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

nflammation 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 wellestablished 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)-1 β , 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 metaanalysis 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 STsegment 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,

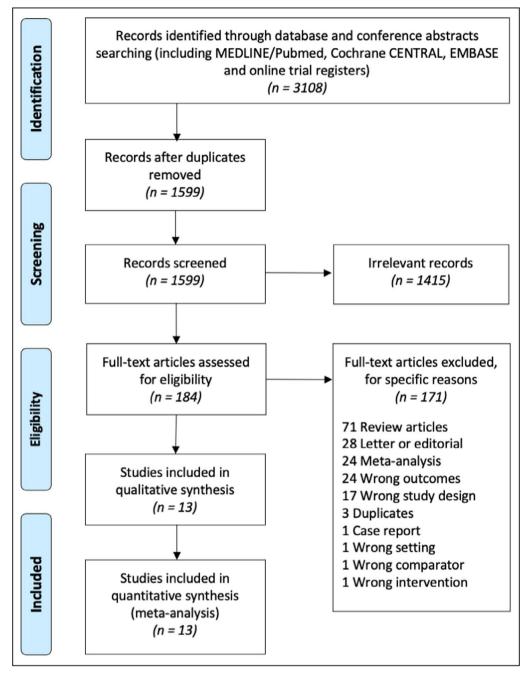


Figure 1. PRISMA flow diagram detailing the article screening process.

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 $l^{2.25}$ 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 metaanalysis 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 heterogeneityadjusted 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 flow-chart 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.

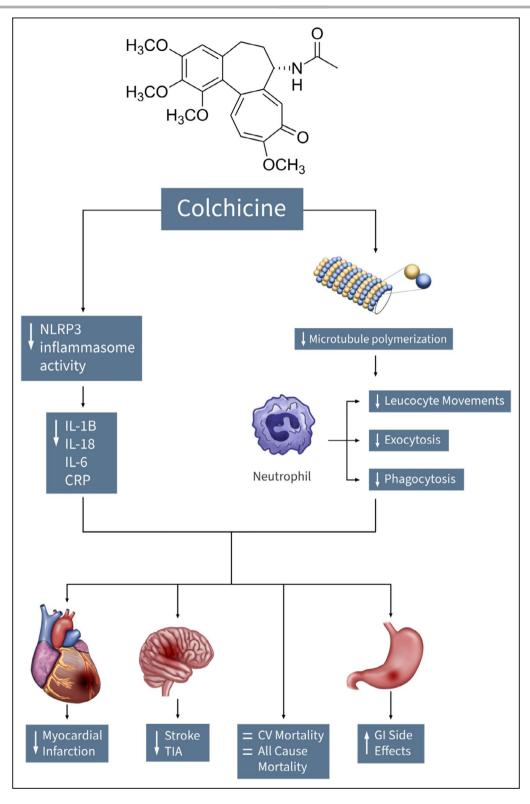


Figure 2. The biological and clinical impact of colchicine among patients with acute and chronic coronary artery disease.

CRP indicates C-reactive protein; CV, cardiovascular; GI, gastrointestinal; and IL, interleukin.

Included Studies

Characteristics of the trials included in the metaanalysis 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

Discontinuation Rate (%)))‡	2		(7)	
Discontir Rate (%)	10 (5.0)	6 (7.5)	62 (11.6) [‡]	26 (12.5)	7 (11.8)	23 (15.2)	RN
FU Duration	5.5 mo*	31 ± 17 d	(median) 36 mo	0 U U	10 d	ى ع	In-hospital: 14.5 ± 11.5 d
Intended Treatment Duration	6 mo	30 d	24 mo	6 mo	10 d	2 Q	Until hospital discharge
Trial Outcomes	 All-cause mortality Recurrent ischemia (assessed by MIBI thallium scan) Angiographic restenosis 	 hs-CRP level at 30 d Platelet function All-cause mortality New MI Stroke/TIA 	 Primary outcome: ACS, out-of hospital cardiac arrest, or (noncardioembolic) ischemic stroke ACS/New MI Lonstable angina Unstable angina Unstable angina Cardiac arrest[§] Cardiac arrest[§] (Noncardioembolic) stroke/TIA 	 In-stent restenosis Parameters of lumen loss All-cause mortality Stroke/TIA 	 Peak hs-troponin T level (within 48 h after CABG) Peak CK-MB level AUC of CK-MB and hs- troponin T 	 AUC of CK-MB Peak hs-troponin T level Absolute MI volume assessed by CMR All-cause mortality 	 Postoperative atrial fibrillation All-cause mortality Length of hospital stay Postoperative infections
Comparator	Placebo	Placebo	Standard therapy	Placebo	Placebo	Placebo	Standard therapy
Colchicine Dose	0.6 mg BID	1 mg OD	0.5 mg OD	0.5 mg BID	0.5 mg BID	2.0 mg LD - 0.5 mg BID	 1.0 mg LD prior to CABG - 0.5 mg BID until discharge
Study Design	Double-blind, placebo controlled RCT (Randomization in 2:1 fashion)	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	RCT, prospective, observer-blinded endpoint (PROBE) trial	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	Double-blind, placebo controlled RCT (Randomization in 1:1 fashion)	RCT, prospective, open-label trial
Study Cohort	CCS patients undergoing PCI (POBA)	ACS patients [†]	CCS patients	Diabetic ACS and CCS patients undergoing PCI with BMS	CCS patients undergoing elective CABG	ACS (STEMI) patients	CCS patients undergoing elective CABG
Randomized Patients (n)	197	08	532	222	60	151	140
Location, Sites	USA/single center	Canada/single center	Australia/single center	Greece/single center	Greece/single center	Greece/ multicenter	Brazil/single center
Study Year	1992	2011	2013	2013	2015	2015	2016
Study	O'Keefe et al. ²⁸	COOL trial ²⁹	LoDoCo trial ³⁰	Deftereos et al. ³¹	Giannopoulos et al. ³²	Deftereos et al. ³³	Zarpelon et al. ³⁴

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Table 1. Cont	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	 CRP peak value during index hospitalization Peak hs-troponin T level Tolerance of colchicine Hospitalization duration Major adverse cardiac events at 1 month 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	 Residual CRP level ≥2 mg/L at 30 d CRP levels Therapy adherence Adverse events All-cause death MACE (MI or stroke) 	30 d	30 q	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	 Primary outcome: cardiovascular mortality, cardiac arrest, MI, stroke, or repeat hospitalization for revascularization All-cause mortality All-cause mortality Cardiovascular mortality Cardiovascular mortality Cardiovascular mortality Cardiovascular mortality All-cause mortality All-tradion All-tradion Atrial fibrillation Atrial fibrillation Adverse events 	24 mo	(median) 22.6 mo	880 (18.5)
COLCHICINE- PCI trial ¹⁶	2020	USA/single center	4001	ACS and CCS patients referred for PCI	Randomized, double blind, placebo- controlled trial (1:1 fashion)	1.8 mg prior to procedure	Placebo	 PCI-related myocardial injury All-cause mortality (Nonfatal) new MI Target vessel revascularization PCI-related MI Change in IL-6, IL-1β and CRP levels 	30 d	30 d	A
											(Continued)

