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FASTTRACK – CLINICAL RESEARCH
Ischaemic heart disease

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

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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%

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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

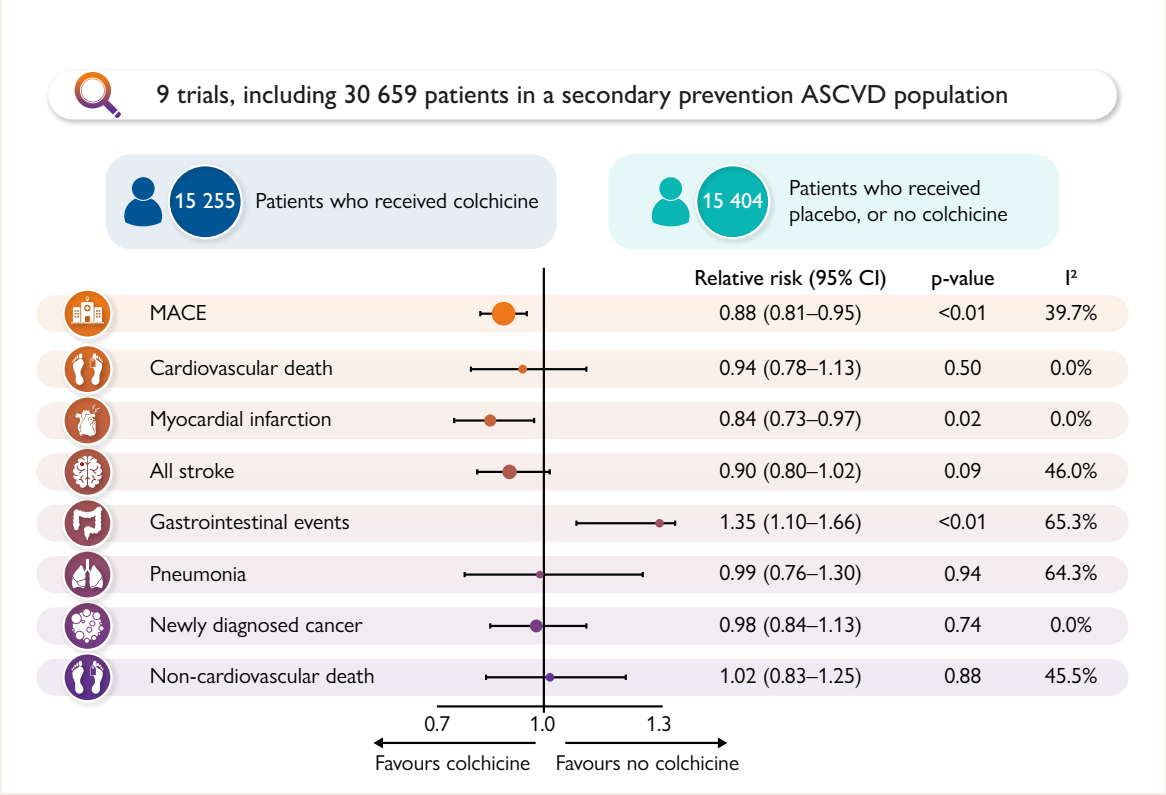
What is the efficacy and safety of colchicine in secondary atherosclerotic cardiovascular disease prevention?

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.[1] Colchicine, an oral medication with broad anti-inflammatory effects, has emerged as a promising, inexpensive therapy to decrease residual atherosclerotic risk.[2]

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.[3] 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].[4] 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].[5]

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.[6] 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.[3,7] 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.[8] 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.[9] 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/(event rate in the no colchicine arm – 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/(event in the colchicine arm – 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.[10]

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.[4,5,11–17]

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, ≥ 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.[4,18] This resulted in 2298 patients above 70 kg who received colchicine 0.5 mg twice daily for the first 3 months after randomization.[4] 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.[16]

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*).[4,5,12–16] 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).[4,12–16]

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),[4,5,12–17] 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),[4,5,12–16] 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).[4,5,12–16] 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),[4,5,12–17] the RR

