterogeneity: rheumatological disorders (rheumatoid arthritis or gout), cardiovascular risk factor, high-sensitivity C-reactive protein level, and rheumatoid arthritis (Deeks 2019).

We plan to carry out the following subgroup analyses:

1. Participants with rheumatological disorders (rheumatoid arthritis or gout) compared to participants without rheumatological disorders. (Hypothesis: rheumatological disorders people could suppose a higher risk).
2. Participants with cardiovascular risk factors (diabetes mellitus, blood hypertension, chronic kidney disease) compared to participants without cardiovascular risk factors. (Hypothesis: Participants with cardiovascular risk factors have a higher risk of cardiovascular outcomes).
3. Participants with high-sensitivity C-reactive protein levels higher than 2 mg/l versus participants with high-sensitivity C-reactive levels protein ≤ 2 mg/l. (Hypothesis: Higher high-sensitivity C-reactive protein could suppose a higher risk).

We will conduct the subgroup analysis for all outcomes. We will use the formal test for subgroup differences in Review Manager (RevMan Web 2019) and base our interpretation on this.

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Trials with a low risk of bias compared to trials with some concerns or a high risk of bias.

2. A fixed-effect meta-analysis compared to random-effects model meta-analysis.
3. Trials without support from a drug company compared to trials with support from the drug company. Trials with support tend to report positive effects.
4. Trials non-published in predatory journals compared to trials published in predatory journals. Trials published in predatory journals tend to report positive effects.

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

We will use the overall risk of bias for a study result, rather than specific domains. We will judge whether or not there is a difference between the primary analysis and sensitivity analysis by comparing changes in P values.

Summary of findings and assessment of the certainty of the evidence

We will create Summary of the findings table using the predefined outcomes in this Cochrane review (all-cause mortality, non-fatal myocardial infarction, stroke, adverse events, cardiovascular mortality, post-cardiac procedure atrial fibrillation, and symptoms or intervention related to peripheral artery disease). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it relates to the RCTs which contribute data to the meta-analyses for the predefined outcomes (Atkins 2004; Guyatt 2008). We will use methods and recommendations described in Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2019) using GRADEpro software (GRADEpro GDT 2020). As listed in Types of interventions, each comparison will get a separate Summary of findings table. We will justify all decisions to downgrade the quality of RCTs using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Judgment about the certainty of evidence will be made by two review authors (AMC, RR) working independently, with disagreements resolved by discussion or involving a third author (DM). Judgments will be justified, documented, and incorporated into reporting of results for each outcome.

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

Acknowledgements

We express our acknowledgments to Nicole Martin, Fiona Stewart, Charlene Bridges from the Cochrane Heart editorial team; peer reviewers Arden Barry, Jean-Claude Tardif, Georgios Tsivgoulis, and an additional peer reviewer who wishes to remain anonymous; and the consumer reviewer Daniel J García Matínez. Their comments and suggestions improved the quality of this Cochrane review.

Contributions of authors

Arturo Martí-Carvajal wrote the draft with inputs from all authors.

Declarations of interest

Review authors declared having no conflicts of interest.

Sources of support

Internal sources

- Universidad UTE and Cochrane Ecuador, Ecuador

Academic and financial.

- Universidad Francisco de Vitoria, Centro Cochrane asociado de Madrid, Spain
  Academic and financial.
- Cátedra Rectoral de Medicina Basada en al Evidencia, Universidad de Carabobo, Venezuela
  Academic and financial.

External sources

- NIHR, UK
  This project was supported by the NIHR via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care.
- Iberoamerican Cochrane Center, Barcelona, Spain
  Academic.

Appendices

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 Colchicine/ (14348)

2 Colchicine.tw. (15915)

3 1 or 2 (20953)

4 randomized controlled trial.pt. (536578)

5 controlled clinical trial.pt. (94267)

6 randomized.ab. (525623)

7 placebo.ab. (219437)

8 clinical trials as topic.sh. (196544)

9 randomly.ab. (360830)

10 trial.ti. (243020)

11 4 or 5 or 6 or 7 or 8 or 9 or 10 (1377865)

12 exp animals/ not humans.sh. (4855957)

13 11 not 12 (1268087)

14 3 and 13 (695)

Appendix 2. Intervention description and replication

1. Brief name: Provide the name or a phrase that describes the intervention
2. Why: describe any rationale, theory, or goal of the elements essential to the intervention
3. What (materials): Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in the training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL)
4. What (procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities

5. Who provided: For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background, and any specific training given
6. How: Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.
7. Where: Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.
8. When and how much: Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.
9. Tailoring: If the intervention was planned to be personalized, titrated, or adapted, then describe what, why, when, and how.
10. Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11. How well (planned): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12. How well (actual): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

Source: Hoffmann 2014.

Appendix 3. Adverse events information domains

1. Name of the adverse events (e.g. dizziness).
2. The reported intensity of the adverse event (e.g. mild, moderate, severe).
3. Whether the trial investigators categorized the adverse event as ‘serious’.
4. Whether the trial investigators identified the adverse event as being related to the intervention.
5. Time point (most commonly measured as a count over the duration of the study).
6. Any reported methods for how adverse events were selected for inclusion in the publication (e.g. ‘We reported all adverse events that occurred in at least 5% of participants’).

Source: Li 2019.

References

Additional references

Akman 2011

Akman T, Sanli O, Uluocak N, Akbulut F, Nane I, Demir S, et al. The most commonly altered type of Peyronie's disease deformity under oral colchicine treatment is lateral curvature that mostly shifts to the dorsal side. Andrologia 2011;43(1):28-33. [DOI: 10.1111/j.1439-0272.2009.01004.x] [PMID: 21219379]

Akman 2018

Akman S, Yazici S, Ozturk C. Gastrointestinal evaluation in colchicine-treated familial Mediterranean fever patients with chronic abdominal pain: cases series. Archivos Argentinos de Pediatria 2018;116(5):e649-54. [DOI: 10.5546/aap.2018.eng.e649] [PMID: 30204991]

Alarcón 1981

Alarcón Zurita A, Dalmau M, Morey A, Marco J, Bestard J, Pizá C, et al. [Treatment of familial Mediterranean fever with colchicine] [Tratamiento de la fiebre familiar Mediterránea con colchicina]. Revista Clinica Española 1981;163(5):311-2. [PMID: 7342187]

Ali 2021

Ali A, Ali A, Kumar D, Kumar R, Elahi K, Suman F, et al. Comparison of incidence of myocardial infarction in patients with rheumatoid arthritis and diabetes mellitus. Cureus 2021;13(6):e15716. [DOI: 10.7759/cureus.15716] [PMID: 34295575]