Table 1. Cont	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	962	ACS patients	Randomized, double blind, placebo- controlled trial (1:1 fashion)	1 month 0.5 mg BID; then 0.5 mg OD	Placebo	 Primary outcome: All- cause mortality, new ACS, ischemia-driven urgent revascularization, and noncardioembolic artoke All-cause mortality All-cause mortality All-cause mortality Stroke Stroke Stroke Stroke Stroke Stroke Stroke Pain 	12 mo	400 d	94 (11.8)
LoDoCo2 trial ⁱ⁸	2020	Multinational/ multicenter	5522	CCS patients	Randomized, double blind, placebo- controlled trial (1:1 fashion)	0.5 mg OD	Placebo	 Primary outcome: cardiovascular mortality, new MI, ischemic stroke, or ischemia-driven revascularization New MI Ischemic stroke Ischemic atroke Schemic atroke Schemic atroke Scardiovascular mortality All-cause mortality 	(minimum) 12 mo	28.6 mo 28.1 mo	580 (10.5) ^{\$}
ACS indicates <i>e</i> myocardial brain fr coronary intervent <i>Trial acronyms:</i> <i>Colchicine Trial:</i> Cx <i>Colchicine in Patie</i> "This represent "This represent #The COOL trial patients with acute #32 and 30 patie \$This included o "The COLCHICI \$During the ope	icute corr action; Cl ion; POBy COOL Tri, 201N Trial nts With / is the mea expander expander of coronary ints ceasi ut-of-hos NE-PCl tr n-label ru	AGS indicates acute coronary syndrome; AUC, area under the curve; E myocardial brain fraction; CMR, cardiac magnetic resonance; CRP, C-react coronary intervention; POBA, plain old balloon angioplasty; PROBE, prosp <i>Trial acronyms:</i> COOL <i>Trial, Colchicine Compared With Placebo to Red.</i> <i>Colchicine Trial:</i> COLIN <i>Trial, Interest of CoLchicine in the Treatment of Pat</i> <i>Colchicine in Patients With Acute Coronary Syndrome.</i> *This represents the mean duration to follow-up coronary angiogram. The COL trial expanded their eligbility criteria over the course of the tr patients with acute coronary syndrome and 7/80, who had a recent stroke #32 and 30 patients ceased colchicine treatment early (within 4 weeks) i \$This included out-of-hospital resuscitated cardiac arrest. The COLCHICINE-PCI trial actually randomized 714 patients, whereas *During the open-label run-in period involving 6528 patients, 437 (6.7%)	C, area under thi cresonance; CRI ngioplasty; PROI ared With Placeb ine in the Treatm frome. Up coronary angli ia over the cours in over the cours who had a recer ent early (within ⁴ foc28 patients, 4 6528 patients, 4	e curve; BID, twic P, C-reactive prote BE, prospective, r o to Reduce hs-C ent of Patients Wit ogram. e of the trial and s in stroke. 4 weeks) and late. 4 weeks) and late. 4 weeks) and late.	ACS indicates acute coronary syndrome: AUC, area under the curve: BID, twice a day; BMS, bare metal stent; CABG, coronary ocardial brain fraction; CMR, cardiac magnetic resonance; CRP, O-reactive protein; FU, follow-up; LD, loading dose; MI, myocardia ronary intervention; POBA, plain old balloon angioplasty; PROBE, prospective, randomized observer-blinded endpoint trial; RCT, ra <i>Trial acronyms: COOL Trial, Colchicine Compared With Placebo to Reduce hs-CRP in Patients With Acute Myocardial INfraction and With Inflammate obtinione Trial, COLIN Trial, Interest of COLchicine in the Treatment of Patients With Acute Myocardial INfraction and With Inflammate <i>Tri</i> his represents the mean duration to follow-up coronary angiogram. This represents the mean duration to follow-up coronary angiogram. 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The COLCHICINE-PCI trial actually randomized 714 patients, whereas only those 400 patients who underwent PCI had complete ^{\$}Tuning the open-label run-in period involving 6528 patients, 437 (6.7%) stopped colchicine for gastrointestinal upset.</i>	I stent; CABG, ading dose; MI, ded endpoint tri <i>Coronary Sync</i> <i>Coronary Sync</i>	coronary artery myocardial infar al; RCT, random <i>tromes or Stroke</i> <i>infammatory Re</i> schemic stroke (spectively. complete follow	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- mycardial brain fraction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ;FU, follow-up; LD, loading dose; MI, myccardial infraction; 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. <i>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 in Patients With Acute Oronary Syndrome.</i> <i>This acronyms: COOL trial contronary Syndrome</i> . <i>This tepresents the mean duration to follow-up corners With Acute Myocardial INfarction and With Inflammatory Response; COLCOT Trial, Colchicine Cardiovascular Outcomes Trial; COPS Trial, <i>Colchicine in Patients With Acute Oronary Syndrome</i>. <i>This tepresents the mean duration to follow-up cornery angiogram.</i> <i>This tepresents the mean duration to follow-up cornery angiogram.</i> <i>This tepresents the mean duration to follow-up acronary angiogram.</i> <i>This tepresents the corneral of Tial, Outcomes and TKB, who had a recornery angiogram.</i> <i>This tepresents that corneral of Tial, Colchicine teatment and With Inflammatory Response; COLCOT Trial, Colchicine Cardiovascular Outcomes Trial; COPS <i>Trial, Colchicine teatment early (within 4 weeks) and late (mean follow-up cornary syndrome or 2.36 years), respectively.</i> <i>32 and 30 patients coreased colchicine teatment early (within 4 weeks) and late (mean follow-up period of 2.36 years), respectively.</i> <i>The COLCHICINE-PCI trial actually randomized cardiac arrest.</i> <i>32 and 30 patients consact and traine teatment whereas only those 400 patients who under went PCI had complete </i></i></i>	iic coronary sy not reported; (transient ische <i>Atheroscleros</i> <i>icine Cardiovas</i> <i>icine Cardiovas</i> sment.	ndrome; CK-Mi DD, once daily; amic attack. <i>is Study; LoDo</i> <i>scular Outcome</i> scular Outcome as. Overall, the t	3, creatine kinase- PCI, percutaneous 20 <i>Trial, Low-Dose</i> <i>s Trial, COPS Trial,</i> rial included 73/80

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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	R	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 cr	pronary artery hypas	CABG indicates coronary artery bypass grafting. MI myocardial infarction: NR not reported: PCI percutaneous coronary intervention: and TIA transition strack	infarction: NB, no	t reported: PCI p	percutaneous corona	rv intervention: and TIA. tr	ransient ischemic attac	×	