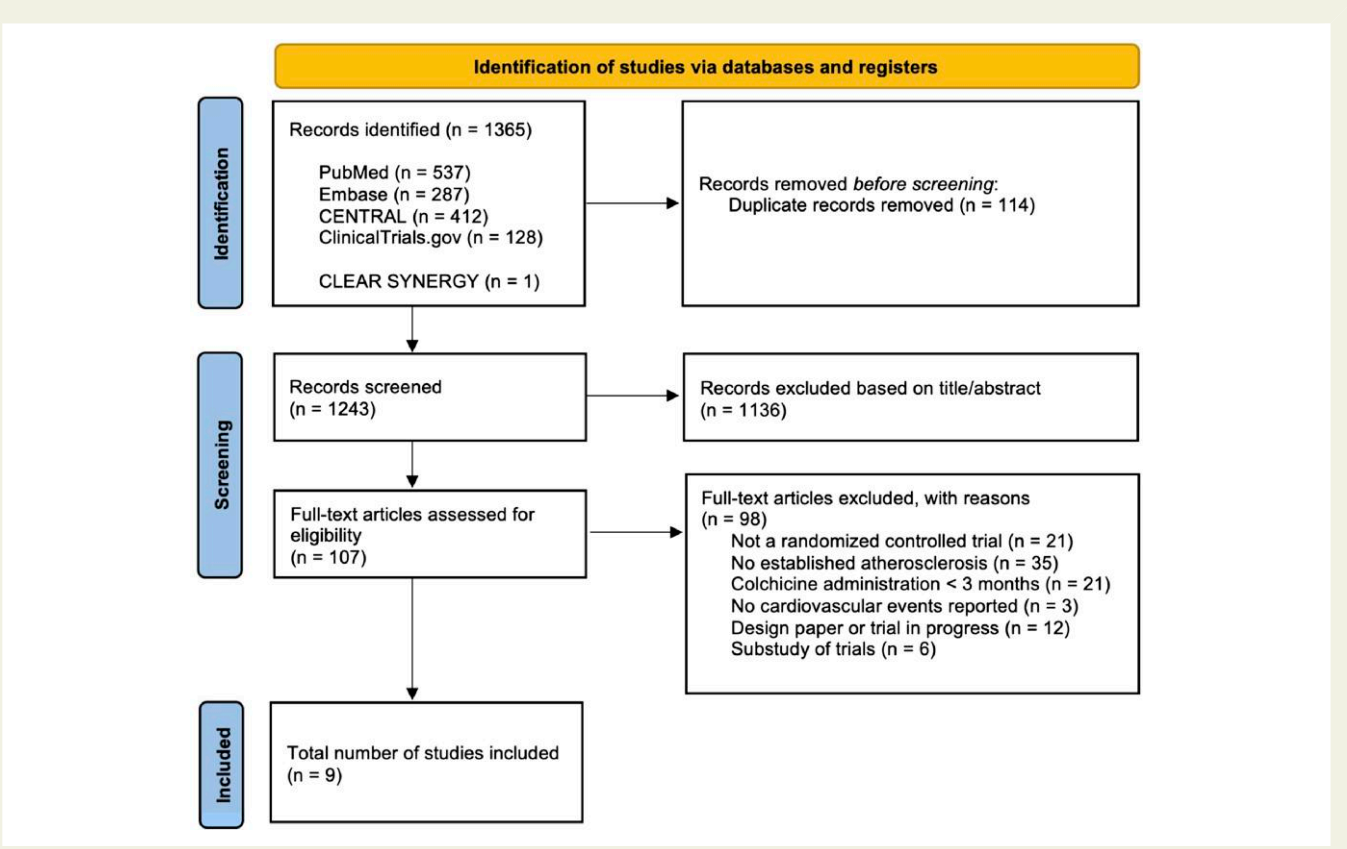


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart

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^2; 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^2); 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^2)	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 >2× 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^2) ; 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^2	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.

