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CLINICAL RESEARCH
Ischaemic heart disease

Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials

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Aims Recent randomized trials demonstrated a benefit of low-dose colchicine added to guideline-based treatment in patients with recent myocardial infarction or chronic coronary disease. We performed a systematic review and meta-analysis to obtain best estimates of the effects of colchicine on major adverse cardiovascular events (MACE).

Methods and results We searched the literature for randomized clinical trials of long-term colchicine in patients with atherosclerosis published up to 1 September 2020. The primary efficacy endpoint was MACE, the composite of myocardial infarction, stroke, or cardiovascular death. We combined the results of five trials that included 11 816 patients. The primary endpoint occurred in 578 patients. Colchicine reduced the risk for the primary endpoint by 25% [relative risk (RR) 0.75, 95% confidence interval (CI) 0.61–0.92; $P = 0.005$], myocardial infarction by 22% (RR 0.78, 95% CI 0.64–0.94; $P = 0.010$), stroke by 46% (RR 0.54, 95% CI 0.34–0.86; $P = 0.009$), and coronary revascularization by 23% (RR 0.77, 95% CI 0.66–0.90; $P < 0.001$). We observed no difference in all-cause death (RR 1.08, 95% CI 0.71–1.62; $P = 0.73$), with a lower incidence of cardiovascular death (RR 0.82, 95% CI 0.55–1.23; $P = 0.34$) counterbalanced by a higher incidence of non-cardiovascular death (RR 1.38, 95% CI 0.99–1.92; $P = 0.060$).

Conclusion Our meta-analysis indicates that low-dose colchicine reduced the risk of MACE as well as that of myocardial infarction, stroke, and the need for coronary revascularization in a broad spectrum of patients with coronary disease. There was no difference in all-cause mortality and fewer cardiovascular deaths were counterbalanced by more non-cardiovascular deaths.

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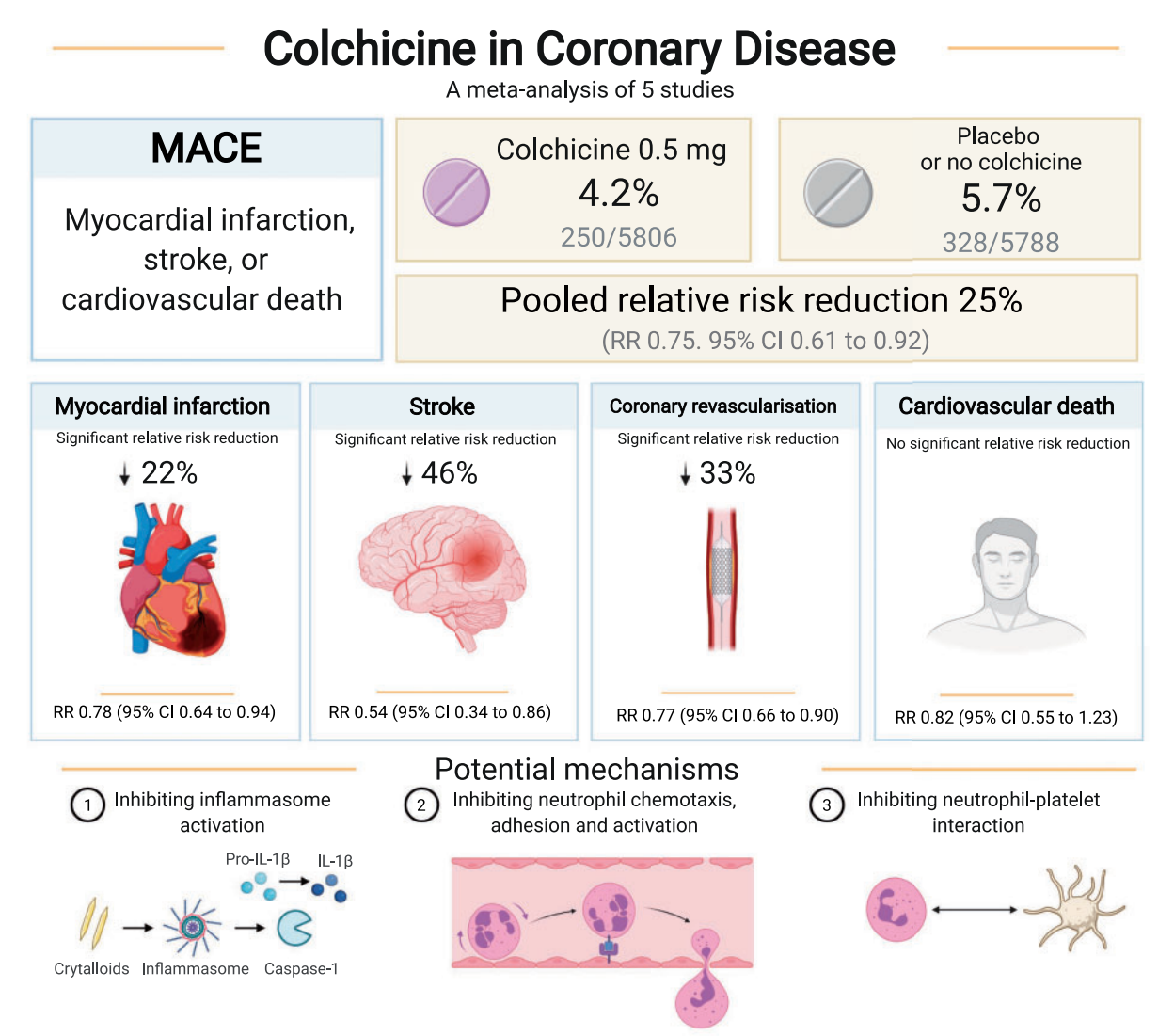
Graphical Abstract



