





# Colchicine for secondary prevention of vascular events: a meta-analysis of trials

Marc-André d'Entremont <sup>1,2,3,†</sup>, Michiel H.F. Poorthuis<sup>4</sup>, Aernoud T.L. Fiolet<sup>5,6</sup>, Pierre Amarenco<sup>1,7</sup>, Kevin Emery Boczar<sup>8</sup>, Ian Buyschaert<sup>9</sup>, Noel C. Chan <sup>10</sup>, Jan H. Cornel<sup>6,11,12</sup>, Jalina Jannink<sup>13</sup>, Shirley Jansen<sup>14</sup>, Sasko Kedev<sup>15</sup>, Anthony C. Keech<sup>16,17</sup>, Jamie Layland<sup>18</sup>, Nathan Mewton<sup>19</sup>, Gilles Montalescot<sup>20</sup>, Domingo A. Pascual-Figal<sup>21,22</sup>, Alfredo E. Rodriguez<sup>23</sup>, Bineta Shah<sup>24,25</sup>, Martin Teraa <sup>26</sup>, Aimee van Zelm<sup>26</sup>, Yongjun Wang<sup>27</sup>, Arend Mosterd <sup>6,13</sup>, Peter Kelly<sup>28,29</sup>, John Eikelboom<sup>1,30</sup>, and Sanjit S. Jolly<sup>1,2,\*</sup>; on behalf of the Colchicine Cardiovascular Trialists Collaboration

<sup>1</sup>Population Health Research Institute, 237 Barton Street East, Hamilton L8L 2X2, Ontario, Canada; <sup>2</sup>Department of Cardiology, Hamilton General Hospital, McMaster University, 237 Barton Street East, Hamilton L8L 2X2, Ontario, Canada; <sup>3</sup>Département de Médecine, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada; <sup>4</sup>Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>5</sup>Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>6</sup>Dutch Network for Cardiovascular Research (WCN), Utrecht, The Netherlands; <sup>7</sup>Department of Neurology, Bichat University Hospital, Paris, France; <sup>8</sup>Department of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; <sup>9</sup>Department of Cardiology, Sint-Jan Hospital, Brugge, Belgium; <sup>10</sup>Department of Medicine, Division of Haematology and Thromboembolism, McMaster University, Hamilton, ON, Canada; <sup>11</sup>Department of Cardiology, Northwest Clinics, Alkmaar, The Netherlands; <sup>12</sup>Department of Cardiology, Radboud University Medical Centre, Nijmegen, The Netherlands; <sup>13</sup>Department of Cardiology, Meander Medical Center, Amersfoort, The Netherlands; <sup>14</sup>Heart and Vascular Research Institute, Harry Perkins Institute for Medical Research, Perth, Australia; <sup>15</sup>Department of Cardiology, University Ss. Cyril and Methodius, Skopje, North Macedonia; <sup>16</sup>NHMRC Clinical Trials Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia; <sup>17</sup>Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia; <sup>18</sup>Department of Cardiology, Peninsula Health, Peninsula Clinical School, Central Clinical School, Monash University, Frankston, VIC, Australia; <sup>19</sup>Department of Cardiology, Institut de Cardiologie des Hospices Civils de Lyon, Lyon, France; <sup>20</sup>Sorbonne University, ACTION Study Group, Centre Hospitalier Universitaire Pitié-Salpêtrière Assistance Publique–Hôpitaux de Paris, Paris, France; <sup>21</sup>Department of Cardiology, Hospital Virgen de la Arrixaca, University of Murcia, Murcia, Spain; <sup>22</sup>Department of Cardiology, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; <sup>23</sup>Department of Cardiology, Otamendi Hospital, Buenos Aires, Argentina; <sup>24</sup>Department of Cardiology, VA New York Harbor Healthcare System, New York, New York, USA; <sup>25</sup>Leon H Charney Division of Cardiology, NYU Grossman School of Medicine, New York, NY, USA; <sup>26</sup>Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>27</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; <sup>28</sup>Department of Neurology, Mater Misericordiae University Hospital and School of Medicine, University College Dublin, Dublin, Ireland; <sup>29</sup>Health Research Board Stroke Clinical Trials Network Dublin Ireland, Dublin, Ireland; and <sup>30</sup>Department of Medicine, McMaster University, Hamilton, ON, Canada

Received 17 December 2024; revised 30 January 2025; accepted 17 March 2025; online publish-ahead-of-print 2 May 2025

See the editorial comment for this article ‘Colchicine in secondary prevention: making sense out of diversity’, by S.J. Pocock and G. Mendieta, <https://doi.org/10.1093/eurheartj/ehaf266>.

## Abstract

**Background and Aims** Randomized trials of colchicine in secondary prevention of atherosclerotic cardiovascular disease have shown mixed results.

**Methods** A systematic review and study-level meta-analysis of randomized controlled trials was performed comparing colchicine vs no colchicine in a secondary-prevention atherosclerotic cardiovascular disease population. A fixed-effect inverse variance model was applied using the intention-to-treat population from the included trials. The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke.

**Results** Nine trials, including 30 659 patients (colchicine 15 255, no colchicine 15 404) with known coronary artery disease or stroke, were included. Compared with no colchicine, patients randomized to colchicine had a relative risk (RR) of 0.88 [95%

\* Corresponding author. Email: [Sanjit.Jolly@phri.ca](mailto:Sanjit.Jolly@phri.ca), Twitter: @SanjitsJolly

†Dr. Marc-André d'Entremont is the first author.

© The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology. All rights reserved. For commercial re-use, please contact [reprints@oup.com](mailto:reprints@oup.com) for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

confidence interval (CI) 0.81–0.95,  $P = .002$ ] for the primary composite outcome, including a RR of 0.94 for cardiovascular death (95% CI 0.78–1.13,  $P = .5$ ), a RR of 0.84 for myocardial infarction (95% CI 0.73–0.97,  $P = .016$ ), and a RR of 0.90 for stroke (95% CI 0.80–1.02,  $P = .09$ ). Colchicine was associated with a RR of 1.35 for hospitalization for gastrointestinal events (95% CI 1.10–1.66,  $P = .004$ ) with no increase in hospitalization for pneumonia, newly diagnosed cancers, or non-cardiovascular death.

**Conclusions** In patients with prior coronary disease or stroke, colchicine reduced the composite of cardiovascular death, myocardial infarction, or stroke by 12%.

**Structured Graphical Abstract**

**Key Question**

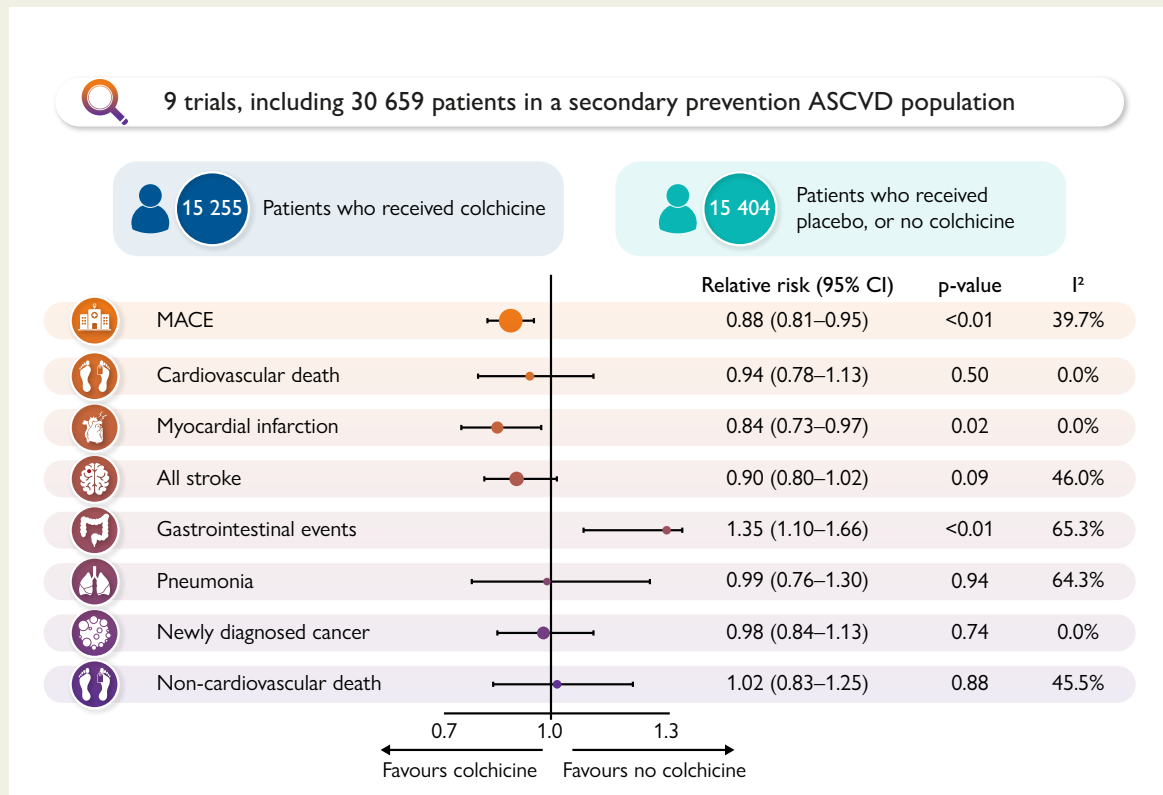
What is the efficacy and safety of colchicine in secondary atherosclerotic cardiovascular disease prevention?

