Colchicine for secondary prevention of ischaemic stroke and atherosclerotic events: a meta-analysis of randomised trials

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Summary

Background Guidelines recommend low-dose colchicine for secondary prevention in cardiovascular disease, but uncertainty remains concerning its efficacy for stroke, efficacy in key subgroups and about uncommon but serious safety outcomes.

Methods In this trial-level meta-analysis, we searched bibliographic databases and trial registries form inception to May 16, 2024. We included randomised trials of colchicine for secondary prevention of ischaemic stroke and major adverse cardiovascular events (MACE: ischaemic stroke, myocardial infarction, coronary revascularisation, or cardiovascular death). Secondary outcomes were serious safety outcomes and mortality. A fixed-effect inverse-variance model was used to generate a pooled estimate of relative risk (RR) with 95% confidence intervals (CI). This study is registered with PROSPERO, CRD42024540320.

Findings Six trials involving 14,934 patients with prior stroke or coronary disease were included. In all patients, colchicine compared with placebo or no colchicine reduced the risk for ischaemic stroke by 27% (132 [1.8%] events versus 186 [2.5%] events, RR 0.73 [95% CI 0.58–0.90]) and MACE by 27% (505 [6.8%] events versus 693 [9.4%] events, with RR 0.73 [0.65–0.81]). Efficacy was consistent in key subgroups (females versus males, age below versus above 70, with versus without diabetes, statin versus non-statin users). Colchicine was not associated with an increase in serious safety outcomes: hospitalisation for pneumonia (109 [1.5%] versus 106 [1.5%], RR 0.99 [0.76–1.30]), cancer (247 [3.5%] versus 255 [3.6%], RR 0.97 [0.82–1.15]), and gastro-intestinal events (153 [2.1%] versus 135 [1.9%]), RR 1.15 [0.91–1.44]. There was no difference in all-cause death (201 [2.7%] versus 181 [2.4%], RR 1.09 [0.89–1.33]), cardiovascular death (70 [0.9%] versus 80 [1.1%], RR 0.89 [0.65–1.23]), or non-cardiovascular death (131 [1.8%] versus 101 [1.4%], RR 1.26 [0.98–1.64]).

Interpretation In patients with prior stroke or coronary disease, colchicine reduced ischaemic stroke and MACE, with consistent treatment effect in key subgroups, and did not increase serious safety events or death.

Funding There was no funding source for this study.

Keywords: Colchicine; Meta-analysis; Stroke; MACE; Safety

Research in context

Evidence before this study
Low-dose colchicine (0.5 mg once daily) prevents major adverse cardiovascular events (MACE) in patients with coronary disease and is recommended by treatment guidelines. However, uncertainty remains concerning the efficacy of colchicine for stroke prevention, benefits in key subgroups and on serious safety events.

Added value of this study
Pooled study-level data from six trials involving 14,934 participants demonstrate that colchicine in patients with prior stroke or coronary disease lowers the risk of ischaemic stroke and MACE, with consistent efficacy in patients with prior stroke or coronary disease, in key subgroups defined by sex, age, diabetes, and statin use at baseline, and without statistically significant increases of serious safety outcomes (hospitalisation for pneumonia, cancer, and gastro-intestinal events) or death (all-cause death, cardiovascular death, and non-cardiovascular death).

Implications of all the available evidence
The results of our meta-analysis support the routine use of colchicine for secondary prevention of stroke and coronary events in a broad population of patients with prior stroke or coronary artery disease.

Introduction

Stroke and coronary disease are the leading causes of death worldwide. Despite the availability of effective prevention strategies, the burden of cardiovascular disease continues to rise, driven in low- and middle-income countries by growing exposure to cardiovascular risk factors, and, in high income countries, by aging populations.[1] Additional effective and affordable therapies are needed to address the growing disease burden. Inflammation is an important risk factor for stroke and cardiovascular outcomes.[2–5] Colchicine is an anti-inflammatory agent with multiple actions on inflammatory pathways, mediated by inhibition of microtubule function.[6] Production costs of colchicine are low and its

widespread availability make it attractive as an inexpensive agent for secondary prevention in regions of varying economic status.

In the Colchicine Cardiovascular Outcomes Trial (COLCOT) and Low-dose Colchicine for secondary prevention of cardiovascular disease (LoDoCo) randomised clinical trials (RCTs), long-term colchicine reduced recurrence of major adverse cardiovascular events (MACE) in patients with coronary disease.[7–9] Multiple treatment guidelines now recommend low-dose colchicine in coronary disease.[10–13] However, key subgroups of patients, particularly those with prior stroke, were underrepresented in the pivotal trials. The recently completed COlchicine for preveNtion of Vascular Inflammation in Non-CardioEmbolic stroke (CONVINCE) trial showed a numerical, but not statistically significant, reduction of MACE in patients with prior stroke or transient ischaemic attack (TIA).[14] Uncertainty thus remains concerning treatment effect of colchicine on stroke outcomes, and in key subgroups including females, older patients, those with diabetes and in statin-untreated patients, and on serious safety events.

The primary aim of this collaborative meta-analysis involving the lead investigators of several trials of colchicine was to evaluate the efficacy of colchicine for the prevention of ischaemic stroke and MACE, as well as to provide comprehensive safety data, and investigate efficacy in key clinical subgroups.