Colchicine in coronary disease

Keywords Colchicine • Atherosclerosis • Coronary disease • Major adverse cardiovascular events • Myocardial infarction • Stroke

Introduction

Despite improvements in prevention, the global burden of cardiovascular disease continues to rise.[1] Guidelines recommend lifestyle changes (exercise, nutrition, smoking cessation), control of risk factors (hypertension, dyslipidaemia, dysglycaemia), and anti-thrombotic therapy in patients with coronary disease,[2–4] but even when these are routinely adopted, a high residual risk remains of myocardial infarction, stroke, coronary revascularization, or cardiovascular death.[5,6]

Atherosclerosis is characterized by inflammation in response to modified lipids and other pro-inflammatory stimuli.[7–9] Colchicine has broad anti-inflammatory effects by inhibiting microtubule formation, mitosis, leucocyte motility, and cytokine release from a range of inflammatory cells[10–12] (*Graphical abstract*). Recent trials have demonstrated that colchicine reduces major adverse cardiovascular events (MACE) in patients with coronary disease.[13,14] These trials involved patients with either acute or chronic coronary disease and were not designed to assess the effect on individual endpoints such as myocardial infarction, stroke, or cardiovascular death. We performed a

systematic review and meta-analysis of randomized clinical trials to obtain estimates of the overall effect of colchicine on MACE and individual components of MACE in patients with coronary disease.

Methods

Protocol

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[15,16] We developed a protocol which was submitted to PROSPERO on 17 July 2020 and registered with the number CRD42020183283.

Search strategy and selection criteria

A search of all randomized trials comparing colchicine to placebo or no colchicine in patients with clinical atherosclerotic disease published up to 1 September 2020 was performed by two independent reviewers (T.S.J.O. and A.T.L.F.) on PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov without language or publication date restrictions. The key search terms used were 'atherosclerosis', 'myocardial ischemia', 'brain ischemia', 'peripheral artery disease', and 'colchicine', including their subheadings and synonyms. Sensitivity-maximizing filters as recommended by the Cochrane Collaboration were applied to identify randomized controlled trials in Embase and PubMed.[17,18] The complete search algorithm is presented in the Supplementary material online, *Appendix*. Studies were eligible if they compared the efficacy of long-term colchicine treatment (≥3 months) with standard treatment with or without placebo in a patient population with established atherosclerosis. Studies were excluded if they lacked reporting of any cardiovascular endpoint, such as myocardial infarction, stroke, coronary revascularization, or cardiovascular death. Discrepancies over eligibility were resolved through consensus with a third reviewer (J.H.C.).

Study endpoints

For this meta-analysis, the pre-specified primary endpoint was the composite of myocardial infarction, stroke, or cardiovascular death and the key secondary endpoint was as above with the addition of coronary revascularization. In the definition of these composite endpoints, we chose the composition, definition, and tallies of the composite endpoints as reported in the original and subsequent publications [Low-dose Colchicine for secondary prevention of cardiovascular disease 2 (LoDoCo2) and the Colchicine Cardiovascular Outcome Trial (COLCOT)]. For the Colchicine in Patients with Acute Coronary Syndrome (COPS) trial and for the LoDoCo trial, we used LoDoCo2 definitions and supplemented the published data with additional data obtained from the principal investigators (J.L. and S.M.N.). In addition, all endpoints were also analysed using the original definitions and published data. The authors did not have access to the composite endpoints of the trial by Deftereos *et al.* (Supplementary material online, *Table S1A*).

The component-oriented endpoints were myocardial infarction, stroke, coronary revascularization, and cardiovascular death. We used the most inclusive definition as reported in the original main trial paper including online supplementary materials, ancillary papers, or by personal communications. Safety endpoints were hospitalization for infection, hospitalization for pneumonia, hospitalization for gastro-intestinal disorders and newly diagnosed cancer, all-cause death, and non-cardiovascular death (Supplementary material online, *Table SA1B*). Endpoint tallies were extracted into a structured data set by two reviewers (T.S.J.O. and A.T.L.F.).