**Key Finding**

In this meta-analysis of nine trials with 30 659 patients, those randomized to colchicine compared to no colchicine had a 12% relative risk reduction for 3-point major cardiovascular adverse events, defined as cardiovascular death, myocardial infarction or all stroke, and a 35% relative risk increase for hospitalization for gastrointestinal events.

**Take Home Message**

Shared decision-making between clinicians and patients is essential when prescribing colchicine in secondary atherosclerotic cardiovascular disease prevention.



**Keywords** Colchicine • Inflammation • Myocardial infarction • Stroke • Coronary revascularization

**Introduction**

Patients diagnosed with atherosclerotic cardiovascular disease (ASCVD) continue to experience significant morbidity and mortality.<sup>1</sup> Colchicine, an oral medication with broad anti-inflammatory effects,

has emerged as a promising, inexpensive therapy to decrease residual atherosclerotic risk.<sup>2</sup>

A meta-analysis from the Colchicine Cardiovascular Trialists Collaboration pooling data from six randomized trials and 14 934 participants with prior myocardial infarction (MI) or stroke demonstrated

that colchicine reduced the composite of cardiovascular mortality, MI, stroke or coronary revascularization by 27% [relative risk (RR) 0.73, 95% confidence interval (CI) 0.65–0.81] with no difference in mortality.<sup>3</sup> Since the publication of this meta-analysis, the two largest randomized trials in coronary artery disease and stroke have shown conflicting results. The 2 × 2 factorial randomized controlled trial of Colchicine vs placebo and spironolactone vs placebo in patients with MI (CLEAR) trial randomized 7062 post-MI patients and did not show a benefit of colchicine over placebo at a median follow-up of 3 years for the composite outcome of cardiovascular death, MI, stroke, or unplanned ischaemia-driven revascularization [322/3528 (9.1%) vs 327/3534 (9.3%), hazard ratio (HR) 0.99, 95% CI 0.85–1.16].<sup>4</sup> The Colchicine in high-risk patients with acute minor-to-moderate ischaemic stroke or transient ischaemic attack (CHANCE3) trial randomized 8343 post-ischaemic stroke or transient ischaemic attack patients with a high-sensitivity C-reactive protein >2 mg/L, showing similar stroke rates in both colchicine and placebo arms at 90 days of follow-up [264/4176 (6.3%) vs 270/4167 (6.5%), HR 0.98, 95% CI 0.83–1.16].<sup>5</sup>

Given the emerging data, a new review of the totality of the evidence evaluating colchicine's efficacy in secondary ASCVD prevention is required. Therefore, we performed a systematic review and meta-analysis to understand the effect of colchicine compared with no colchicine on the background of usual care in patients with ASCVD on important cardiovascular outcomes.

## Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for the writing of the manuscript.<sup>6</sup> Given the current manuscript contains study-level data, ethics approval was not required.

### Search strategy, selection criteria, and data extraction

Our investigator group completed a systematic review of PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to 16 June 2024, without language restriction. We included all randomized trials that compared colchicine with no colchicine on a background of usual care in participants with known ASCVD. [Supplementary data online, Table S1](#) demonstrates our complete search strategy. We used sensitivity-maximizing filters as recommended by the Cochrane Collaboration to identify randomized trials in PubMed and Embase.

Trials were eligible if the treatment duration was 90 days or more and data on efficacy or safety outcomes was available, consistent with previous meta-analyses.<sup>3,7</sup> Unpublished data, observational studies, narrative reviews, editorials, case series and duplicate studies were excluded. Three authors (A.T.L.F., M.H.F.P., and M.D.) independently screened abstracts and evaluated full-text articles for eligibility, with conflicts resolved by consensus discussion. For each included trial, descriptive and outcome data from the principal and subsidiary publications were compiled, with additional outcome and subgroup data collected directly from collaborating investigators whenever possible.

### Outcomes

The primary efficacy outcome was defined as three-point major adverse cardiovascular events (MACE), defined as cardiovascular death, MI, or stroke. We used the definitions of outcomes utilized by the original trials. Other efficacy outcomes included four-point MACE defined as cardiovascular death, MI, stroke, or coronary revascularization, and its individual components, along with ischaemic stroke and all-cause death. For safety

outcomes, we collected data on hospitalization for gastrointestinal events, hospitalization for pneumonia, newly diagnosed cancer and non-cardiovascular death. We requested additional study-level data from investigators of relevant trials as needed when available. Trials for which outcome data were unavailable were excluded for that specific outcome analysis.

### Risk of bias assessment

The included trials' risk of bias was assessed using Cochrane's Collaboration Risk-of-Bias Tool 2.<sup>8</sup> Three authors (A.T.L.F., M.H.F.P., and M.D.) independently evaluated the five domains of risk of bias.

### Statistical analysis

All analyses were performed using the intention-to-treat population, meaning all randomized participants were included in their initially allocated study group. We used a fixed-effect model with inverse variance as our primary analysis to calculate pooled RR and 95% CI. We used random effects using the restricted maximum likelihood estimator with the DerSimonian-Laird method as a sensitivity analysis. We used the  $I^2$  statistic to evaluate heterogeneity.<sup>9</sup> As per the Cochrane Collaboration,  $I^2$  statistic thresholds were defined as 0–40% for low, 30–60% for moderate, 50–90% for substantial, and 75–100% for considerable. We planned to assess for publication bias if ten or more studies were included.

We performed prespecified subgroup analyses for the primary outcome using the following baseline characteristics collected from the trial investigators: (i) age <70 years vs ≥70 years, (ii) male vs female, (iii) diabetes vs no diabetes, and (iv) statin therapy vs no-statin therapy. Furthermore, trial-level subgroup analyses compared cerebrovascular disease vs coronary artery disease trials and placebo-controlled vs non-placebo-controlled trials. Given its shorter treatment and follow-up time, we conducted a sensitivity analysis excluding the CHANCE-3 trial for outcomes containing data from CHANCE-3.

The number needed to treat (NNT) for benefit was calculated using the pooled event rate of the no colchicine arm as the baseline risk with the following formula:  $1/(\text{event rate in the no colchicine arm} - \text{event rate in the colchicine arm})$ . NNT or harm was calculated using the pooled event rate in the no colchicine arm as the baseline risk with the following formula:  $1/(\text{event in the colchicine arm} - \text{event rate in the no colchicine arm})$ . A weighted (by the sample size of the individual trials) average of medians was calculated as an approximate measure of median follow-up across all trials. NNT (benefit) and NNT (harm) were calculated for the primary composite outcomes, its components, and coronary revascularization, and for statistically significant safety outcomes.<sup>10</sup>

All analyses were performed using Stata (version 15.1) and R (The R Foundation of Statistical Computing version 3.6.0). A  $P$ -value < .05 was considered statistically significant. We did not adjust for multiplicity.