Amanova 2014

Amanova A, Celebi ZK, Bakar F, Caglayan MG, Keven K. Colchicine levels in chronic kidney diseases and kidney transplant recipients using tacrolimus. Clinical Transplantation 2014;28:(10):1177-83. [DOI: 10.1111/ctr.12448] [PMID: 25125128]

Anonymous 2008

Anonymous. Colchicine: serious interactions. Prescrire International 2008;17(96):151-3. [PMID: 19492485]

Anyfanti 2021

Anyfanti P, Gavriilaki E, Nikolaidou B, Yiannaki E, Lazaridis A, Papadopoulos N, et al. Patients with autoimmune chronic inflammatory diseases present increased biomarkers of thromboinflammation and endothelial dysfunction in the absence of flares and cardiovascular comorbidities. Journal of Thrombosis and Thrombolysis 2021;Jul 5:Online ahead of print. [DOI: 10.1007/s11239-021-02517-0] [PMID: 34224067]

Aran 2011

Aran S, Malekzadeh S, Seifirad S. A double-blind randomized controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. Clinical and Experimental Rheumatology 2011;29(3):513-8. [PMID: 21640042]

Arbel 2018

Arbel Y, Abuzeid W, Rosenson RS, Weisman A, Farkouh ME. Old drugs for new indications in cardiovascular medicine. Cardiovascular Drugs and Therapy 2018;32(2):223-32. [PMID: 10.1007/s10557-018-6785-y] [PMID: 29633048]

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490. [DOI: 10.1136/bmj.328.7454.1490] [PMID: 15205295]

Bäck 2015

Bäck M, Hansson GK. Anti-inflammatory therapies for atherosclerosis. Nature Reviews. Cardiology 2015;12(4):199-211. [DOI: 10.1038/nrcardio.2015.5] [PMID: 25666404]

Barrett 2020

Barrett TJ. Macrophages in atherosclerosis regression. Arteriosclerosis, Thrombosis, and Vascular Biology 2020;40(1):20-33. [DOI: 10.1161/ATVBAHA.119.312802]

[PMID: 31722535]

Bershadsky 1988

Bershadsky AD, Vasiliev JM. Cytoskeleton. New York: Plenum Press, 1988. [DOI: 10.1007/978-1-4684-5278-]

Borenstein 2009

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Chapter 17 Prediction interval. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors(s). Introduction to Meta-Analysis. First edition. Chichester, West Sussex, United Kingdom: John Wiley & Sons, Ltd, 2009:127-33. [ISBN: 978-0-470-05724-7]

Borenstein 2017

Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. Research Synthesis Methods 2017;8(1):5-18. [PMID: 28058794]

Borron 1996

Borron SW, Scherrmann JM, Baud FJ. Markedly altered colchicine kinetics in a fatal intoxication: examination of contributing factors. Human and Experimental Toxicology 1996;15(11):885-90. [DOI: 10.1177/096032719601501104] [PMID: 8938483]

Boutron 2019

Boutron I, Page M J, Higgins J P T, Altman D G, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:177-204.

Calkins 2017

Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14(10):e275-e444. [DOI: 10.1016/j.hrthm.2017.05.012] [PMID: 28506916]

Cerquaglia 2005

Cerquaglia C, Diaco M, Nucera G , La Regina M, Montalto M, Manna R. Pharmacological and clinical basis of treatment of Familial Mediterranean Fever (FMF) with colchicine or analogues: an update. Current Drug Targets. Inflammation and Allergy. 2005;4(1):117-24. [DOI: 10.2174/1568010053622984] [PMID: 15720245]

Chaldakov 2018

Chaldakov GN. Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases. Cell Biology International 2018;42(8):1079-84. [DOI: 10.1002/cbin.10988] [PMID: 29762881]

Chappey 1993

Chappey ON, Niel E, Wautier JL, Hung PP, Dervichian M, Cattan D, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. Clinical Pharmacology and Therapeutics 1993;54(4):360-7. [DOI: 10.1038/clpt.1993.161] [PMID: 8222477]

Chen 2017

Chen K, Schenone AL, Borges N, Militello M, Menon V. Teaching an old dog new tricks: colchicine in cardiovascular medicine. American Journal of Cardiovascular Drugs 2017;17(5):347-60. [DOI: 10.1007/s40256-017-0226-3] [PMID: 28353024]

Chistiakov 2018

Chistiakov D A, Melnichenko A A, Grechko A V, Myasoedova V A, Orekhov A N. Potential of anti-inflammatory agents for treatment of atherosclerosis. Experimental and Molecular Pathology 2018;104(2):114-24. [DOI: 10.1016/j.yexmp.2018.01.008] [PMID: 29378168]

Cocco 2010

Cocco G, Chu DCC, Pandolfi S. Colchicine in clinical medicine. A guide for internists. European Journal of Internal Medicine 2010;21(6):503-8. [DOI: 10.1016/j.ejim.2010.09.010] [PMID: 21111934]

Cochain 2017

Cochain C, Zernecke A. Macrophages in vascular inflammation and atherosclerosis. Pflugers Archiv 2017;469(3-4):485-99. [DOI: 10.1007/s00424-017-1941-y] [PMID: 28168325]

Croca 2017

Croca S, Rahman A. Atherosclerosis in systemic lupus erythematosus. Best Practice and Research. Clinical Rheumatology 2017;31(3):364-72. [PMID: 10.1016/j.berh.2017.09.012] [PMID: 29224678]

Cronstein 1995

Cronstein BN, Molad Y , J Reibman J, Balakhane E , Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. Journal of Clinical Investigation 1995;96:994-1002. [DOI: 10.1172/JCI118147] [PMID: 7543498]

Cronstein 2013

Cronstein BN, Sunkureddi P. Mechanistic aspects of inflammation and clinical management of inflammation in acute gouty arthritis. Journal of Clinical Rheumatology 2013;19(1):19-29. [DOI: 10.1097/RHU.0b013e31827d8790] [PMID: 23319019]

Curiel 2012

Curiel RV, Guzman NJ. Challenges associated with the management of gouty arthritis in patients with chronic kidney disease: a systematic review. Seminars in Arthritis and Rheumatism 2012;42(2):166-78. [DOI: 10.1016/j.semarthrit.2012.03.013] [PMID: 22560299]

d'Alessandro 2020

d'Alessandro E, Becker C, Bergmeier W, Bode C, Bourne JH, Brown H, Scientific Reviewer Committee. Thrombo-inflammation in cardiovascular disease: an expert consensus document from the third Maastricht consensus conference on thrombosis. Thrombosis and Haemostasis 2020;120(4):538-64. [DOI: 10.1055/s-0040-1708035] [PMID: 32289858]

