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SYSTEMATIC REVIEW AND META-ANALYSIS

Colchicine in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Trials

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BACKGROUND: Inflammation plays a pivotal role in coronary artery disease (CAD). The anti-inflammatory drug colchicine seems to reduce ischemic events in patients with CAD. So far there is equipoise about its safety and impact on mortality.

METHODS AND RESULTS: To evaluate the utility of colchicine in patients with acute and chronic CAD, we performed a systematic review and meta-analysis. MEDLINE, EMBASE, Cochrane CENTRAL and conference abstracts were searched from January 1975 to October 2020. Randomized trials assessing colchicine compared with placebo/standard therapy in patients with CAD were included. Data were combined using random-effects models. The reliability of the available data was tested using trial sequential analyses . Of 3108 citations, 13 randomized trials (n=13 125) were included. Colchicine versus placebo/standard therapy in patients with CAD reduced risk of myocardial infarction (odds ratio [OR] 0.64; 95% CI, 0.46–0.90; P=0.01; I^2 41%) and stroke/transient ischemic attack (OR 0.50; 95% CI, 0.31–0.81; P=0.005; I^2 0%). But treatment with colchicine compared with placebo/standard therapy had no influence on all-cause and cardiovascular mortality (OR 0.96; 95% CI, 0.65–1.41; P=0.83; I^2 24%; and OR 0.82; 95% CI, 0.55–1.22; P=0.45; I^2 0%, respectively). Colchicine increased the risk for gastrointestinal side effects (P<0.001). According to trial sequential analyses, there is only sufficient evidence for a myocardial infarction risk reduction with colchicine.

CONCLUSIONS: Among patients with CAD, colchicine reduces the risk of myocardial infarction and stroke, but has a higher rate of gastrointestinal upset with no influence on all-cause mortality.

Key Words: colchicine ■ coronary artery disease ■ inflammation ■ myocardial infarction ■ systematic review

Inflammation plays a pivotal role in the development and progression of coronary artery disease (CAD).[1] The main mechanisms for cardiovascular events in afflicted patients represent plaque activation and rupture.[2] Experimental studies have demonstrated, that inflammatory cells release specific cytokines and enzymes, which ultimately promote plaque erosion and rupture.[1] By specifically targeting inflammation in patients with CAD, it has been suggested that the risk for cardiovascular events can be reduced.[3,4]

Colchicine is an ancient drug, which is traditionally used for treatment of various rheumatic disorders (eg, gout and Behçet's disease), but has also become a well-established therapy for pericarditis.[5] It primarily impedes tubulin polymerization and microtubule formation and thus inhibits the leukocytes´ migratory, exocytotic and phagocytotic function by suppressing the expression of selectins, which are upregulated in atherosclerosis, particularly following myocardial infarction (MI).[5] Moreover, colchicine executes anti-inflammatory effects via NLRP3 inflammasome inactivation and a decrease in release of interleukin (IL)-1β, IL-18, IL-6, and C-reactive protein.[5–7]

Over the past 3 decades, several observational and randomized studies evaluated the impact of colchicine

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CLINICAL PERSPECTIVE

What Is New?

- In this systematic review and meta-analysis of >13 000 patients with acute and chronic coronary artery disease, we highlight that the adjunctive treatment with the anti-inflammatory drug colchicine reduces the risk for ischemic events, namely, new myocardial infarction, stroke, and repeat revascularization procedures.
- Whilst colchicine seems related to an increased risk of gastrointestinal side effects, there was no significant increased risk for infectious complications or mortality with this treatment.

What Are the Clinical Implications?

- Colchicine represents a promising supplementary drug for secondary prevention of ischemic events among patients with acute and chronic coronary artery disease.
- The reduced risk of potentially debilitating secondary coronary vascular or cerebrovascular events will need to be balanced against the side effect and interaction profile of colchicine.
- Nonetheless, several questions regarding colchicine treatment in coronary artery disease patients remain uncertain and warrant more research, including patient selection, drug dosing, and therapy duration.

Nonstandard Abbreviations and Acronyms

TSA	trial sequential analysis

on outcomes of patients with acute or chronic CAD and indicated potential benefits, including a reduction in ischemic events, including repeat revascularization, MI, and stroke/transient ischemic attack (TIA).[8] Moreover, a series of recent meta-analyses showed somewhat conflicting results, and some even suggested potential harm due to a higher risk of gastrointestinal-related adverse events.[9–15] However, some of them did not consider a series of large clinical trials, which have recently been published and certainly brought new perspectives to this field.[16–18] In addition, the optimal treatment duration and dosing of colchicine have also been debated.[14,17] Therefore, we conducted a comprehensive systematic review and meta-analysis, incorporating a trial sequential analysis, of all randomized trials assessing the efficacy of colchicine in patients with acute or chronic CAD.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. We conducted this systematic review and meta-analysis in agreement with the latest version of Cochrane Handbook for Systematic Reviews and Interventions and reported following the PRISMA statement for meta-analysis in health care interventions.[19–21] We followed an internal protocol for the reviewing process and data collection. There was no external funding in place to support this work. The authors are solely responsible for the design and execution of this systematic review and meta-analysis, the drafting and editing of the paper, and its final content. Additionally, no individual or organization not listed as an author contributed under any circumstances to the drafting or editing of this manuscript or performance of any analyses presented therein. This meta-analysis has been registered at the PROSPERO international database for registered systematic reviews in health and social care (ID CRD42021242792).

Study Selection

Only randomized clinical trials (RCT) were included in this meta-analysis since data derived from observational studies and case series are more susceptible to bias and therefore have been excluded. We extensively searched for any RCT evaluating colchicine compared to placebo or standard therapy among patients with acute or chronic CAD.

Regarding the CAD definitions, (i) acute CAD comprised unstable angina presentation, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), and (ii) chronic CAD included for example patients presenting with stable angina equivalents, silent myocardial ischemia or history of myocardial revascularization (eg, recent non-urgent percutaneous coronary intervention).

Two independent reviewers (T.K. and R.K.) reviewed all titles and abstracts for eligibility. Reviewers then assessed full text articles for inclusion. The reviewers selected then all full texted citations and abstracts (ie, unpublished) and screened for eligibility. Incongruences in assessment were resolved involving a third-party opinion (M.B.). Unpublished citations would have also been considered to address negative publication bias. A flow chart describing study exclusion is presented in Figure 1.

Data Sources

Data was extracted for matching RCTs in MEDLINE/PUBMED, Cochrane CENTRAL, EMBASE and online trial registers (including https://clinicaltrials.gov) published any time since January 1, 1975. The search process was terminated by October 1, 2020. Of note,

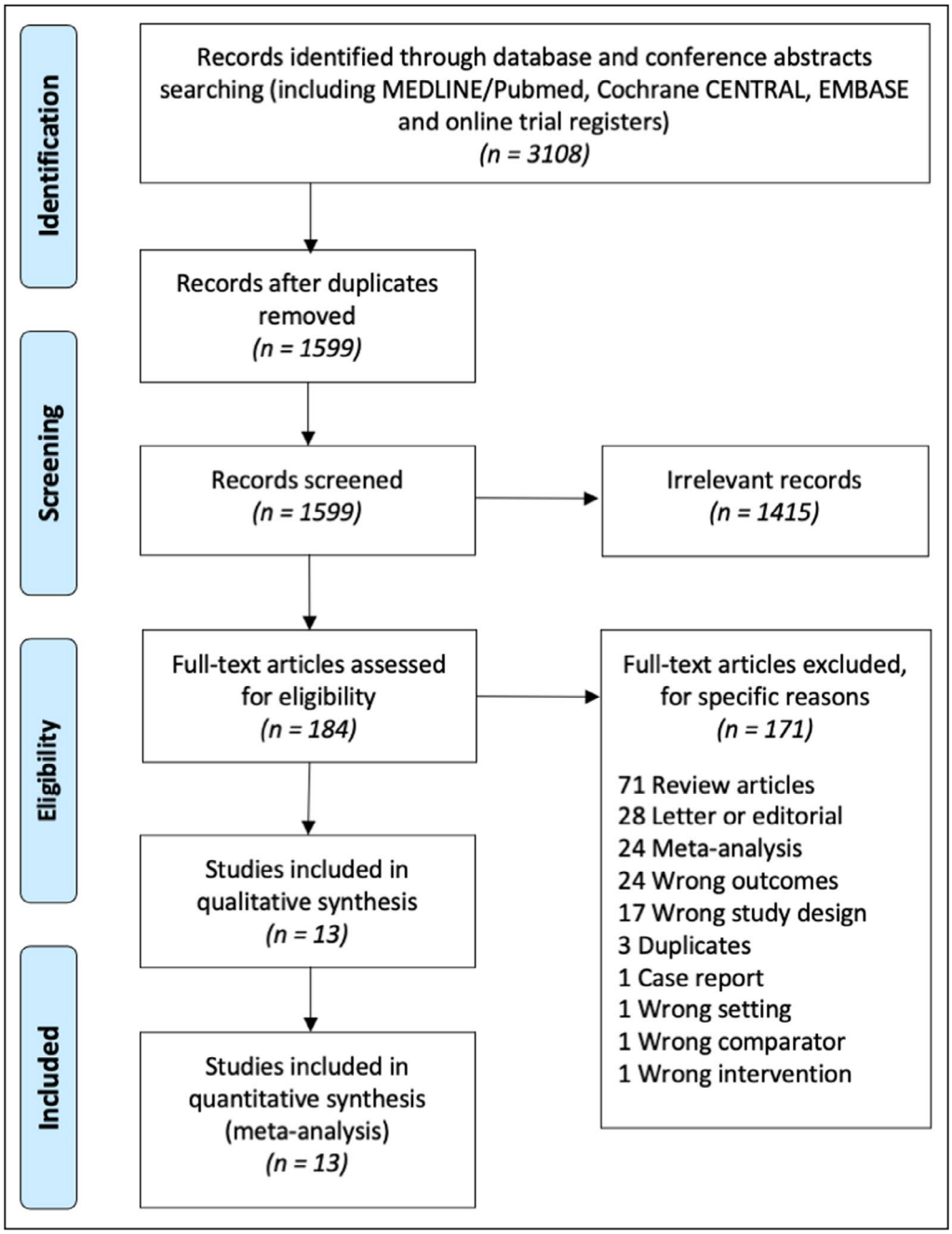

Figure 1. PRISMA flow diagram detailing the article screening process.

the search was repeated prior to submission in order to keep the data up to date. Any article published after that date was not included. Additionally, we manually searched the abstracts submitted to the American College of Cardiology (ACC), the American Heart Association (AHA), the European Society of Cardiology (ESC), and Transcatheter Therapeutics (TCT) up to October 10, 2020. In addition, we searched the clinicaltrials.gov registry for ongoing or recently finished trials. We reviewed the reference lists of original studies identified by the electronic search to ensure all pertinent studies had been considered. The applied search terms are listed in Data S1. To ensure data completeness, we contacted the included study's corresponding author, if necessary.

Data Collection, Extraction, and Quality Assessment

The 2 reviewers (T.K. and R.K) extracted the data independently using the Covidence software package

(Melbourne VIC, Australia). Any disagreements were resolved by consensus and residual uncertainty was clarified with the senior author (M.B.). The Kappa (κ) statistic, calculated to assess the degree of agreement between the 2 authors (κ=0.90), indicates a substantial agreement. The data were extracted independently and verified by the senior author (M.B.). Publication bias was assessed by visual analysis of funnel plots. The included trials were evaluated for risk of bias in 5 domains (sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and incomplete outcome data) according to the risk of bias tool from the Cochrane collaboration.21[20,22,23] The correlating table is shown in Table S1. The quality of the studies was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool for RCTs (Table S2).[24]

Outcomes

We obtained the outcomes for the longest available follow-up. The following outcomes were evaluated as reported by the studies: all-cause mortality, cardiovascular mortality, MI, and stroke/TIA. The details of the MI and stroke/TIA definitions are highlighted in the Table S3. Other outcomes, which were considered, included ischemia driven revascularization (eg, percutaneous coronary intervention or coronary artery bypass grafting for recurrent ischemic symptoms) and noncardiovascular mortality (if reported).

In order to discern the impact of colchicine on outcomes of patients with acute versus chronic CAD and the role of short (≤30 days) versus long-term colchicine treatment (>30 days) and high- (>0.5 mg per day) versus low-dose (≤0.5 mg per day), we performed dedicated sensitivity analyses involving the main outcomes. Further sensitivity analyses were conducted that pooled large trials separately from the smaller trials which contributed just very few events.

In order to establish the tolerability and safety, we reviewed and analyzed the rate of drug discontinuation and adverse outcomes/side effects (eg, gastrointestinal side effects, infections) among patients with CAD treated with colchicine compared to placebo/standard therapy.

Statistical Analysis

We analyzed the pooled data, number of events and number of patients in each subgroup from the included RCTs. Between-study heterogeneity was determined using I^2.[25] We preferred intention-to-treat analyzes, which involved all randomized probands. In order to account for the between-study variation, we applied random-effect models, using the Mantel-Haenszel approach as implemented in Review Manager 5.3 (Rev Man, The Nordic Cochrane Centre, Copenhagen, Denmark) for dichotomous outcome variables.[14] We reported the results as odds ratio (OR) and the corresponding 95% CI. To assess the robustness of the results, we performed separate sensitivity analyses for the main outcomes applying fixed-effects models utilizing the Mantel-Haenszel estimation method (Figure S2). Those analyses were conducted using Stata/SE version 16.1 (StataCorp, College Station, Texas, USA). A P value <0.05 was considered statistically significant.