Methods

Search strategy, selection criteria, and data-extraction

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[15] The protocol was submitted to international prospective register of systematic reviews PROSPERO on April 26, 2024, prior to commencement of the analyses.

PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov were searched from inception to May 16, 2024, without restriction on language of publication, to identify RCTs published in peer-reviewed journals that compared colchicine to an active comparator (i.e., placebo or no colchicine control) in patients with cardiovascular disease. The key search terms were 'atherosclerosis', 'myocardial ischemia', 'stroke', 'transient ischaemic attack', 'brain ischemia', 'peripheral artery disease' and 'colchicine', including their subheadings and synonyms. Sensitivity-maximising filters were used as recommended by the Cochrane Collaboration to identify RCTs in PubMed and EMBASE.[16,17] The search algorithm is presented in Supplemental Table S1.

RCTs were eligible for inclusion if they compared colchicine to an active comparator (placebo or no colchicine) for secondary prevention after stroke or coronary disease, with a least 3 months of treatment duration, reporting data on any of the efficacy or safety outcomes. Unpublished data, observational studies, non-randomised registry studies, narrative reviews, editorials, case series, and duplicate studies were excluded. Two authors (ATLF and MHFP) independently screened titles and abstracts for relevance and duplicates and evaluated full text articles for eligibility with conflicts resolved by consensus discussion with a third reviewer (PJK). For each included trial, summary data were extracted from the principal and relevant subsidiary peer-reviewed publications.

Data analysis

The primary efficacy outcomes were ischaemic stroke and MACE (i.e., the composite of ischaemic stroke, myocardial infarction, coronary revascularisation, or cardiovascular death). We used the definitions of outcomes used in the original trials (Supplemental Table S2). We requested additional data from the principal investigators to create the pre-specified composite outcome for this meta-analysis if needed. Other secondary efficacy outcomes included all stroke (ischaemic and haemorrhagic, including intracerebral haemorrhage and subarachnoid haemorrhage); myocardial infarction; and coronary revascularisation. The main safety outcome was death, which was further classified as all-cause death, cardiovascular death, and non-cardiovascular death. Other serious safety outcomes evaluated included hospitalisation for pneumonia, newly diagnosed cancer, and gastro-intestinal events.

The primary analysis was done in all patients and a sensitivity analysis was done restricting the cohort to patients with prior stroke or TIA. For subgroup analyses, lead investigators of included trials provided outcome data for the primary efficacy outcomes according to prespecified subgroups: sex (female versus male); age (<70 versus ≥70 years); diabetes mellitus (yes versus no); and statin treatment at randomisation (yes versus no).

The relative risks of each outcome from each individual trial were determined and pooled estimates were subsequently calculated by applying inverse-variance weighting using a fixed-effect model. Additional sensitivity analyses encompassed a separate analysis using a random-effect model with a DerSimonian–Laird estimator. The treatment effect was formally tested at a two-sided alpha level of 0.05. Inter-study heterogeneity was assessed with the Higgins and Thompsons' I^2 index. Heterogeneity was considered low if the percentage was approximately 25%, moderate if 50%, and high if 75%.[18] Interactions between studies and between subgroups were examined with a test for heterogeneity, with a p value below 0.05 considered significant. Publication bias was assessed if sufficient (i.e., 10 or more) studies were available.

All analyses were performed in STATA (version 15.1) and R (The R Foundation for Statistical Computing, version 3.6.0).

Risk of bias assessment

The methodological quality of the randomised controlled trials was assessed by the Cochrane Collaboration's revised Risk-of-Bias 2 tool.[19,20] Two investigators (ATLF and MHFP) independently assessed the five domains for risk of bias: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.

Role of the funding source

There was no funding source for this study.

Results

Six eligible trials involving 14,934 participants, of whom 7487 received colchicine and 7473 received placebo or no colchicine, were identified (Fig. 1).[7–9,14,21,22] Table 1 provides a summary of trial designs. One trial was performed in patients with prior non-cardioembolic stroke or TIA (CONVINCE, n = 3144), and five trials evaluated patients with coronary disease (LoDoCo2, n = 5522 participants; Colchicine in Patients With Acute Coronary Syndrome [COPS], n = 795; COLCOT, n = 4745; LoDoCo, n = 532; Deftereos et al., n = 196). LoDoCo2, COLCOT, COPS and the trial by Deftereos et al. were randomised, placebo-controlled, double-blind trials. CONVINCE and LoDoCo were open-label trials with blinded endpoint adjudication.