Dahan 2009

Dahan A, Amidon GL. Grapefruit juice and its constituents augment colchicine

intestinal absorption: potential hazardous interaction and the role of p-glycoprotein. Pharmaceutical Research 2009;26(4):883-92. [DOI: 10.1007/s11095-008-9789-7] [PMID: 19048359]

Das 2002

Das SK, Mishra K, Ramakrishnan S, Srivastava R, Agarwal GG, Singh R, et al. A randomized controlled trial to evaluate the slow-acting symptom modifying effects of a regimen containing colchicine in a subset of patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2002;10(4):247-52. [DOI: 10.1053/joca.2002.0516] [PMID: 11950246]

Dasgeb 2018

Dasgeb B, Kornreich D, McGuinn K, Okon L, Brownell I, Sackett DL. Colchicine: an ancient drug with novel applications. British Journal of Dermatology 2018;178(2):350-6. [DOI: 10.1111/bjd.15896] [PMID: 28832953]

Davis 2013

Davis MW, Wason S, Digiacinto JL. Colchicine-antimicrobial drug interactions: what pharmacists need to know in treating gout. Consultant Pharmacist 2013;28(3):176-83. [DOI: 10.4140/TCP.n.2013.176] [PMID: 23462027]

Deeks 2019

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:241-84.

Deftereos 2013

Deftereos S, Giannopoulos G, Papoutsidakis N, Panagopoulou V, Kossyvakis C, Raisakis K, et al. Colchicine and the heart: pushing the envelope. Journal of the American College of Cardiology 2013;62(20):1817-25. [PMID: 24036026]

Dubé 2021

Dubé MP, Legault MA, Lemaçon A, Perreault LPL, Fouodjio R, Waters DD, et al. Pharmacogenomics of the efficacy and safety of colchicine in COLCOT. Circulation. Genomic and Precision Medicine 2021;Feb 9:Online ahead of print. [DOI: 10.1161/CIRCGEN.120.003183] [PMID: 33560138]

Eshghjoo 2021

Eshghjoo S, Jayaraman A, Sun Y, Alaniz RC. Microbiota-mediated immune regulation in atherosclerosis. Molecules 2021;26(1):179. [DOI: 10.3390/molecules26010179] [PMID: 33401401]

Essame 2020

Essame J, Grossberg S, Mahomed A. Colchicine overdose: A South African experience, a case report. African Journal of Emergency Medicine 2020;10(3):167-9. [DOI: 10.1016/j.afjem.2019.12.005] [PMID: 32923329]

Fazeli 2021

Fazeli MS, Khaychuk V, Wittstock K, Breznen B, Crocket G, Pourrahmat MM, et al. Cardiovascular disease in rheumatoid arthritis: risk factors, autoantibodies, and the effect of antirheumatic therapies. Clinical Medicine Insights. Arthritis and Musculoskeletal Disorders 2021;14:11795441211028751. [DOI: 10.1177/11795441211028751] [PMID: 34262386]

FDA 2021

Food and Drug Administration. Approval package for application number: 22-351. www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022351s000_SumR.pdf. (accessed 4 March 2021).

FDA 2021a

Food and Drug Administration. Approval package for application number 210942Orig1s000. www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210942Orig1s000Approv.pdf (accessed 4 March 2021).

Ferraz-Amaro 2021

Ferraz-Amaro I, Corrales A, Quevedo-Abeledo JC, Vegas-Revenga N, Blanco R, Portilla V, et al. Disease activity influences the reclassification of rheumatoid arthritis into very high cardiovascular risk. Arthritis Research and Therapy 2021;23(1):162. [DOI: 10.1186/s13075-021-02542-7] [PMID: 34088356]

Finkelstein 2002

Finkelstein Y, Shemesh J, Mahlab K, Abramov D, Bar-El Y, Sagie A, et al. Colchicine for the prevention of postpericardiotomy syndrome. Herz 2002;27(8):791-4. [DOI: 10.1093/eurheartj/ehab221] [PMID: 33961006]

Finkelstein 2010

Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: the dark side of an ancient drug. Clinical Toxicology 2010;48(5):407-14. [DOI: 10.3109/15563650.2010.495348] [PMID: 20586571]

Fiolet 2020

Fiolet A T L, Nidorf S M, Cornel J H. Colchicine for secondary prevention in coronary disease. European Heart Journal 2020;Dec 21:Online ahead of print. [DOI: 10.1093/eurheartj/ehaa974] [PMID: 33346343]

Flora 2019

Flora GD, Nayak MK. A brief review of cardiovascular diseases, associated risk factors and current treatment regimes. Current Pharmaceutical Design 2019;25(38):4063-84. [DOI: 10.2174/1381612825666190925163827] [PMID: 31553287]

Forkosh 2020

Forkosh E, Kenig A, Ilan Y. Introducing variability in targeting the microtubules: Review of current mechanisms and future directions in colchicine therapy. Pharmacology Researches and Perspectives 2020;8(4):e00616. [DOI: 10.1002/prp2.616] [PMID: 32608157]

Frostegård 2013

Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Medicine 2013;11:117. [DOI: 10.1186/1741-7015-11-117] [PMID: 23635324]

Fujii 2021

Fujii M, Kishibe M, Ishida-Yamamoto A. Case of hypocomplementemic urticarial vasculitis with Sjogren's syndrome successfully treated with oral corticosteroid and colchicine. Journal of Dermatology 2021;48(2):e112-3. [DOI: 10.1111/1346-8138.15712] [PMID: 33264439]

Gellman 2013

Gellman MC, Turner RJ. Encyclopedia of Behavioral Medicine. 1st edition. New York, Heidelberg, Dordrecht, London: Springer, 2013. [DOI: 10.1007/978-1-4419-1005-9] [ISBN: 978-1-4419-1004-2]

Geovanini 2018

Geovanini GR, Libby P. Atherosclerosis and inflammation: overview and updates. Clinical Science 2018;132(12):1243-52. [DOI: 10.1042/CS20180306] [PMID: 29930142]

Ghawanmeh 2020

Ghawanmeh AA, Al-Bajalan HM, Mackeen MM, Alali FQ, Chong KF. Recent developments on (-)-colchicine derivatives: Synthesis and structure-activity relationship. European Journal Medicine Chemistry 2020;185:111788. [PMID: 10.1016/j.ejmech.2019.111788] [PMID: 31655432]

Gisterå 2017

Gisterå A, Hansson GK. The immunology of atherosclerosis. Nature Reviews. Nephrology 2017;13(6):368-80. [DOI: 10.1038/nrneph.2017.51] [PMID: 28392564]