Data synthesis and analysis

To estimate the pooled treatment effect, pooled relative risks (RR) were calculated using the cumulative incidence rates as reported, by applying inverse-variance weighting combined with a random-effect model with a DerSimonian–Laird estimator. Overall treatment effect was formally tested at a two-sided alpha level of 0.05 without adjustment for multiplicity. Treatment effect modification by subgroups for the primary and secondary endpoint was tested using random-effects models, applying the method of restricted maximum likelihood estimation. In order to obtain absolute risk reductions and number needed to treat, risk estimates of the 1- and 3-year cumulative incidences were calculated from the original data or estimated from the published Kaplan–Meier estimator curves. Weighted-average estimates were calculated with the use of the weights from the overall meta-analysis of reported endpoints.

The presence of heterogeneity of treatment effect among studies was assessed by calculating a Higgins and Thompsons' I^2 index, in which heterogeneity was considered to be low if the I^2 index was around 25%, moderate if around 50%, and high if around 75%.[19,20] Publication bias was not assessed due to the small number of included studies.

The methodological quality of the randomized trials was assessed by the Cochrane Collaboration's revised Risk-of-Bias 2 tool.[21,22] Two investigators (T.S.J.O. and A.T.L.F.) independently assessed the five domains for risk of bias: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. All statistical analyses were performed using R (The R Foundation for Statistical Computing, version 3.6.0) using the metaphor package (version 2.4-0). Illustrations were made with BioRender.com. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. The data underlying this article will be shared on reasonable request to the corresponding author.

Results

From 536 initial citations identified by the search, we included five randomized trials that met the inclusion criteria (Supplementary material online, *Figure SA1*).[13,14,23–25] These five trials involved 11 816 patients randomly allocated to colchicine ($n = 5918$) or placebo or standard treatment ($n = 5898$). The key study features of the five trials are reported in *Table 1* and Supplementary material online, *Table SA1*.

The trial by Deftereos *et al.*, the COLCOT trial, the COPS trial and the LoDoCo2 trial were all randomized, placebo-controlled, double-blind, clinical trials.[13,14,23,25] The LoDoCo was a single-centre, open-label trial of colchicine vs. control on a background of optimal medical treatment in patients with chronic coronary disease, with blinded endpoint adjudication (a PROBE design).[24] The trial by Deftereos *et al.*[23] was single-centre and enrolled stable patients with diabetes who underwent percutaneous coronary intervention with bare-metal stent insertion. COLCOT and COPS enrolled patients with recent myocardial infarction (<30 days) or acute coronary syndrome, respectively.[13,25] The LoDoCo2 was a multi-centre international trial enrolling patients with chronic coronary disease that used an open-label run-in period of 30 days.[14] All trials used a dose regimen of colchicine 0.5 mg once daily except the trial by Deftereos *et al.*,[23] which used a dose regimen of 0.5 mg twice daily and the COPS trial, which used 0.5 mg twice daily during the first month, then

Table 1 Key features of included trials

Trial acronym	Author	Year	Trial size	Key inclusion criteria	Key exclusion criteria	Active treatment	Comparator	Multi-centre	Open-label run-in	Follow-up (median, months)
LoDoCo2	Nidorf[14]	2020	5522	Chronic coronary disease, clinically stable >6 months	Heart failure (NYHA class 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[25]	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 1 month, followed by 0.5 mg once daily	Placebo	Yes	No	12
COLCOT	Tardif[13]	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
NA	Deftereos[23]	2013	222	Diabetes and undergoing percutaneous coronary revascularization	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[24]	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.

Table 2 Baseline characteristics of included trials

	Age (years)	Females (%)	Diabetes (%)	eGFR <60 mL/min/1.73 m^2 (%)	History of ACS (%)	Antiplatelet therapy (%)	Statin therapy (%)	Beta-blocker therapy (%)
LoDoCo2	65.8 ± 8.6	15.3	18.3	5.5	84.4	90.9	94.0	62.1
COPS	59.9 ± 10.3	20.8	19.0	NA	100.0	98.6	98.9	82.6
COLCOT	60.6 ± 10.7	19.2	20.2	NA	100.0	98.8	99.0	88.9
Deftereos	63.3 ± 7.0	34.7	100.0	33.2	31.1	NA	NA	NA
LoDoCo	67 ± 9.4	11.1	30.3	NA	23.5	93.4	95.1	66.5

ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; NA, not available.