## Results

The PRISMA flowchart ([Figure 1](#)) describes the selection of studies. Of the initial 1365 records identified, 107 full-text studies were reviewed. After excluding 98 studies, nine eligible trials involving 30 659 participants, of whom 15 255 participants were randomized to colchicine and 15 404 randomized to no colchicine, were included.<sup>4,5,11–17</sup>

### Trial characteristics

[Table 1](#) provides a summary of the trial characteristics. Seven trials evaluated participants with known coronary artery disease (CLEAR,  $n = 7062$ ; Effect of colchicine on coronary plaque stability in acute coronary syndrome as assessed by optical coherence tomography (COLOCT),  $n = 128$ ; Low-dose colchicine for secondary prevention

of cardiovascular disease 2 (LoDoCo2),  $n = 5522$ ; Colchicine in patients with acute coronary syndrome (COPS),  $n = 795$ ; Colchicine cardiovascular outcomes trial (COLCOT),  $n = 4745$ ; LoDoCo,  $n = 532$ ; Deftereos,  $n = 222$ ). Two trials evaluated participants with known cerebrovascular disease [CHANCE-3,  $n = 8343$ ; long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE),  $n = 3144$ ]. Median follow-ups ranged from 90 days (CHANCE-3) to 36 months (CLEAR). All trials were placebo-controlled except for CONVINCE and LoDoCo, which were open-label trials with blinded endpoint adjudication. Participants of the LoDoCo2 trial had a 1-month open-label run-in phase before being randomized. All trials used colchicine 0.5 mg once daily except for Deftereos *et al.*, who used 0.5 mg twice daily, and the COPS trial, which used 0.5 mg twice daily for the first month before stepping down to 0.5 mg once daily. The CLEAR trial used weight-based dosing for the first 3 months after randomization (<70 kg received colchicine 0.5 mg daily,  $\geq 70$  kg received colchicine 0.5 mg twice daily), then colchicine 0.5 mg daily until the steering committee decided to treat uniformly with 0.5 mg daily in September 2020.<sup>4,18</sup> This resulted in 2298 patients above 70 kg who received colchicine 0.5 mg twice daily for the first 3 months after randomization.<sup>4</sup> The weighted average of medians for follow-up was 22.4 months.

## Baseline characteristics

Table 2 highlights the main baseline characteristics of the trials' participants. The mean age ranged from 58 to 67 years, and female participation ranged from 11.1% to 37.6%. Participants all had an uptake in antiplatelet and statin therapy above 90%.

## Risk of bias

We summarized the risk of bias in [Supplementary data online, Table S2](#). COLOCT and Deftereos *et al.* were deemed to have 'some concern' of bias because a prespecified research protocol could not be verified. We judged the LoDoCo trial to have some 'some concern' of bias, given that the research assistant was allowed to assign a newly recruited participant to treatment if a participant discontinued colchicine because of intolerance in the first month.<sup>16</sup>

## Outcomes

Participants randomized to colchicine had a RR of 0.88 for the primary outcome of three-point MACE as compared with those randomized to no colchicine (935/15079 vs 1067/15064; 95% CI 0.81–0.95,  $P = .002$ ;  $I^2 = 39.7\%$ ,  $P = .13$ ; seven studies) (Figure 2) (Structured Graphical Abstract).<sup>4,5,12–16</sup> Similarly, participants allocated to colchicine had a relative risk of 0.81 for four-point MACE compared with no colchicine (826/10903 vs 1020/10897; 95% CI 0.74–0.89,  $P < .001$ ;  $I^2 = 70.3\%$ ,  $P = .01$ ; six studies).<sup>4,12–16</sup>

For the individual components of the composite outcomes, participants who received colchicine had a RR 0.94 for cardiovascular death (205/15191 vs 221/15174; 95% CI 0.78–1.13,  $P = .5$ ;  $I^2 = 0\%$ ,  $P = .63$ ; eight studies),<sup>4,5,12–17</sup> a RR of 0.84 MI (332/15079 vs 396/15064; 95% CI 0.73–0.97,  $P = .016$ ;  $I^2 = 0\%$ ,  $P = .61$ ; seven studies),<sup>4,5,12–16</sup> a RR of 0.90 for stroke (463/15079 vs 518/15064; 95% CI 0.80–1.02,  $P = .09$ ;  $I^2 = 46\%$ ,  $P = .09$ ; seven studies).<sup>4,5,12–16</sup> Furthermore, the RR for all-cause death was 0.97 (396/15191 vs 405/15174; 95% CI 0.85–1.11,  $P = .66$ ;  $I^2 = 25.4\%$ ,  $P = .23$ ; eight studies),<sup>4,5,12–17</sup> the RR