Gomer 2010

Gomer RH, Lupher Jr ML. Investigational approaches to therapies for idiopathic pulmonary fibrosis. Expert Opinion on Investigational Drugs 2010;19(6):737-45. [DOI: 10.1517/13543784.2010.484018] [PMID: 20443753]

Gong 2004

Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No: CD004481. [DOI: 10.1002/14651858.CD004481.pub2] [PMID: 15106254]

Gotlieb 1991

Gotlieb AI, Langille BL, Fedoroff S (editors). Atherosclerosis: cellular and molecular interactions in the artery wall. New York: Springer Science+Business Media New York, 1991. [DOI: 10.1007/978-1-4615-3754-0] [ISBN (EBOOK): 978-1-4615-3754-0]

GRADEpro GDT 2020 [Computer program]

GRADEpro GDT. Version accessed 9 January 2020. Hamilton (ON): McMaster University (developed by Evidence Prime), 2020. Available at gradepro.org.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist G E, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336(7651):995-8. [PMID: 10.1136/bmj.39490.551019.BE] [PMID: 18456631]

Halabe-Cherem 2009

Halabe-Cherem J, Hamui-Sutton A, Cohen-Cohen S, Sacal-Dumani E, Shuchleib-Cung A, Nellen-Hummel H, et al. [Recurrent pericardial effusion due to familiar Mediterranean fever]. Revista Médica del Instituto Mexicano del Seguro Social 2009;47(2):211-4. [PMID: 19744393]

Hannawi 2021

Hannawi SM, Hannawi H, Al Salmi I. Cardiovascular risk in rheumatoid arthritis:

literature review. Oman Medical Journal 2021;36(3):e262. [DOI: 10.5001/omj.2021.25] [PMID: 34164156]

Hansson 2006

Hansson G K, Robertson A K, Söderberg-Nauclèr C. Inflammation and atherosclerosis. Annual Review of Pathology 2006;1:297-329. [DOI: 10.1146/annurev.pathol.1.110304.100100] [PMID: 18039117]

Harrison 2017

Harrison S, Jones HE, Martin RM, Lewis SJ, Higgins JPT. The albatross plot: a novel graphical tool for presenting results of diversely reported studies in a systematic review. Research Synthesis Methods 2017;8(3):281–9. [DOI: 10.1002/jrsm.1239] [PMID: 28453179]

Hemkens 2016

Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, et al. Colchicine for prevention of cardiovascular events. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No: CD011047. [DOI: 10.1002/14651858.CD011047.pub2] [PMID: 26816301]

Hermans 2010

Hermans MP, Fruchart JC. Reducing residual vascular risk in patients with atherogenic dyslipidemia: Where do we go from here? Clinical Lipidology 2010;5(6):811-26. [DOI: https://doi.org/10.2217/clp.10.65]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60. [DOI: 10.1136/bmj.327.7414.557] [PMID: 12958120]

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019. [ISBN: 9781119536611 (adobe pdf)]

Higgins 2019a

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:205–28.

Higgins 2019b

Higgins JPT, Savović J, Page MJ, Sterne JAC on behalf of the RoB2 Development Group. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) template for completation. drive.google.com/file/d/1Q4Fk3HCuBRwIDWTGZa5oH11OdR4Gbhdo/view. Accessed 12 March 2021 2019.

Higgins 2019c

Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019:569–94.

Ho 2019

Ho GCH, Lau WH, Leung MH. Colchicine gastrotoxicity in a patient with chronic kidney disease. Rheumatology 2019;58(12):2229. [DOI: 10.1093/rheumatology/kez178] [PMID: 31056709]

Hoffmann 2014

Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687. [DOI: 10.1136/bmj.g1687] [PMID: 24609605]

Hoffmann 2017

Hoffmann TC, Oxman AD, Ioannidis JP, Moher D, Lasserson TJ, Tovey DI, et al. Enhancing the usability of systematic reviews by improving the consideration and description of interventions. BMJ 2017;358:j2998. [DOI: 10.1136/bmj.j2998] [PMID: 28729459]

Hollis 1999

Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319(7211):670-4. [DOI: 10.1136/bmj.319.7211.670] [PMID: 10480822]

Hu 2021

Hu D, Wang Z, Wang Y, Liang C. Targeting macrophages in atherosclerosis. Current Pharmaceutical Biotechnology 2021;Jan 22:Online ahead of print. [DOI: 10.2174/1389201022666210122142233] [PMID: 33480337]

Hung 2005

Hung IFN, Wu AKL, Cheng VCC, Tang BSF, To KW, Yeung CK, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clinical Infectious Diseases 2005;41(3):291-300. [DOI: 10.1086/431592.] [PMID: 16007523]

Hussain 2020

Hussain SM, Dawson C, Wang Y, Tonkin AM, Chou L, Wluka AE, et al. Vascular pathology and osteoarthritis: a systematic review. Journal of Rheumatology 2020;47(5):748-60. [DOI: 10.3899/jrheum.181236] [PMID: 31154415]

Ibrahim 2019

Ibrahim A, Gazzard L, Alharbi M, Rompré-Brodeur A, Aube M, Carrier S. Evaluation of oral pentoxifylline, colchicine, and penile traction for the management of Peyronie's disease. Sexual Medicine 2019;7(4):459-63. [DOI: 10.1016/j.esxm.2019.07.003] [PMID: 31445974]

Imai 2020

Imai S, Momo K, Kashiwagi H, Miyai T, Sugawara M, Takekuma Y. Prescription of colchicine with other dangerous concomitant medications: a nation-wide survey using the Japanese claims database. Biological and Pharmaceutical Bulletin 2020;43(10):1519-25. [DOI: 10.1248/bpb.b20-00314] [PMID: 32999162]

Imazio 2005

Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for

REcurrent pericarditis) trial. Archives of Internal Medicine 2005;165(17):1987-91. [DOI: 10.1001/archinte.165.17.1987] [PMID: 16186468]

Imazio 2005a

Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation 2005;112(13):2012-16. [DOI: 10.1161/CIRCULATIONAHA.105.542738] [PMID: 16186437]

Imazio 2010

Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, COPPS Investigators. Colchicine for the prevention of the post-pericardiotomy syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. European Heart Journal 2010;31(22):2749-54. [DOI: 10.1093/eurheartj/ehq319] [PMID: 20805112]

Imazio 2011

Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. Annals of Internal Medicine 2011;155(7):409-14. [DOI: 10.7326/0003-4819-155-7-201110040-00359] [PMID: 21873705]

Imazio 2011a

Imazio M, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, et al. Colchicine prevents early postoperative pericardial and pleural effusions. American Heart Journal 2011;162(3):527-32. [DOI: 10.1016/j.ahj.2011.05.017] [PMID: 21884871]

Imazio 2014

Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. Lancet 2014;383(9936):2232-37. [DOI: 10.1016/S0140-6736(13)62709-9] [PMID: 24694983]