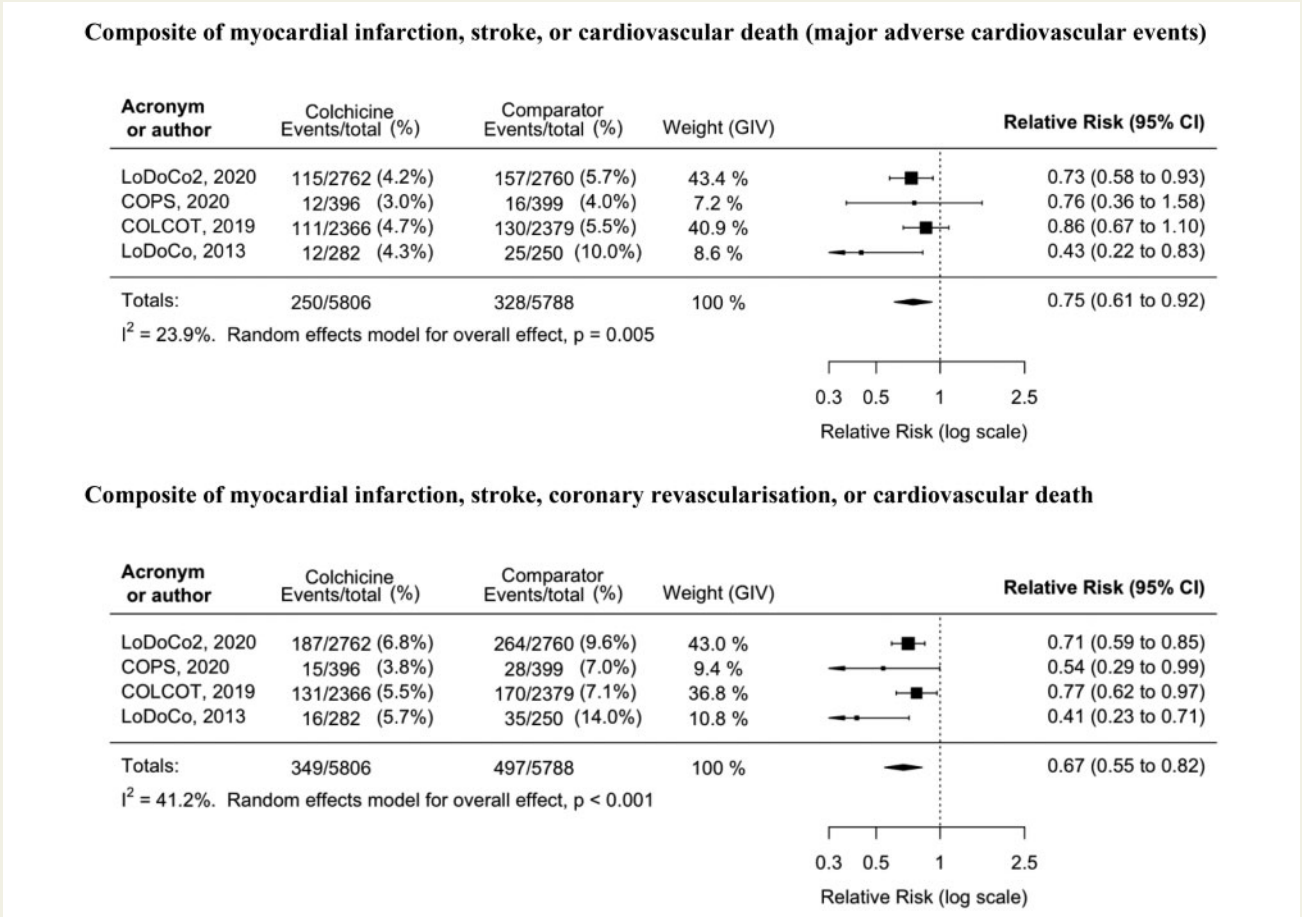


Figure 1 Primary and secondary endpoint. Pooled relative risks and 95% confidence intervals for the composite of myocardial infarction, stroke, or cardiovascular death (upper panel) and for the composite of myocardial infarction, stroke, coronary revascularization, or cardiovascular death (lower panel) in patients treated with colchicine as compared with placebo or no colchicine. CI, confidence interval; GIV, generic inverse variance.

0.5 mg daily thereafter.[25] Risk of bias assessment with the Risk-of-Bias 2 tool is summarized in Supplementary material online, *Table SA2*.

Baseline characteristics of patients included in our analyses are summarized in *Table 2*. All 11 816 patients had established coronary disease, 5540 (46.9%) were enrolled within 30 days of acute coronary syndrome, and 6276 (53.1%) were enrolled with chronic coronary disease. Patients had a median age of 63.3 ± 9.6 years and were mostly male (84.0%). Medication at baseline was reported for 11 594 patients. Of these, 10 988 (94.8%) were taking single or dual antiplatelet therapy, 11 176 (96.4%) were taking statins and 8655 (74.7%) were taking beta-blockers. The majority (87.9%) had a history of acute coronary syndrome prior to randomization. Heart failure was uncommon as this was an exclusion criterion for most trials.

The trial by Deftereos *et al.*[23] followed patients for 6 months and the COPS trial for 1 year, while the other trials followed patients for a median between 23 and 36 months.[13,14,24,25] Permanent discontinuation of trial regimen was reported in 487 (8.2%) colchicine patients vs. 385 (6.8%) placebo patients. Proportions of patients lost to follow-up were low in both the colchicine (0.9%) and the control groups (1.0%). The trial by Deftereos *et al.* did not report on composite endpoints, myocardial infarction, or stroke.