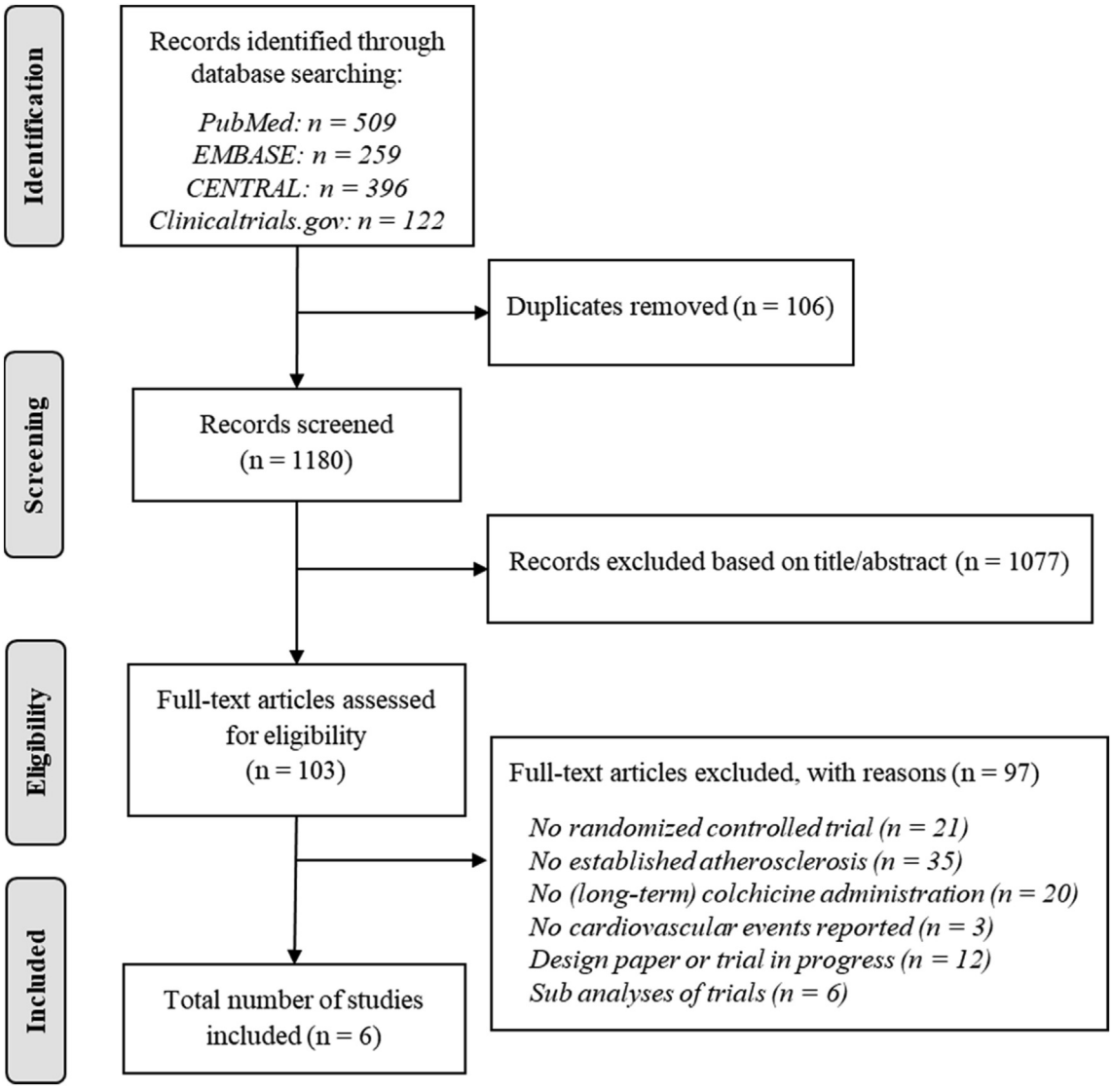

Fig. 1: **Flowchart of included studies.**

Acronym	Author	Year	Trial size	Key inclusion criteria	Key exclusion criteria	Active treatment	Comparator	Multi-centre	Open label run-in	Follow-up (median, months)
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 >2x upper limit of normal); bypass surgery <3 years or planned	Colchicine 0.5 mg once daily	Placebo	Yes	No	23
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
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	36

eGFR, estimated glomerular filtration rate. LVEF, left ventricular ejection fraction. NA, not available. NYHA, New York Heart Association. TIA, transient ischaemic attack.

Table 1: **Key features of included trials.**

Deftereos et al. studied colchicine at a dose of 0.5 mg by mouth twice daily and COPS used this dose for the first month only, followed by 0.5 mg once daily. All other trials used 0.5 mg once daily. The LoDoCo2 trial used an open-label run-in period of 30 days during which all participants received colchicine at a dose of 0.5 mg once daily. Trial medication discontinuation in the colchicine group at the end of the trials ranged from 10.5% to 22.0% (Supplemental Table S4). CONVINCE was finished before the anticipated number of outcomes was accrued due to budget constraints attributable to the Coronavirus disease 2019 (COVID-19) pandemic. Risk of bias was overall low for the primary outcomes the trials. We assigned unclear risk of bias to Deftereos et al., since selection of the reported outcomes could not be verified with a prespecified research protocol (Supplemental Table S3).

Baseline characteristics for each study are shown in Table 2. Percentage of female participants ranged from 11.1% to 34.7%. Median age ranged from 59.9 to 65.5 years. Percentage of current smokers ranged from 4.5% to 37.8% and those of patients with history of hypertension ranged from 48.5% to 65.4%. Percentage of patients with diabetes mellitus ranged from 18.3% to 100%. Prior stroke or TIA ranged from 2% to 100% in the four trials that reported this. Patients were treated according to recommended standards for secondary cardiovascular disease prevention, with 93.5%–99.0% of patients treated with statin therapy and 90.9%–98.8% treated with antiplatelet therapy at the time of randomisation.