Baseline Characteristics of the Patients With Acute and Chronic Coronary Artery Disease Among the Included Studies Table 2. CABG indicates coronary artery bypass gratting; MI, myocardial intarction; NH, not reported; PCI, percutaneous coronary intervention; and IIA, 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 \geq 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% Cl, 0.65–1.41; P=0.83; l^2 24%), as shown in Figure 3A. Cardiovascular mortality was reported

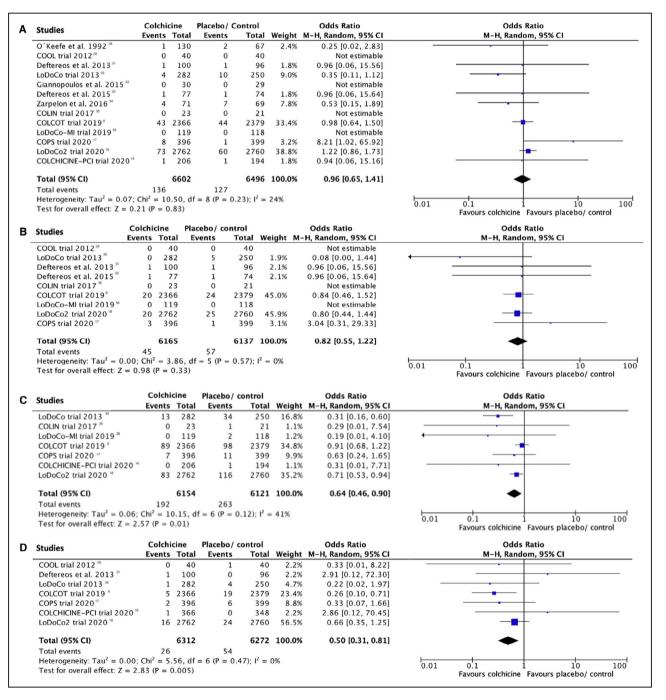


Figure 3. (A) All-cause mortality, (B) cardiovascular mortality, (C) new myocardial infarction, and (D) stroke/transient ischemic attack with colchicine compared to placebo/standard therapy.

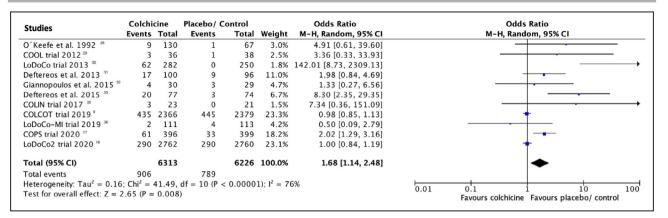


Figure 4. Rate of therapy discontinuation/withdrawal with colchicine compared to placebo/standard therapy. 95% CI indicates 95% confidence interval.

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% Cl, 0.55–1.22; P=0.45; P 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% Cl, 0.90–2.02; P=0.15; P 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 longterm 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; l^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 \leq 30 days versus >30 days, and at a lowerversus 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; I² 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% Cl, 1.45-3.36; P=0.0002; l^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; I² 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.

Chudian	Colchi	cine	Placebo/ co	ontrol		Odds Ratio	Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
O'Keefe et al. 1992 28	41	130	8	67	9.8%	3.40 [1.49, 7.76]	
COOL trial 2012 29	14	40	7	40	8.0%	2.54 [0.89, 7.20]	
LoDoCo trial 2013 30	32	282	0	250	2.0%	65.00 [3.96, 1067.34]	
Deftereos et al. 2013 31	16	100	7	96	8.9%	2.42 [0.95, 6.18]	
Deftereos et al. 2015 33	18	77	1	74	3.3%	22.27 [2.89, 171.74]	
Giannopoulos et al. 2015 32	5	30	1	29	2.9%	5.60 [0.61, 51.24]	
COLIN trial 2017 35	10	23	0	21	1.8%	33.44 [1.81, 618.57]	_
LoDoCo-MI trial 2019 36	12	111	6	113	8.2%	2.16 [0.78, 5.98]	
COLCOT trial 2019 8	408	2330	414	2346	15.6%	0.99 [0.85, 1.15]	+
LoDoCo2 trial 2020 18	53	2762	50	2760	14.0%	1.06 [0.72, 1.57]	- - -
COLCHICINE-PCI trial 2020 16	34	206	11	194	10.9%	3.29 [1.62, 6.70]	
COPS trial 2020 17	91	396	83	399	14.5%	1.14 [0.81, 1.59]	
Total (95% CI)		6487		6389	100.0%	2.21 [1.45, 3.36]	•
Total events	734		588				
Heterogeneity: $Tau^2 = 0.29$;	$Chi^2 = 50$).11, di	f = 11 (P < 0)	0.00001	$I^2 = 789$	6	
Test for overall effect: Z = 3.1	70 (P = 0)	0.0002)					0.01 0.1 1 10 100 Favours colchicine Favours placebo/ control
							ravours coleniente ravours placeboy control

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

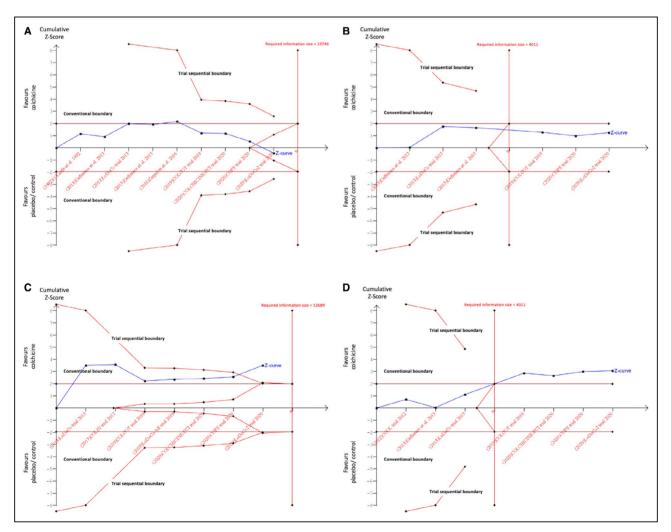


Figure 6. Trial sequential analyses (TSA) of studies assessing impact colchicine vs placebo/standard therapy on (A) allcause mortality, (B) cardiovascular mortality, (C) new myocardial infarction, and (D) stroke/transient ischemic attack (TIA).

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-1B 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. $^{\rm 18}$

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 longterm 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 antiinflammatory 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 (eq, 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.