The primary and secondary endpoints are summarized in *Figure 1* and the *Graphical abstract*. A total of 578 patients developed a primary endpoint. Overall, colchicine reduced the risk for the primary endpoint of MACE, the composite of myocardial infarction, stroke, or cardiovascular death, by 25% [RR 0.75; 95% confidence interval (CI) 0.61–0.92; $P = 0.005$, with low heterogeneity, $I^2 = 23.9\%$]. For the key secondary endpoint of myocardial infarction, stroke, coronary revascularization, or cardiovascular death, the pooled RR reduction was 33% (RR 0.67; 95% CI 0.55–0.82, $P < 0.001$). Subgroup analysis showed no significant interaction between treatment and acute coronary syndrome or chronic coronary disease for the primary ($P = 0.279$) or the secondary ($P = 0.620$) endpoint (Supplementary material online, *Figure SA3A*). No significant interaction between treatment and sex for the primary ($P = 0.402$) or the secondary ($P = 0.083$) endpoint was observed (Supplementary material online, *Figure SA3B*). The number needed to treat for the composite of myocardial infarction, stroke, coronary revascularization, or cardiovascular death varied greatly between trials from 30 to 98 patients for 1 year with a weighted-average estimate of 84 and from 9 to 60 for 3 years with a weighted-average estimate of 40 (Supplementary material online, *Table SA3*).

Treatment effect was directionally consistent for components of the composite endpoint (*Figure 2*). Overall, colchicine significantly reduced the risk for myocardial infarction by 22% (RR 0.78; 95% CI 0.64–0.94; $P = 0.010$), for stroke by 46% (RR 0.54; 95% CI 0.34–0.86 $P = 0.009$), and for coronary revascularization by 23% (RR 0.77; 95% CI 0.66–0.90; $P < 0.001$). The risk reduction for stroke was mostly driven by ischaemic stroke (RR 0.49; 95% CI 0.30–0.81; $P = 0.005$), as the incidence of haemorrhagic strokes was very low with 10 events (Supplementary material online, *Figure S2*).

Fatalities are summarized in *Figure 3*. We observed no difference in all-cause death (RR 1.08; 95% CI 0.71–1.62; $P = 0.726$), with a lower incidence of cardiovascular death (RR 0.82; 95% CI 0.55–1.23; $P = 0.339$) counterbalanced by a higher incidence of non-cardiovascular death (RR 1.38; 95% CI 0.99–1.92; $P = 0.060$).

Safety information is summarized in *Figure 4* and was available from three trials: COLCOT, COPS, and LoDoCo2.[13,14,25] Overall, colchicine was not associated with an increased risk for hospitalization for infection in general (RR 1.08; 95% CI 0.78–1.51; $P = 0.636$) or hospitalization for pneumonia (RR 1.67; 95% CI 0.58–4.77, $P = 0.339$, with high level of heterogeneity, $I^2 = 75.0\%$). Hospitalizations for gastrointestinal disorders did not differ between treatment groups (RR 1.13; 95% CI 0.81–1.56; $P = 0.470$). Overall, no differences in the risk for new cancer was seen in those allocated colchicine vs. no colchicine or placebo (RR 0.987, 95% CI 0.80–1.21; $P = 0.861$).

Results for the primary and secondary composite endpoints, for the individual endpoints, and for fatalities were essentially unchanged in a sensitivity analysis that removed the non-placebo-controlled LoDoCo trial. Sensitivity analyses using a fixed-effects model and analyses using the original endpoint definitions of the trials showed consistent results, albeit with slightly smaller estimated effect sizes (Supplementary material online, *Figures S4–S6*).

Discussion

This meta-analysis includes five trials and endpoints in 11 816 randomized patients and shows consistent cardiovascular benefits of colchicine in a wide range of patients with coronary disease. The most notable observations include the following: first, we found that colchicine, as compared with no colchicine or placebo, reduced the risk of the composite of myocardial infarction, stroke, or cardiovascular death by 25% with a low between-trial heterogeneity. With the addition of coronary revascularization to the composite endpoint, similar treatment benefits were observed. In addition, we observed significant reductions separately in the risks of myocardial infarction (22%), any stroke (46%), and coronary revascularization (23%). Second, we found no differences in all-cause death, with a lower incidence of cardiovascular death counterbalanced by a higher incidence of non-cardiovascular death. Third, risk for infectious or gastrointestinal adverse events and cancer were similar between colchicine and no colchicine or placebo groups.

Our results accord with the clinical benefit of targeted anti-inflammatory therapy in atherosclerosis which was found in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS).[26] The anti-inflammatory mechanisms of action of colchicine are not yet fully elucidated. Multiple pathways are suggested, involving inhibition of microtubule formation, inhibition of leucocyte adhesion, and modulation of the nucleotide-binding oligomerization domain leucine-rich repeat-containing receptor family pyrin domain-containing 3 (NLRP3) inflammasome with reduced expression of interleukin-1β, interleukin-6, and other pro-inflammatory cytokines.[11,12,27]

The benefits of colchicine observed in these analyses were achieved against a background of standard secondary preventive therapies and are consistent with the concept of a residual inflammatory risk in patients with atherosclerosis.[28] The observed risk reduction matched that of other secondary preventive strategies in chronic coronary disease such as lipid-lowering or anti-thrombotic therapy.[29,30] The effects appeared to be consistent in both acute coronary syndrome and chronic coronary disease, and in women and men.