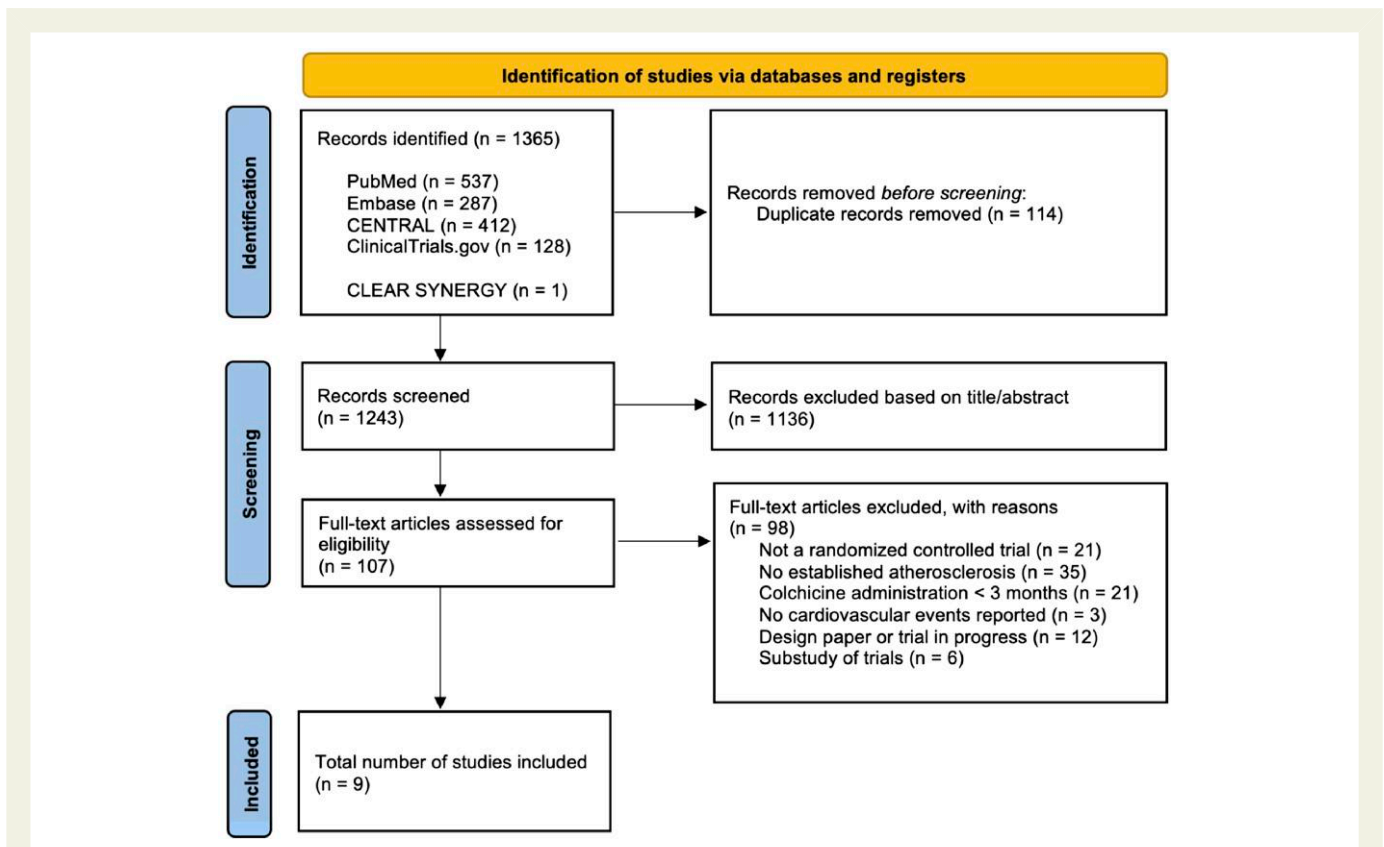


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart

**Table 1** Key trial characteristics

| Acronym  | Author    | Year | Trial size | Key inclusion criteria                                          | Key exclusion criteria                                                                                                          | Active treatment                                                           | Comparator    | Multi-centre | Open-label run-in | Follow-up (median, months) |
|----------|-----------|------|------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------|--------------|-------------------|----------------------------|
| CLEAR    | Jolly     | 2024 | 7062       | Myocardial infarction having undergone PCI                      | Creatinine clearance of < 30 mL/min/1.73 m <sup>2</sup> ; contraindication to spironolactone                                    | Colchicine 0.5 mg once daily                                               | Placebo       | Yes          | No                | 36                         |
| COLOCT   | Yu        | 2024 | 128        | Acute coronary syndrome with lipid rich plaque on OCT           | History of CABG or plan for CABG; PCI within the last 6 months; Significant left main disease                                   | Colchicine 0.5 mg once daily                                               | Placebo       | No           | No                | 12                         |
| CHANCE3  | Li        | 2024 | 8343       | Ischaemic stroke or TIA with a hs-CRP > 2 mg/L                  | Stroke/TIA caused by cardio-embolism or other defined cause                                                                     | Colchicine 0.5 mg twice daily for 3 days, then 0.5 mg daily                | Placebo       | Yes          | No                | 3                          |
| CONVINCE | Kelly     | 2024 | 3144       | Non-severe ischaemic stroke or high-risk TIA                    | Stroke/TIA caused by cardio-embolism or other defined cause                                                                     | Colchicine 0.5 mg once daily                                               | No colchicine | Yes          | No                | 34                         |
| LoDoCo2  | Nidorf    | 2020 | 5522       | Chronic coronary disease, clinically stable > 6 months          | Heart failure (NYHA III/IV); renal failure (eGFR < 50 mL/min/1.73 m <sup>2</sup> ); severe valvular heart disease               | Colchicine 0.5 mg once daily                                               | Placebo       | Yes          | Yes               | 29                         |
| COPS     | Tong      | 2020 | 795        | Acute coronary syndrome with presence of coronary disease       | Requiring bypass surgery; severe liver impairment; severe renal impairment (eGFR < 30 mL/min/1.73 m <sup>2</sup> )              | Colchicine 0.5 mg twice daily for one month, followed by 0.5 mg once daily | Placebo       | Yes          | No                | 12                         |
| COLCOT   | Tardif    | 2019 | 4745       | Post myocardial infarction                                      | Heart failure (LVEF < 35%); renal impairment (creatinine level > 2X upper limit of normal); bypass surgery < 3 years or planned | Colchicine 0.5 mg once daily                                               | Placebo       | Yes          | No                | 23                         |
| LoDoCo   | Nidorf    | 2013 | 532        | Chronic coronary disease, clinically stable > 6 months          | Bypass surgery < 10 years, major competing comorbidities                                                                        | Colchicine 0.5 mg once daily                                               | No colchicine | No           | No                | 28                         |
| NA       | Deftereos | 2013 | 222        | Diabetes and undergoing percutaneous coronary revascularisation | Acute myocardial infarction; renal impairment (eGFR < 20 mL/min/1.73 m <sup>2</sup> ); liver failure                            | Colchicine 0.5 mg twice daily                                              | Placebo       | No           | No                | 6                          |

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

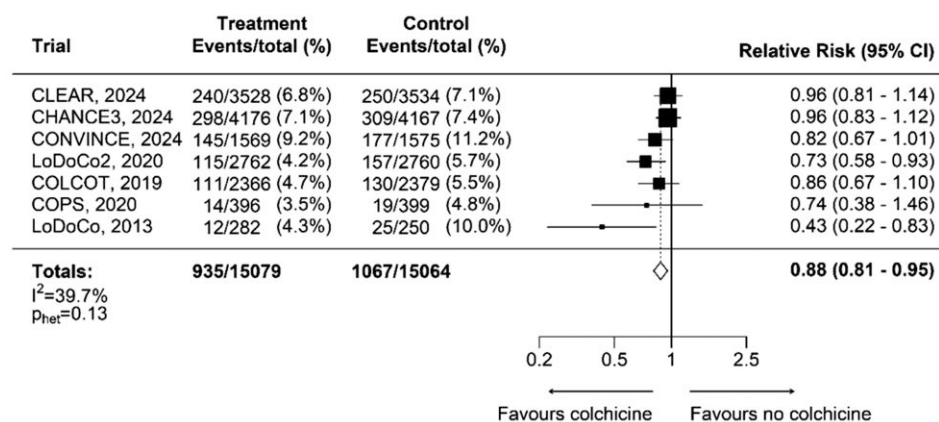
**Table 2** Baseline characteristics of included trials

|           | Age         | Females | Diabetes | eGFR < 60 mL/min/1.73 m <sup>2</sup> | Smoking | History of stroke or TIA | History of ACS | Antiplatelet therapy | Statin therapy | Beta-blocker therapy |
|-----------|-------------|---------|----------|--------------------------------------|---------|--------------------------|----------------|----------------------|----------------|----------------------|
| CLEAR     | 60.6 ± 10.3 | 20.4%   | 18.5%    | 8.1%                                 | 40.8%   | 2.2%                     | 100%           | 96.8%                | 96.6%          | NA                   |
| COLOCT    | 58 ± 9.8    | 25%     | 25%      | 5.4%                                 | 39.1%   | 2.3%                     | 100%           | 100%                 | 95.3%          | 75%                  |
| CHANCE3   | 65.9 ± 11   | 37.6%   | 32%      | NA                                   | 24.3%   | 100%                     | 1.5%           | 95.4%                | 95.5%          | NA                   |
| CONVINCE  | 66.3 ± 10.0 | 30.5%   | 22.3%    | NA                                   | 22.1%   | 100%                     | 9%             | 97.5%                | 93.5%          | NA                   |
| LoDoCo2   | 65.8 ± 8.6  | 15.3%   | 18.3%    | 5.5%                                 | 11.7%   | 4.0%                     | 84.4%          | 90.9%                | 94.0%          | 62.1%                |
| COPS      | 59.9 ± 10.3 | 20.8%   | 19.0%    | NA                                   | 34.8%   | 2.0%                     | 100%           | 98.6%                | 98.9%          | 82.6%                |
| COLCOT    | 60.6 ± 10.7 | 19.2%   | 20.2%    | NA                                   | 29.8%   | 2.6%                     | 100%           | 98.8%                | 99.0%          | 88.9%                |
| Deftereos | 63.3 ± 7.0  | 34.7%   | 100%     | 33.2%                                | 52.3%   | NA                       | 31.1%          | NA                   | NA             | NA                   |
| LoDoCo    | 67 ± 9.4    | 11.1%   | 30.3%    | NA                                   | 4.5%    | NA                       | 23.5%          | 93.4%                | 95.1%          | 66.5%                |

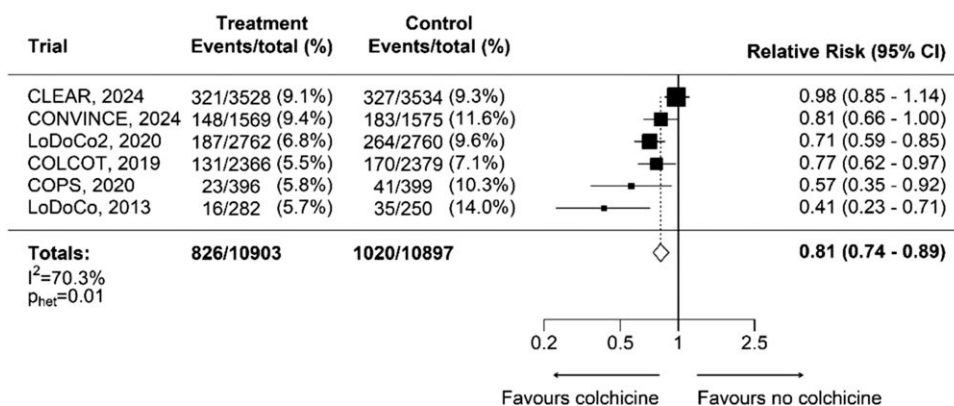
History of stroke or TIA was available for 3318 patients in LoDoCo2.

ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; NA, not available; TIA, transient ischaemic attack.

#### Pooled estimate of colchicine therapy for the prevention of MACE

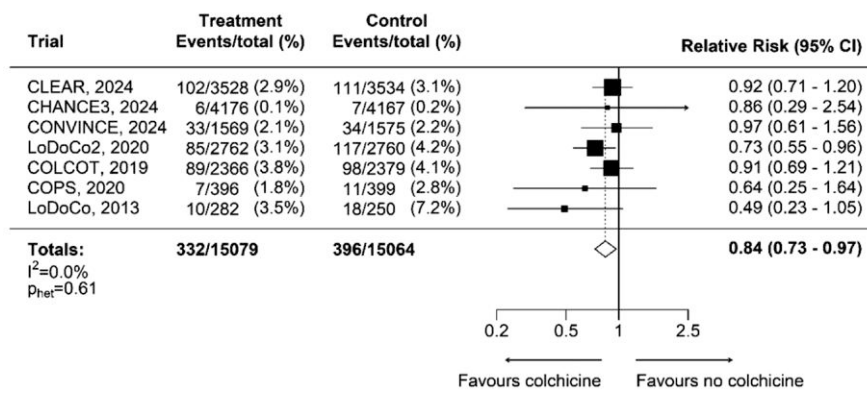


#### Pooled estimate of colchicine therapy for the prevention of MACE+

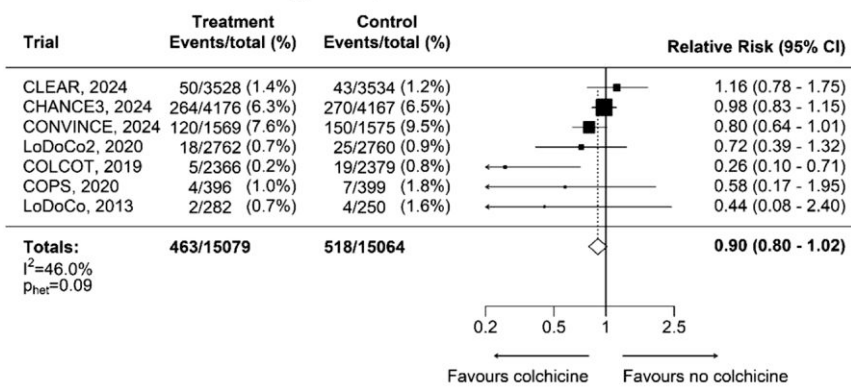


**Figure 2** Primary outcome of major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke) and MACE+ (composite of cardiovascular death, myocardial infarction, stroke, or coronary revascularization). MACE, major adverse cardiovascular events

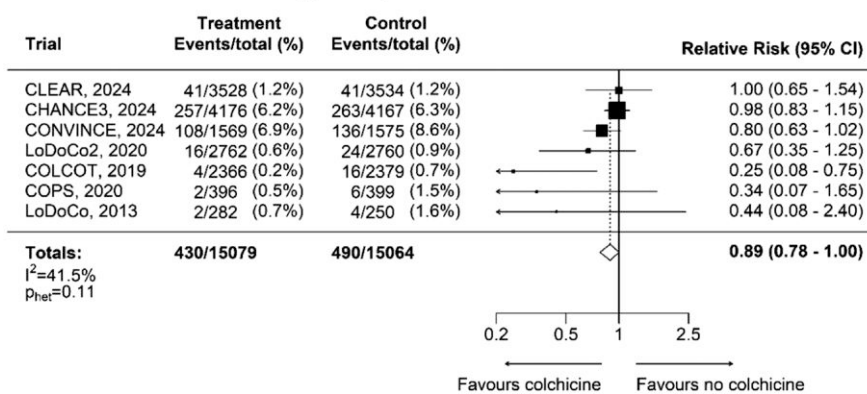
**Pooled estimate of colchicine therapy for the prevention of myocardial infarction**



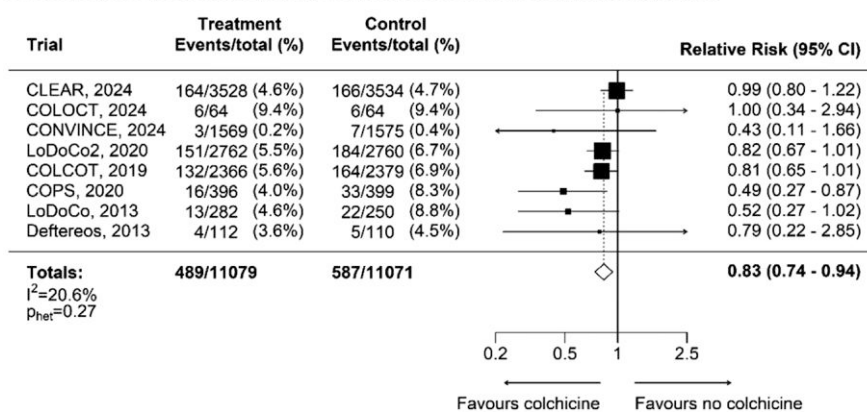
**Pooled estimate of colchicine therapy for the prevention of all stroke**