Trial Sequential Analysis

Trial sequential analysis (TSA) represents a meta-analysis technique, which can be applied to assess the accumulated evidence from previous trials in a sequential manner to evaluate if sufficient evidence is available to draw firm conclusions.[26] Due to the small number of RCTs with limited number of patients, a meta-analysis of this type may be susceptible to type I and II errors. By using TSA, monitoring boundaries are formed to establish whether the P value for a particular outcome is sufficient for the accrued evidence to indicate the anticipated effect once the boundary is crossed.[26] In the event monitoring boundaries are not crossed, continued evaluation for evidence was recommended. The red dashed lines make up the trial sequential monitoring boundaries. The interpretation has similarities to DeMets' stopping boundaries, which are used in clinical trials. We estimated the information size required to demonstrate or reject a priori anticipated intervention effect of a 25% relative risk reduction. With respect to the latest major trials assessing colchicine in patients with CAD, the value of 25% was chosen to represent a reasonable intervention effect for colchicine compared to placebo/standard therapy.[8,18] The heterogeneity-adjusted required information size to demonstrate or reject a 25% relative risk reduction of the different end points is estimated with an alpha of 5%, and a beta of 20%. The trial sequential analyses were performed using the Copenhagen Trial Unit's Centre for Clinical Intervention Research software package (version 0.9.5.10 Beta).[27]

RESULTS

Overall, we identified 3108 citations, of which 184 were selected for full text review, as displayed in the flowchart in Figure 1. Finally, 13 RCTs comparing colchicine versus placebo/standard therapy in patients with acute or chronic CAD fulfilled the eligibility criteria and were considered for meta-analysis.[8,16–18,28–36] The inverted funnel plots for the main end points did not suggest any significant publication bias (Figure S1). Figure 2 encapsulates the main results.

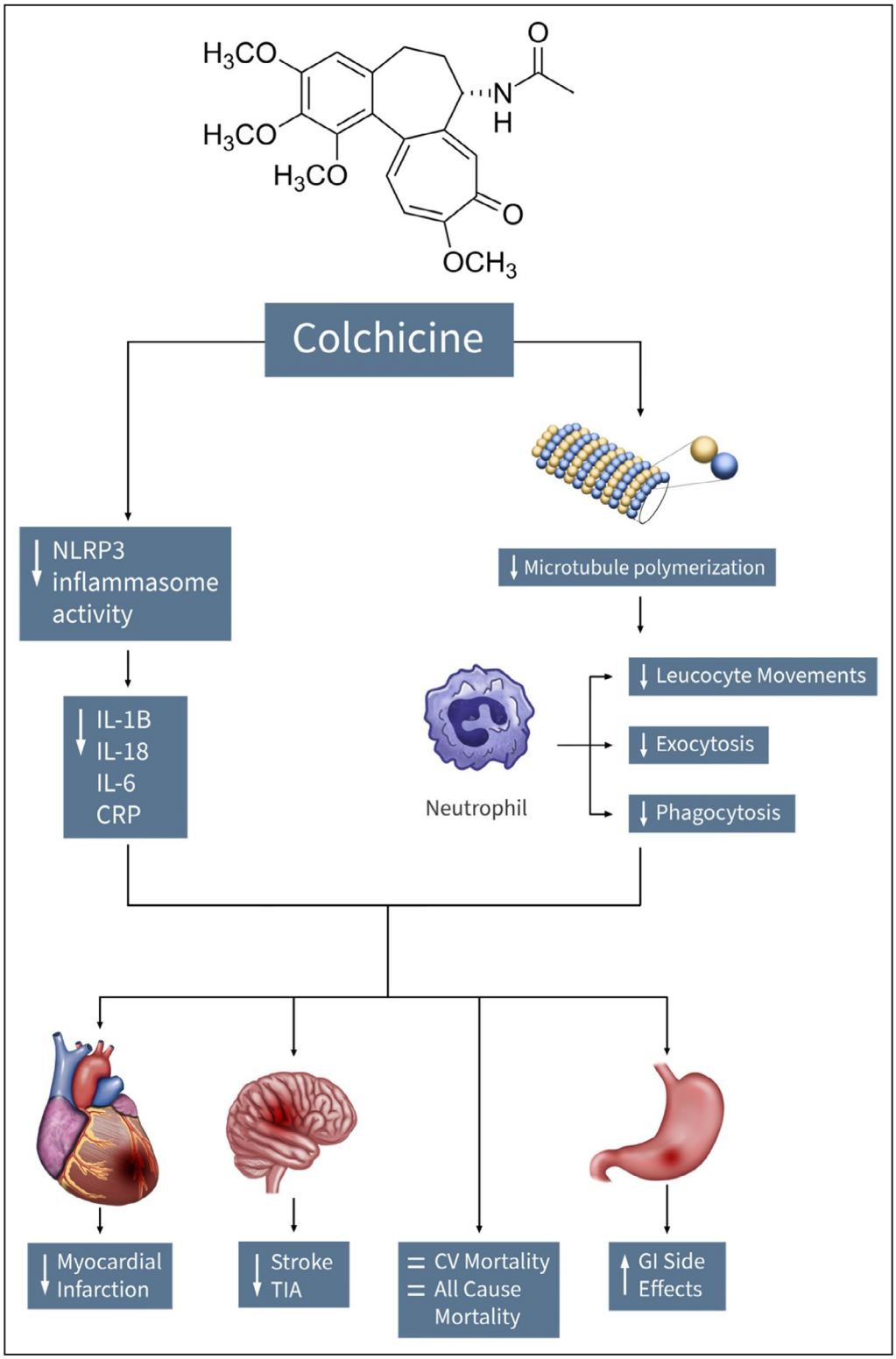

Figure 2. The biological and clinical impact of colchicine among patients with acute and chronic coronary artery disease.
CRP indicates C-reactive protein; CV, cardiovascular; GI, gastrointestinal; and IL, interleukin.

Included Studies

Characteristics of the trials included in the meta-analysis are presented in Tables 1 and 2. The 13 included studies comprised 13 125 patients. The median follow-up was 6 (interquartile range [IQR] 1; 15) months. Colchicine doses were single dose or

Table 1. Summary of the Included Study Population

Study	Study Year	Location, Sites	Randomized Patients (n)	Study Cohort	Study Design	Colchicine Dose	Comparator	Trial Outcomes	Intended Treatment Duration	FU Duration	Discontinuation Rate (%)
O'Keefe et al.[28]	1992	USA/single center	197	CCS patients undergoing PCI (POBA)	Double-blind, placebo controlled RCT (Randomization in 2:1 fashion)	0.6 mg BID	Placebo	1. All-cause mortality 2. Recurrent ischemia (assessed by MIBI thallium scan) 3. Angiographic restenosis	6 mo	5.5 mo*	10 (5.0)
COOL trial[29]	2011	Canada/single center	80	ACS patients†	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	1 mg OD	Placebo	1. hs-CRP level at 30 d 2. Platelet function 3. All-cause mortality 4. New MI 5. Stroke/TIA	30 d	31 ± 17 d	6 (7.5)
LoDoCo trial[30]	2013	Australia/single center	532	CCS patients	RCT, prospective, observer-blinded endpoint (PROBE) trial	0.5 mg OD	Standard therapy	1. *Primary outcome*: ACS, out-of hospital cardiac arrest, or (noncardioembolic) ischemic stroke 2. ACS/New MI 3. Unstable angina 4. All-cause mortality 5. Cardiovascular mortality 6. Cardiac arrest§ 7. (Noncardioembolic) stroke/TIA	24 mo	(median) 36 mo	62 (11.6)‡
Deftereos et al.[31]	2013	Greece/single center	222	Diabetic ACS and CCS patients undergoing PCI with BMS	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	0.5 mg BID	Placebo	1. In-stent restenosis 2. Parameters of lumen loss 3. All-cause mortality 4. Stroke/TIA	6 mo	6 mo	26 (12.5)
Giannopoulos et al.[32]	2015	Greece/single center	60	CCS patients undergoing elective CABG	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	0.5 mg BID	Placebo	1. Peak hs-troponin T level (within 48 h after CABG) 2. Peak CK-MB level 3. AUC of CK-MB and hs-troponin T	10 d	10 d	7 (11.8)
Deftereos et al.[33]	2015	Greece/ multicenter	151	ACS (STEMI) patients	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	2.0 mg LD – 0.5 mg BID	Placebo	1. AUC of CK-MB 2. Peak hs-troponin T level 3. Absolute MI volume assessed by CMR 4. All-cause mortality	5 d	5 d	23 (15.2)
Zarpelon et al.[34]	2016	Brazil/single center	140	CCS patients undergoing elective CABG	RCT, prospective, open-label trial	1.0 mg LD prior to CABG – 0.5 mg BID until discharge	Standard therapy	1. Postoperative atrial fibrillation 2. All-cause mortality 3. Length of hospital stay 4. Postoperative infections	Until hospital discharge	In-hospital: 14.5 ± 11.5 d	NR

(*Continued*)

Table 1. Continued

Study	Study Year	Location, Sites	Randomized Patients (n)	Study Cohort	Study Design	Colchicine Dose	Comparator	Trial Outcomes	Intended Treatment Duration	FU Duration	Discontinuation Rate (%)
COLIN trial[35]	2017	France/single center	44	ACS (STEMI) patients	RCT, prospective, open-label trial	1 mg OD	Standard therapy	1. CRP peak value during index hospitalization 2. Peak hs-troponin T level 3. Tolerance of colchicine 4. Hospitalization duration 5. Major adverse cardiac events at 1 month 6. Cardiac remodeling on echocardiography and cardiac MRI	1 month	1 month	3 (13.0)
LoDoCo-MI trial[36]	2019	Australia/single center	237	ACS (acute MI) patients	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	0.5 mg OD	Placebo	1. Residual CRP level ≥2 mg/L at 30 d 2. CRP levels 3. Therapy adherence 4. Adverse events 5. All-cause death 6. MACE (MI or stroke)	30 d	30 d	6 (2.5)
COLCOT trial[8]	2019	Multinational/ Multicenter	4745	ACS patients (within 30 d after MI)	Randomized, double blind, placebo-controlled trial (1:1 fashion)	0.5 mg OD	Placebo	1. *Primary outcome*: cardiovascular mortality, cardiac arrest, MI, stroke, or repeat hospitalization for revascularization 2. All-cause mortality 3. Cardiovascular mortality 4. Cardiac arrest[§] 5. New MI 6. Stroke 7. Revascularization 8. Hospitalization for HF 9. Atrial fibrillation 10. DVT/PE 11. Adverse events	24 mo	(median) 22.6 mo	880 (18.5)
COLCHICINE-PCI trial[16]	2020	USA/single center	400[¶]	ACS and CCS patients referred for PCI	Randomized, double blind, placebo-controlled trial (1:1 fashion)	1.8 mg prior to procedure	Placebo	1. PCI-related myocardial injury 2. All-cause mortality 3. (Nonfatal) new MI 4. Target vessel revascularization 5. PCI-related MI 6. Change in IL-6, IL-1β and CRP levels	30 d	30 d	NA

(*Continued*)

Table 1. Continued

Study	Study Year	Location, Sites	Randomized Patients (n)	Study Cohort	Study Design	Colchicine Dose	Comparator	Trial Outcomes	Intended Treatment Duration	FU Duration	Discontinuation Rate (%)
COPS trial[17]	2020	Australia/ multicenter	795	ACS patients	Randomized, double blind, placebo-controlled trial (1:1 fashion)	1 month 0.5 mg BID; then 0.5 mg OD	Placebo	1. *Primary outcome*: All-cause mortality, new ACS, ischemia-driven urgent revascularization, and noncardioembolic stroke 2. All-cause mortality 3. Cardiovascular mortality 4. New ACS/MI 5. Stroke 6. Ischemia-driven urgent revascularization 7. Hospitalization for chest pain	12 mo	400 d	94 (11.8)
LoDoCo2 trial[18]	2020	Multinational/ multicenter	5522	CCS patients	Randomized, double blind, placebo-controlled trial (1:1 fashion)	0.5 mg OD	Placebo	1. *Primary outcome*: cardiovascular mortality, new MI, ischemic stroke, or ischemia-driven revascularization 2. New MI 3. Ischemic stroke 4. Ischemia-driven revascularization 5. Cardiovascular mortality 6. All-cause mortality	(minimum) 12 mo	(median) 28.6 mo	580 (10.5)[$]

ACS indicates acute coronary syndrome; AUC, area under the curve; BID, twice a day; BMS, bare metal stent; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CK-MB, creatine kinase-myocardial brain fraction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ; FU, follow-up; LD, loading dose; MI, myocardial infarction; NA, not applicable; NR, not reported; OD, once daily; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; PROBE, prospective, randomized observer-blinded endpoint trial; RCT, randomized controlled trial; and TIA, transient ischemic attack.

Trial acronyms: COOL Trial, Colchicine Compared With Placebo to Reduce hs-CRP in Patients With Acute Coronary Syndromes or Strokes – Targeting Inflammation in Atherosclerosis Study; LoDoCo Trial, Low-Dose Colchicine Trial; COLIN Trial, Interest of COLchicine in the Treatment of Patients With Acute Myocardial INfarction and With Inflammatory Response; COLCOT Trial, Colchicine Cardiovascular Outcomes Trial; COPS Trial, Colchicine in Patients With Acute Coronary Syndrome.

*This represents the mean duration to follow-up coronary angiogram.

†The COOL trial expanded their eligibility criteria over the course of the trial and started also enrolling patients with acute ischemic stroke due to slower than expected recruitment rates. Overall, the trial included 73/80 patients with acute coronary syndrome and 7/80, who had a recent stroke.

‡32 and 30 patients ceased colchicine treatment early (within 4 weeks) and late (mean follow-up period of 2.36 years), respectively.

§This included out-of-hospital resuscitated cardiac arrest.

¶The COLCHICINE-PCI trial actually randomized 714 patients, whereas only those 400 patients who underwent PCI had complete follow-up and thus outcome assessment.

$During the open-label run-in period involving 6528 patients, 437 (6.7%) stopped colchicine for gastrointestinal upset.