The results for the main outcomes are presented in Fig. 2. Ischaemic stroke occurred in 132 (1.8%) of 7375 patients assigned to colchicine and in 186 (2.5%) of 7363 patients assigned to placebo or no colchicine. Colchicine reduced the risk of ischaemic stroke by 27% (RR 0.73, 95% CI 0.58–0.90; p < 0.004; Fig. 2a), with low heterogeneity among trials. The effect estimates were

	Mean age	Females	Current smoking	Hypertension	Diabetes mellitus	eGFR <60 ml/min/1.73m^2	History of stroke or TIA	History of ACS	Antiplatelet therapy	Statin therapy	Beta-blocker therapy
CONVINCE	66.3 ± 10.0	30.5%	22.1%	65.4%	22.3%	NA	100%	9%	97.5%	93.5%	NA
LoDoCo2	65.8 ± 8.6	15.3%	11.8%	50.9%	18.3%	5.5%	4.0%	84.4%	90.9%	94.0%	62.1%
COPS	59.9 ± 10.3	20.8%	34.8%	50.3%	19.0%	NA	2.0%	100%	98.6%	98.9%	82.6%
COLCOT	60.6 ± 10.7	19.2%	29.9%	51.0%	20.2%	NA	2.6%	100%	98.8%	99.0%	88.9%
Deftereos	63.3 ± 7.0	34.7%	37.8%	48.5%	100%	33.2%	NA	31.1%	NA	NA	NA
LoDoCo	67 ± 9.4	11.1%	4.5%	NA	30.3%	NA	NA	23.5%	93.4%	95.1%	66.5%

ACS, acute coronary syndrome. eGFR, estimated glomerular filtration rate. NA, not available. TIA, transient ischaemic attack. History of stroke or TIA was available for 3318 patients, and smoking status was missing for 21 patients in LoDoCo2.

Table 2: **Baseline characteristics of included trials.**

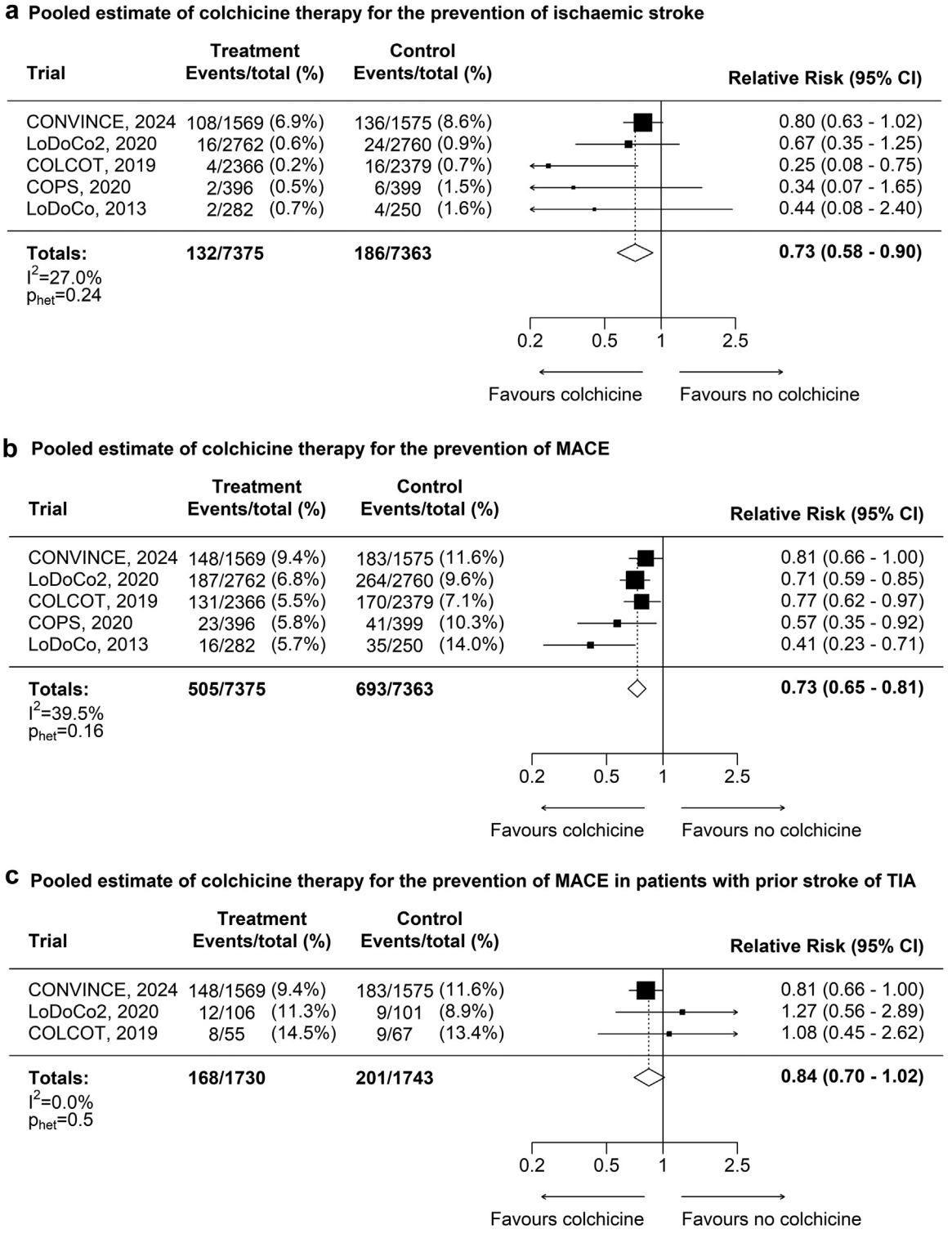

Fig. 2: a: Pooled estimate of colchicine treatment for prevention of ischaemic stroke. b: Pooled estimate of colchicine therapy for prevention of ischaemic stroke, myocardial infarction, coronary revascularisation, or cardiovascular death (MACE). c: Pooled estimate of colchicine therapy for prevention of ischaemic stroke, myocardial infarction, coronary revascularisation, or cardiovascular death (MACE) in patients with prior stroke or TIA.