Imazio 2014a

Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, COPPS-2 Investigators. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. JAMA 2014;312(10):1016-23. [DOI: 10.1001/jama.2014.11026] [PMID: 25172965]

Imazio 2016

Imazio M, Gaita F. Colchicine for cardiovascular medicine. Future Cardiology 2016;12(1):9-16. [DOI: 10.2217/fca.15.59] [PMID: 26632860]

Imazio 2021

Imazio M, Nidorf N. Colchicine and the heart. European Heart Journal 2021;42(28):2745-60. [PMID: 10.1093/eurheartj/ehab221] [PMID: 33961006]

IntHout 2016

IntHout J, Ioannidis JP, Rovers M M, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 2016;6(7):e010247. [DOI: 10.1136/bmjopen-2015-010247] [PMID: 27406637]

Janke 2020

Janke C, Magiera MM. The tubulin code and its role in controlling microtubule properties and functions. Nature Reviews. Molecular Cell Biology 2020;21(6):307-26. [DOI: 10.1038/s41580-020-0214-3] [PMID: 32107477]

January 2014

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology 2014;64(21):e1-76. [DOI: 10.1016/j.jacc.2014.03.022] [PMID: 24685669]

Karamanou 2018

Karamanou M, Tsoucalas G, Pantos K, Androutsos G. Isolating colchicine in 19th Century: an old drug revisited. Current Pharmaceutical Design 2018;24(6):654-58. [PMID: 10.2174/1381612824666180115105850] [PMID: 29336251]

Kaur 2020

Kaur I, Singal A, Rohatgi J. Conjunctival ulcers in Behcet's disease and response to colchicine. Indian Dermatology Online Journal 2020;11(6):1005-6. [DOI: 10.4103/idoj.IDOJ_362_20. eCollection 2020] [PMID: 33344359]

Kiraz 1998

Kiraz S, Ertenli I, Arici M, Calgüneri M, Haznedaroglu I, Celik I, et al. Effects of colchicine on inflammatory cytokines and selectins in familial Mediterranean fever. Clinical and Experimental Rheumatology 1998;16(6):721-4. [PMID: 9844766]

Kirchhof 2016

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal 2016;37(8):2893-962. [DOI: 10.1093/eurheartj/ehw210] [PMID: 27567408]

Kobiyama 2018

Kobiyama K, Ley K. Atherosclerosis. Circulation Research 2018;123(10):1118-20. [DOI: 10.1161/CIRCRESAHA.118.313816] [PMID: 30359201]

Kontopantelis 2010

Kontopantelis E, Reeves D. Metaan: Random-effects meta-analysis. Stata Journal 2010;10(3):395–407. [DOI: 10.1177/1536867X1001000307]

Kottoor 2018

Kottoor SJ, Arora RR. The utility of anti-inflammatory agents in cardiovascular disease: a novel perspective on the treatment of atherosclerosis. Journal of Cardiovascular Pharmacology and Therapeutics 2018;23(6):483-93. [DOI: 10.1177/1074248418778548] [PMID: 29783850]

Lazaros 2018

Lazaros G, Imazio M, Brucato A, Vlachopoulos C, Lazarou E, Vassilopoulos D, et al. The role of colchicine in pericardial syndromes. Current Pharmaceutical Design 2018;24(6):702-9. [PMID: 10.2174/1381612824666180116101823] [PMID: 29336245]

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M- I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:67–108.

Lennerz 2017

Lennerz C, Barman M, Tantawy M, Sopher M, Whittaker P. Colchicine for primary prevention of atrial fibrillation after open-heart surgery: Systematic review and meta-analysis. International Journal of Cardiology 2017;249:127-37. [DOI: 10.1016/j.ijcard.2017.08.039] [PMID: 28918897]

Leung 2015

Leung YY, Hui LLY, Kraus VB. Colchicine--Update on mechanisms of action and therapeutic uses. Seminars in Arthritis and Rheumatism 2015;45(3):341-50. [DOI: 10.1016/j.semarthrit.2015.06.013] [PMID: 26228647]

Li 2019

Li T, Higgins JPT, Deeks JJ (editors). Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:109–142.

Li 2021

Li X, Sundquist J, Nymberg V, Sundquist K. Association of autoimmune diseases with cardiomyopathy: a nationwide follow-up study from Sweden. European Heart Journal. Quality of Care and Clinical Outcomes 2021;Jun 21:Online ahead of print. [DOI: 10.1093/ehjqcco/qcab044] [PMID: 34152406]

Liang 2019

Liang X, Xiu C, Liu M, Lin C, Chen H, Bao R, et al. Platelet-neutrophil interaction aggravates vascular inflammation and promotes the progression of atherosclerosis by activating the TLR4/NF-κB pathway. Journal of Cellular Biochemistry 2019;120(4):5612-19. [DOI: 10.1002/jcb.27844] [PMID: 30302814]

Liantinioti 2018

Liantinioti G, Argyris AA, Protogerou AD, Vlachoyiannopoulos P. The role of colchicine in the treatment of autoinflammatory diseases. Current Pharmaceutical Design 2018;24(6):690-4. [DOI: 10.2174/1381612824666180116095658] [PMID: 29336247]

Libby 2019

Libby P, Buring J E, Badimon L, Hansson G K, Deanfield J, Bittencourt M S, et al. Atherosclerosis. Nature Reviews. Disease Primers 2019;5(1):56. [PMID: 10.1038/s41572-019-0106-z] [PMID: 31420554]

Liberati 2009

Liberati A, Altman D G, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Medicine 2009;6(7):e1000100. [DOI: 10.1371/journal.pmed.1000100] [PMID: 19621070]

Liu 2018

Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. Current Opinion in Rheumatology 2018;30(5):441-8. [PMID: 10.1097/BOR.0000000000000528] [PMID: 29870498]

Liu 2019

Liu W, Balu N, Canton G, Hippe DS, Watase H, Waterton JC, et al. Understanding atherosclerosis through an osteoarthritis data set. Arteriosclerosis, Thrombosis, and Vascular Biology 2019;39(6):1018-25. [DOI: 10.1161/ATVBAHA.119.312513] [PMID: 31070477]

Liuzzo 1994

Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. New England Journal of Medicine 1994;331(7):417-24. [PMID: 10.1056/NEJM199408183310701] [PMID: 7880233]

Ma 2019

Ma WT, Gao F, Gu K, Chen DK. The role of monocytes and macrophages in autoimmune diseases: a comprehensive review. Frontiers in Immunology 2019;10:1140. [DOI: 10.3389/fimmu.2019.01140] [PMID: 31178867]

Magro 2021

Magro L, Arzento E, Leone R, Stano MG, VezzaroM, Rudolph A, et al. Identifying and characterizing serious adverse drug reactions associated with drug-drug interactions in a spontaneous reporting database. Frontiers in Pharmacology 2021;11:622862. [PMID: 10.3389/fphar.2020.622862] [PMID: 33536925]

Maisch 2004

Maisch B, Seferović PM, Ristiá AD, Erbel R, Rienmüller R, Adler Y, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; The task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology. European Heart Journal 2004;25(7):587-610. [DOI: 10.1016/j.ehj.2004.02.002] [PMID: 15120056]

Martinez 2018

Martinez BK, White CM. The emerging role of inflammation in cardiovascular disease. Annals of Pharmacotherapy 2018;52(8):801-9. [DOI: 10.1177/1060028018765939] [PMID: 29557210]

McKenzie 2019

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV. Chapter 9: Summarizing study characteristics and preparing for synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019:229-40.