Table 2. Baseline Characteristics of the Patients With Acute and Chronic Coronary Artery Disease Among the Included Studies

Study	Patients, n (% Male)	Mean Age (Years)	Previous MI, n (%)	Previous PCI, n (%)	Previous CABG, n (%)	History of Stroke/ TIA, n (%)	Hypertension,n (%)	Diabetes mellitus, n (%)	History of Smoking, n (%)
O'Keefe et al.[28]	197 (85.8)	60.5	NR	NR	51 (25.9)	NR	NR	24 (12.2)	NR
COOL trial[29]	40 (88.7)	57.2	14 (17.5)	NR	NR	3 (3.7)	34 (42.5)	13 (16.2)	63 (78.7)
LoDoCo trial[30]	532 (88.9)	66	64 (23.4)	307 (57.7)	101 (18.9)	NR	NR	161 (30.2)	24 (4.5)
Deftereos et al.[31]	196 (65)	63.7	28 (28)	NR	NR	NR	95 (49)	196 (100)	74 (38)
Giannopoulos et al.[32]	59 (69.4)	65.2	11 (18.6)	13 (22.0)	NR	NR	48 (81.3)	25 (42.3)	29 (49.1)
Deftereos et al.[33]	151 (68.8)	58.0	NR	NR	NR	NR	60 (39.7)	22 (21.2)	79 (52.3)
Zarpelon et al.[34]	140 (67.8)	60.9	31 (22.1)	20 (14.2)	NR	NR	124 (88.6)	72 (51.4)	57 (40.7)
COLIN trial[35]	44 (79.5)	59.9	NR	2 (4.5)	1 (2.3)	NR	19 (43.1)	6 (13.6)	31 (70.4)
LoDoCo-MI trial[36]	237 (77)	61	36 (15)	NR	NR	NR	112 (47)	52 (22)	143 (60)
COLCOT trial[8]	4745 (80.8)	60.6	767 (16.2)	798 (16.8)	150 (3.2)	122 (2.6)	2421 (51.0)	959 (20.2)	1416 (29.8)
COLCHICINE PCI trial[16]	400 (93.5)	66.3	103 (25.7)	150 (37.5)	NR	36 (9)	367 (91.7)	231 (57.7)	282 (70.5)
COPS trial[17]	795 (79.0)	59.8	118 (14.8)	101 (12.7)	34 (4.2)	16 (2.0)	400 (50.3)	151 (18.9)	277 (34.8)
LoDoCo2 trial[18]	5522 (84.7)	66.0	4658 (84.3)	4177 (75.6)	710 (12.8)	NR	2808 (50.8)	1007 (18.2)	648 (11.7)

CABG indicates coronary artery bypass grafting; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.
*Deftereos et al. reported baseline demographics only from those 196 patients, who completed follow-up after 6 mo. However, they had actually randomized 222 patients.

<1 mg per day in 6 trials,[8,16,18,30,34,36] and most of the other studies used ≥1 mg per day.[17,28,29,31–33,35] Of note, 12.3% of all patients enrolled in the colchicine group discontinued the treatment early. A summary of the quality of the RCTs can be found in Table S1. Ten RCTs were of high quality incorporating a double-blind placebo-controlled design, but 3 studies had some qualitative drawbacks, eg, open label designs.[30,34,35]

Effects of Colchicine on All-Cause, Cardiovascular Mortality, and Noncardiovascular Mortality

All-cause mortality was reported in all 13 trials (n=13 098).[8,16–18,28–36] Colchicine compared with placebo/standard therapy did not reduce the risk of death from any cause (OR, 0.96; 95% CI, 0.65–1.41; *P*=0.83; I^2 24%), as shown in Figure 3A. Cardiovascular mortality was reported

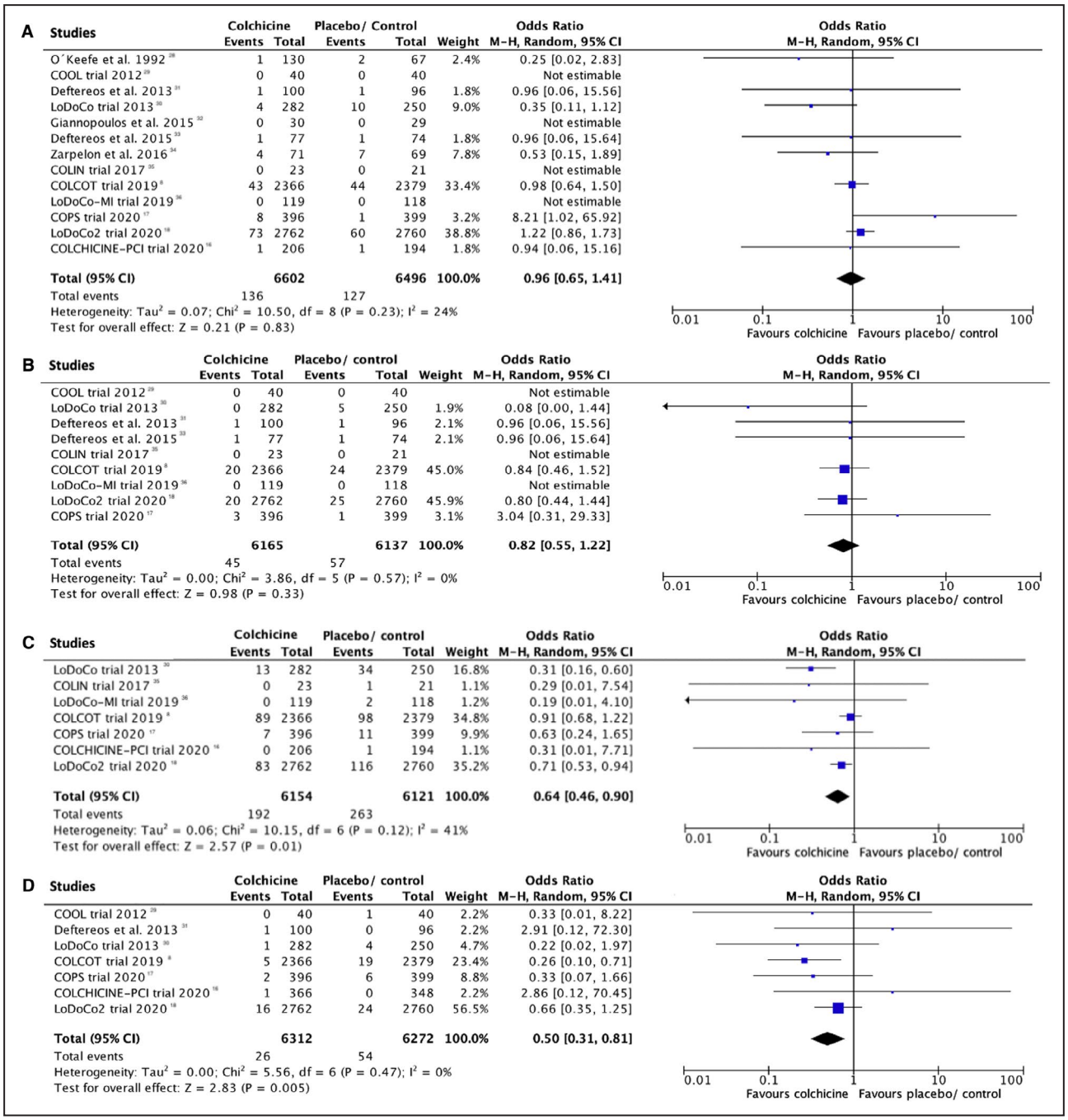

Figure 3. (A) All-cause mortality, (B) cardiovascular mortality, (C) new myocardial infarction, and (D) stroke/transient ischemic attack with colchicine compared to placebo/standard therapy.

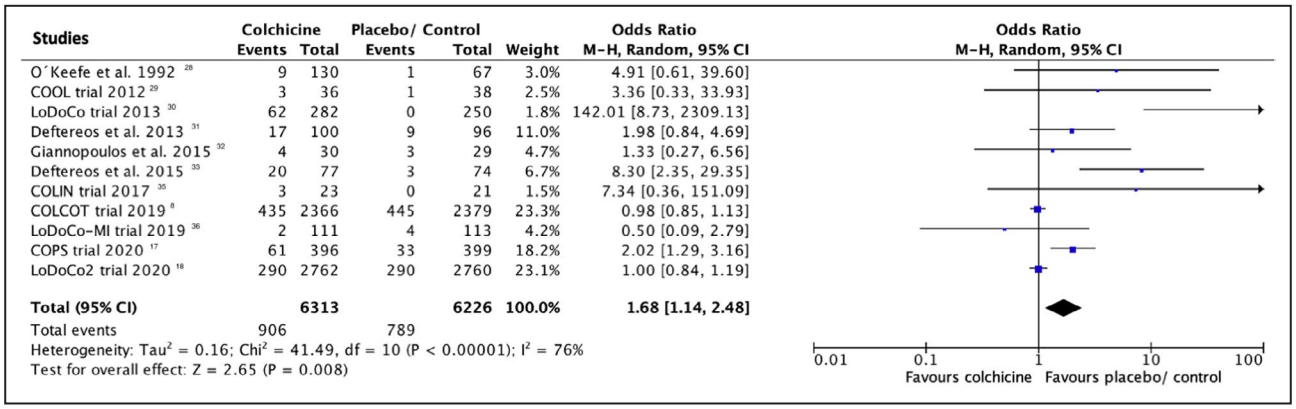

Figure 4. Rate of therapy discontinuation/withdrawal with colchicine compared to placebo/standard therapy.
95% CI indicates 95% confidence interval.

in 9 studies (n=12 302).[8,17,18,29–31,33,35,36] This outcome was also not affected by colchicine compared to placebo or standard therapy (OR, 0.82; 95% CI, 0.55–1.22; *P*=0.45; I^2 0%), as displayed in Figure 3B. Additionally, 4 studies reported noncardiovascular mortality.[8,17,18,30] Colchicine compared with placebo or standard therapy led to a numerically higher number of noncardiovascular deaths (85 [1.4%] versus 60 [1.0%] cases [OR, 1.35; 95% CI, 0.90–2.02; *P*=0.15; I^2 16%]), see Figure S2.

There were no differences across the performed subgroup analyses for all-cause and cardiovascular mortality, including comparisons of lower- versus higher-dose colchicine regimens, short- versus long-term colchicine administration and colchicine compared with placebo/standard therapy in acute versus chronic CAD (Figure S3 and S4).

Effects of Colchicine on MI, Stroke/TIA, and Ischemia Driven Revascularization Rate

New or recurrent MI was reported in 7 trials (n=12 275).[8,16–18,30,35,36] Compared with placebo/standard medical therapy, colchicine reduced the rate of MI, but there was moderate heterogeneity across the included studies (OR, 0.64; 95% CI, 0.46–0.90; *P*=0.01; I^2 41%) (Figure 3C).

Stroke/TIA incidence with colchicine in comparison to placebo/standard therapy was evaluated in 7 studies.[8,16–18,29–31] In these trials, colchicine treatment led to a reduction of stroke/TIA rate (OR, 0.50; 95% CI, 0.31–0.81; *P*=0.005; I^2 0%) (Figure 3D).

Again, we found no significant interaction among the conducted sub-group analyses assessing those 2 outcomes in patients receiving colchicine compared with placebo/standard therapy in acute versus chronic CAD, for ≤30 days versus >30 days, and at a lower- versus higher-dose regimen (Figure S5 and S6).

Five studies also reported information about repeat revascularization procedures/ischemia driven revascularization (n=11 684).[8,16–18,31] Administration of colchicine compared with placebo led to a lower risk of ischemia driven revascularization (OR, 0.61; 95% CI, 0.42–0.88; *P*=0.008; I^2 37%) (Figure S7).

Therapy Adherence and Adverse Effects With Colchicine

All of the included studies reported adverse effects.[8,16–18,28–36] The rate of treatment discontinuation was higher among patients taking colchicine compared with placebo/standard therapy (14.3% versus 12.6%; OR, 1.68; 95% CI, 1.14–2.48; *P*<0.00001; I^2 76%), see Figure 4. The most commonly reported side effects during treatment with colchicine compared with placebo/standard therapy comprised gastrointestinal complaints, namely nausea and diarrhea (OR 2.21; 95% CI, 1.45–3.36; *P*=0.0002; I^2 78%) (Figure 5). Three studies provided data regarding relevant infections (eg, pneumonia), but a difference between the 2 treatment regimens could not be shown (OR 1.42; 95% CI, 0.81–2.47; *P*=0.22; I^2 77) as displayed in (Figure S8).[8,18,34] Noteworthy, other side effects, which have been reported across the analyzed studies, included myalgia, myositis, peripheral neuritis, transaminitis, neutropenia, thrombopenia, rash, alopecia, and itching.[8,17,29–31,33,35,36]

Outcomes in Small Versus Large Trials

The dedicated sensitivity analyses comparing the main outcomes among the smaller compared to the largest 3 trials are presented in Figure S3. In fact, 3 trials comprised 11 062 patients (84.4% of the analyzed population).[8,17,18] Regarding all-cause mortality, this end point was lower in patients treated with colchicine compared with placebo/standard therapy among the smaller compared with the largest trials. Also, we found differences in the smaller versus the large 3 trials in terms of drug discontinuation and gastrointestinalside effects rates.

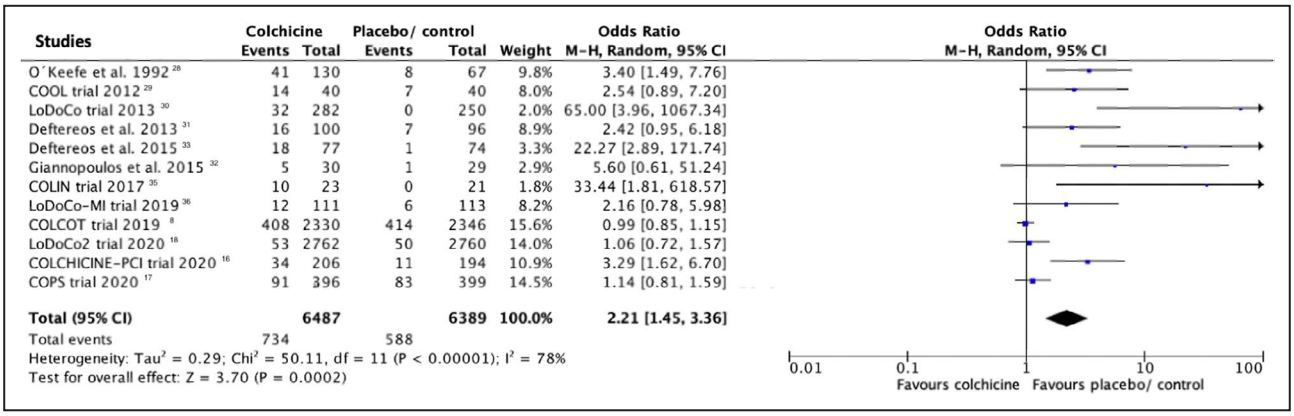

Figure 5. Gastrointestinal side effects with colchicine compared with placebo/standard therapy.