**Pooled estimate of colchicine therapy for the prevention of ischaemic stroke**

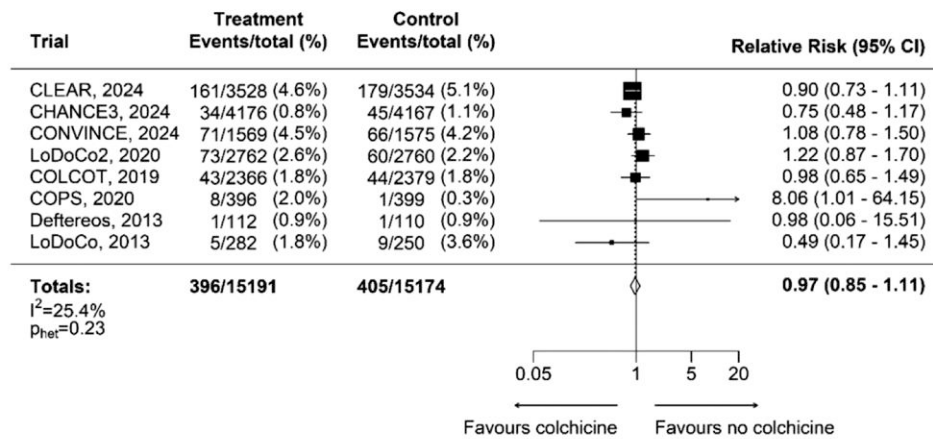


**Pooled estimate of colchicine therapy for the prevention of coronary revascularisation**

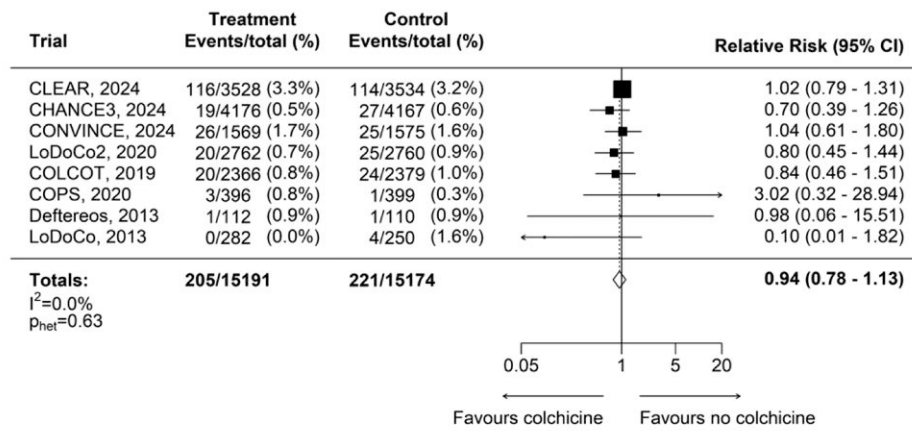


**Figure 3** Individual non-fatal outcomes

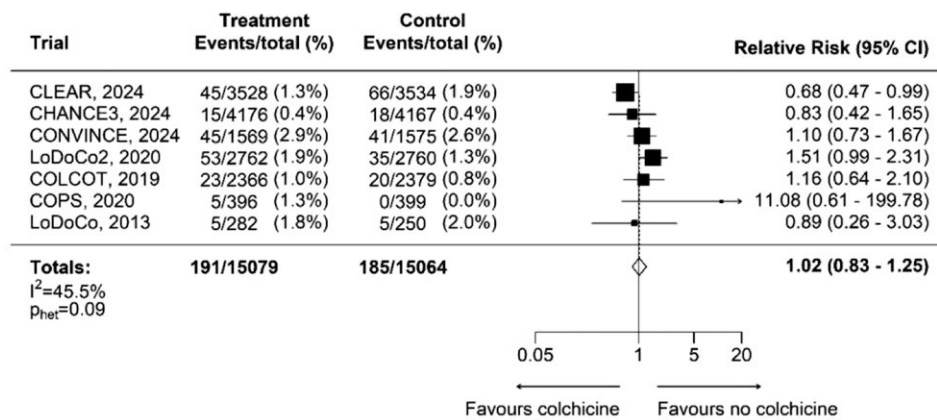
**Pooled estimate of colchicine therapy for the prevention of all-cause death**



**Pooled estimate of colchicine therapy for the prevention of cardiovascular death**



**Pooled estimate of colchicine therapy for the prevention of non-cardiovascular death**

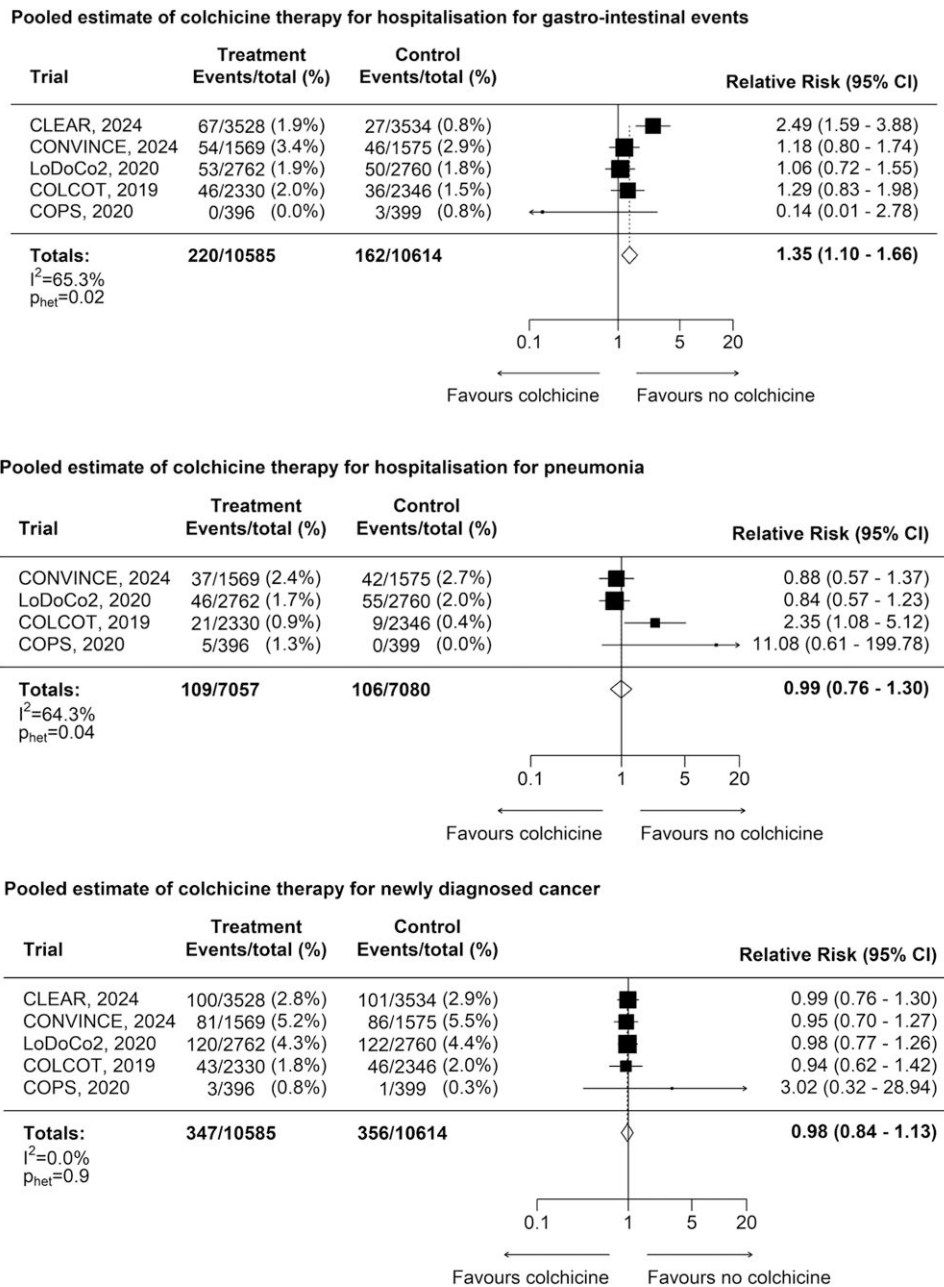


**Figure 4** Mortality (all-cause death, cardiovascular death, and non-cardiovascular death)

for ischaemic stroke was 0.89 (430/15079 vs 490/15064; 95% CI 0.78–1.00,  $P = .06$ ;  $I^2 = 41.5%$ ;  $P = .11$ ; seven trials)<sup>4,5,12–16</sup> and the RR for coronary revascularization was 0.83 (489/11079 vs 587/11071; 95% CI 0.74–0.94,  $P = .002$ ;  $I^2 = 20.6%$ ;  $P = .27$ ; eight trials)<sup>4,5,12–17</sup> (Figures 3 and 4).

Colchicine-treated participants had a RR of 1.35 of requiring hospitalization for gastrointestinal events (220/10585 vs 162/10614; 95% CI

1.10–1.66,  $P = .004$ ;  $I^2 = 65.3%$ ,  $P = .02$ ; five trials),<sup>4,12–15</sup> but hospitalization for pneumonia (109/7057 vs 106/7080; RR 0.99, 95% CI 0.76–1.30,  $P = .94$ ;  $I^2 = 64.3%$ ,  $P = .04$ ; four trials),<sup>12–15</sup> newly diagnosed cancer (347/10585 vs 356/10614; RR 0.98, 95% CI 0.84–1.13,  $P = .74$ ;  $I^2 = 0%$ ,  $P = .9$ ; 5 trials),<sup>4,12–15</sup> and non-cardiovascular death (191/15079 vs 185/15064; RR 1.02, 95% CI 0.83–1.25,  $P = .88$ ;  $I^2 = 45.5%$ ,  $P = .09$ ; 7 trials)<sup>4,5,12–16</sup> were not different between groups (Figures 4 and 5).