Meta-analyses of current available data provide strong evidence for the efficacy of low-dose colchicine on composite cardiovascular endpoints and individual components. However, evaluation of safety of colchicine is currently limited to adverse events with high incidence rates such as hospitalizations for infection. None of the trials reported on infections that did not lead to hospitalization. Addressing safety on the level of serious but rarely occurring adverse events such as serious myotoxicity or neutropenia is limited by the low occurrence of such events necessitating longer follow-up and larger cohorts than are currently available. Other meta-analyses focusing on the safety of long-term colchicine for varied indications confirmed diarrhoea as a side effect of colchicine but did not identify increased frequency of other serious adverse events.[31,32]

By reducing myocardial infarction and stroke, colchicine might be expected to affect related mortality. Although the incidence of

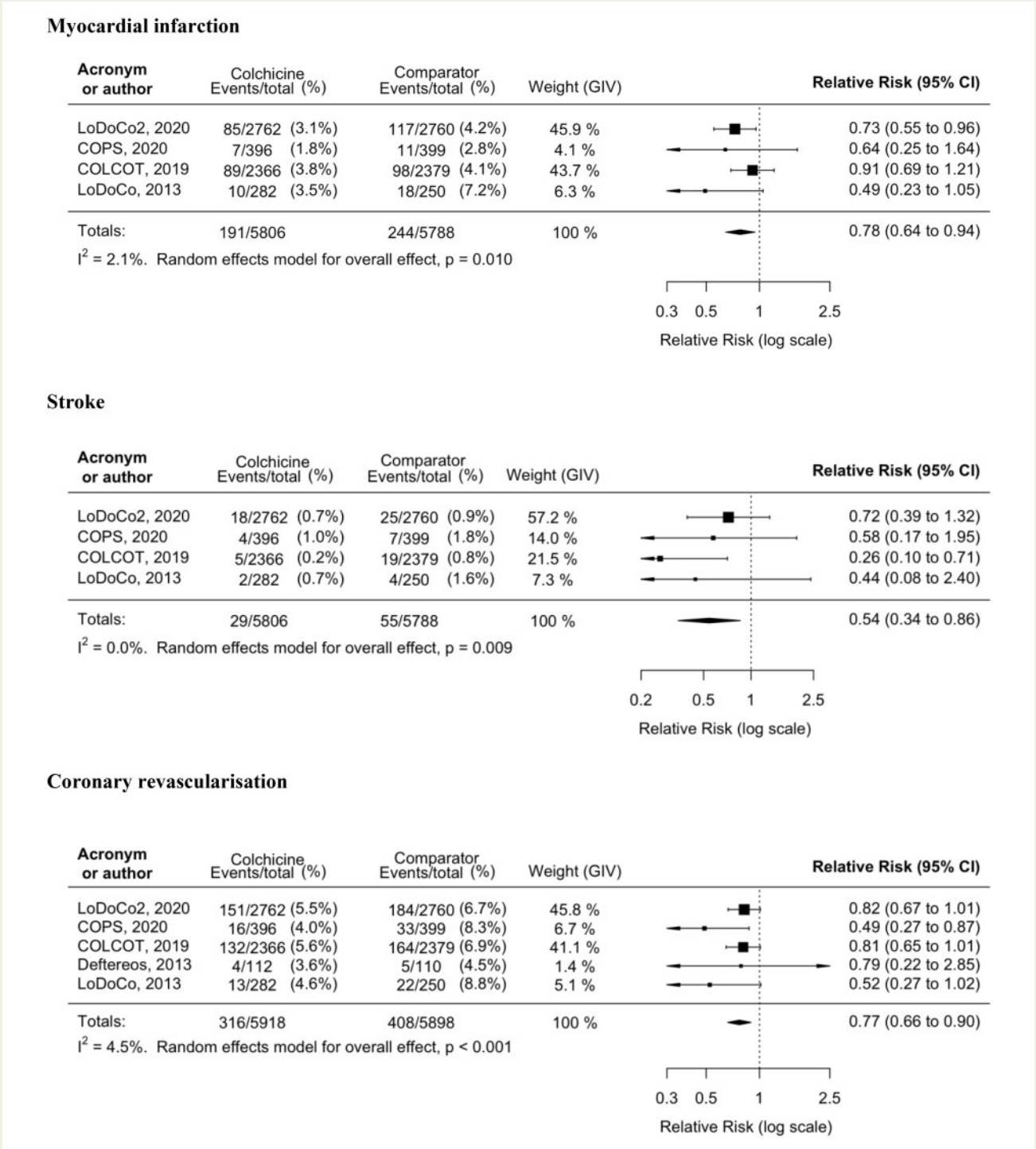


Figure 2 Myocardial infarction, stroke, and coronary revascularization. Pooled relative risks and 95% confidence intervals for the individual components of the composite endpoints in patients treated with colchicine as compared with placebo or no colchicine. CI, confidence interval; GIV, generic inverse variance.