consistent when comparing CONVINCE to the four trials that included patients with coronary disease (p for heterogeneity = 0.09), and comparing the two acute to the two chronic coronary disease trials (p for heterogeneity = 0.13). The risk of all stroke (ischaemic and haemorrhagic) was reduced by 26% in colchicine-treated patients (RR 0.74, 0.60–0.91; p < 0.004; Supplemental Figure S1). The number of haemorrhagic strokes during follow-up was low and did not differ by treatment group (17 [0.2%] in the colchicine group versus 19 [0.3%] in the no colchicine group).

MACE occurred in 505 (6.8%) of 7375 patients assigned to colchicine and 693 (9.4%) of 7363 assigned to no colchicine. Colchicine reduced the risk of MACE by 27% (RR 0.73, 0.65–0.81; p < 0.001; Fig. 2b), with low to moderate heterogeneity among trials. The effect estimates were consistent when comparing CONVINCE to the four trials that included patients with coronary disease (p for heterogeneity = 0.22) and comparing the two acute to the two chronic coronary disease trials (p for heterogeneity = 0.51). Risk reduction was 22% when omitting coronary revascularisation from the composite outcome between the colchicine and no colchicine arms (395 [5.4%] versus 505 [6.9%], RR 0.78, 0.69–0.89; p < 0.001; Supplemental Figure S2). Effects were consistent for the individual components of the composite, with a risk reduction of 20% for myocardial infarction (224 [3.0%] versus 278 [3.8%], RR 0.80, 0.68–0.96, p = 0.01; Supplemental Figure S3), and a risk reduction of 26% for coronary revascularisation (319 [4.3%] versus 415 [5.6%], RR 0.77, 0.67–0.89; p < 0.001; Supplemental Figure S4). Among all trials, 3473 patients had prior stroke or TIA, and 2864 patients had prior stroke at randomisation. Although not meeting the threshold for statistical significance, the direction of effect of colchicine for reduction of MACE was consistent in patients with prior stroke or TIA (RR 0.84, 0.70–1.02; p = 0.09, Fig. 2c) and in prior stroke alone (RR 0.85, 0.69–1.05; p = 0.13, Supplemental Figure S5).

The benefit of low-dose colchicine in reducing the risk of ischaemic stroke was consistent across all subgroups examined, with neither a significant interaction in treatment between those aged below 70 or over 70 years of age (p for heterogeneity = 0.37), nor by sex (p for heterogeneity = 0.43), those with or without diabetes (p for heterogeneity = 0.57), and those using statin therapy at baseline or not (p for heterogeneity = 0.57) (Fig. 3a). The direction of the pooled estimates for the risk of MACE was consistent in all subgroups, without evidence of treatment interaction by subgroup categories (Fig. 3b).

Colchicine-treated patients had no excess of hospitalisation for pneumonia (109 [1.5%] versus 106 [1.5%], RR 0.99, 0.76–1.30; p = 0.94), newly diagnosed cancer (247 [3.5%] versus 255 [3.6%], RR 0.97, CI 0.82–1.15; p = 0.72), or gastro-intestinal events (153 [2.2%] versus 135 [1.9%], RR 1.15, CI 0.91–1.44; p = 0.24) (Supplemental Figure S6).

There was no significant difference in all-cause death (201 [2.7%] versus 181 [2.4%], RR 1.09, CI 0.89–1.33; p = 0.39; Fig. 4a); cardiovascular death (70 [0.9%] versus 80 [1.1%], RR 0.89, 0.65–1.23; p = 0.50; Fig. 4b), or non-cardiovascular death (131 [1.8%] versus 101 [1.4%], RR 1.26 CI 0.97–1.64; p = 0.08; Fig. 4c).

Sensitivity analyses using random-effects models showed similar findings for all outcomes (Supplemental Table S3).