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Supplementary Material

Data S1 Tables S1–S3 Figures S1–S10

REFERENCES

- 1. Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844–2850. DOI: 10.1161/01.CIR.91.11.2844.
- Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014;276:618–632. DOI: 10.1111/ joim.12296.
- Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. J Intern Med. 2015;278:483–493. DOI: 10.1111/joim.12406.
- Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377:1119–1131. DOI: 10.1056/NEJMoa1707914.
- Imazio M, Andreis A, Brucato A, Adler Y, De Ferrari GM. Colchicine for acute and chronic coronary syndromes. *Heart.* 2020;106:1555–1560. DOI: 10.1136/heartjnl-2020-317108.
- Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. *Circ Res.* 2016;118:145–156. DOI: 10.1161/CIRCRESAHA.115.306656.
- Tucker B, Kurup R, Barraclough J, Henriquez R, Cartland S, Arnott C, Misra A, Martínez G, Kavurma M, Patel S. Colchicine as a novel therapy for suppressing chemokine production in patients with an acute coronary syndrome: a pilot study. *Clin Ther.* 2019;41:2172–2181. DOI: 10.1016/j.clinthera.2019.07.015.
- Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* 2019;381:2497– 2505. DOI: 10.1056/NEJMoa1912388.
- Ullah W, Gowda SN, Fischman D. Safety and efficacy of colchicine in patients with coronary artery disease: a systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2021;23:1–6. DOI: 10.1016/j. carrev.2020.06.004.
- Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. *Am J Cardiol.* 2021;140:33–38. DOI: 10.1016/j.amjcard.2020.10.043.
- Xiang Z, Yang J, Yang J, Zhang J, Fan Z, Yang C, Di L, Ma C, Wu J, Huang Y. Efficacy and safety of colchicine for secondary prevention of coronary heart disease: a systematic review and meta-analysis. *Intern Emerg Med.* 2021;16:487–496. DOI: 10.1007/s11739-020-02606-7.
- Tien YY, Huang HK, Shih MC, Tu YK. Drug repurposing? Cardiovascular effect of colchicine on patients with coronary artery disease: a systematic review and meta-analysis. *J Cardiol.* 2021;77:576–582. DOI: 10.1016/j.jjcc.2020.11.010.
- Samuel M, Tardif JC, Bouabdallaoui N, Khairy P, Dubé MP, Blondeau L, Guertin MC. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Can J Cardiol*. 2021;37:776–785. DOI: 10.1016/j.cjca.2020.10.006.
- Aimo A, Pascual Figal DA, Bayes-Genis A, Emdin M, Georgiopoulos G. Effect of low-dose colchicine in acute and chronic coronary syndromes: a systematic review and meta-analysis. *Eur J Clin Invest.* 2021;51:e13464. DOI: 10.1111/eci.13464.
- Samuel M, Tardif JC, Bouabdallaoui N, Khairy P, Dube MP, Blondeau L, Guertin MC. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Can J Cardiol*. 2021;37:776–785. DOI: 10.1016/j.cjca.2020.10.006.
- Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, Smilowitz NR, Feit F, Ratnapala N, Keller NM, et al. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. *Circ Cardiovasc Interv.* 2020;13:e008717. DOI: 10.1161/CIRCINTERVENTIONS.119.008717.
- Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, et al. Colchicine in patients with acute coronary syndrome: the Australian cops randomized

clinical trial. *Circulation*. 2020;142:1890–1900. DOI: 10.1161/CIRCU LATIONAHA.120.050771.

- Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu X-F, Ireland MA, Lenderink T, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med.* 2020;383:1838–1847. DOI: 10.1056/NEJMoa2021372.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. DOI: 10.1136/ bmj.327.7414.557.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. DOI: 10.1136/bmj.b2700.
- 21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021)*. Cochrane, 2021. Available at: www.training.cochrane.org/handbook.
- Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. DOI: 10.1136/bmj.d5928.
- Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. DOI: 10.1136/bmj.i4919.
- Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, et al. GRADE guidelines:
 Rating the quality of evidence–study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407–415. DOI: 10.1016/j.jclinepi.2010.07.017.
- Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*. 2007;335:914–916. DOI: 10.1136/ bmj.39343.408449.80.
- Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol.* 2017;17:39. DOI: 10.1186/s12874-017-0315-7.
- Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol.* 2008;61:763–769. DOI: 10.1016/j.jclinepi.2007.10.007.
- O'Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol.* 1992;19:1597–1600. DOI: 10.1016/0735-1097(92)90624-V.
- Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. *J Thromb Thrombolysis*. 2012;33:88–94. DOI: 10.1007/s11239-011-0637-y.
- Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61:404–410. DOI: 10.1016/j.jacc.2012.10.027.
- Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, Driva M, Hahalis G, Pyrgakis V, Alexopoulos D, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol*. 2013;61:1679–1685. DOI: 10.1016/j. jacc.2013.01.055.
- 32. Giannopoulos G, Angelidis C, Kouritas VK, Dedeilias P, Filippatos G, Cleman MW, Panagopoulou V, Siasos G, Tousoulis D, Lekakis J, et al. Usefulness of colchicine to reduce perioperative myocardial damage in patients who underwent on-pump coronary artery bypass grafting. *Am J Cardiol.* 2015;115:1376–1381. DOI: 10.1016/j.amjcard.2015.02.036.
- Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G, Goudevenos J, Alexopoulos D, Pyrgakis V, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation*. 2015;132:1395–1403. DOI: 10.1161/ CIRCULATIONAHA.115.017611.
- Zarpelon CS, Netto MC, Jorge JC, Fabris CC, Desengrini D, Jardim Mda S, Silva DG. Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization. *Arg Bras Cardiol*. 2016;107:4–9. DOI: 10.5935/abc.20160082.
- Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol J-P, Leclercq F, Macia J-C, Gervasoni R, Cung T-T, et al. COLIN trial: value of colchicine in the treatment of patients with acute myocardial infarction

and inflammatory response. Arch Cardiovasc Dis. 2017;110:395–402. DOI: 10.1016/j.acvd.2016.10.004.

- Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, Hillis GS. The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: a pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. *Am Heart J*. 2019;215:62–69. DOI: 10.1016/j.ahj.2019.06.003.
- Horioka K, Tanaka H, Isozaki S, Konishi H, Fujiya M, Okuda K, Asari M, Shiono H, Ogawa K, Shimizu K. Acute colchicine poisoning causes endotoxemia via the destruction of intestinal barrier function: the curative effect of endotoxin prevention in a murine model. *Dig Dis Sci.* 2020;65:132–140. DOI: 10.1007/s10620-019-05729-w.
- Tochinai R, Suzuki K, Nagata Y, Ando M, Hata C, Komatsu K, Suzuki T, Uchida K, Kado S, Kaneko K, et al. Cardiotoxic changes of colchicine intoxication in rats: electrocardiographic, histopathological and blood chemical analysis. *J Toxicol Pathol.* 2014;27:223–230. DOI: 10.1293/ tox.2014-0013.
- Frommeyer G, Krawczyk J, Dechering DG, Kochhäuser S, Leitz P, Fehr M, Eckardt L. Colchicine increases ventricular vulnerability in an experimental whole-heart model. *Basic Clin Pharmacol Toxicol*. 2017;120:505–508. DOI: 10.1111/bcpt.12702.
- Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, Pollak U, Koren G, Bentur Y. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol.* 2010;48:407–414. DOI: 10.3109/15563 650.2010.495348.
- Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. *Semin Arthritis Rheum.* 1991;21:143–155. DOI: 10.1016/0049-0172(91)90003-I.
- 42. Li Y, Wang P, Yang X, Wang W, Zhang J, He Y, Zhang W, Jing T, Wang B, Lin R. SIRT1 inhibits inflammatory response partly through regulation

of NLRP3 inflammasome in vascular endothelial cells. *Mol Immunol.* 2016;77:148–156. DOI: 10.1016/j.molimm.2016.07.018.