cardiovascular deaths was lower in patients treated with colchicine, it was not significantly reduced. The trials all included patients with established cardiovascular disease, but the majority of fatalities were of non-cardiovascular origin. The increased incidence in non-cardiovascular death for colchicine cannot be explained by increased numbers of infections or cancer, has not been related to other causes, and was not observed in prior observational studies. The wide CIs reflect the limited power for these observations. To evaluate whether this finding represents a true signal, extended follow-up of patients enrolled in prior colchicine studies is required, and future

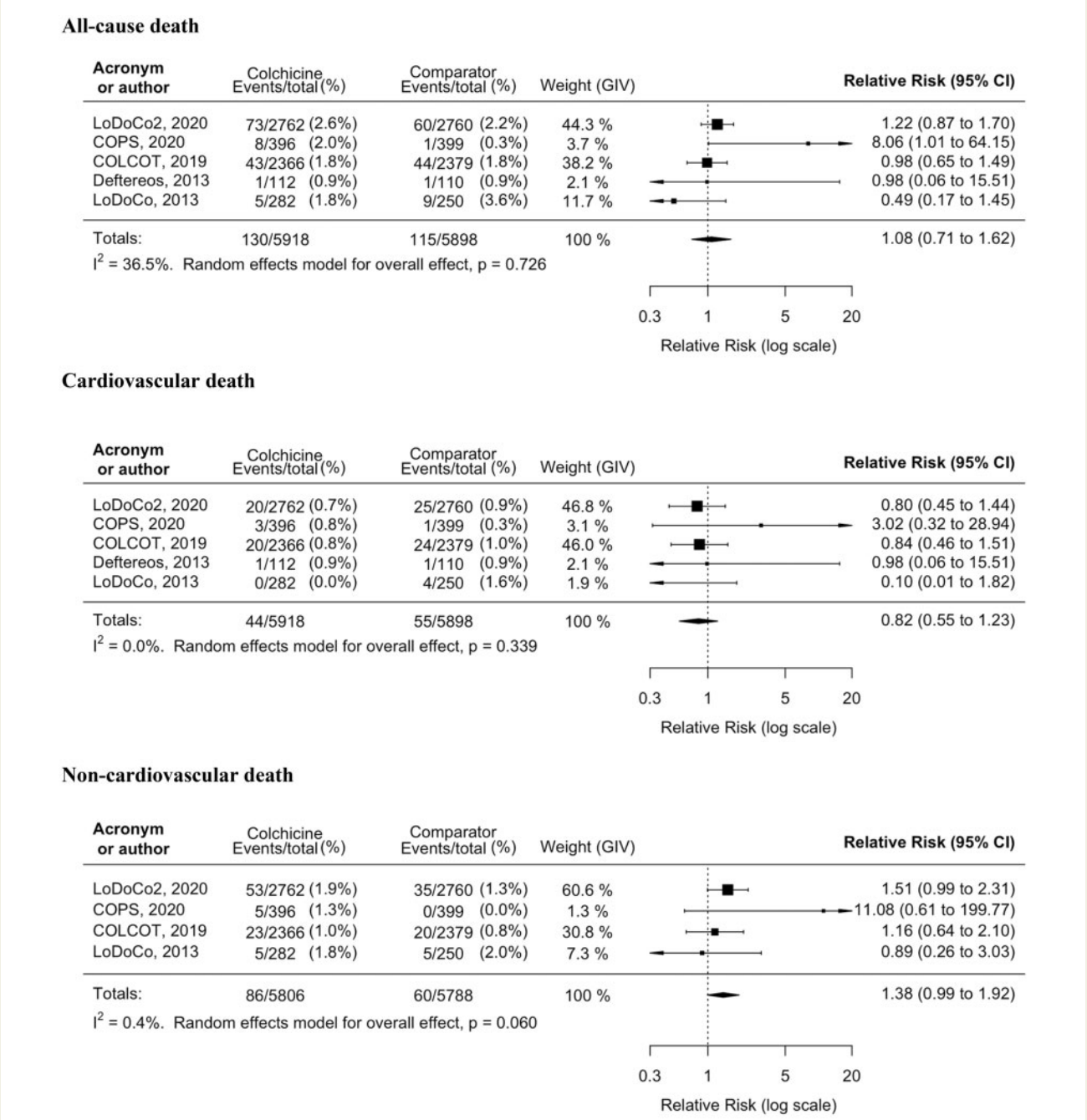


Figure 3 Death. Pooled relative risks and 95% confidence intervals for all-cause death, cardiovascular death, and non-cardiovascular death in patients treated with colchicine as compared with placebo or no colchicine. Patient-level data for the LoDoCo trial were retrieved by personal communication, which revealed an error in the tally of deaths in the original paper, resulting in one additional cardiovascular death in the placebo group and one less non-cardiovascular death in the colchicine group, which was corrected in the current tally. CI, confidence interval; GIV, generic inverse variance.

trials should collect granular information on the origin of fatalities.[33,34] Although interpretation of fatality data is currently limited by low event numbers and statistical uncertainty, future data will contribute in more precise assessment of the net clinical benefit of colchicine in coronary disease.