**Figure 5** Adverse events

## Subgroup and sensitivity analyses

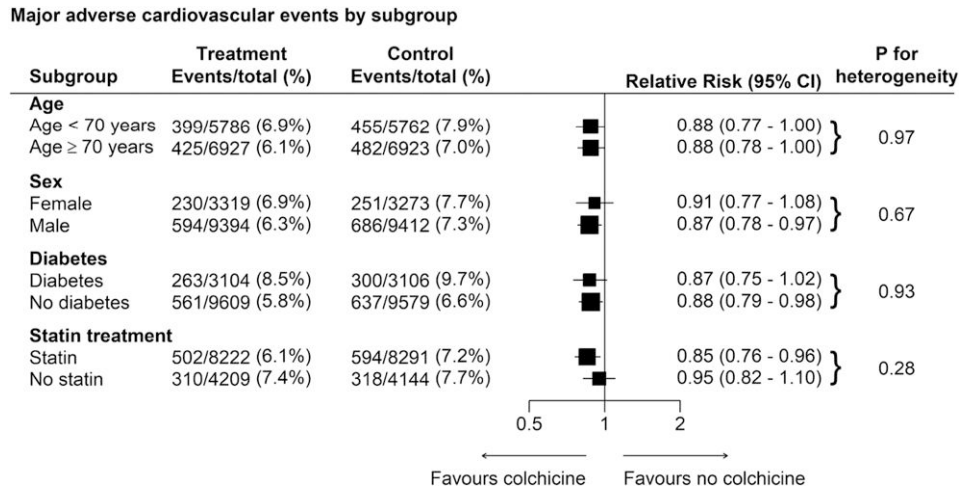
Subgroup data for three-point MACE were available from the CLEAR, CHANCE-3, CONVINCE, LoDoCo2, COPS and LoDoCo trials. The effect of colchicine was consistent across all examined subgroups, including age, sex, diabetes status, and statin prescription (Figure 6). At the trial level, the effect of colchicine on three-point MACE was consistent in the coronary and cerebrovascular trials (see Supplementary data online, Figure S1) and in the placebo vs non-placebo trials (see Supplementary data online, Figure S2).

Sensitivity analyses using random effects were consistent with the primary fixed-effect analyses but with wider 95% CIs (see Supplementary data online, Table S3). Sensitivity analyses excluding the CHANCE-3 trial were overall consistent with the primary analyses,

except for a significant downward shift of effect estimates for stroke (RR 0.81, 95% CI 0.68–0.98) and ischaemic stroke (RR 0.78, 95% CI 0.64–0.94) (see Supplementary data online, Figure S3).

## NNT for benefit and harm

Considering the baseline risk for three-point MACE of 7.08% in the overall control group with a weighted average of medians for follow-up of 22.4 months across trials, the NNT (benefit) for three-point MACE for colchicine vs no colchicine was 114 (95% CI 74–285) reflecting an absolute risk reduction of 0.88%. Hospitalization for gastrointestinal events was associated with an NNT (harm) of 181 (95% CI 667–99), calculated from an absolute risk increase of 0.55% (see Supplementary data online, Table S4).



**Figure 6** Subgroup analyses for major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke)

## Discussion

In this study-level meta-analysis combining evidence from nine randomized trials and 30 659 participants, we demonstrated that colchicine provides a 12% RR reduction (0.88% absolute risk reduction) in decreasing three-point MACE in a secondary ASCVD prevention population compared with no colchicine on a background of usual care. For the individual components of the primary composite outcome, there was a 16% RR reduction for MI, while there was no significant difference in cardiovascular death or all stroke. Colchicine was associated with a 35% RR increase (0.55% absolute risk increase) of hospitalization for gastrointestinal events. There were no other adverse safety signals; notably, there was no difference between groups for non-cardiovascular death.

## Comparison with prior evidence

The last three large colchicine trials, including two cerebrovascular disease trials (CONVINCE and CHANCE-3) and the largest coronary artery disease trial (CLEAR), have not shown a significant benefit of colchicine in secondary prevention of ASCVD.<sup>5,12</sup> This has led to a less pronounced effect estimated of three-point MACE, from a 25% relative risk reduction in a previous meta-analysis published in 2021 to a 12% relative risk reduction in the current meta-analysis with the accrual of more than twice the number of participants and events.<sup>3,7</sup> Our finding of increased adverse gastrointestinal events with colchicine is concordant with a previous systematic review and meta-analysis across various indications for colchicine.<sup>19</sup> While most patients and clinicians will put more weight on reducing three-point MACE over the potential increase in hospitalization for gastrointestinal events, the NNT may help clinicians and patients decide when colchicine is considered in ASCVD prevention.

Differences over time in effect estimates of colchicine compared with no colchicine in secondary prevention of ASCVD are likely multifactorial. One hypothesis is regression to the mean, where earlier trials with fewer events initially demonstrated more pronounced effects.<sup>20</sup> Secular trends in cardiovascular healthcare and improvements in co-intervention should also be considered.<sup>21</sup>

On the other hand, the CONVINCE trial, numerically favouring colchicine, was stopped before the anticipated number of outcomes were

accrued and was likely underpowered due to the COVID-19 pandemic.<sup>12</sup> Although we included the CHANCE-3 trial for completeness, the design of CHANCE-3 differed from longer-term colchicine trials with randomization of patients within 24 h of stroke/transient ischaemic attack onset, having a large proportion of events occurring within 7 days after randomization and a total follow-up time of 90 days.<sup>5</sup> The treatment duration may not have been sufficient to demonstrate a possible benefit.<sup>5</sup> Finally, the CLEAR trial had a 26% drug discontinuation rate and ran before, during and after the COVID-19 pandemic.<sup>4</sup> However, the intention-to-treat and on-treatment analyses were consistent, and no significant interaction was found in the different periods across the pandemic.<sup>4</sup>

## Implications for clinical practice and research

Despite being a recommended therapy in coronary artery disease, colchicine has not been widely adopted for ASCVD prevention.<sup>22,23</sup> Given the totality of evidence suggests a more modest benefit than previously demonstrated along with an increase in gastrointestinal events, the role of colchicine in secondary ASCVD prevention is currently less certain.

New emerging trial data may suggest that the benefit of the anti-inflammatory hypothesis is dependent on specific pathways rather than an overall effect. The Cardiovascular Inflammation Reduction Trial randomized 4786 high-risk coronary artery disease participants to methotrexate vs placebo and did not demonstrate a reduction of the composite outcome of MACE at a median follow-up of 2.3 years.<sup>24</sup> The PULSE-MI trial randomized 530 participants to pre-hospital pulse-dose glucocorticoid vs placebo in ST-elevation MI participants and did not show a decreased infarct size on cardiac magnetic resonance at 3 months.<sup>25</sup> However, the Canakinumab Antiinflammatory Thrombosis Outcomes Study trial demonstrated that canakinumab, an interleukin-1 inhibitor, was associated with a 15% RR reduction for cardiovascular events, but at the risk of increased fatal infections.<sup>26</sup> While additional data on colchicine will be informative, more evidence regarding additional targets of the inflammatory pathways involved in atherosclerotic disease progression is also essential. The Research study to look at how ziltivekimab (interleukin-6 inhibitor) works compared with placebo in people with cardiovascular disease, chronic kidney disease

and inflammation (ZEUS) (ClinicalTrials.gov NCT05021835) and the Research study to look at how ziltivekimab works compared with placebo in people with a heart attack (ARTEMIS) (ClinicalTrials.gov NCT06118281) will be important in determining new ideal targets for new anti-inflammatory therapies. Mechanistic studies have shown that colchicine inhibits the NLRP3 inflammasome, reducing interleukin-1 and interleukin-6 levels.<sup>27</sup> Modulating this inflammatory mechanism may lead to greater coronary plaque stabilization, as per the COLOCT trial.<sup>11</sup> Specifically, targeting interleukin-6 downstream may provide important insights into the anti-inflammatory pathway in atherosclerosis.

## Limitations

Our meta-analysis has several limitations. First, we did not analyse individual participant-level data. Therefore, our capacity to explore the main reasons for variability in trial results, perform landmark analyses, and assess efficacy and safety outcomes with greater granularity, including the NNT, is limited. Second, we acknowledge the wide range of follow-up times, such as 3 months for the CHANCE-3 trial and 36 months for the CLEAR trial. For this reason, we provided a sensitivity analysis excluding the CHANCE-3 to provide additional insight. Third, differences in outcome definition between trials may have introduced some variability, especially regarding adverse events (gastrointestinal events, pneumonia and newly diagnosed cancer), which were not uniformly adjudicated. Significant between-trial heterogeneity was observed for the association of colchicine with hospitalization for gastrointestinal events ( $I^2$  65.3%,  $P = .02$ ). More granular, patient-level analyses regarding the specific types of events, the timing of events, and whether particular subgroups of patients were more vulnerable to gastrointestinal hospitalization are needed to gain additional insights into this finding.