Discussion

Randomised trials of long-term colchicine in patients with coronary disease reported few patients with ischaemic stroke outcomes and a numerical but not statistically significant reduction of recurrent stroke was observed in patients with stroke in the CONVINCE trial, leading to uncertainty about the efficacy of colchicine for secondary prevention of stroke. This study-level meta-analysis of six randomised trials involving 14,934 patients with prior stroke or coronary disease showed consistent benefit for prevention of stroke and MACE, with consistent effects in patients with prior stroke and in key subgroups. The observed risk reductions of 27% for both ischaemic stroke and MACE provide compelling evidence for a benefit of colchicine in high-risk patients with atherosclerosis. The substantial increase in number of stroke outcome events compared with earlier meta-analyses now provides the most robust estimate of treatment effect for stroke prevention by colchicine to date.[23–25] The evidence for benefit in stroke prevention is strengthened by the plausibility of the effect size compared with the earlier reported large effect sizes of colchicine in smaller studies, the consistency of effect when haemorrhagic stroke is included in the stroke outcome definition, the alignment of treatment effect in the pre-specified subgroups, and the reproducibility of our findings in sensitivity analyses using a random-effects model. The magnitude of benefit of these pooled estimates are larger than those seen in contemporary secondary prevention trials of adjunctive lipid-lowering agents such as Ezetimibe or Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibition.[26] Colchicine can be produced at low-cost and addition of colchicine to contemporary secondary prevention therapies is highly cost-effective at commonly accepted thresholds.[27–29] This favourable combination of a clinically relevant treatment effect and low expense is of importance when considering strategies to address rising cardiovascular disease burden in middle and low-income countries. In the large coronary trials, the curves diverged by 6 months and remain consistently separated after this time. The lack of heterogeneity across trials of differing durations suggests a consistent effect over time, which was also seen in earlier landmark analyses.[30] Future individual patient and long-term follow up data will help to confirm consistency of treatment effect over time.

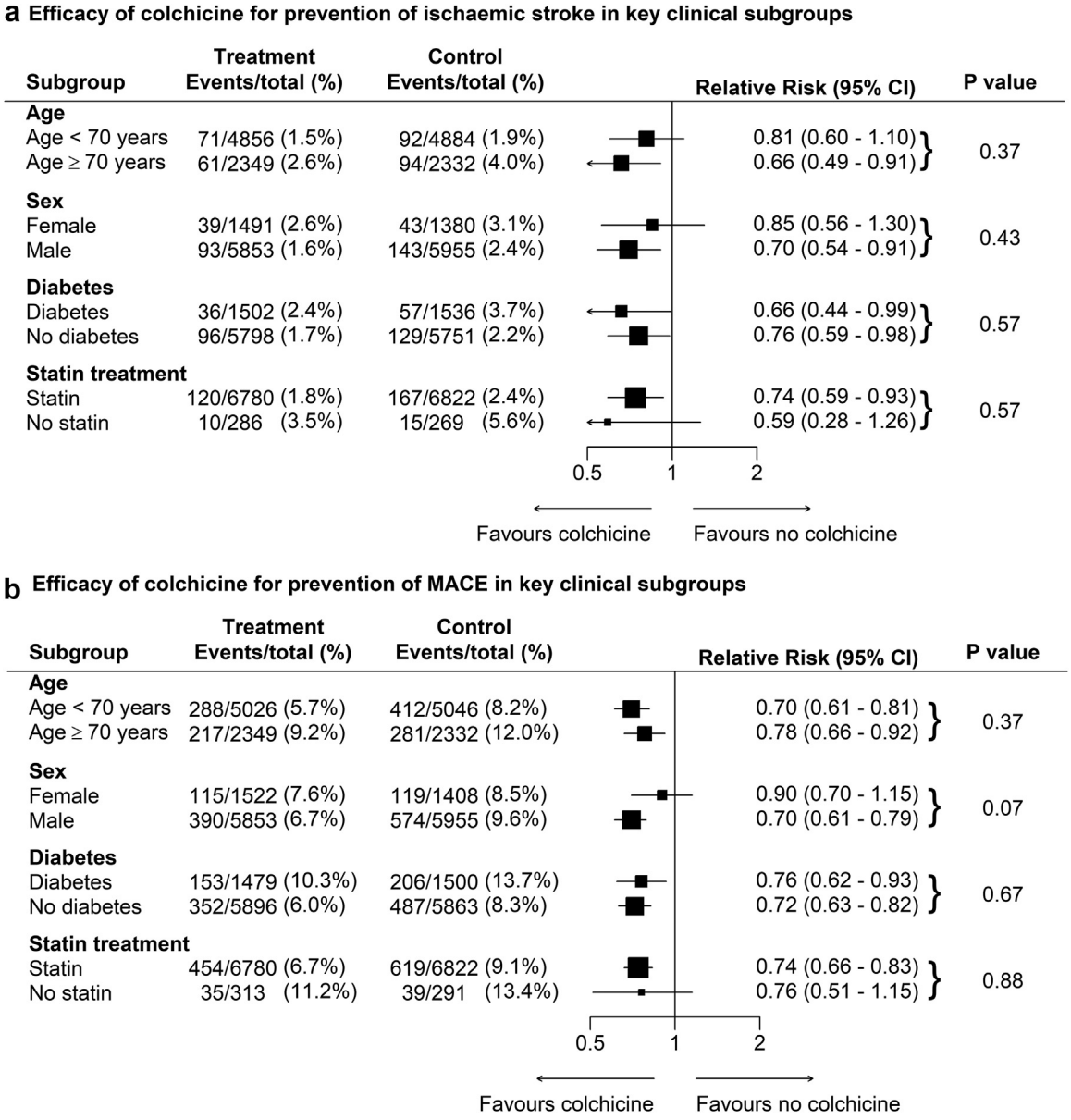

Fig. 3: **a: Efficacy of colchicine for prevention of ischaemic stroke in key clinical subgroups. b: Efficacy of colchicine for prevention of MACE in key clinical subgroups**.