We acknowledge several limitations of our study. We used aggregated study-level data rather than individual participant data, However, while this limits our ability to examine subgroups of interest, this will not materially alter the overall conclusions drawn. The trials included patients with recent myocardial infarction as well as

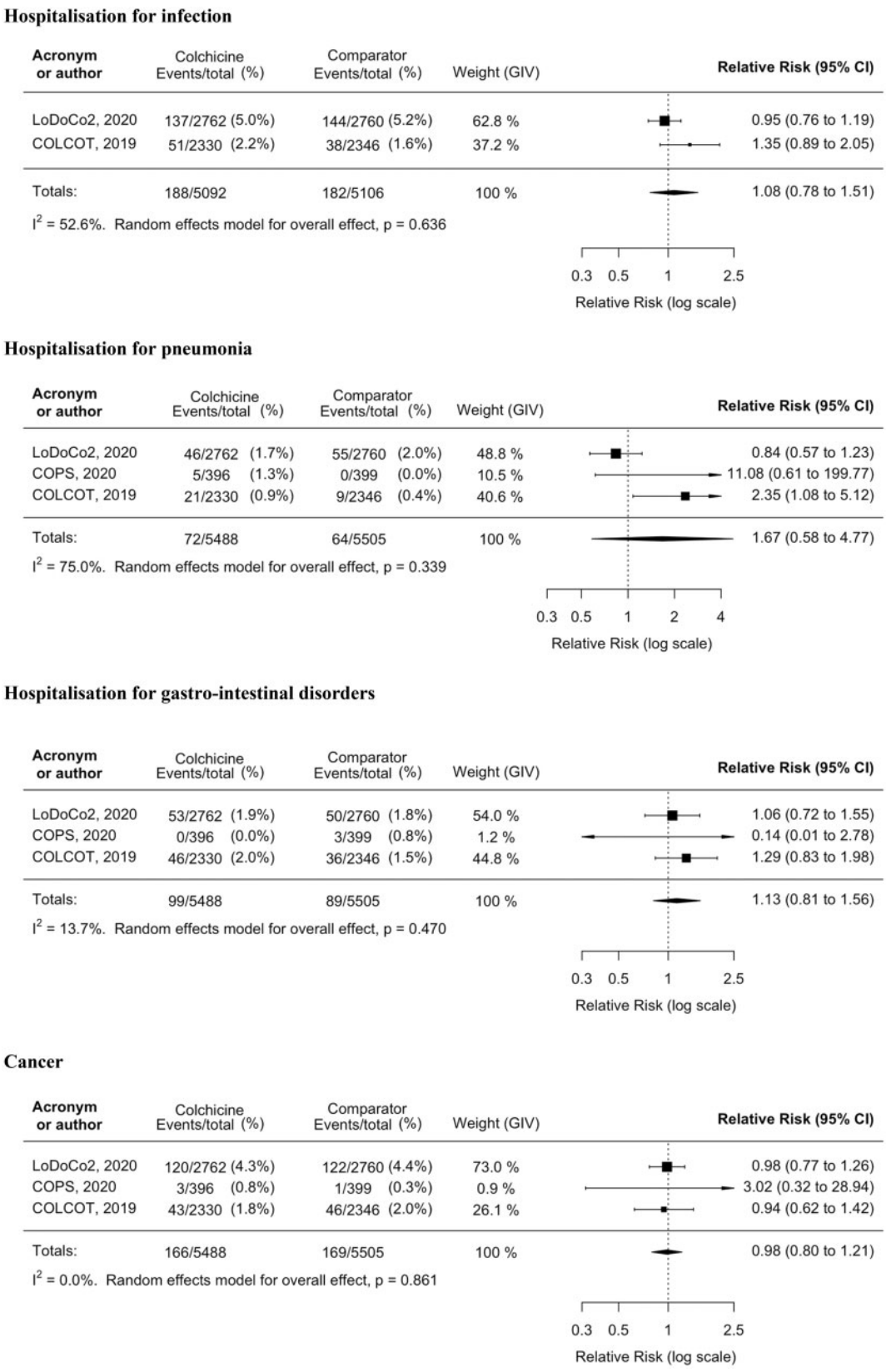


Figure 4 Adverse events. Pooled relative risks and 95% confidence intervals for hospitalization for infection, hospitalization for pneumonia, and cancer in patients treated with colchicine as compared with placebo or no colchicine. CI, confidence interval; GIV, generic inverse variance.

patients with chronic coronary disease. The inclusion criteria and definitions of endpoints varied among the included trials, but this did not lead to heterogeneity of the results. Furthermore, all trials included mostly older male patients without heart failure or renal failure. This limitation will need to be addressed in future and ongoing studies. Finally, data about ethnicity were lacking in all trials except COLCOT, potentially limiting generalizability of the results.

In conclusion, the best available evidence indicates that low-dose colchicine reduced composite and individual cardiovascular outcomes in patients with coronary disease, when added to contemporary treatment with antiplatelet agents and lipid-lowering therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

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