Trial Sequential Analyses

We performed trial sequential analyses focusing on the following outcomes: all-cause mortality, cardiovascular death, MI, and stroke/TIA, as displayed in Figure 6.

The cumulative z-curve for all-cause and cardiovascular death failed to cross the trial sequential monitoring boundaries indicating a lack of firm evidence for a 25% reduction in all-cause and cardiovascular death

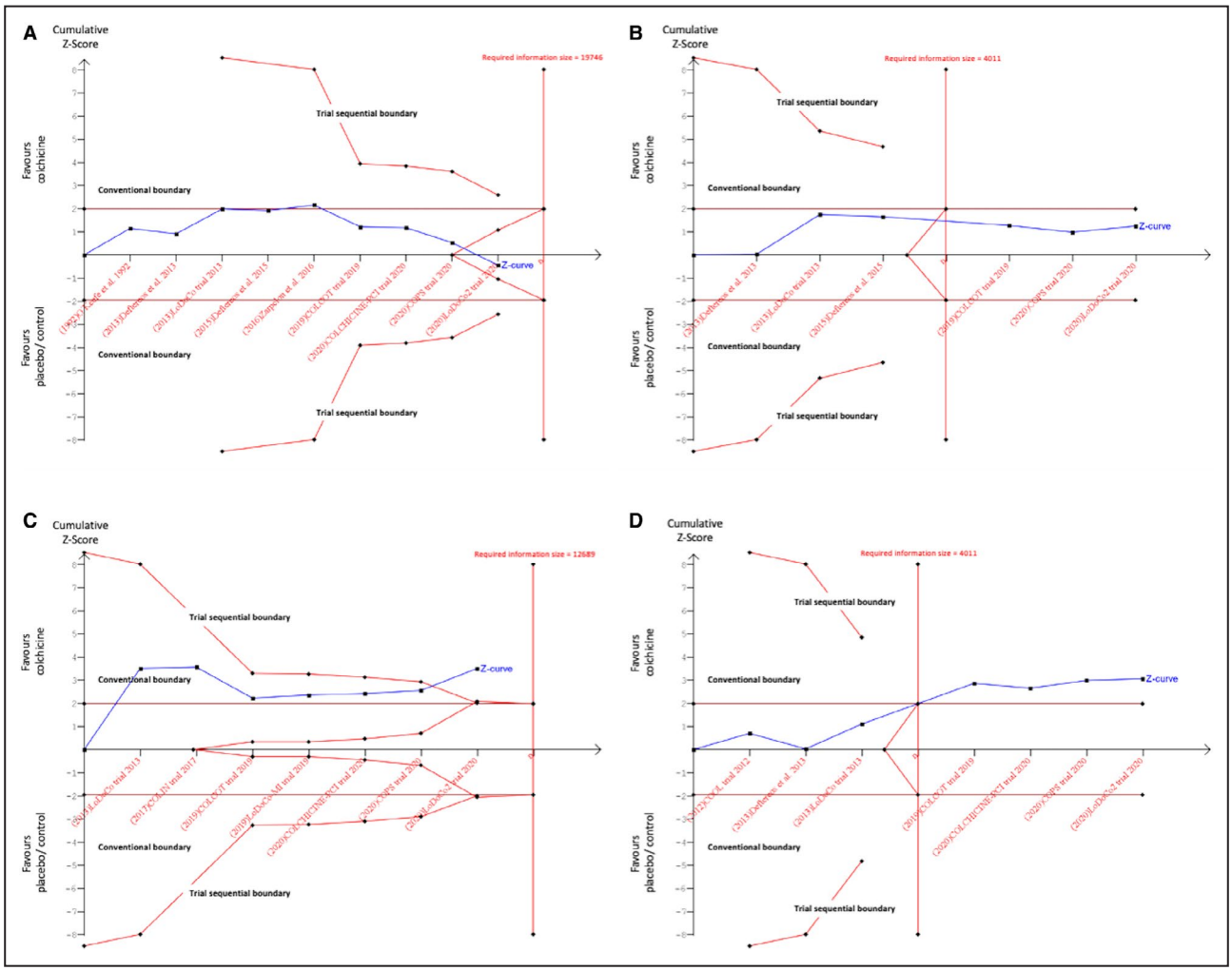

Figure 6. Trial sequential analyses (TSA) of studies assessing impact colchicine vs placebo/standard therapy on (A) all-cause mortality, (B) cardiovascular mortality, (C) new myocardial infarction, and (D) stroke/transient ischemic attack (TIA).

with colchicine compared with placebo/standard therapy (Figure 6A and 6B). Interestingly, the cumulative z-curve for the outcome new MI crossed the conventional boundary and the trial sequential boundary suggesting possible evidence for a 25% risk reduction with colchicine compared to placebo/standard therapy (Figure 6C). However, the cumulative z-curve for stroke/TIA with colchicine compared with placebo/standard therapy crossed only the conventional boundary, but not the trial sequential monitoring boundary, which does implicate the lack of firm evidence with respect to this end point (Figures 6D).

DISCUSSION

Currently, the role of colchicine in patients with acute and chronic CAD is unclear in the absence of strong evidence to guide clinical decision making. Colchicine which modulates both local inflammatory cells as well expression of cytokines (e.g. IL-1β release) by leukocytes and thus also systemic inflammation could therefore reasonably be expected to improve secondary cardiovascular prevention outcomes. From a theoretical perspective, colchicine therapy to counter vascular disease makes sense. By performing a comprehensive systematic review and meta-analysis of all 13 relevant RCTs currently accessible, including 13 125 patients, we have strived to clarify the evidence in this area, which in turn could help to guide the use of this anti-inflammatory drug among patients with established CAD.

This systematic review and meta-analysis provides some important insights about the utility of colchicine in patients with CAD, which are highlighted in Figure 2. Our analysis revealed that patients with CAD treated with colchicine seem to have lower rates of ischemic events, particularly MI and stroke/TIA, compared with patients treated with placebo or standard medical therapy. Additionally, there was lower risk for repeat revascularization procedures. However, irrespective of dose and therapy duration, treatment with colchicine did not show any relevant association with all-cause or cardiovascular mortality. Nevertheless, our data also indicated a numerical increase in noncardiovascular death cases in patients treated with colchicine compared to placebo or standard therapy.

With respect to relevant side effects, there has been some concerns regarding higher infection, specifically pneumonia, rates under colchicine treatment. However, our pooled data demonstrated no differences and may weaken this safety concern.[8] Furthermore, the number of patients suffering from gastrointestinal-related side effects, mostly diarrhea, was higher among colchicine treated patients, possibly related to disrupted intestinal barrier function and higher intestinal permeability.[37] This may also reflect one of the main reasons for colchicine treatment interruption.

Although colchicine has been clinically used for many decades, the safety and tolerability of this drug continue to raise some concerns. Our data seem to underscore a high rate of gastrointestinal upset and therapy discontinuation (>10%) with colchicine, albeit some variability has been observed across the pooled trials. Indeed, one needs to take into account that this drug has a narrow therapeutic window and some considerable toxic side effects if overdosed or not appropriately monitored. Besides gastrointestinal, hematological and neuromuscular side effects as well as drug interactions, experimental studies and case reports also suggested the possibility of colchicine related cardiotoxicity mediated by increased ventricular excitability and changes in autonomic nervous activity, potentially contributing to a higher risk for sudden cardiac death.[38–41]

In this context, the safety among patients with CAD has also been debated. In fact, the recent LoDoCo2 trial reported a reduction in the risk of cardiovascular events, but a numerically higher number of noncardiovascular deaths among patients treated with colchicine compared with placebo (hazard ratio [HR, 95%CI] 1.51 [0.99–2.31]).[18] In the Australian COPS trial, the number of noncardiovascular deaths was also higher (HR [95%CI] 8.20 [1.03–65.61]).[17] When pooling the data from the major trials reporting noncardiovascular death, we found a trend towards higher noncardiovascular death rates in the colchicine groups. Hence, it requires more data to establish whether immunomodulating therapy using colchicine in CAD is related to higher mortality by other mechanisms independent, but additive to infections.[17]

By highlighting a reduced rate of ischemia driven revascularization, MI and stroke/TIA among patients with CAD taking colchicine compared with placebo, our analyses expand the signals, derived from the 4major trials in this field.[8,17,18,30] Of note, experimental studies highlight colchicine´s anti-inflammatory effects, via NLRP3 inflammasome inactivation, may enhance endothelial function and thus promote atheroprotection and mitigate the risk for cardiovascular events.[6,42]

Although our results indicate a reduction in ischemic events with colchicine in patients with acute and chronic CAD, more data are warranted. First, it needs to be seen if the observed reduction in ischemic events also translates into a mortality reduction in the long term. According to the currently available data, it may not. Second, more studies are necessary in order to identify and target those patients, who will benefit most from this anti-inflammatory drug. Thus far, one might carefully weigh the benefits and possible side effects of colchicine before prescribing it to patients with CAD. This should certainly comprise detailed patient

information and possibly a drug run-in phase, as for instance performed in the LoDoCo2 trial.[18]

Whereas secondary prevention in CAD represents a long-term commitment, the optimal duration of the colchicine therapy in patients with CAD will reflect an important subject of future studies and guideline discussions. Our analyses might indicate a signal towards a need for a treatment duration with colchicine of >30 days, which could be plausible from a mechanistic standpoint since the anti-inflammatory effects of colchicine are not only mediated by direct interaction with microtubules and regulation in cytokine secretion, but also modifications on the transcriptional level, which may necessitate a longer therapy duration to establish their full effect.[43]

By including a trial sequential analysis, we aimed to further establish the current evidence for colchicine in patients with CAD. As such, we found that the evidence deriving from the current data indicates that colchicine in patients with CAD lowers the risk for MI. But when considering other vigorous end points, such as all-cause death, cardiovascular death as well as stroke, we found that the accrued evidence may not be sufficient to draw firm inferences about colchicine's role in secondary prevention of patients with CAD yet. To ultimately define the role of colchicine in patients with acute and chronic CAD, there is a demand for further adequately powered trials focusing on hard end points and providing long-term follow-up data beyond 2 to 3 years.[44] The ongoing CLEAR-SYNERGY trial (ClinicalTrials.gov identifier: NCT03048825), which plans to enroll 7000 patients with MI and follow up for up to 5 years, will hopefully clarify many of those issues in due course.[45]

Following the publication of the latest major trials (eg, COLCOT and LoDoCo2), researchers now also showed a growing interest in colchicine and its anti-inflammatory capabilities in the limelight of the global COVID-19 pandemic.[46] Since coronavirus SARS-CoV2 infections are commonly associated with unbalanced systemic inflammatory reactions, mediated by eg, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF- α), colchicine may have the potential to mitigate this systemic reaction and thus improve outcomes of patients with COVID-19.[46,47] In fact, the recent GREECO-19 and COLCORONA trials demonstrated some potential clinical benefits.[48,49] But both trials had limitations and there is still a need for more data in this context.

Limitations

These results need to be interpreted in the context of some limitations. Primarily, among the analyzed studies, different dosing regimens of colchicine had been studied among various CAD cohorts (eg, MI versus chronic coronary disease patients), which might limit the interpretation and generalizability of the results somewhat. Secondly, the considered studies in this meta-analysis applied slightly different MI and stroke definitions. Thirdly, some of the studies had been conducted in earlier eras, where revascularization using contemporary drug eluting stents and medical therapy, including for example potent statins and antiplatelets, were not standard of care, which might have also impacted those studies' outcomes. We also observed considerable heterogeneity among the included trials of some comparisons (eg, risk of MI with colchicine compared to placebo/standard therapy), which needs to be taken in account. Additionally, 3 open label studies had been included in the analyses. Those studies are by their nature more susceptible to bias than placebo controlled RCTs and may have consequently influenced the overall results. Finally, one needs to be aware that the COLCOT, COPS, and LoDoCo2 trials, not only contributed more than 80% of all patients with CAD included in this meta-analysis, but more importantly, the majority of events, which in turn somewhat hampers the validity of some of our analyses.[8,17,18]

CONCLUSIONS

In patients with acute and chronic CAD, adding colchicine to standard therapy seems to reduce the risk for ischemic events, namely MI and stroke/TIA. In addition, it reduces the risk for repeat revascularization procedures. Overall, colchicine therapy may have an increased risk for gastrointestinal side effects and therapy withdrawal. Whilst we did not find any signal for major infectious complications or mortality associated with colchicine therapy, the reduced risk of potentially debilitating secondary coronary vascular or cerebrovascular events will need to be balanced against the known side effect profile of colchicine, confirmed in our meta-analysis on a case-by-case basis. However, our analyses also underscore the need for more prospective studies assessing the role, dosing and optimal duration of colchicine therapy among patients with CAD.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S3
Figures S1–S10

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Supplemental Material

Data S1.

Supplemental Methods

The applied search terms

Search terms applied with MEDLINE/PUBMED:

The used search terms: “colchicine“, “colgout”, “colcemid“, “beta-lumicolchicine” “colchiquim”, “colchisol”, “colchicum”, “colchicin”, ”colchicinum”, “colchizin” AND (All-cause mortality OR Cardiovascular mortality OR Myocardial infarction fatal and non-fatal OR adverse events OR Acute Coronary Syndrom OR coronary artery disease OR CAD OR Stroke fatal and non-fatal OR cardiovascular revascularization OR Non-scheduled cardiovascular interventions OR Non-scheduled hospitalizations OR cardiovascular disease OR STEMI OR NSTEMI or percutaneous coronary intervention OR cardiac arrest.

Table S1. Risk of bias assessment.