Our study was not designed to investigate the mechanism of stroke prevention by colchicine, but the combined findings correspond to evidence from earlier experimental and clinical mechanistic studies. The causative role of inflammation in large artery and small vessel stroke has been by confirmed by mendelian randomization studies, in which genetically determined lower levels of interleukin-6 are associated with lower risk for stroke, and higher activity of monocyte chemoattractant protein-1 with higher risk for stroke.[2,31] In carotid atherosclerosis, inflammation and unstable plaque morphology are associated with higher risk for ischaemic stroke.[32,33] Correspondingly, increased carotid plaque inflammation detected with 18F-fluorodeoxyglucose uptake independently predicts early recurrent stroke.[34] In addition to these findings in large vessel disease, evidence from experimental studies also have highlighted the causal role of inflammation in the pathogenesis of cardio-embolic stroke, small vessel disease, and cryptogenic stroke.[32] Colchicine may have benefit for several stroke subtypes via inhibition of inflammation and platelet activation, such as reduced

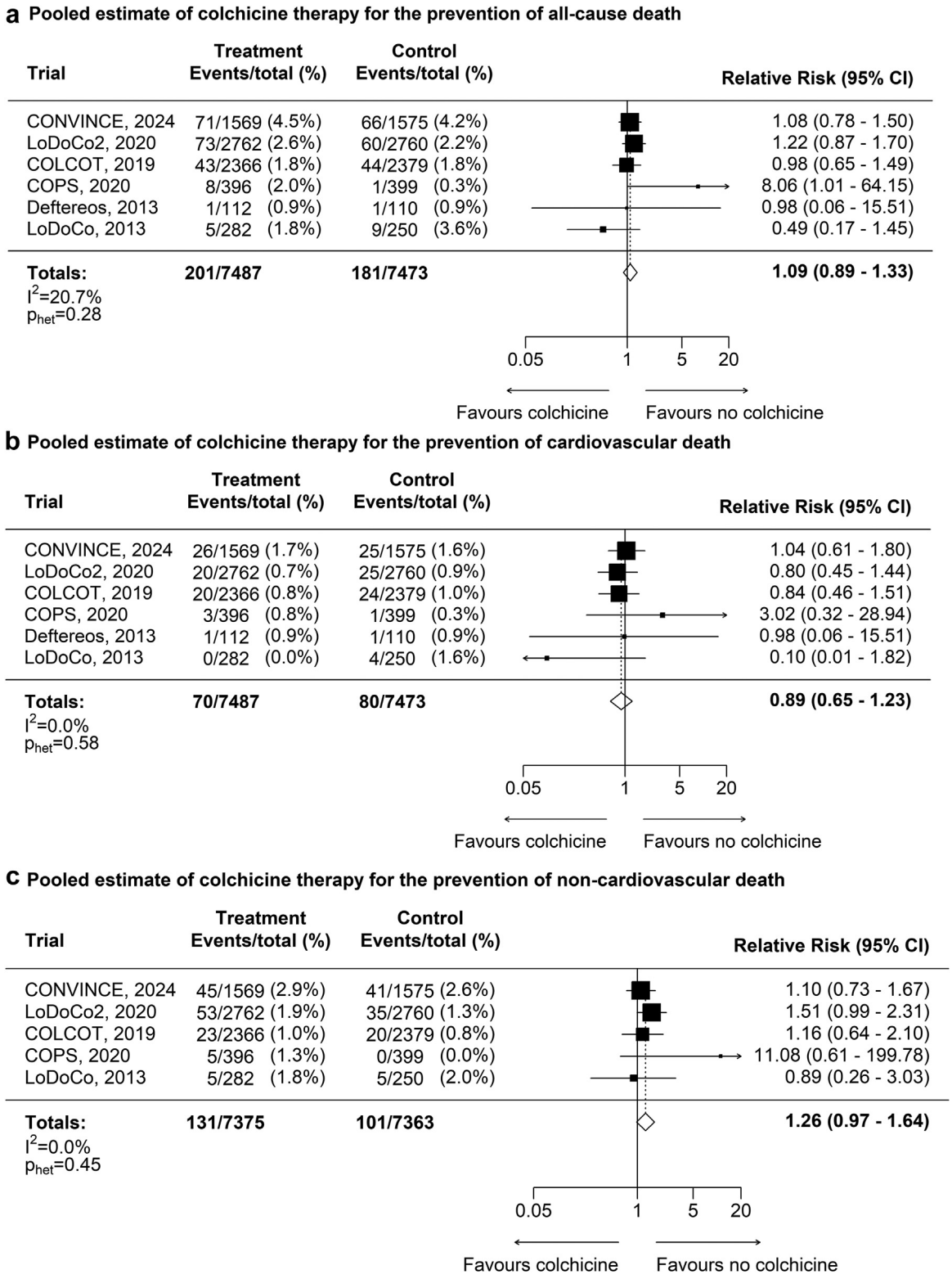

Fig. 4: **Mortality (all-cause death, cardiovascular death, and non-cardiovascular death). a: Pooled estimate of colchicine treatment for prevention of all-cause death. b: Pooled estimate of colchicine treatment for prevention of cardiovascular death. c: Pooled estimate of colchicine treatment for prevention of non-cardiovascular death.** CONVINCE included 51 cardiovascular deaths, among which are 18 late deaths (10 in the colchicine arm and 8 in the control arm) beyond 30 days of the qualifying event. Deftereos et al., 2013 reported no non-cardiovascular deaths in both treatment and control arm and was therefore omitted in this meta-analysis.