Meneses 2015

Meneses CF, Egües CA, Uriarte M, Belzunegui J, Rezola M. Colchicine use in isolated renal AA amyloidosis. Reumatologia Clinica 2015;11(4):242-3. [DOI: 10.1016/j.reuma.2014.09.007] [PMID: 25453598]

Meurin 2015

Meurin P, Lelay-Kubas S, Pierre B, Pereira H, Pavy B, Iliou MC, French Society of Cardiology. Colchicine for postoperative pericardial effusion: a multicentre, double-blind, randomised controlled trial. Heart 2015;101(21):1711-6. [PMID: 10.1093/eurheartj/ehab221] [PMID: 26076938]

Micheletti 2020

Micheletti RG, Pagnoux C. Management of cutaneous vasculitis. Presse Medicale 2020;49(3):104033. [DOI: 10.1016/j.lpm.2020.104033] [PMID: 32645416]

Ministrini 2021

Ministrini S, Carbone F. PCSK9 and inflammation. Maybe a role in autoimmune diseases? Focus on rheumatoid arthritis and systemic lupus erythematosus. Current Medicinal Chemistry 2021;Aug 10:Online ahead of print.. [DOI: 10.2174/0929867328666210810150940] [PMID: 34375179]

Mizuno 2011

Mizuno Y, Jacob RF, Mason RP. Inflammation and the development of atherosclerosis. Journal of Atherosclerosis and Thrombosis 2011;18(5):351-8. [PMID: 10.5551/jat.7591] [PMID: 21427505]

Moriya 2019

Moriya J. Critical roles of inflammation in atherosclerosis. Journal of Cardiology 2019;73(1):22-7. [DOI: 10.1016/j.jjcc.2018.05.010] [PMID: 29907363]

Morton 1999

Morton IKM, Hall JM. Concise Dictionary of Pharmacological Agents Properties and Synonyms. First edition. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1999. [ISBN: 075-1404-993]

Nidorf 2013

Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. Journal of the American College of Cardiology 2013;61(4):404-10. [DOI: 10.1016/j.jacc.2012.10.027] [PMID: 23265346]

Nidorf 2014

Nidorf SM, Eikelboom JW, Thompson PL. Colchicine for secondary prevention of cardiovascular disease. Current Atherosclerosis Reports 2014;16(3):391. [DOI: 10.1007/s11883-013-0391-z] [PMID: 24425060]

Nording 2020

Nording H, Baron L, Langer HF. Platelets as therapeutic targets to prevent atherosclerosis. Atherosclerosis 2020;307:97-108. [DOI: 10.1016/j.atherosclerosis.2020.05.018] [PMID: 32653088]

Nuki 2008

Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. Current Rheumatology Reports 2008;10(3):218-27. [DOI: 10.1007/s11926-008-0036-3] [PMID: 18638431]

Oikonomou 2020

Oikonomou E, Leopoulou M, Theofilis P, Antonopoulos AS, Siasos G, Latsios G, et al. A link between inflammation and thrombosis in atherosclerotic cardiovascular

diseases: Clinical and therapeutic implications. Atherosclerosis 2020;309:16-26. [DOI: 10.1016/j.atherosclerosis.2020.07.027] [PMID: 32858395]

Ozen 2021

Ozen G, Pedro S, Schumacher R, Simon T, Michaud K. Risk factors for venous thromboembolism and atherosclerotic cardiovascular disease: do they differ in patients with rheumatoid arthritis? RMD Open 2021;7(2):e001618. [DOI: 10.1136/rmdopen-2021-001618] [PMID: 34193517]

Pant 2014

Pant S, Deshmukh A, Gurumurthy GS, Pothineni NV, Watts TE, Romeo F, et al. Inflammation and atherosclerosis--revisited. Journal of Cardiovascular Pharmacology and Therapeutics 2014;19(2):170-8. [DOI: 10.1177/1074248413504994] [PMID: 24177335]

Papageorgiou 2017

Papageorgiou N, Briasoulis A, Lazaros G, Imazio M, Tousoulis D. Colchicine for prevention and treatment of cardiac diseases: a meta-analysis. Cardiovascular Therapeutics 2017;35(1):10-8. [PMID: 10.1111/1755-5922.12226] [PMID: 27580061]

Paschke 2013

Paschke S, Weidner AF, Paust T, Marti O, Beil M, Ben-Chetrit E. Technical advance: Inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. Journal of Leukocyte Biology 2013;94(5):1091-6. [DOI: 10.1189/jlb.1012510] [PMID: 23901122]

Patel 2021

Patel NH, Dey AK, Sorokin AV, Teklu M, Petrole R, Zhou W, et al. Chronic inflammatory diseases and coronary heart disease: Insights from cardiovascular CT. Journal of Cardiovascular Computed Tomography 2021;S1934-5925(21)00086-1:Online ahead of print. [DOI: 10.1016/j.jcct.2021.06.003] [PMID: 34226164]

Perico 1996

Perico N, Ostermann D, Bontempeill M , Morigi M, Amuchastegui CS , Zoja C, et al. Colchicine interferes with L-selectin and leukocyte function-associated antigen-1 expression on human T lymphocytes and inhibits T cell activation. Journal of the American Society of Nephrology 1996;7(4):594-601. [DOI: 8724893]

Pircher 2019

Pircher J, Engelmann B, Massberg S, Schulz C. Platelet-neutrophil crosstalk in atherothrombosis. Thrombosis and Haemostasis 2019;119(8):1274-82. [DOI: 10.1055/s-0039-1692983] [PMID: 31254975]

Plotz 2021

Plotz B, Pillinger M, Samuels J. Colchicine and clinical trials for hand osteoarthritis. Osteoarthritis and Cartilage 2021;S1063-4584(21)00618-X:Online ahead of print. [DOI: 10.1016/j.joca.2020.12.026] [PMID: 33636316]