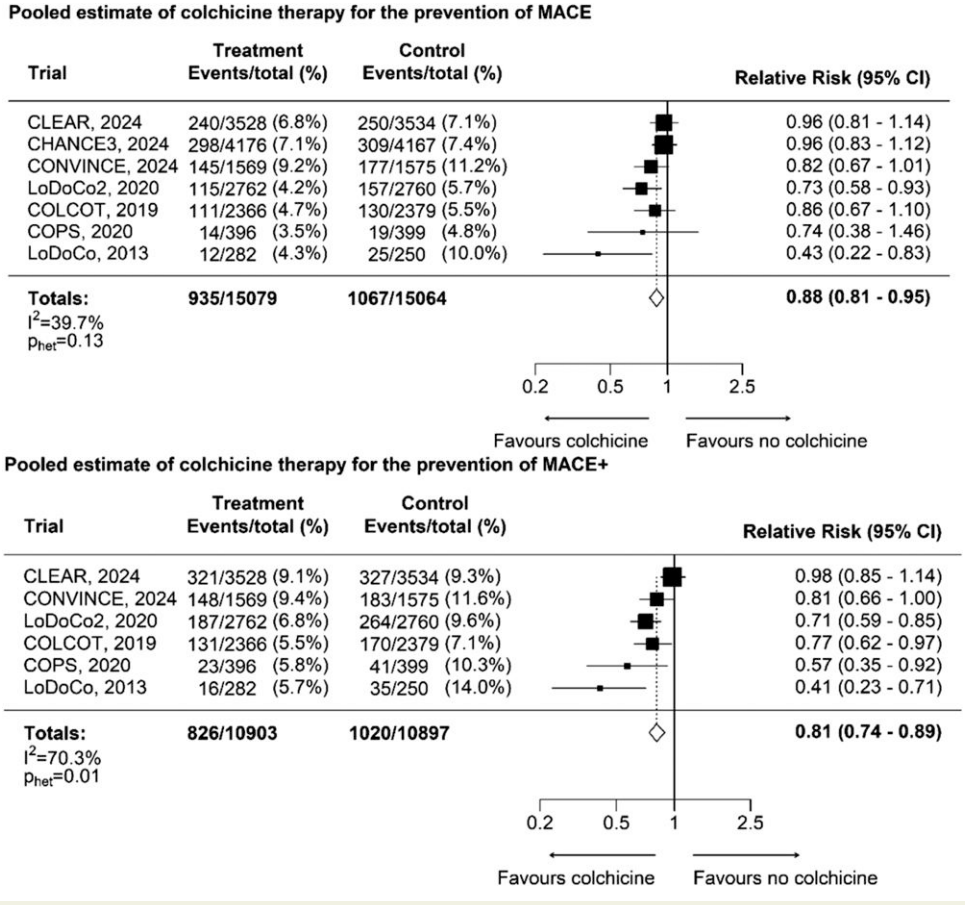


Figure 2 Primary outcome of major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke) and MACE+ (composite of cardiovascular death, myocardial infarction, stroke, or coronary revascularization). MACE, major adverse cardiovascular events