- Ben-Chetrit E, Bergmann S, Sood R. Mechanism of the antiinflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis. *Rheumatology (Oxford, England)*. 2006;45:274–282. DOI: 10.1093/rheumatology/kei140.
- 44. Hemkens LG, Ewald H, Briel M. Colchicine and prevention of cardiovascular events. *JAMA*. 2016;316:1106–1107. DOI: 10.1001/jama.2016.11044.
- Jolly SS. ClinicalTrials.gov. A 2x2 Factorial Randomized Controlled Trial of Colchicine and Spironolactone in Patients With Myocardial Infarction/SYNERGY Stent Registry - Organization to Assess Strategies for Ischemic Syndromes 9. https://clinicaltrials.gov/ct2/show/NCT03 048825
- Kaul S, Gupta M, Bandyopadhyay D, Hajra A, Deedwania P, Roddy E, Mamas M, Klein A, Lavie CJ, Fonarow GC, et al. Gout pharmacotherapy in cardiovascular diseases: a review of utility and outcomes. *Am J Cardiovasc Drugs*. 2020;28:1–14. https://doi.org/10.1007/s40256-020-00459-1
- Lavie CJ. In reply use of famotidine and risk of severe course of illness in patients with COVID-19: a meta-analysis. *Mayo Clin Proc.* 2021;96:1367–1368. DOI: 10.1016/j.mayocp.2021.03.002.
- Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, Metallidis S, Sianos G, Baltagiannis S, Panagopoulos P, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open.* 2020;3:e2013136. DOI: 10.1001/jamanetwor kopen.2020.13136.
- Tardif JCBN, L'Allier PL, Gaudet D, Shah B, Pillinger MH, Lopez-Sendon J, da Luz P, Verret L, Audet S, Dupuis J, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. *medRxiv*. 2021. DOI: 10.1101/2021.01.26.21250494

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	Н	Н	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	Н	Н	Н	L	L	Unclear	Yes
COLIN trial ³⁵	2016	1 month	L	Н	Н	Н	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 a	assessment			Nº of p	atients	Effe	et		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	placebo / control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All cause	e mortality in	CAD patients	5									
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
Cardiova	ascular (CV)	mortality in C	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	r 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)		CRITICAL
New myo	ocardial infa	rction (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)		CRITICAL
Ischemia	a-driven reva	scularization								·		
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
Gastroin	testinal side	effects	•	•				•	1	•		

			Certainty a	assessment			№ of p	atients	Effec	et		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	placebo / control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
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
Infectiou	us complication	ons								· · · · · · · · · · · · · · · · · · ·		
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)		IMPORTANT
Therapy	discontinuat	ion / withdray	val 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-car	diovascular n	nortality										
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): ischemic chest pain occurring at rest or increasing in frequency and lasting >10 min ECG changes of ischemia with ST elevation, ST depression or new left bundle branch block 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 <i>First Universal definition of</i> <i>Myocardial Infarction</i>[†] <i>Unstable angina</i> 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 <i>European Society of</i> <i>Cardiology (ESC) Guidelines</i> 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

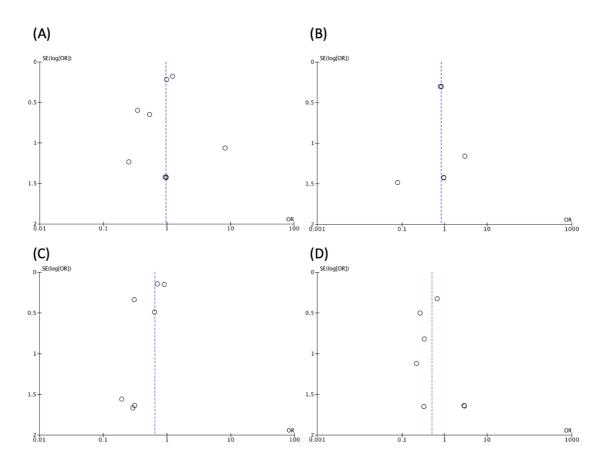
LoDoCo-MI trial ³⁶	2019	• MI definition as per 3 rd Universal Definition of Myocardial Infarction [‡]	• Not further specified
COLCOT trial ⁸	2019	• MI defined according to national guidelines (the exact guidelines had not been defined in the protocol)	• Stroke or TIA (exact definitions were not further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

	Cold	chicine	Placebo	/ control		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
O´Keefe et al., 1992 28	1	129	2	65	_	0.25 [0.02, 2.83]	2.06
COOL trial, 2011 29	0	40	0	40 -		1.00 [0.02, 51.63]	0.39
Deftereos et al., 2013 31	1	99	1	95		0.96 [0.06, 15.56]	0.79
LoDoCo trial, 2013 30	4	278	10	240		0.35 [0.11, 1.12]	8.21
Giannopoulos et al. 2015 32	0	30	0	29 -		0.97 [0.02, 50.36]	0.39
Deftereos et al., 2015 33	1	76	1	73		0.96 [0.06, 15.64]	0.79
Zarpelon et al., 2016 34	4	67	7	62		0.53 [0.15, 1.89]	5.26
COLIN trial, 2017 35	0	23	0	21 -		0.91 [0.02, 48.15]	0.40
LoDoCo-MI trial, 2019 36	0	119	0	118 -		0.99 [0.02, 50.39]	0.39
COLCOT trial, 2019 8	43	2,323	44	2,335	+	0.98 [0.64, 1.50]	33.84
COLCHICINE-PCI trial, 2020 16	1	205	1	193		0.94 [0.06, 15.16]	0.81
COPS trial, 2020 17	8	388	1	398		- 8.21 [1.02, 65.92]	0.77
LoDoCo2 trial, 2020 18	73	2,689	60	2,700		1.22 [0.86, 1.73]	45.90
Overall					+	1.06 [0.83, 1.35]	
Heterogeneity: I ² = -14.21%, H ²	= 0.88	3					
Test of $\theta_i = \theta_j$: Q(12) = 10.51, p =	= 0.57	7		Fav	ors colchicine Favors placeb	o/ control	
Test of θ = 0: z = 0.44, p = 0.66							
				1	/32 1/4 2 16	-	