Rahman 2017

Rahman M S, Woollard K. Atherosclerosis. Advances in Experimental Medicine and Biology 2017;1003:121-44. [DOI: 10.1007/978-3-319-57613-8_7] [PMID: 28667557]

Rajapakse 2001

Rajapakse R, Warman J, Korelitz BI. Colchicine for persistent constipation after total abdominal colectomy with ileorectostomy for colonic inertia. Journal of Clinical Gastroenterology 2001;33(1):81-4. [DOI: 10.1097/00004836-200107000-00022] [PMID: 11418801]

Rambaldi 2001

Rambaldi A, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No: CD002148. [DOI: 10.1002/14651858.CD002148.pub2]

Reglero-Real 2021

Reglero-Real N, Pérez-Gutiérrez L, Yoshimura A, Rolas L, Garrido-Mesa J, Barkaway A, et al. Autophagy modulates endothelial junctions to restrain neutrophil diapedesis during inflammation. Immunity 2021;S1074-7613(21)00298-3:online ahead of print.

RevMan Web 2019 [Computer program]

The Cochrane Collaboration Review Manager Web (RevManWeb). Available at revman.cochrane.org.. The Cochrane Collaboration, 2019.

Richette 2010

Richette P, Bardin T. Colchicine for the treatment of gout. Expert Opinion on Pharmacotherapy 2010;11(17):2933-8. [PMID: 10.1517/14656566.2010.529432] [PMID: 21050036]

Ridker 2018

Ridker PM. Clinician's guide to reducing inflammation to reduce atherothrombotic risk: JACC review topic of the week. Journal of the American College of Cardiology 2018;72(25):3320-31. [DOI: 10.1016/j.jacc.2018.06.082] [PMID: 30415883]

Riley 2011

Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549. [DOI: 10.1136/bmj.d549] [PMID: 21310794]

Roll-Mecak 2020

Roll-Mecak A. The tubulin code in microtubule dynamics and information encoding. Developmental Cell 2020;54(1):7-20. [DOI: 10.1016/j.devcel.2020.06.008] [PMID: 32634400]

Rollot 2004

Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kélaïdi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. Annals of Pharmacotherapy 2004;38(12):2074-7. [PMID: 10.1345/aph.1E197] [PMID: 15494379]

Roman 2020

Roman YM, Hernandez AV, White CM. The role of suppressing inflammation in the treatment of atherosclerotic cardiovascular disease. Annals of Pharmacotherapy 2020;54(10):1021-9. [DOI: 10.1177/1060028020922994] [PMID: 32425120]

Roth 2020

Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM,

GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. Journal of the American College of Cardiology 2020;76(25):2982-3021. [DOI: 10.1016/j.jacc.2020.11.010] [PMID: 33309175]

Roubille 2020

Roubille F, Tardif JC. Colchicine for secondary cardiovascular prevention in coronary disease. Circulation 2020;142(20):1901-4. [DOI: 10.1161/CIRCULATIONAHA.120.051240] [PMID: 33196312]

Rudolph 1977

Rudolph SA , Greengard P, Malawista SE. Effects of colchicine on cyclic AMP levels in human leukocytes. Proceedings of the National Academy of Sciences of the United States of America 1977;74(8):3404-8. [DOI: 10.1073/pnas.74.8.3404] [PMID: 198784]

Sabouraud 1994

Sabouraud A, Chappey O, Dupin T, Scherrmann JM. Binding of colchicine and thiocolchicoside to human serum proteins and blood cells. International Journal of Clinical Pharmacology and Therapeutics 1994;32(8):429-32. [PMID: 7981928]

Salih 2017

Salih M, Smer A, Charnigo R, Ayan M, Darrat YH, Traina M, et al. Colchicine for prevention of post-cardiac procedure atrial fibrillation: Meta-analysis of randomized controlled trials. International Journal of Cardiology 2017;243:258-62. [DOI: 10.1016/j.ijcard.2017.04.022] [PMID: 28747027]

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of Clinical Epidemiology 2020;119:126-35. [DOI: 10.1016/j.jclinepi.2019.10.014] [PMID: 31711912]

Schrottmaier 2020

Schrottmaier WC, Mussbacher M, Salzmann M, Assinger A. Platelet-leukocyte interplay during vascular disease. Atherosclerosis 2020;307:109-20. [DOI: 10.1016/j.atherosclerosis.2020.04.018] [PMID: 32439204]

Schünemann 2019

Schünemann HJ, Higgins JPT, Vist G E, Glasziou P, Akl E A, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2019:375-402.

Semb 2017

Semb AG. Handbook of cardiovascular disease management in rheumatoid arthritis. First edition. Switzerland: Springer International Publishing AG, 2017. [ISBN: 978-3-319-26782-1 (eBook)]

Shi 2010

Shi GP. Immunomodulation of vascular diseases: atherosclerosis and autoimmunity. European Journal of Vascular and Endovascular Surgery 2010;39(4):485-94. [DOI: 10.1016/j.ejvs.2010.01.028] [PMID: 20188603]

Siak 2021

Siak J, Flint N, Shmueli H G, Siegel RJ, Rader F. The use of colchicine in cardiovascular diseases - a systematic review. American Journal of Medicine 2021;S0002-9343(21)00098-X:Online ahead of print. [DOI: 10.1016/j.amjmed.2021.01.019] [PMID: 33609528]

Sinanoglu 2018

Sinanoglu O, Kurtulus FO, Akgün FS. Long-term effect of colchicine treatment in preventing urethral stricture recurrence after internal urethrotomy. Urology Journal 2018;15(4):204-8. [DOI: 10.22037/uj.v0i0.4198] [PMID: 29681046]

Slobodnick 2015

Slobodnick A, Shah B, PillingerMH, Krasnokutsky S. Colchicine: old and new. American Journal of Medicine 2015;128(5):461-70. [DOI: 10.1016/j.amjmed.2014.12.010] [PMID: 25554368]

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002. [DOI: 10.1136/bmj.d4002] [PMID: 21784880]

Stewart 2020

Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Research and Therapy 2020;22(1):28. [DOI: 10.1186/s13075-020-2120-7] [PMID: 32054504]

Tardif 2019

Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. New England Journal of Medicine 2019;381(26):2497-2505. [DOI: 10.1056/NEJMoa1912388] [PMID: 31733140]

Taylor 1965

Taylor EW. The mechanism of colchicine inhibition of mitosis. I. Kinetics of inhibition and the binding of H3-colchicine. Journal of Cell Biology 1965;25(1 Suppl):145-60. [DOI: 10.1083/jcb.25.1.145] [PMID: 14342828]