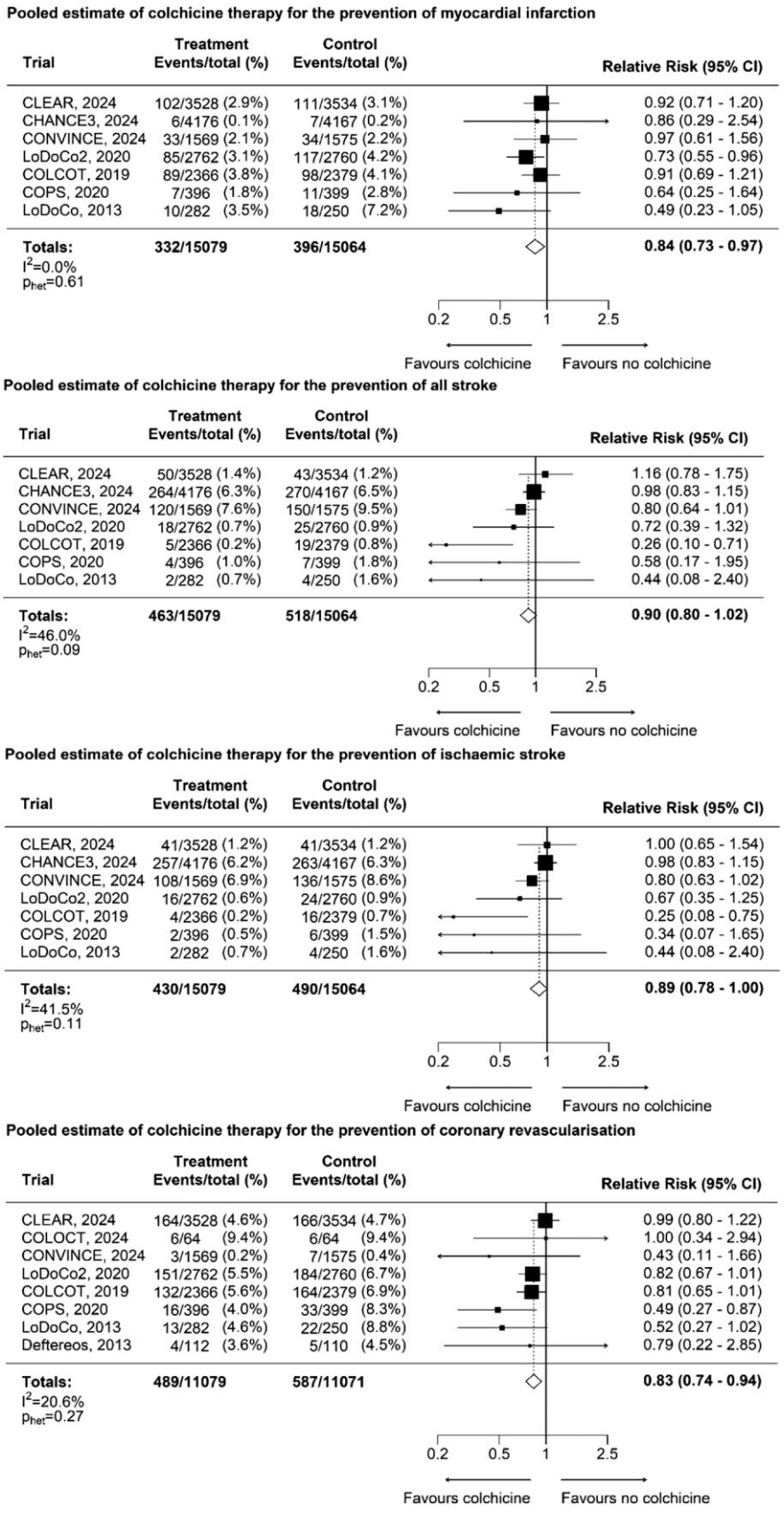


Figure 3 Individual non-fatal outcomes

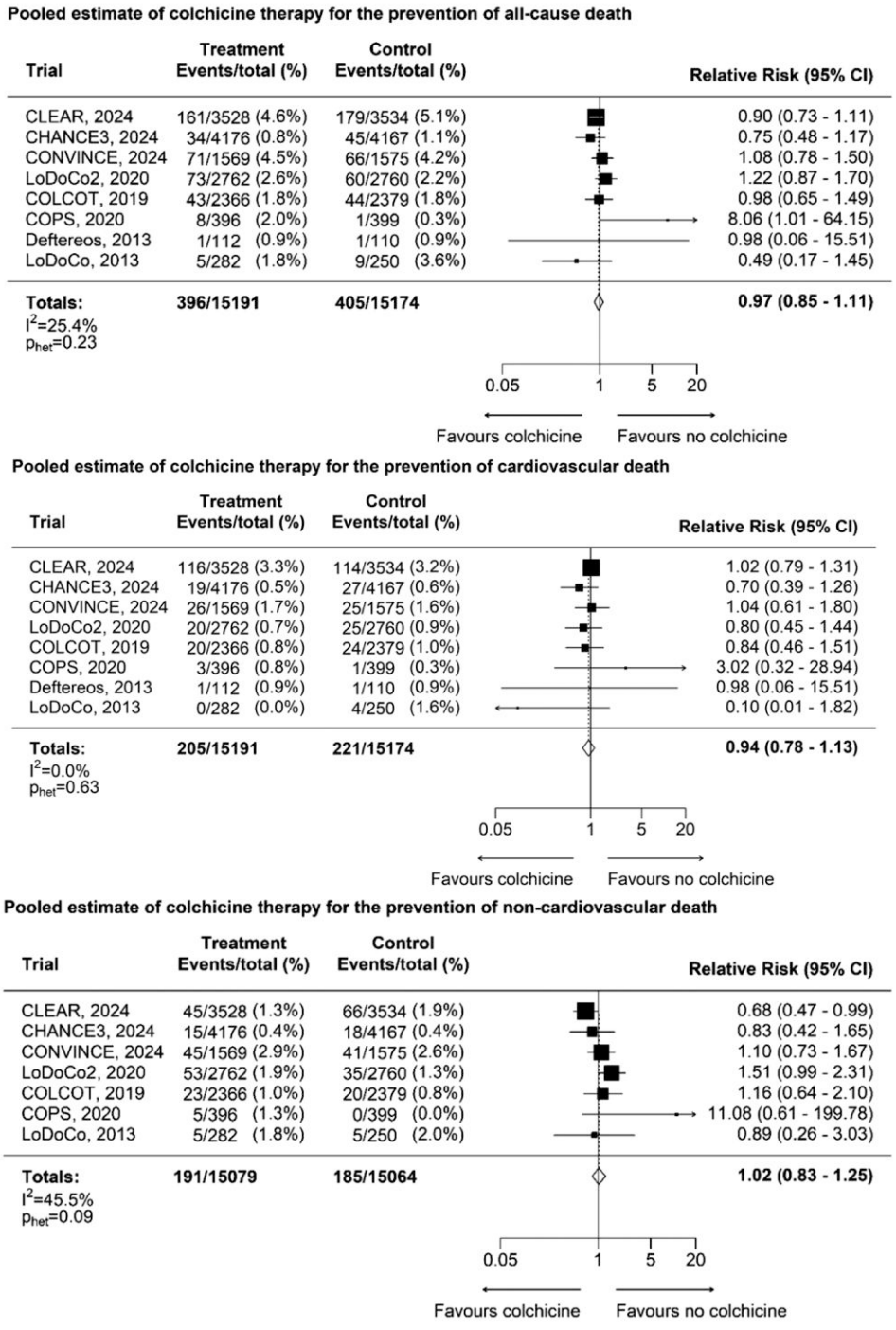


Figure 4 Mortality (all-cause death, cardiovascular death, and non-cardiovascular death)

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)[4,5,12–16] 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)[4,5,12–17] (*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),[4,12–15] 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),[12–15] 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),[4,12–15] 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)[4,5,12–16] were not different between groups (*Figures 4* and *5*).