Study	Year	Follow-up duration	Random sequence generation	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Intention to treat analysis	<5% patients with missing outcome data
O´Keefe et al.[28]	1992	6 months	L	L	L	L	L	L	Yes	Yes
COOL trial[29]	2011	30 days	L	L	L	L	L	L	Yes	No
LoDoCo trial[30]	2013	36 months	L	H	H	L	L	L	Yes	Yes
Deftereos et al.[31]	2013	6 months	L	L	L	L	L	L	Yes	No
Giannopoulos et al.[32]	2015	10 days	L	L	L	L	L	L	Yes	Yes
Deftereos et al.[33]	2015	5 days	L	L	L	L	L	L	Yes	Yes
Zarpelon et al.[34]	2016	14 days	L	H	H	H	L	L	Unclear	Yes
COLIN trial[35]	2016	1 month	L	H	H	H	L	L	Yes	Yes
LoDoCo-MI trial[36]	2019	30 days	L	L	L	L	L	L	Yes	Yes
COLCOT trial[8]	2019	22.6 months	L	L	L	L	L	L	Yes	Yes
COLCHICINE-PCI trial[16]	2020	30 days	L	L	L	L	L	L	Yes	Yes
COPS trial[17]	2020	400 days	L	L	L	L	L	L	Yes	Yes
LoDoCo2 trial[18]	2020	(median) 28.6 months	L	L	L	L	L	L	Yes	Yes

H = high risk; L = low risk; U = unclear risk.

Table S2. Assessment of the studies´ quality according to the *GRADE* (Grading of Recommendations, Assessment, Development and Evaluations) tool

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	placebo / control	Relative (95% CI)	Absolute (95% CI)		
All cause mortality in CAD patients												
13	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	136/6602 (2.1%)	127/6496 (2.0%)	**OR 0.96** (0.65 to 1.41)	**1 fewer per 1,000** (from 7 fewer to 8 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cardiovascular (CV) mortality in CAD patients												
9	randomized trials	not serious	not serious	not serious	not serious	none	45/6165 (0.7%)	57/6137 (0.9%)	**OR 0.82** (0.55 to 1.22)	**2 fewer per 1,000** (from 4 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke or TIA												
7	randomized trials	not serious	serious [c]	not serious	serious [b]	none	26/6312 (0.4%)	54/6272 (0.9%)	**OR 0.50** (0.31 to 0.81)	**4 fewer per 1,000** (from 6 fewer to 2 fewer)	⊕⊕◯◯ LOW	CRITICAL
New myocardial infarction (MI)												
7	randomized trials	not serious	serious [d]	not serious	serious [b,e]	none	192/6154 (3.1%)	263/6121 (4.3%)	**OR 0.64** (0.46 to 0.90)	**15 fewer per 1,000** (from 23 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL
Ischemia-driven revascularization												
5	randomized trials	not serious	serious [f]	not serious	not serious [e]	none	167/5842 (2.9%)	244/5842 (4.2%)	**OR 0.61** (0.42 to 0.88)	**16 fewer per 1,000** (from 24 fewer to 5 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Gastrointestinal side effects												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	placebo / control	Relative (95% CI)	Absolute (95% CI)		
12	randomized trials	not serious	not serious	not serious	serious [b,e]	none	734/6487 (11.3%)	588/6389 (9.2%)	**OR 2.21** (1.45 to 3.36)	**91 more per 1,000** (from 36 more to 162 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Infectious complications												
3	randomized trials	not serious	serious [g]	not serious	serious [e]	none	207/5163 (4.0%)	188/5175 (3.6%)	**OR 1.42** (0.81 to 2.47)	**14 more per 1,000** (from 7 fewer to 49 more)	⨁⨁◯◯ LOW	IMPORTANT
Therapy discontinuation / withdrawal rate												
11	randomized trials	not serious	not serious	not serious	serious [b,e]	none	906/6313 (14.4%)	789/6226 (12.7%)	**OR 1.68** (1.14 to 2.48)	**69 more per 1,000** (from 15 more to 138 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Non-cardiovascular mortality												
4	randomized trials	not serious	serious [g]	not serious	not serious	none	85/5806 (1.5%)	60/5788 (1.0%)	**OR 1.35** (0.90 to 2.02)	**4 more per 1,000** (from 1 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL

95%CI = 95% Confidence interval; CAD = Coronary artery disease; OR: Odds ratio; TIA = Transient ischemic attack.

* *Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.)*

Explanations:

a. 3 out of 13 randomized studies had an open-label design, which is prone to some bias.
b. Wide confidence intervals (CI), which were observed among some of the included studies, may lower the quality of evidence.
c. Definition of transient ischemic attack (TIA) or stroke varied across the included studies.
d. Definition of myocardial infarction (MI) differed among the included studies.
e. There was a considerable heterogeneity (I2 >25%) among the included studies.
f. Definition of ischemia driven revascularization (IDR) varied among the included studies.
g. This adverse outcome has not been systematically reported by all trials.

Table S3. Applied definitions of myocardial infarction and stroke per the individual studies.

Study	Year	Myocardial infarction*	Stroke
O´Keefe et al.[28]	1992	• Not further specified	• Not further specified
COOL trial[29]	2011	• **ACS definition** (at least 2 of the following 3 criteria were required): o ischemic chest pain occurring at rest or increasing in frequency and lasting >10 min o ECG changes of ischemia with ST elevation, ST depression or new left bundle branch block o Elevated cardiac biomarkers.	• New focal neurological deficit of vascular origin lasting >24 h. CT scan or MRI imaging results were reviewed for all patients with stroke.
LoDoCo trial[30]	2013	• **MI definition** as per *First Universal definition of Myocardial Infarction*† • *Unstable angina* as evidenced by a recent acceleration of angina unassociated with a rise in serum troponin but angiographic evidence of change in coronary anatomy (as per Braunwald classification types IB and IIB)	• Computed tomography or magnetic resonance imaging proven ischemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial hemorrhage.
Deftereos et al.[31]	2013	• Not further specified	• Not further specified
Giannopoulos et al.[32]	2015	• Not further specified	• Not further specified
Deftereos et al.[33]	2015	• Not further specified	• Not further specified
Zarpelon et al.[34]	2016	• Not further specified	• Not further specified
COLIN trial[35]	2016	• **MI definition** as per *European Society of Cardiology (ESC) Guidelines* for the Management of Acute Myocardial Infarction in patients presenting with ST-segment elevation 2012 (Eur Heart J 2012; 33:2569-619)	• Not further specified

LoDoCo-MI trial[36]	2019	• **MI definition** as *per 3rd Universal Definition of Myocardial Infarction*‡	• Not further specified
COLCOT trial[8]	2019	• **MI** defined according to national guidelines (the exact guidelines had not been defined in the protocol)	• Stroke or TIA (exact definitions were not further specified)
COLCHICINE-PCI trial[16]	2020	• **MI definition** as per *3rd Universal Definition of Myocardial Infarction*‡	• Ischemic stroke, not further specified.

COPS trial[17]	2020	• **ACS definition**:
		  ○ Elevated cardiac troponin
		  ○ ECG changes
		  ○ *STEMI* and *NSTEMI* are defined as ischaemic symptoms, positive troponin and ECG changes.
		• *Unstable angina* is defined as history consistent with coronary ischaemia with objective evidence of ischaemia (i.e. ECG change) and negative troponin.
			• **Non-cardioembolic ischaemic stroke**: CT or MRI-proven ischaemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial haemorrhage.

LoDoCo2 trial[18]	2020	• **MI definition** as per *3rd Universal definition of Myocardial Infarction*‡ • *Unstable angina* as evidenced by a recent acceleration of angina unassociated with a rise in serum troponin but angiographic evidence of change in coronary anatomy (as per Braunwald classification types IB and IIB)	• **Non-cardioembolic ischaemic stroke**: as evidenced by CT or MRI and coded as such by the treating neurologist occurring in the absence of atrial fibrillation, cerebral hemorrhage, lacunae infarction or small vessel disease.

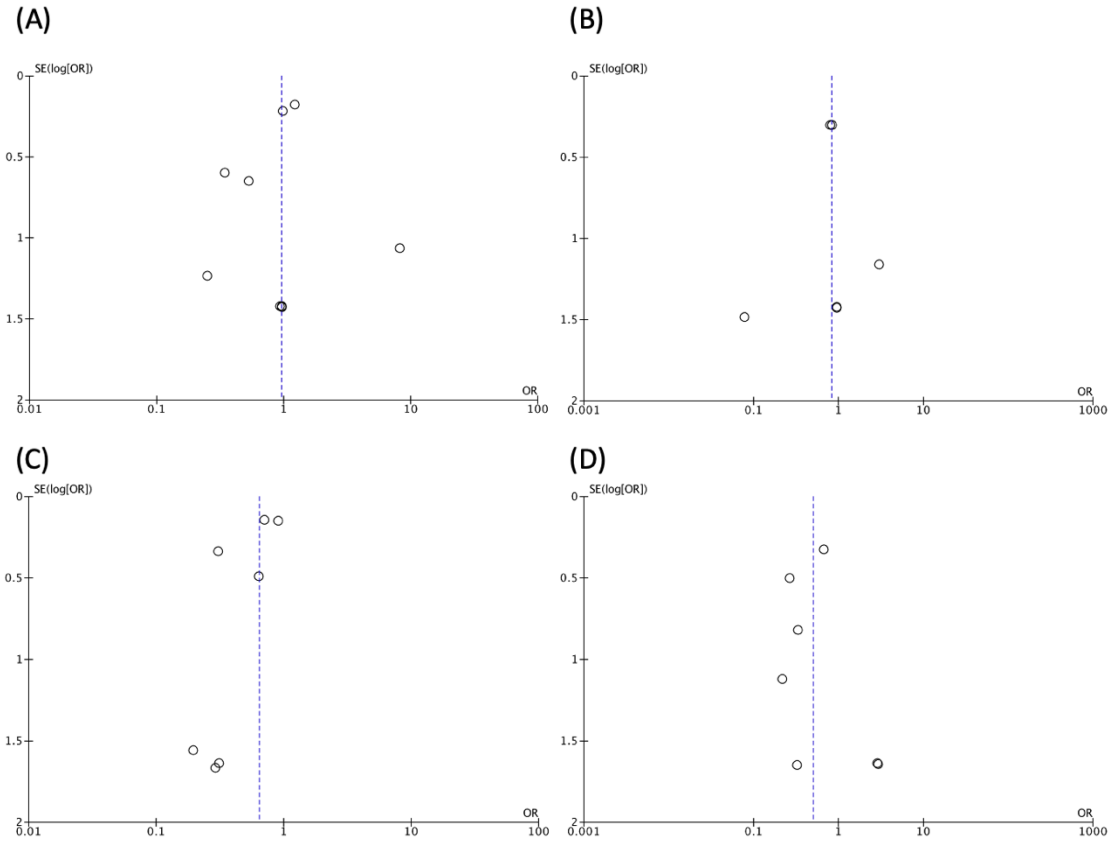
ACS = Acute coronary syndrome; CT = Computed tomography; MRI = magnetic resonance imaging; NSTEMI = Non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIA = Transient ischemic attack.

* Of note, some studies only reported their acute coronary syndrome (ACS) definition (e.g. Raju et al.)

† Thygesen K., Alpert J.S., White H.D. and Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: "Universal definition of myocardial infarction". J Am Coll Cardiol 2007; **50**: 2173.

‡ Thygesen K., Alpert J.S., Jaffe A.S. and Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: "Third universal definition of myocardial infarction". Circulation 2012; **126**: 2020-2035

Figure S1. Funnel plot of logarithmized odds ratio for assessment of publication bias among the included studies for the following outcomes: (A) all-cause mortality; (B) cardiovascular mortality (CV); (C) new myocardial infarction; and (D) stroke / TIA

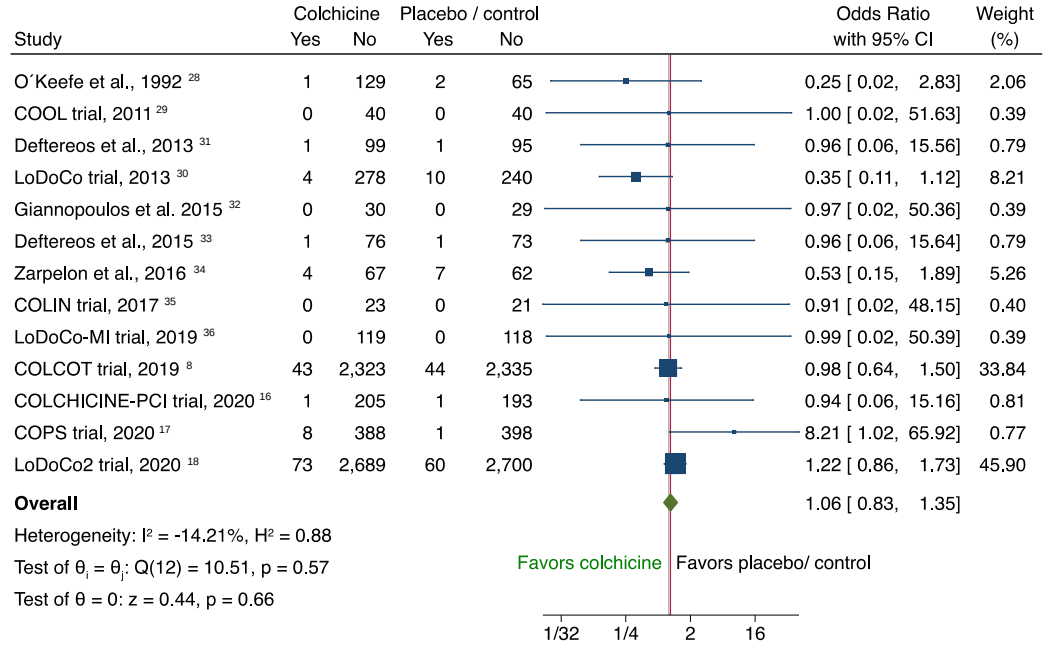


OR = Odds ratio; SE = Standard error.