Terkeltaub 2009

Terkeltaub RA. Colchicine update: 2008. Seminars in Arthritis and Rheumatism 2009;38(6):411-9. [DOI: 10.1016/j.semarthrit.2008.08.006 Abstract] [PMID: 18973929]

Thompson 2019

Thompson PL. Colchicine in cardiovascular disease: repurposing an ancient gout drug. Clinical Therapeutics 2019;41(1):8-10. [PMID: 10.1016/j.clinthera.2018.11.014] [PMID: 30594311]

Tong 2016

Tong DC, Wilson AM, Layland J. Colchicine in cardiovascular disease: an ancient drug with modern tricks. Heart 2016;102(13):995-1002. [DOI: 10.1136/heartjnl-2015-309211] [PMID: 26993138]

Trivedi 2014

Trivedi C, Sadadia M. Colchicine in prevention of atrial fibrillation following cardiac surgery: systematic review and meta-analysis. Indian Journal of Pharmacology 2014;46(6):590-5. [DOI: 10.4103/0253-7613.144905] [PMID: 25538328]

Tsivgoulis 2018

Tsivgoulis G, Katsanos AH, Giannopoulos G, Panagopoulou V, Jatuzis D, Lemmens R , et al. The role of colchicine in the prevention of cerebrovascular ischemia. Current Pharmaceutical Design 2018;24(6):668-74. [DOI: 10.2174/1381612824666180116100310] [PMID: 29336246]

Van Nuland 2017

Van Nuland SE, Rogers KA. Academic nightmares: Predatory publishing. Anatomical Sciences Educationc 2017;10:392–4. [DOI: 10.1002/ase.1671] [PMID: 27911990]

Vanuzzo 2011

Vanuzzo D. The epidemiological concept of residual risk. Internal and Emergency Medicine 2011;6(Suppl 1):45-51. [DOI: 10.1007/s11739-011-0669-5] [PMID: 22009612]

Verma 2015

Verma S, Eikelboom JW, Nidorf SM, Al-Omran M, Gupta N, Teoh H, et al. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovascular Disorders 2015;15:96. [DOI: 10.1186/s12872-015-0068-3] [PMID: 26318871]

Verne 1997

Verne GN, Eaker EY, Davis RH, Sninsky CA. Colchicine is an effective treatment for patients with chronic constipation: an open-label trial. Digestive Diseases and Sciences 1997;42(9):1959-63. [DOI: 10.1023/a:1018883731556] [PMID: 9331162]

Verne 2003

Verne GN, Davis RH, Robinson ME, Gordon JM, Eaker EY, Sninksy CA. Treatment of chronic constipation with colchicine: randomized, double-blind, placebo-controlled, crossover trial. American Journal of Gastroenterology 2003;98(5):1112-6. [DOI: 10.1111/j.1572-0241.2003.07417.x] [PMID: 12809836]

Veronese 2018

Veronese N, Stubbs B, Solmi M, Smith TO, Reginster JY, Maggi S. Osteoarthristis increases the risk of cardiovascular disease: data from the osteoarthritis initiative. Journal of Nutrition, Health, and Aging 2018;22(3):371-6. [DOI: 10.1007/s12603-017-0941-0] [PMID: 29484350]

Vicente 2021

Vicente GNS, Pereira IA, de Castro GRW, da Mota LMH, Carnieletto AP, de Souza DGS, et al. Cardiovascular risk comorbidities in rheumatoid arthritis patients and the use of anti-rheumatic drugs: a cross-sectional real-life study. Advances in Rheumatology 2021;61(1):38. [DOI: 10.1186/s42358-021-00186-4] [PMID: 34172097]

Vilardell 1978

Vilardell F. [Prolonged remission with colchicine in a case of familial Mediterranean fever]. Revista Clinica Española 1978;149(1):97-8. [PMID: 674762]

Villa Zapata 2020

Villa Zapata L, Hansten PD, Horn JR, Boyce RD, Gephart S, Subbian V, et al. Evidence of clinically meaningful drug-drug interaction with concomitant use of colchicine and clarithromycin. Drug Safety 2020;43(7):661-8. [DOI: 10.1007/s40264-020-00930-7] [PMID: 32274687]

Wang 2016

Wang MX, Deng XL, Mu BY, Cheng YJ, Chen YJ, Wang Q, et al . Effect of colchicine in prevention of pericardial effusion and atrial fibrillation: a meta-analysis. International and Emergency Medicine 2016 ;11(6):867-76. [DOI: 10.1007/s11739-016-1496-5] [PMID: 27378573]

Wang 2021

Wang Q, Zhang M, Wang M, Tai Y, Tao J, Zhou W, et al. Triggers of cardiovascular diseases in rheumatoid arthritis. Current Problems in Cardiology 2021;Apr 6:10.1016/j.cpcardiol.2021.100853. [DOI: 10.1016/j.cpcardiol.2021.100853] [PMID: 34016483]

Whayne 2021

Whayne TF Jr. Inflammation may be the future of cardiovascular risk reduction: Does colchicine have a current Indication? American Journal of Cardiovascular Drugs 2021;21(1):1-10. [DOI: 10.1007/s40256-020-00408-y] [PMID: 32356107]

Wilson 1976

Wilson L. Microtubules as drug receptors: pharmacological properties of microtubule protein. Annals of the New York Academy of Sciences 1976;253:213-31. [DOI: 10.1111/j.1749-6632.1975.tb19201.x.] [PMID: 1096718]

Wolf 2019

Wolf D, Ley K. Immunity and inflammation in atherosclerosis. Circulation Research 2019;124(2):315-37. [DOI: 10.1161/CIRCRESAHA.118.313591] [PMID: 30653442]

Xia 2021

Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. American Journal of Cardiology 2021;140:33-38. [DOI: 10.1016/j.amjcard.2020.10.043] [PMID: 33137319]

Yalcinkaya 2021

Yalcinkaya D, Yarlioglues M, Ergun E, Celik IE, Oksuz F, Cicek G, et al. Severe cardiovascular involvement in a patient with rheumatoid arthritis. Kardiologia Polska 2021;79(5):577-8. [DOI: 10.33963/KP.15879]

Zhao 2021

Zhao M, Wu J, Wu H, Sawalha A, Qianjin L. Clinical treatment options in scleroderma: recommendations and comprehensive review. Clinical Reviews in Allergy and Immunology 2021;Jan 15:Online ahead of print. [DOI: 10.1007/s12016-020-08831-4] [PMID: 33449302]

Zhu 2018

Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, et al. Research progress on the relationship between atherosclerosis and inflammation. Biomolecules 2018;8(3):80. [DOI: 10.3390/biom8030080] [PMID: 30142970]

Figures and tables