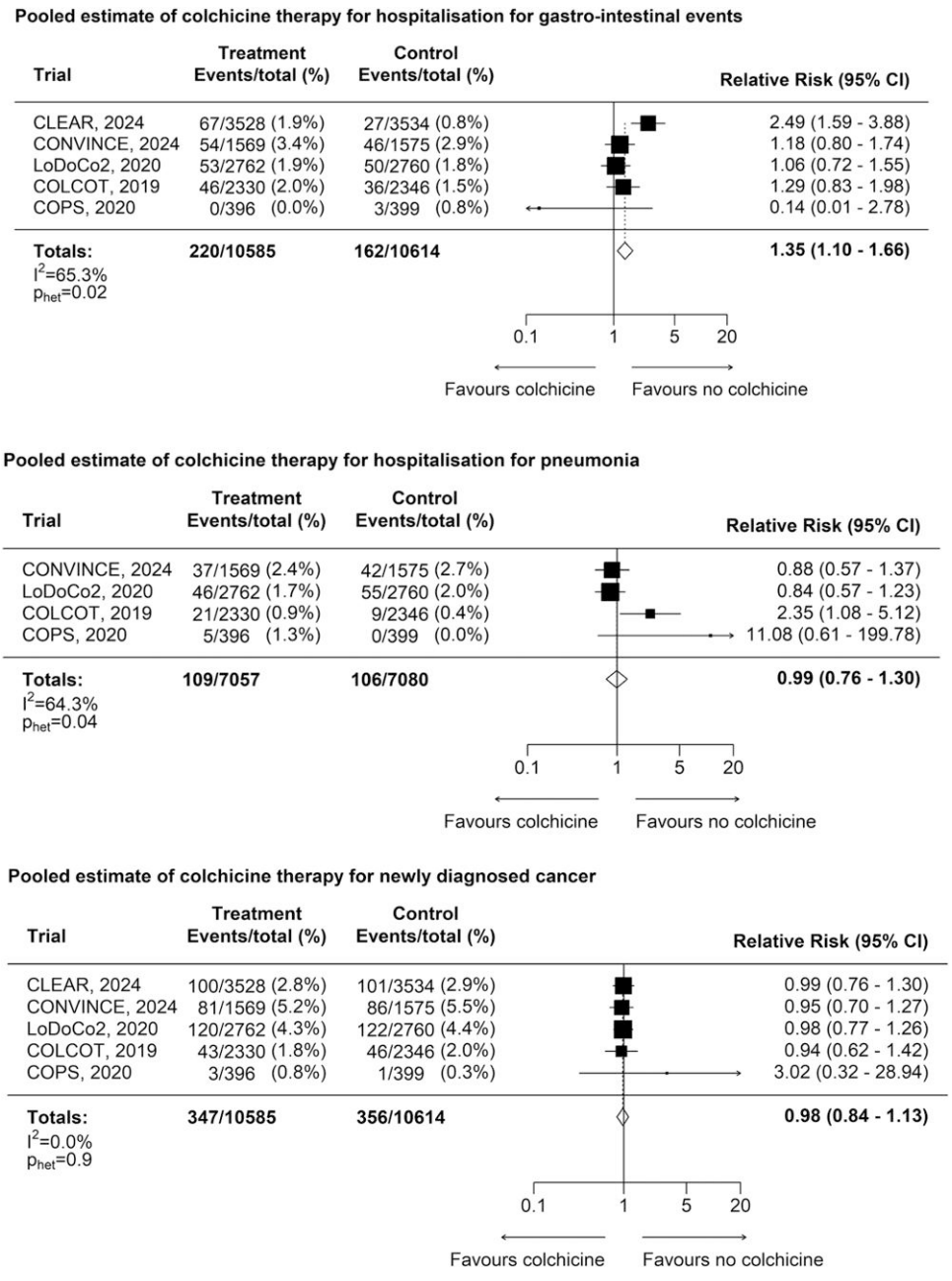


Figure 5 Adverse events

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*).

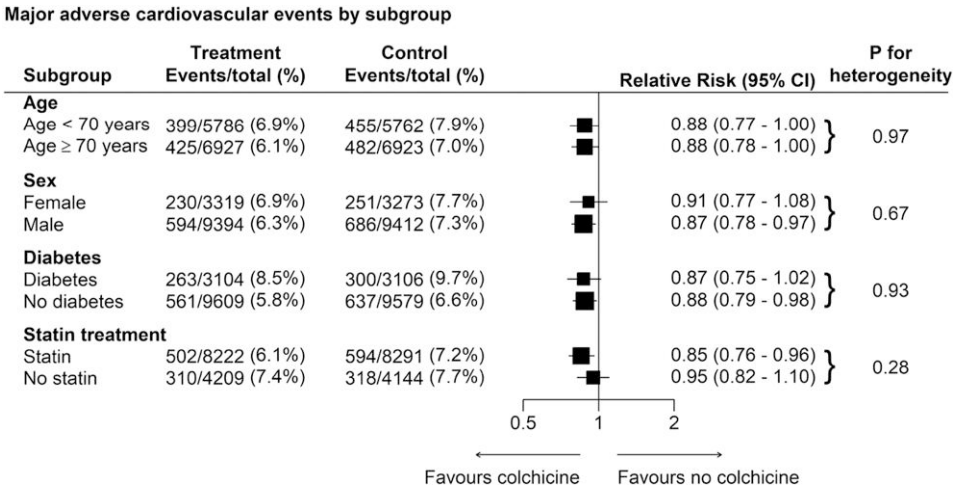


Figure 6 Subgroup analyses for major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke)

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.[5,12] 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.[3,7] Our finding of increased adverse gastrointestinal events with colchicine is concordant with a previous systematic review and meta-analysis across various indications for colchicine.[19] 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.[20] Secular trends in cardiovascular healthcare and improvements in co-intervention should also be considered.[21]

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.[12] 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.[5] The treatment duration may not have been sufficient to demonstrate a possible benefit.[5] Finally, the CLEAR trial had a 26% drug discontinuation rate and ran before, during and after the COVID-19 pandemic.[4] However, the intention-to-treat and on-treatment analyses were consistent, and no significant interaction was found in the different periods across the pandemic.[4]

Implications for clinical practice and research

Despite being a recommended therapy in coronary artery disease, colchicine has not been widely adopted for ASCVD prevention.[22,23] 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.[24] 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.[25] 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.[26] 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.[27] Modulating this inflammatory mechanism may lead to greater coronary plaque stabilization, as per the COLOCT trial.[11] 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.

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Supplementary data

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

Declarations

Disclosure of Interest

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Data Availability

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

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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).

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