neutrophil adhesion at sites of inflamed or injured endothelium, decreased expression of platelet activation surface markers, and reduced leukocyte-platelet aggregation.[35,36] This leads to changes in plaque morphology and plaque vulnerability.[32,37–39] These mechanisms and the findings of our meta-analysis suggest therapeutic benefit is mainly gained with prolonged treatment, in particular when considering the neutral outcomes of short term treatment in the Colchicine in High-risk Patients with Acute Minor-to-moderate Ischemic Stroke or Transient Ischemic Attack (CHANCE3) trial.[40]

In our study, the increased number of outcome events and collaborative involvement of individual trialists allowed in-depth analysis of the effect of colchicine in key clinical subgroups. We found consistent treatment effects in patients aged over 70 years as compared to younger patients, which is reassuring since implementation in real-world populations will likely be in older patients than those participating in trials.[41] Individual trials of colchicine recruited fewer women than men and were underpowered to detect a treatment differences by sex.[42] Our analyses now include the largest-available sample of female participants, with data of 2628 women. The direction of treatment effect was consistent in males and females, albeit with some variation in effect size which was not statistically significant. Although diabetes is associated with a pro-inflammatory state, we observed equal benefit in patients with and without diabetes, consistent with findings from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial.[43] Finally, we observed a similar benefit in both statin and non-statin treated patients, supporting an independent and additive effect of anti-inflammatory therapy on top of lipid-lowering therapy and for treatment of statin-intolerant patients. These data support the finding that in patients who receive contemporary statin therapy, inflammation assessed by high-sensitivity C-Reactive protein is a stronger predictor for risk of future cardiovascular events and death than cholesterol assessed by low-density lipoprotein (LDL) cholesterol.[44]

Randomised trials are not designed to detect uncommon serious safety events, which may be important when new treatments are adopted for widespread clinical use. Consistent with large observational studies of colchicine for various indications, we found no increased risk of pre-specified serious safety outcomes, although rates of nausea and diarrhoea are known to be increased.[45–47] Five of the six trials included in our meta-analysis demonstrated a favourable but non-significant direction of effect of colchicine on cardiovascular death, and four of the five trials which reported non-cardiovascular death reported a higher number of such deaths in the colchicine arm. The numerically higher but statistically non-significant, increase in non-cardiovascular deaths is based on a low absolute number of events, and the surplus almost completely arises from one trial (LoDoCo2). Ancillary analyses on drivers of mortality in this trial and prolonged follow-up of the COPS trial revealed a wide spectrum of causes of death without a clear overarching or consistent signal.[48,49] The current meta-analysis showed no increase in specific major causes of death (hospitalisations for new cancer, pneumonia, or gastro-intestinal events). In addition, experience from life-long treatment with colchicine in Familial Mediterranean Fever, in which it is used in children, pregnant and nursing women, has not shown concerns relating to excess non-cardiovascular death.[47,50] Since the apparent increase is not consistently seen in studies and lacks a biological explanation at this time this issue requires further study with long term follow-up in future randomised trials and real-world data. The upcoming CLEAR SYNERGY (OASIS 9) trial will provide valuable data for both efficacy and safety data in this regard.[51] When introducing colchicine to current regimes of secondary prevention, patients should be counselled about known drug interactions and adverse effects, and renal function should be regularly monitored. Priorities for future trials include further investigation of the effect of colchicine for prevention of vascular events and cognitive decline in patients with stroke, investigating safety in patients with renal impairment, further randomised data of non-cardiovascular death in colchicine-treated patients and controls, and establishing the effect of colchicine therapy on long-term cardiovascular outcomes.

We acknowledge some limitations. Some relevant subgroups, such as ethnicity or race, were not collected at baseline, or were not assessed in this study, such as hypertension or smoking status. Differences in stroke outcome definition between trials may have introduced some variability, although this is unlikely to have materially impacted our overall findings. The possibility of performance bias in the two non-placebo-controlled trials could not be fully excluded, but we believe is unlikely since these trials involved blinded adjudication of outcomes supported by objective biomarker and imaging data. In this meta-analysis, we did not analyse individual patient data which would have allowed more detailed exploration of outcomes, subgroups and interactions based on stroke aetiology.

In conclusion, in patients with prior stroke or coronary disease, low-dose colchicine reduced the risk for ischaemic stroke and MACE, with consistent treatment effects in key clinical subgroups, and without significant increases in other serious safety events or all-cause mortality. Our findings support the use of low-dose colchicine for secondary prevention of stroke and coronary events in clinical practice.

Contributors

ATLF, MHFP, SMN, JE, AM, and PJK wrote the protocol and the statistical analysis plan. ATLF and MHFP performed statistical analyses with oversight from PJK. PIs of individual trials (ATLF (LoDoCo2), JL (COPS), SMN (LoDoCo, LoDoCo2), J-CT (COLCOT), PT (LoDoCo), AM

(LoDoCo2), PJK (CONVINCE)) accessed and verified the data. ATLF, MHFP, JE, AM, and PJK wrote the first draft of the manuscript. All authors critically reviewed drafts of this manuscript and approved the final version.

Data sharing statement

Study-level data not published within the article can be shared with researchers who submit a research proposal and request access to the data, for use pending approval of the authors and of the individual trial funders, and after a data access agreement has been signed.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102835.

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