## Conclusions

In conclusion, in patients with prior ASCVD, colchicine was associated with a 12% RR reduction of cardiovascular death, MI or stroke as compared with no colchicine on a background of usual care. However, there was an increased risk of hospitalization for gastrointestinal events. Shared decision-making between clinicians and patients is essential in balancing the benefits and harms when prescribing colchicine in secondary ASCVD prevention.

## Acknowledgements

The authors are grateful to Paul Sherliker (Nuffield Department of Population Health, University of Oxford) for the assistance in creating the figures.

## Supplementary data

Supplementary data are available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

M.-A.d'E. is a Canadian Institutes of Health Research Canada Graduate Scholarship awardee. P.A. reports receiving research grants from Pfizer, AstraZeneca, and Novartis, being on an advisory board for Novartis, and

receiving speaker fees from Novartis, Sanofi and Viatrix. K.E.B. reports advisory board activity with MedTrace and research relationships with MedTrace, Novartis and Novo Nordisk that are not related to the current work. N.C.C. has received a Canadian Institutes of Health Research project grant to examine the risk-benefit of colchicine in patients with peripheral artery disease (LEADER-PAD trial). A.C.K. has research support from the Australian National Health and Medical Research Council and Medical Research Future Fund, plus research support and/or honoraria for lectures from Abbott, Abbvie, Amgen, Aspen, Kowa, Mylan, Novartis, Pfizer and Sanofi. Jamie Layland is on an advisory board for Novo Nordisk. G.M. reports receiving research funds from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celcor, CSL Behring, Hexacath, Idorsia, Lilly, Novo Nordisk, Pfizer, SMT, and Terumo. B.S. is supported, in part, by the National Heart, Lung, and Blood Institute of the National Institutes of Health (1R01HL146206, 3R01HL146206-02S1) and VA Office of Research and Development (CSP 2002, I01CX002358); serves on the advisory board for Philips Volcano and NovoNordisk; serves on the steering committee for the Elevate Pivotal Study sponsored by Magenta Medical; and serves on the Data Safety Monitoring Board for the EnCompass trial sponsored by Insight Medical. M.T. reports receiving institutional research grants from Philips Medical B.V. and payment for consultancy, lectures, presentations, or educational events from W.L. Gore & Associates, Terumo Aortic, and Cook Medical. S.S.J. reports receiving grants or contracts from Boston Scientific and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Penumbra, Teleflex, and Abiomed.

## Data Availability

The data supporting the study's findings are available from the Colchicine Cardiovascular Trialists Collaboration upon reasonable request.

## Funding

There is nothing to declare.

## Ethical Approval

Given the current manuscript contains study-level data, ethics approval was not required.

## Pre-registered Clinical Trial Number

We registered the present meta-analysis in the International Prospective Register of Systematic Reviews (PROSPERO, CRD2024595059).

## References

- Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;**76**:2982–3021. <https://doi.org/10.1016/j.jacc.2020.11.010>
- Deftereos SG, Beerkens FJ, Shah B, Giannopoulos G, Vrachatis DA, Giotaki SG, et al. Colchicine in cardiovascular disease: in-depth review. *Circulation* 2022;**145**:61–78. <https://doi.org/10.1161/CIRCULATIONAHA.121.056171>
- Fiolet ATL, Poorthuis MHF, Opstal TSJ, Amarenco P, Boczar KE, Buyschaert I, et al. Colchicine for secondary prevention of ischaemic stroke and atherosclerotic events: a meta-analysis of randomised trials. *EClinicalMedicine* 2024;**76**:102835. <https://doi.org/10.1016/j.eclinm.2024.102835>
- Jolly SS, d'Entremont M-A, Lee SF, Mian R, Tyrwhitt J, Kedev S, et al. Colchicine in acute myocardial infarction. *N Engl J Med* 2025;**392**:633–42. <https://doi.org/10.1056/NEJMoa2405922>
- Li J, Meng X, Shi F-D, Jing J, Gu H-Q, Jin A, et al. Colchicine in patients with acute ischaemic stroke or transient ischaemic attack (CHANCE-3): multicentre, double blind,

- randomised, placebo controlled trial. *BMJ* 2024;**385**:e079061. <https://doi.org/10.1136/bmj-2023-079061>
6. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;**372**:n160. <https://doi.org/10.1136/bmj.n160>
  7. Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC, et al. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. *Eur Heart J* 2021;**42**:2765–75. <https://doi.org/10.1093/eurheartj/ehab115>
  8. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. <https://doi.org/10.1136/bmj.l4898>
  9. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58. <https://doi.org/10.1002/sim.1186>
  10. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;**317**:1309–12. <https://doi.org/10.1136/bmj.317.7168.1309>
  11. Yu M, Yang Y, Dong S-L, Zhao C, Yang F, Yuan Y-F, et al. Effect of colchicine on coronary plaque stability in acute coronary syndrome as assessed by optical coherence tomography: the COLOCT randomized clinical trial. *Circulation* 2024;**150**:981–93. <https://doi.org/10.1161/CIRCULATIONAHA.124.069808>
  12. Kelly P, Lemmens R, Weimar C, Walsh C, Purroy F, Barber M, et al. Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial. *Lancet* 2024;**404**:125–33. [https://doi.org/10.1016/S0140-6736\(24\)00968-1](https://doi.org/10.1016/S0140-6736(24)00968-1)
  13. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;**383**:1838–47. <https://doi.org/10.1056/NEJMoa2021372>
  14. Tong DC, Quinn S, Nasir A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. *Circulation* 2020;**142**:1890–900. <https://doi.org/10.1161/CIRCULATIONAHA.120.050771>
  15. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–505. <https://doi.org/10.1056/NEJMoa1912388>
  16. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;**61**:404–10. <https://doi.org/10.1016/j.jacc.2012.10.027>
  17. Devereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol* 2013;**61**:1679–85. <https://doi.org/10.1016/j.jacc.2013.01.055>
  18. d'Entremont M-A, Lee SF, Mian R, Kedev S, Montalescot G, Cornel JH, et al. Design and rationale of the CLEAR SYNERGY (OASIS 9) trial: a 2 × 2 factorial randomized controlled trial of colchicine versus placebo and spironolactone vs placebo in patients with myocardial infarction. *Am Heart J* 2024;**275**:173–82. <https://doi.org/10.1016/j.ahj.2024.06.007>
  19. 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 Res Ther* 2020;**22**:28. <https://doi.org/10.1186/s13075-020-2120-7>
  20. Morton V, Torgerson DJ. Effect of regression to the mean on decision making in health care. *BMJ* 2003;**326**:1083–4. <https://doi.org/10.1136/bmj.326.7398.1083>
  21. Conrad N, Molenberghs G, Verbeke G, Zaccardi F, Lawson C, Friday JM, et al. Trends in cardiovascular disease incidence among 22 million people in the UK over 20 years: population based study. *BMJ* 2024;**385**:e078523. <https://doi.org/10.1136/bmj-2023-078523>
  22. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;**45**:3415–537. <https://doi.org/10.1093/eurheartj/ehae177>
  23. Khorsandi M, Mhaimed O, Dzaye O, Tasdighi E, Alexander GC, Blaha MJ. Brief report: U.S. Trends in use of colchicine by cardiologists and other specialties, 2018 to 2024. *Am Heart J* 2025;**279**:76–80. <https://doi.org/10.1016/j.ahj.2024.10.011>
  24. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;**380**:752–62. <https://doi.org/10.1056/NEJMoa1809798>
  25. Madsen JM, Engstrøm T, Obling LER, Zhou Y, Nepper-Christensen L, Beske RP, et al. Prehospital pulse-dose glucocorticoid in ST-segment elevation myocardial infarction: the PULSE-MI randomized clinical trial. *JAMA Cardiol* 2024;**9**:882–91. <https://doi.org/10.1001/jamacardio.2024.2298>
  26. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–31. <https://doi.org/10.1056/NEJMoa1707914>
  27. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. *Atherosclerosis* 2018;**269**:262–71. <https://doi.org/10.1016/j.atherosclerosis.2017.12.027>