Fixed-effects Mantel-Haenszel model

(B) Cardiovascular (CV) mortality

	Colo	chicine	Placebo	/ contro		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% Cl	(%)
COOL trial, 2011 29	0	40	0	40		- 1.00 [0.02, 51.63]	0.84
Deftereos et al., 2013 31	1	99	1	95		0.96 [0.06, 15.56]	1.72
LoDoCo trial, 2013 30	0	282	5	245		0.08 [0.00, 1.44]	9.88
Deftereos et al., 2015 33	1	76	1	73		0.96 [0.06, 15.64]	1.71
COLIN trial, 2017 ³⁵	0	23	0	21		- 0.91 [0.02, 48.15]	0.87
LoDoCo-MI trial, 2019 36	0	119	0	118		- 0.99 [0.02, 50.39]	0.85
COLCOT trial, 2019 8	20	2,346	24	2,355	-#-	0.84 [0.46, 1.52]	40.30
COPS trial, 2020 17	З	393	1	398		3.04 [0.31, 29.33]	1.68
LoDoCo2 trial, 2020 18	20	2,742	25	2,735		0.80 [0.44, 1.44]	42.16
Overall					•	0.79 [0.54, 1.16]	
Heterogeneity: I ² = -106.	02%,	$H^2 = 0.4$	9				
Test of $\theta_i = \theta_i$: Q(8) = 3.8	8, p =	0.87			avors colchicine Favors pla	cebo/ control	
Test of θ = 0: z = -1.20, p	0 = 0.2	23					
					/128 1/8 2 3	2	

Fixed-effects Mantel-Haenszel model

(C) New myocardial infarction

Chudu		chicine		/ control		Odds Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
LoDoCo trial, 2013 30	13	269	34	216		0.31 [0.16, 0.60]	13.36
COLIN trial, 2017 35	0	23	1	20		0.29 [0.01, 7.54]	0.60
LoDoCo-MI trial, 2019 36	0	119	2	116		0.19 [0.01, 4.10]	0.97
COLCOT trial, 2019 8	89	2,277	98	2,281	-	0.91 [0.68, 1.22]	36.55
COLCHICINE-PCI trial, 2020 16	0	206	1	193		0.31 [0.01, 7.71]	0.60
COPS trial, 2020 17	7	389	11	388		0.63 [0.24, 1.65]	4.18
LoDoCo2 trial, 2020 18	83	2,679	116	2,644	-	0.71 [0.53, 0.94]	43.74
Overall					•	0.71 [0.59, 0.86]	
Heterogeneity: l ² = 40.88%, H ² =	= 1.69						
Test of $\theta_i = \theta_j$: Q(6) = 10.15, p =	0.12				Favors colchicine	Favors placebo/ control	
Test of θ = 0: z = -3.49, p = 0.00)						
					1/64 1/16 1/4	1 4	

Fixed-effects Mantel-Haenszel model

(D) Stroke or transient ischemic attack (TIA)

	Cold	chicine		/ control		Odds Ratio Weig	0
Study	Yes	No	Yes	No		with 95% CI (%	,)
COOL trial, 2011 29	0	40	1	39 —		0.33 [0.01, 8.22] 2.6	37
Deftereos et al., 2013 31	1	99	0	96		2.91 [0.12, 72.30] 0.9) 1
LoDoCo trial, 2013 30	1	281	4	246		— 0.22 [0.02, 1.97] 7.6	32
COLCOT trial, 20198	5	2,361	19	2,360		0.26[0.10, 0.71] 34.1	0
COLCHICINE-PCI trial, 2020 16	1	365	0	348		2.86 [0.12, 70.45] 0.9) 2
COPS trial, 2020 17	2	394	6	393		— 0.33 [0.07, 1.66] 10.7	'3
LoDoCo2 trial, 2020 18	16	2,746	24	2,736	-	- 0.66 [0.35, 1.25] 43.0)5
Overall					•	0.49 [0.31, 0.77]	
Heterogeneity: I ² = -7.95%, H ² =	0.93						
Test of $\theta_i = \theta_i$: Q(6) = 5.56, p = 0	.47			Favo	ors colchicine	Favors placebo/ control	
Test of θ = 0: z = -3.05, p = 0.00							
				1/6	4 1/4	4 64	

Fixed-effects Mantel-Haenszel model

	Colo	hicine	Placebo	/ control					Odds Ra	atio	Weight
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
O'Keefe et al., 1992 28	9	121	1	66	_				4.91 [0.61,	39.60]	0.18
COOL trial, 2011 29	3	33	1	37					3.36 [0.33,	33.93]	0.13
Deftereos et al., 2013 31	17	83	9	87	-	-			1.98 [0.84,	4.69]	1.14
LoDoCo trial, 2013 30	62	220	0	250					142.01 [8.73,	2309.13]	0.06
Giannopoulos et al. 2015 32	4	26	3	26		•			1.33 [0.27,	6.56]	0.40
Deftereos et al., 2015 33	20	57	3	71					8.30 [2.35,	29.35]	0.34
COLIN trial, 2017 35	3	20	0	21				-	7.34 [0.36,	151.09]	0.07
LoDoCo-MI trial, 2019 36	2	109	4	109 -		<u> </u>			0.50 [0.09,	2.79]	0.58
COLCOT trial, 2019 8	435	1,931	445	1,934					0.98 [0.85,	1.13]	54.13
COPS trial, 2020 17	61	335	33	366					2.02 [1.29,	3.16]	4.16
LoDoCo2 trial, 2020 18	290	2,472	290	2,470		•			1.00 [0.84,	1.19]	38.81
Overall						•			1.17 [1.05,	1.29]	
Heterogeneity: I ² = 75.90%,	$H^2 = 4$	4.15									
Test of $\theta_i = \theta_j$: Q(10) = 41.49	9, p =	0.00	Fa	avors colo	hicine	Favor	s placeb	o/ control			
Test of $\theta = 0$: z = 2.93, p = 0	0.00										
				1	/8	2	32	512			
Fixed-effects Mantel-Haenszo	el moc	del									

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

(F) Gastrointestinal side effects

	Colo	chicine	Placebo	/ control		Odds F	latio	Weight
Study	Yes	No	Yes	No		with 95°	% CI	(%)
O'Keefe et al., 1992 28	41	89	8	59		3.40 [1.49,	7.76]	1.48
COOL trial, 2011 29	14	26	7	33		2.54 [0.89,	7.20]	0.93
Deftereos et al., 2013 31	16	84	7	89		2.42 [0.95,	6.18]	1.23
LoDoCo trial, 2013 30	32	250	0	250		— 65.00 [3.96,	1067.34]	0.10
Giannopoulos et al. 2015 32	5	25	1	28 -		5.60[0.61,	51.24]	0.17
Deftereos et al., 2015 33	18	59	1	73	· · · · · · · · · · · · · · · · · · ·	22.27 [2.89,	171.74]	0.16
COLIN trial, 2017 35	10	13	0	21		33.44 [1.81,	618.57]	0.06
LoDoCo-MI trial, 2019 36	12	99	6	107		2.16 [0.78,	5.98]	1.09
COLCOT trial, 2019 8	408	1,922	414	1,932		0.99 [0.85,	1.15]	69.74
COLCHICINE-PCI trial, 2020 16	34	172	11	183		3.29 [1.62,	6.70]	1.94
COPS trial, 2020 17	91	305	83	316	-	1.14 [0.81,	1.59]	13.05
LoDoCo2 trial, 2020 18	53	2,709	50	2,710	-	1.06 [0.72,	1.57]	10.05
Overall					•	1.26 [1.12,	1.42]	
Heterogeneity: l ² = 78.05%, H ² =	= 4.56							
Test of $\theta_i = \theta_i$: Q(11) = 50.11, p =	= 0.00		Favors	colchicine	Favors placebo/ control			
Test of θ = 0: z = 3.88, p = 0.00								
				-	1 8 64 512	2		
Fixed offects Mental Heeneral m	odol							