Figure S2. Colchicine in patients with coronary artery disease (CAD) – Sensitivity analyzes using Mantel-Haenszel (M-H) fixed effect models

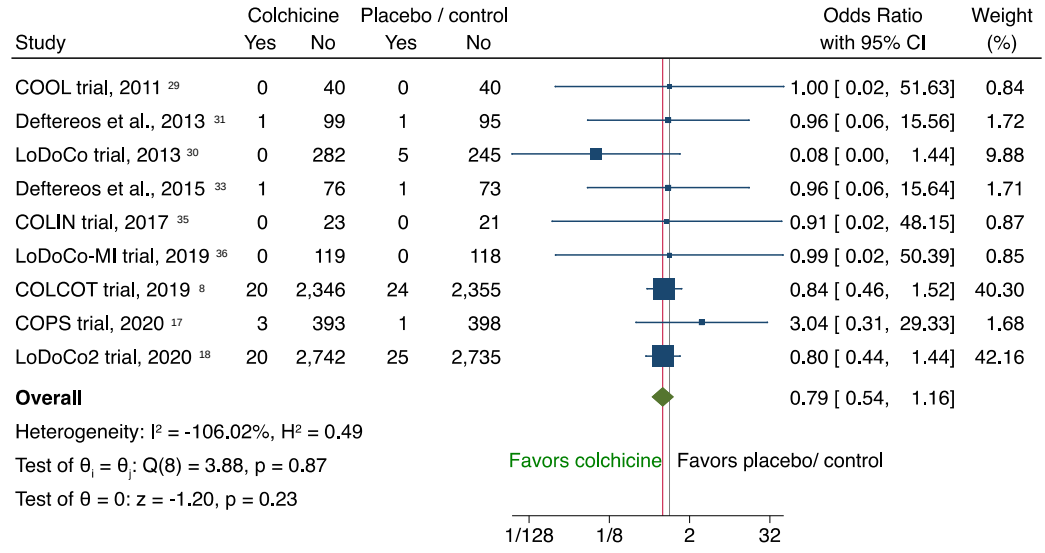
Main outcomes with colchicine compared to placebo / standard therapy in patients with CAD:

(A) All-cause mortality



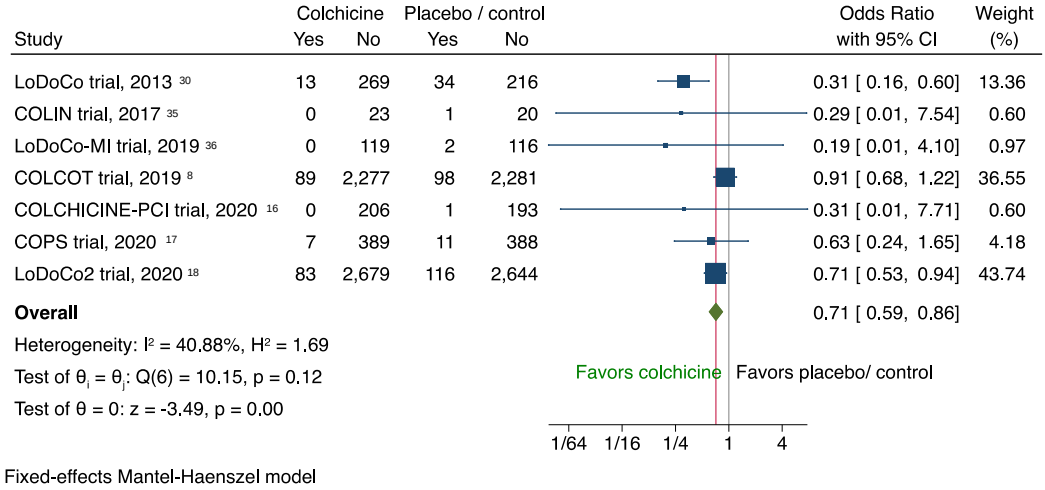
Fixed-effects Mantel-Haenszel model

(B) Cardiovascular (CV) mortality



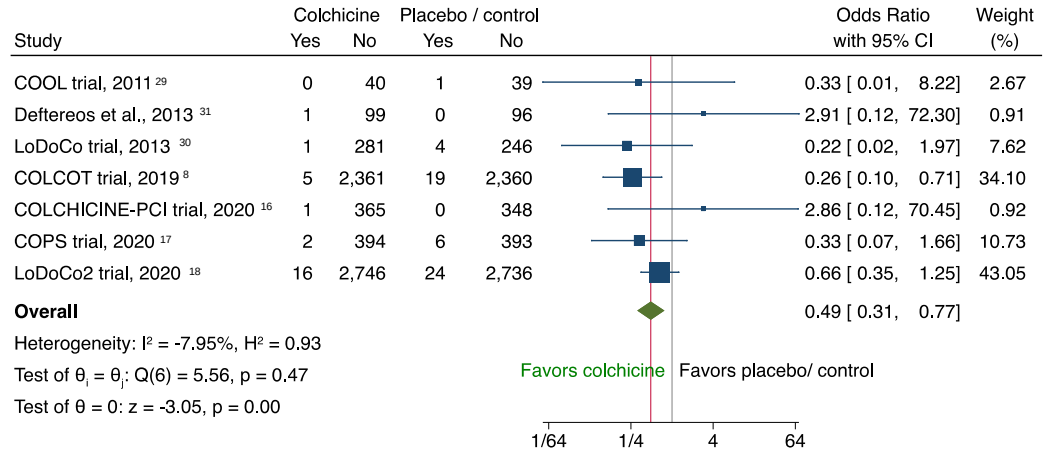
Fixed-effects Mantel-Haenszel model

(C) New myocardial infarction



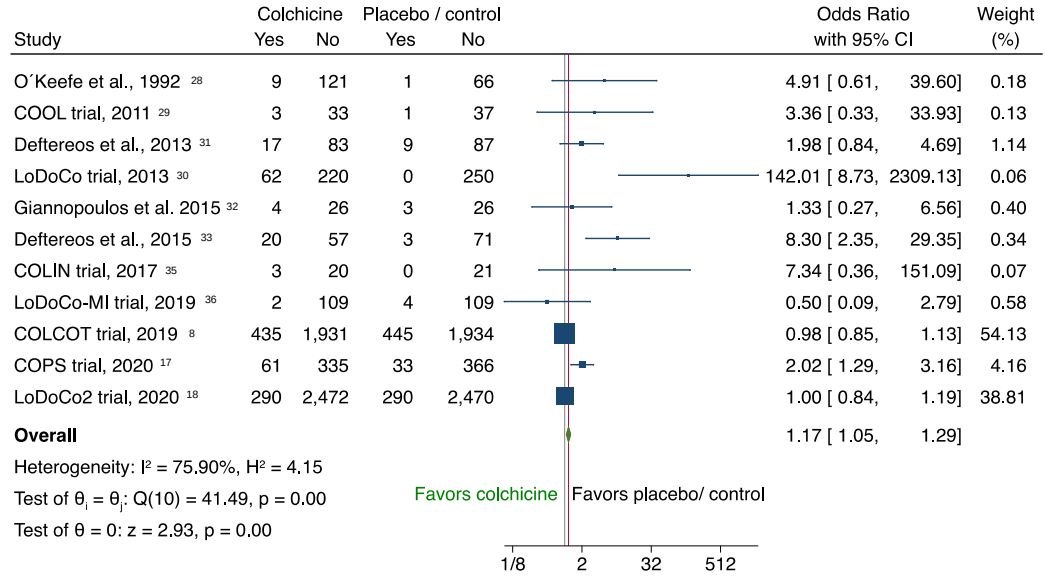
Fixed-effects Mantel-Haenszel model

(D) Stroke or transient ischemic attack (TIA)



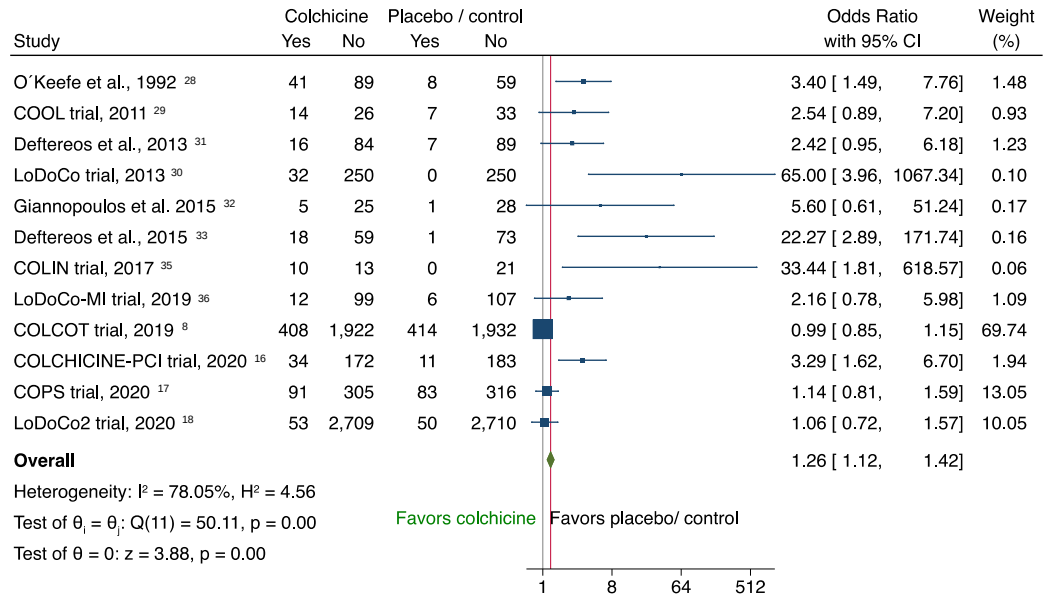
Fixed-effects Mantel-Haenszel model

(E) Therapy discontinuiation with colchicine compared to placebo/ standard therapy



Fixed-effects Mantel-Haenszel model

(F) Gastrointestinal side effects

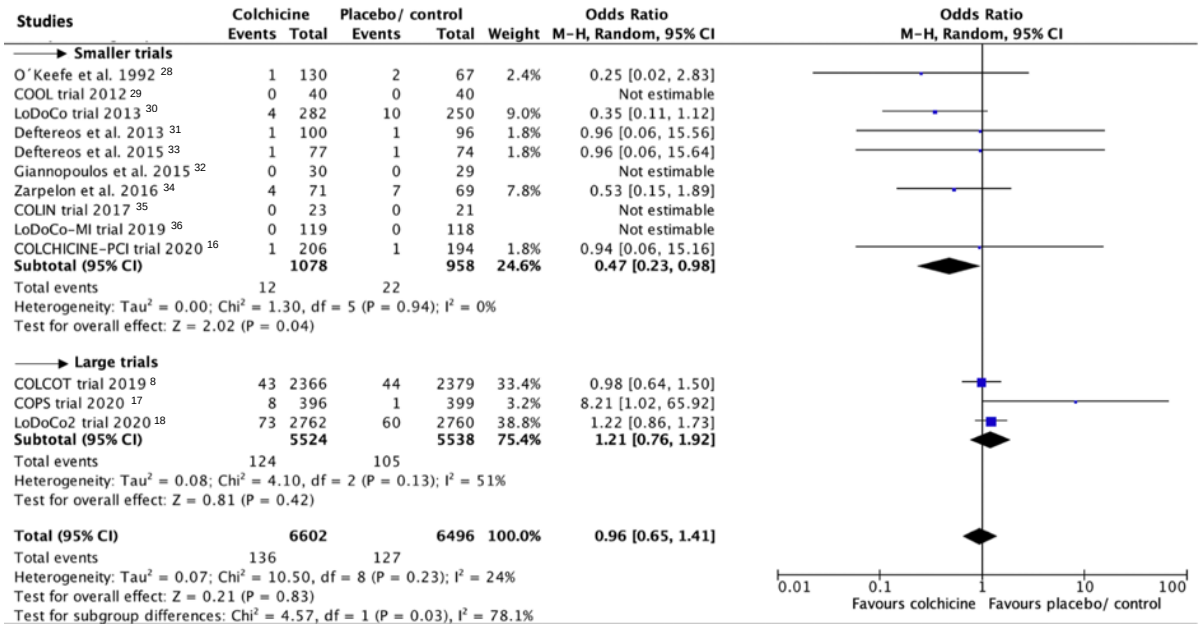


Fixed-effects Mantel-Haenszel model

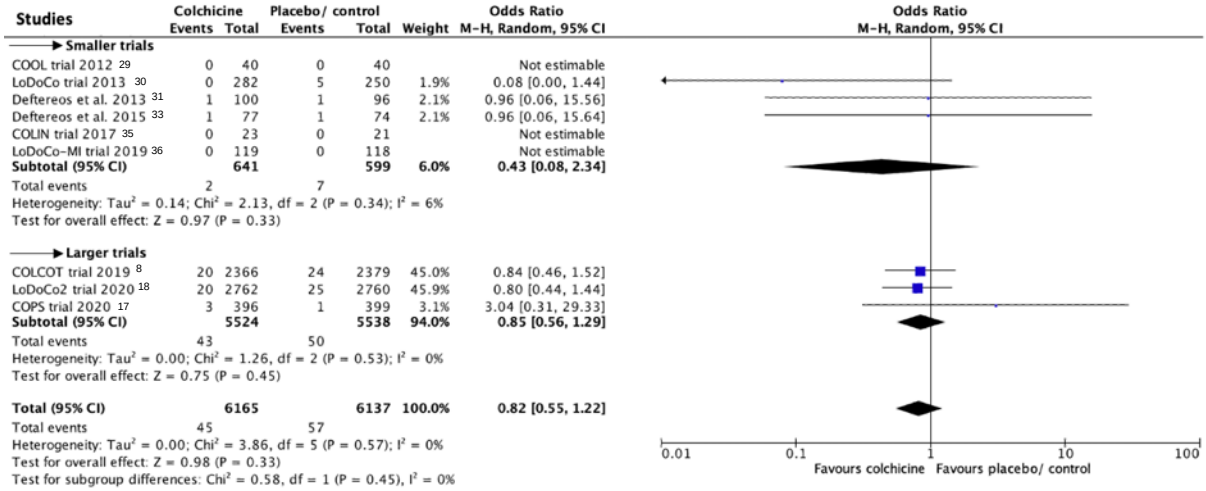
Figure S3. Sensitivity analyzes: Colchicine in patients with coronary artery disease (CAD) – Outcomes in small versus large, randomized trials

Main outcomes with colchicine compared to placebo / standard therapy in patients with CAD:

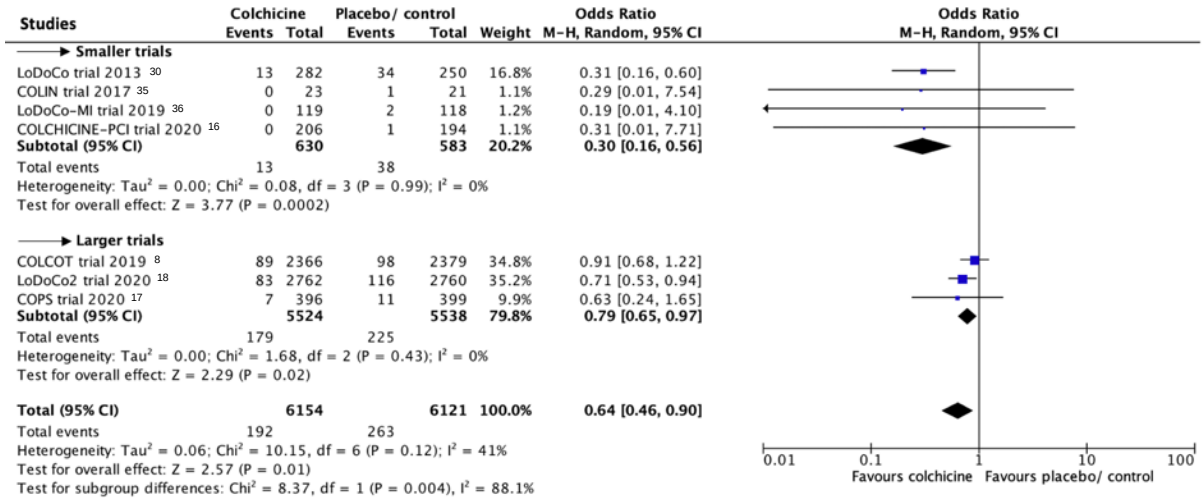
(A) All-cause mortality



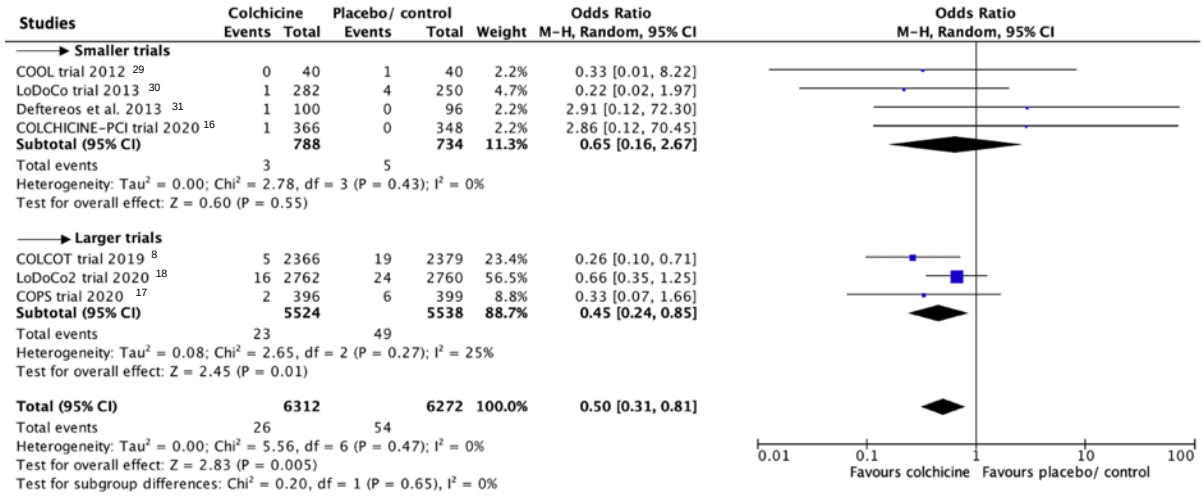
(B) Cardiovascular (CV) mortality



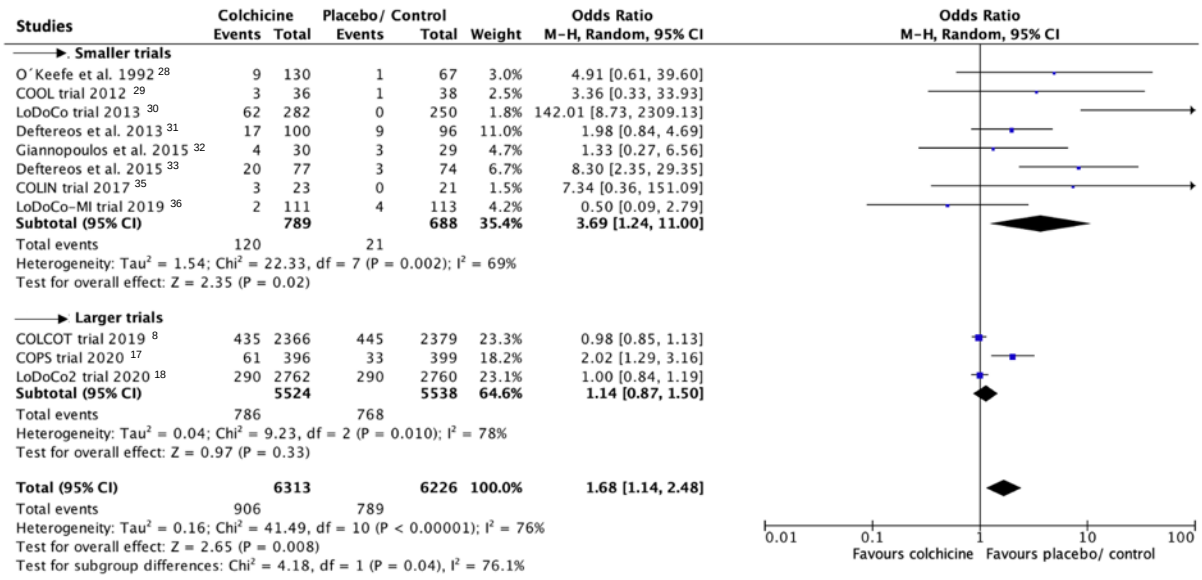
(C) New myocardial infarction



(D) Stroke or transient ischemic attack (TIA)



(E) Therapy discontinuiation with colchicine compared to placebo/ standard therapy



(F) Gastrointestinal side effects

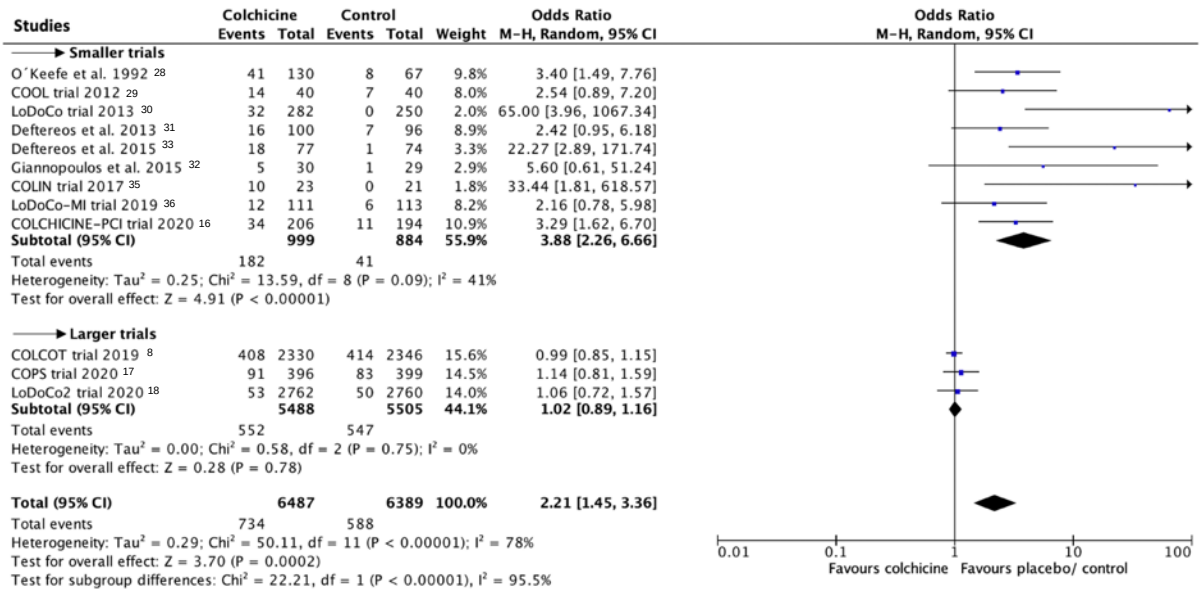
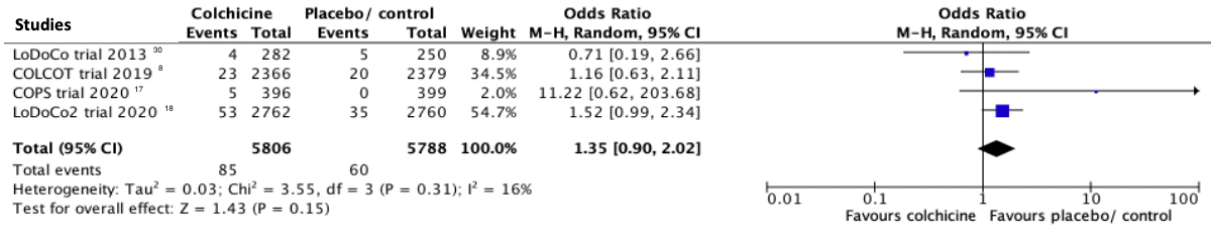
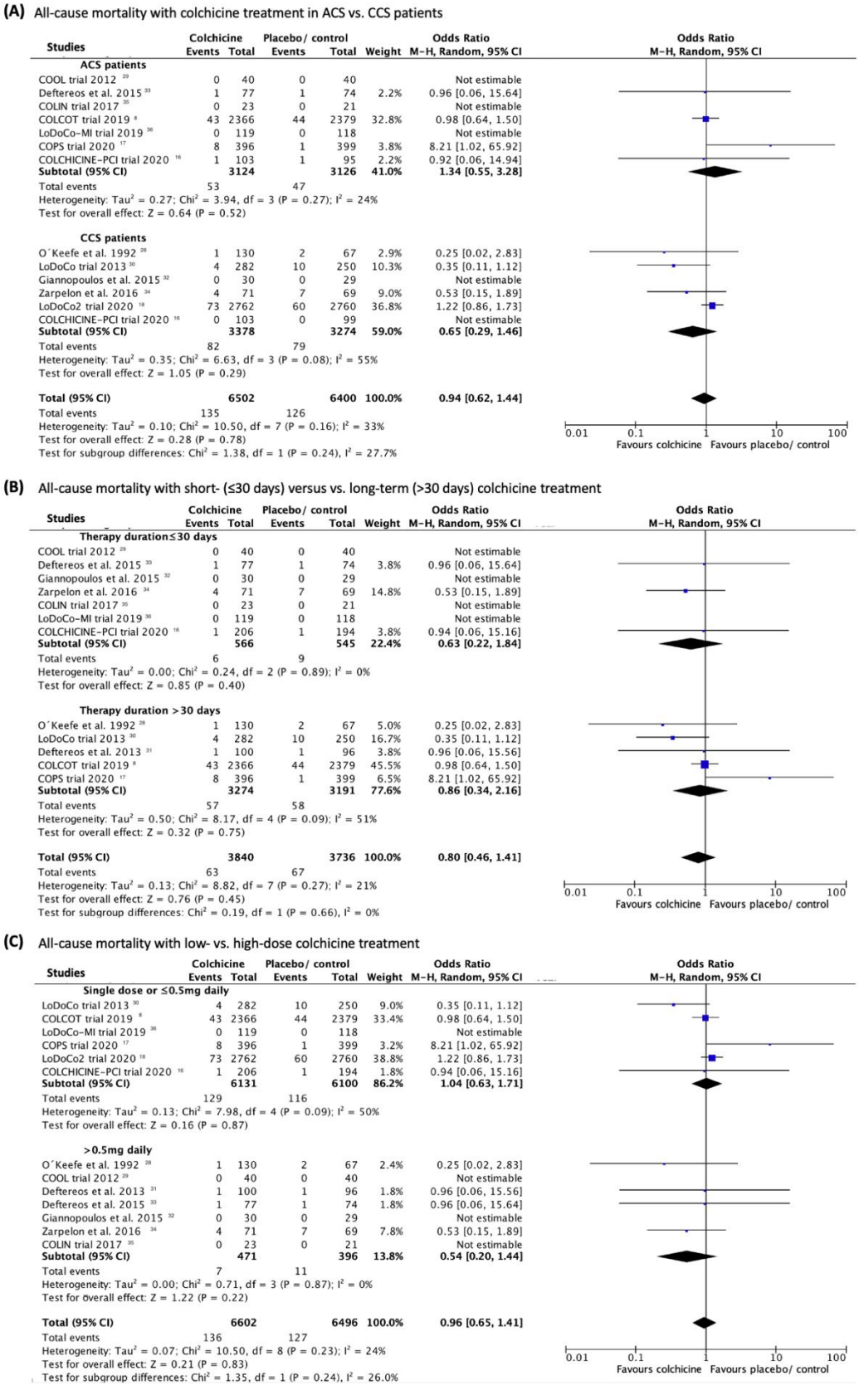


Figure S4. Non-cardiovascular mortality with colchicine compared to placebo/ standard therapy.



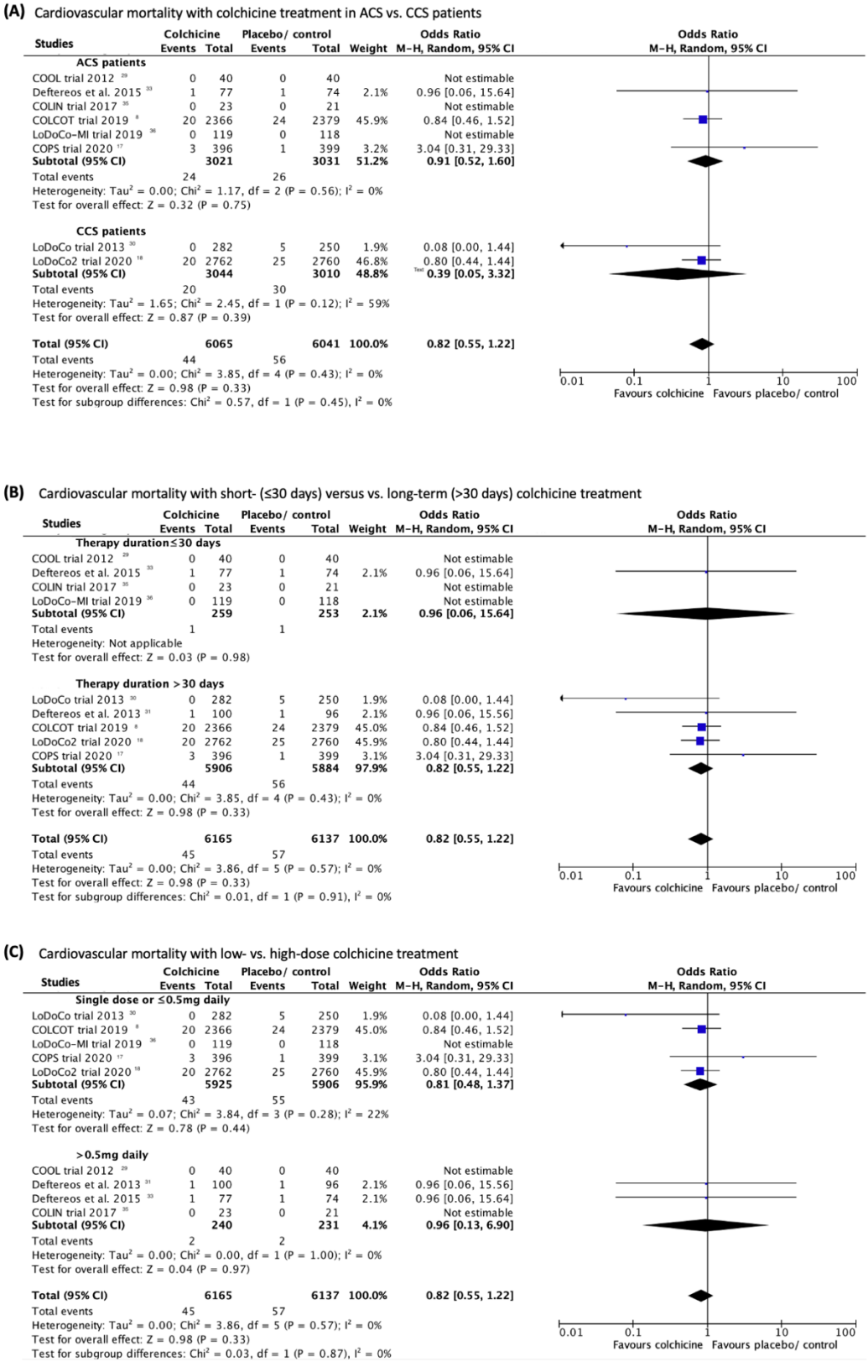
95% CI = 95% confidence interval.

Figure S5. Sub-group analyses assessing all-cause mortality with colchicine versus placebo/ standard therapy in (A) acute versus chronic CAD, (B) for ≤30 days versus >30 days, and (C) at a lower- versus higher-dose regimen.



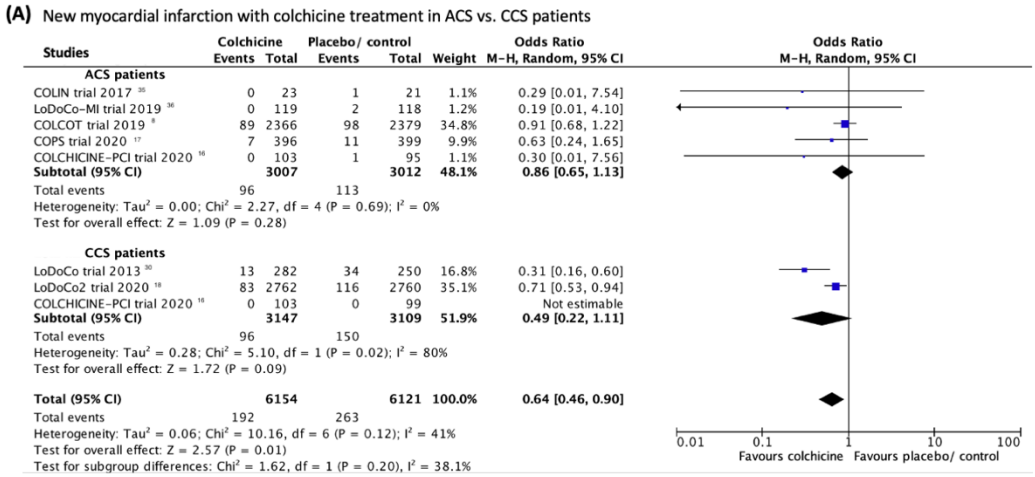
95% CI = 95% confidence interval.

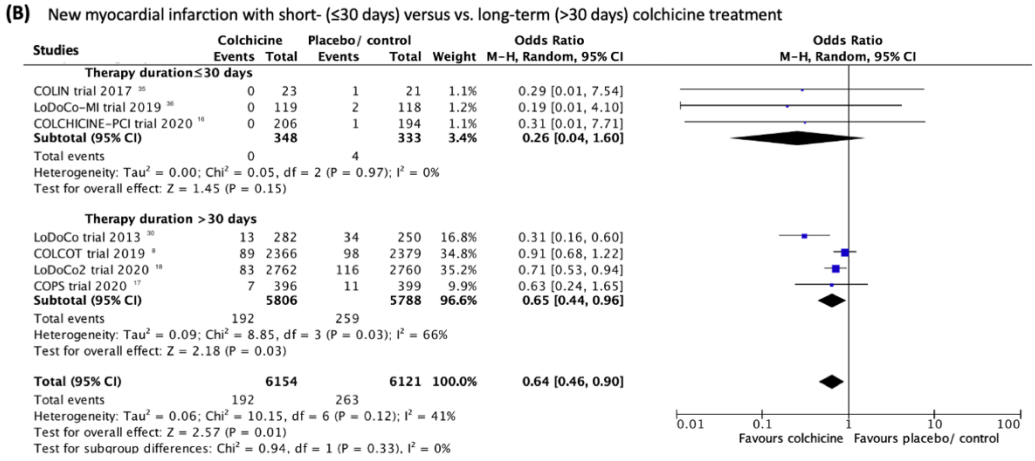
Figure S6. **Sub-group analyses assessing cardiovascular mortality with colchicine versus placebo/ standard therapy in (A) acute versus chronic CAD, (B) for ≤30 days versus >30 days, and (C) at a lower- versus higher-dose regimen**

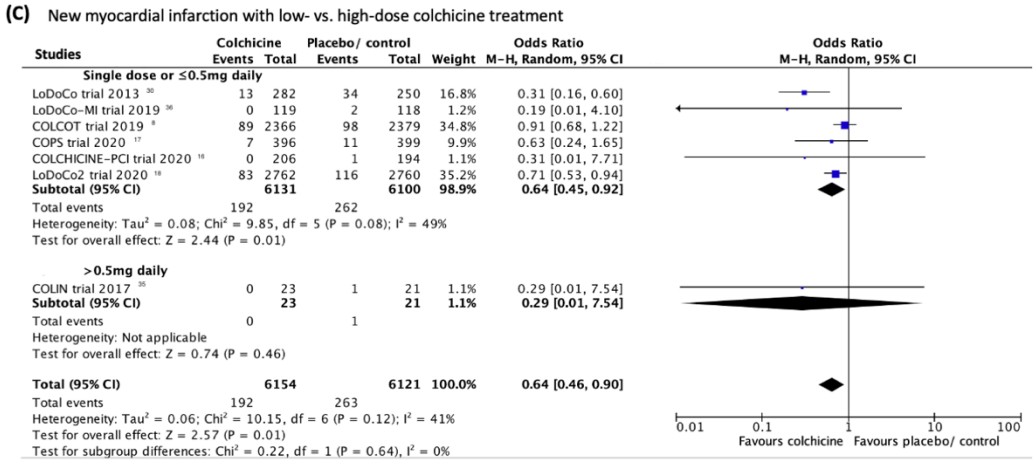


95% CI = 95% confidence interval.

Figure S7. **Sub-group analyses assessing new myocardial infarction with colchicine versus placebo/ standard therapy in (A) acute versus chronic CAD, (B) for ≤30 days versus >30 days, and (C) at a lower- versus higher-dose regimen**

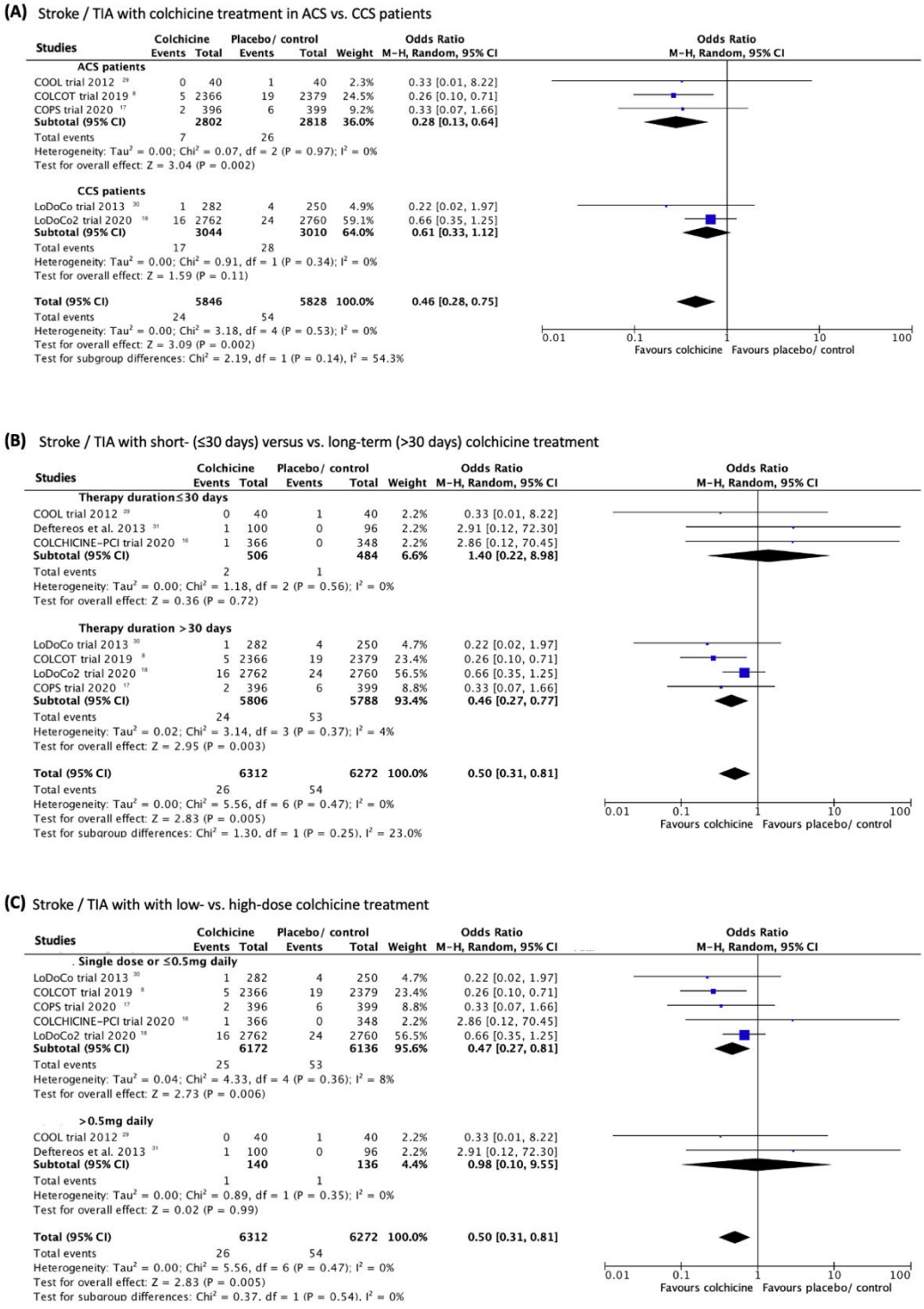






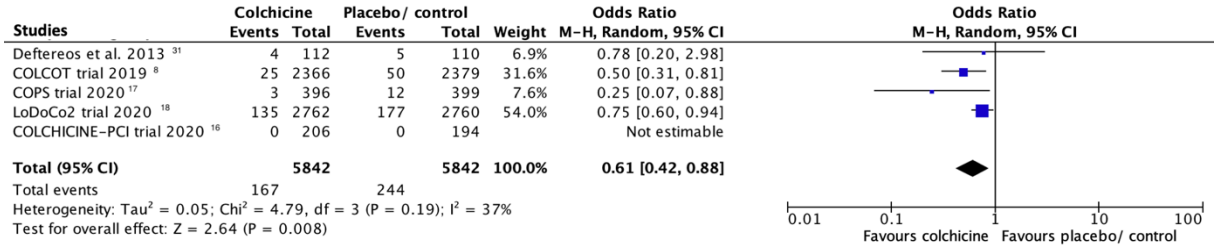
95% CI = 95% confidence interval.

Figure S8 **Sub-group analyses assessing stroke with colchicine versus placebo/ standard therapy in (A) acute versus chronic CAD, (B) for ≤30 days versus >30 days, and (C) at a lower- versus higher-dose regimen**



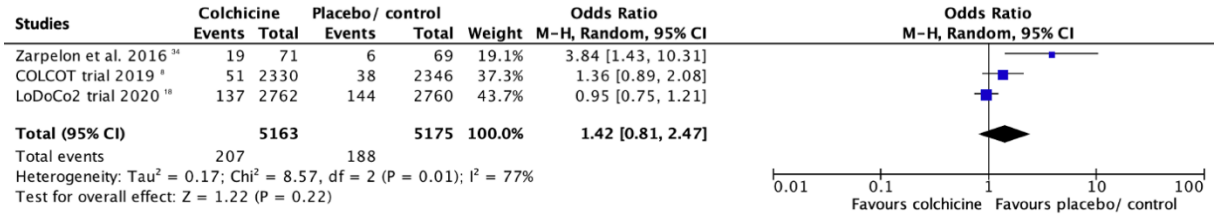
95% CI = 95% confidence interval.

Figure S9. **Ischemia driven or urgent revascularization with colchicine compared to placebo/ standard therapy**



95% CI = 95% confidence interval.

Figure S10. **Infectious complications with colchicine compared to placebo/ standard therapy**



95% CI = 95% confidence interval.