Fixed-effects Mantel-Haenszel model

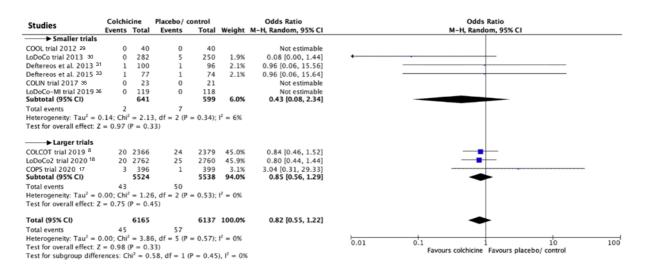
Figure S3. Sensitivity analyzes: Colchicine in patients with coronary artery disease (CAD) – Outcomes in small versus large, randomized trials

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

(A) All-cause mortality

Colchi	cine	Placebo/ c	ontrol		Odds Ratio	Odds Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
1	130	2	67	2.4%	0.25 [0.02, 2.83]	
0	40	0	40		Not estimable	
4	282	10	250	9.0%	0.35 [0.11, 1.12]	
1	100	1	96	1.8%	0.96 [0.06, 15.56]	
1	77	1	74	1.8%	0.96 [0.06, 15.64]	
0	30	0	29		Not estimable	
4	71	7	69	7.8%	0.53 [0.15, 1.89]	
0	23	0	21		Not estimable	
0	119	0	118		Not estimable	
1	206	1	194	1.8%	0.94 [0.06, 15.16]	
	1078		958	24.6%	0.47 [0.23, 0.98]	
12		22				-
$chi^2 = 1.$	30, df	= 5 (P = 0.9)	(4); $I^2 = 0$	0%		
02 (P = 0)	0.04)					
43	2366	44	2379	33.4%	0.98 [0.64, 1.50]	_ _
8	396	1	399			
73	2762	60	2760			
	5524		5538	75.4%	1.21 [0.76, 1.92]	+
124		105				-
$hi^2 = 4$.	10. df	= 2 (P = 0.1)	3): $I^2 = 5$	51%		
	6602		6496	100.0%	0.96 [0.65, 1.41]	•
136		127				Ť
	0.50. di		$(23) \cdot I^2 =$	24%		+
		- 0 (1 - 0)				0.01 0.1 i 10 10
						Favours colchicine Favours placebo/ control
	Events 1 0 4 1 0 4 0 1 1 0 4 0 1 1 1 0 4 0 1	$\begin{array}{ccccccc} 0 & 40 \\ 4 & 282 \\ 1 & 100 \\ 0 & 1 & 77 \\ 0 & 30 \\ 4 & 71 \\ 0 & 23 \\ 0 & 119 \\ 1 & 206 \\ 1078 \\ 12 \\ 2 & (P = 0.04) \\ \end{array}$	Events Total Events 1 130 2 0 40 0 4 282 10 1 100 1 1 77 1 0 30 0 4 71 7 0 23 0 0 119 0 1 206 1 1078 22 22 2(h² = 1.30, df = 5 (P = 0.5) 2 2(P = 0.04) 43 2366 44 8 396 1 73 2762 60 5524 124 105 11 10 127 6602 136 127 136 127 1.0.50, df = 8 (P = 0 1 1 1 0.53 1 1	Events Total Events Total 1 130 2 67 0 40 0 40 4 282 10 250 1 100 1 96 1 77 1 74 0 30 0 29 4 71 7 69 0 23 0 21 0 119 0 118 1 206 1 194 1078 958 122 2/bit 2 10 1399 73 2762 60 2760 5524 5538 124 105 1/bit 2 (P = 0.13); l ² = 5 1 6602 6496 136 127 1/bit 1.0.50, df = 8 (P = 0.23); l ² = 1 1 1	Events Total Events Total Weight 1 130 2 67 2.4% 0 40 0 40 4 282 10 250 9.0% 1 100 1 96 1.8% 1 77 1 74 1.8% 0 30 0 29 4 4 71 7 69 7.8% 0 23 0 21 0 0 190 118 1 206 1 194 1.8% 1078 958 24.6% 122 22 24.6% 122 22 24.6% 124 128 128 128 129 3.2% 3.2% 3.2% 3.2% 3.2% 5538 75.4% 124 105 514'2 4.10, df = 2 (P = 0.13); l² = 51% 14 14 14 14 14 14 14 14 14 14 14 </td <td>Events Total Events Total Weight M-H, Random, 95% CI 1 130 2 67 2.4% 0.25 [0.02, 2.83] 0 40 0 40 Not estimable 4 282 10 250 9.0% 0.35 [0.11, 1.12] 1 100 1 96 1.8% 0.96 [0.06, 15.64] 0 30 0 29 Not estimable 4 71 7 69 7.8% 0.53 [0.15, 1.89] 0 119 0 118 Not estimable 1 206 1 194 1.8% 0.94 [0.06, 15.16] 1078 958 24.6% 0.47 [0.23, 0.98] 122 212 22 22 22 24.6% 0.47 [0.26, 1.73] 5524 5538 75.4% 1.21 [0.76, 1.92] 124 107 2.0 5538 75.4% 1.21 [0.76, 1.92] 124 105 5538 75.4% 1.21 [0.76, 1.</td>	Events Total Events Total Weight M-H, Random, 95% CI 1 130 2 67 2.4% 0.25 [0.02, 2.83] 0 40 0 40 Not estimable 4 282 10 250 9.0% 0.35 [0.11, 1.12] 1 100 1 96 1.8% 0.96 [0.06, 15.64] 0 30 0 29 Not estimable 4 71 7 69 7.8% 0.53 [0.15, 1.89] 0 119 0 118 Not estimable 1 206 1 194 1.8% 0.94 [0.06, 15.16] 1078 958 24.6% 0.47 [0.23, 0.98] 122 212 22 22 22 24.6% 0.47 [0.26, 1.73] 5524 5538 75.4% 1.21 [0.76, 1.92] 124 107 2.0 5538 75.4% 1.21 [0.76, 1.92] 124 105 5538 75.4% 1.21 [0.76, 1.

(B) Cardiovascular (CV) mortality



(C) New myocardial infarction

Charles .	Colchic	ine	Placebo/ c	ontrol		Odds Ratio	Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Smaller trials							
LoDoCo trial 2013 30	13	282	34	250	16.8%	0.31 [0.16, 0.60]	_
COLIN trial 2017 35	0	23	1	21	1.1%	0.29 [0.01, 7.54]	
LoDoCo-MI trial 2019 36	0	119	2	118	1.2%	0.19 [0.01, 4.10]	· · · · · · · · · · · · · · · · · · ·
COLCHICINE-PCI trial 2020 ¹ Subtotal (95% CI)	6 0	206 630	1	194 583	1.1% 20.2%		•
Total events	13		38				
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 0.0$	08, df =	= 3 (P = 0.9)	$(99); I^2 = ($	0%		
Test for overall effect: $Z = 3$.	77 (P = 0)	.0002)					
→ Larger trials							
COLCOT trial 2019 8	89	2366	98	2379	34.8%	0.91 [0.68, 1.22]	+
LoDoCo2 trial 2020 18	83	2762	116	2760	35.2%	0.71 [0.53, 0.94]	
COPS trial 2020 17	7	396	11	399	9.9%	0.63 [0.24, 1.65]	
Subtotal (95% CI)		5524		5538	79.8%	0.79 [0.65, 0.97]	\blacklozenge
Total events	179		225				
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 1.6$	58, df =	= 2 (P = 0.4)	13); I ² = (0%		
Test for overall effect: $Z = 2$.	29 (P = 0)	.02)					
Total (95% CI)		6154		6121	100.0%	0.64 [0.46, 0.90]	◆
Total events	192		263				
Heterogeneity: Tau ² = 0.06;	$Chi^{2} = 10$.15, df	f = 6 (P = 0)	.12); I ² =	41%		0.01 0.1 1 10 10
Test for overall effect: $Z = 2$.	57 (P = 0	.01)					Favours colchicine Favours placebo/ control
Test for subgroup difference	c Chi ² - Chi ²	227 4	f = 1 /P = 0	0.004) 12	- 88 1%		ravours continente ravours placebo/ control

(D) Stroke or transient ischemic attack (TIA)

Studies	Colchi		Placebo/ o			Odds Ratio	Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
→ Smaller trials							
COOL trial 2012 29	0	40	1	40	2.2%	0.33 [0.01, 8.22]	
LoDoCo trial 2013 30	1	282	4	250	4.7%	0.22 [0.02, 1.97]	
Deftereos et al. 2013 31	1	100	0	96	2.2%	2.91 [0.12, 72.30]	
COLCHICINE-PCI trial 2020 16	1	366	0	348	2.2%	2.86 [0.12, 70.45]	
Subtotal (95% CI)		788		734	11.3%		
Total events	3		5				
Heterogeneity: $Tau^2 = 0.00$; 0	$Chi^2 = 2$.	78. df	= 3 (P = 0.4)	3); $I^2 = ($	0%		
Test for overall effect: $Z = 0.6$				- // ·			
→ Larger trials							
COLCOT trial 2019 8	5	2366	19	2379	23.4%	0.26 [0.10, 0.71]	
LoDoCo2 trial 2020 18	16	2762	24	2760	56.5%	0.66 [0.35, 1.25]	— • +
COPS trial 2020 17	2		6	399	8.8%	0.33 [0.07, 1.66]	
Subtotal (95% CI)	-	5524		5538			◆
Total events	23		49				-
Heterogeneity: Tau ² = 0.08; 0	$Chi^2 = 2$.	65. df	= 2 (P = 0.2)	7): $I^2 = 2$	25%		
Test for overall effect: $Z = 2.4$.,,.			
Total (95% CI)		6312		6272	100.0%	0.50 [0.31, 0.81]	◆
Total events	26		54				
Heterogeneity: Tau ² = 0.00; 0	$Chi^2 = 5$.	56. df	= 6 (P = 0.4)	7); $I^2 = ($	0%		
Test for overall effect: $Z = 2.8$							0.01 0.1 i 10
Test for subgroup differences			f = 1 (P = 0)	.65), I ² =	0%		Favours colchicine Favours placebo/ control

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

Studies	Colchie Events		Placebo/ C Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
Smaller trials	Lvents	Total	Lvents	Total	weight	M-H, Kalluolli, 55% Cl	
O'Keefe et al. 1992 28	9	130	1	67	3.0%	4.91 [0.61, 39.60]	
COOL trial 2012 29	3	36	1	38	2.5%	3.36 [0.33, 33.93]	
LoDoCo trial 2013 30	62	282	0	250	1.8%	142.01 [8.73, 2309.13]	
Deftereos et al. 2013 31	17	100	9	96	11.0%	1.98 [0.84, 4.69]	
Giannopoulos et al. 2015 32	4	30	3	29	4.7%	1.33 [0.27, 6.56]	
Deftereos et al. 2015 33	20	77	3	74	6.7%	8.30 [2.35, 29.35]	
COLIN trial 2017 35	3	23	0	21	1.5%	7.34 [0.36, 151.09]	
LoDoCo-MI trial 2019 36	2	111	4	113	4.2%	0.50 [0.09, 2.79]	
Subtotal (95% CI)		789		688	35.4%	3.69 [1.24, 11.00]	
Total events	120		21				
Heterogeneity: Tau ² = 1.54	: Chi ² =	22.33.	df = 7 (P =	0.002); I ⁱ	$^{2} = 69\%$		
Test for overall effect: $Z = 2$							
► Larger trials							
COLCOT trial 2019 ⁸	435	2366	445	2379	23.3%	0.98 [0.85, 1.13]	+
COPS trial 2020 ¹⁷	61	396	33	399	18.2%	2.02 [1.29, 3.16]	
LoDoCo2 trial 2020 18	290	2762	290	2760	23.1%	1.00 [0.84, 1.19]	<u>+</u>
Subtotal (95% CI)		5524		5538	64.6%	1.14 [0.87, 1.50]	♠
Total events	786		768				
Heterogeneity: Tau ² = 0.04	; Chi ² = 9	9.23, d	f = 2 (P = 0)	.010); I ²	= 78%		
Test for overall effect: $Z = 0$).97 (P =	0.33)					
Total (95% CI)		6313		6226	100.0%	1.68 [1.14, 2.48]	•
Total events	906		789				+
Heterogeneity: $Tau^2 = 0.16$		41.49.		0.0000	1): $ ^2 = 70$	5%	
					-,,,.		0.01 0.1 1 10 10
Test for overall effect: $Z = 2$)				Favours colchicine Favours placebo/ control

(F) Gastrointestinal side effects

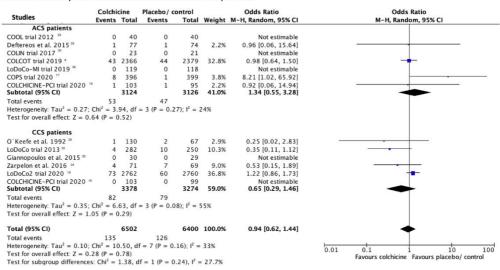
Studies	Colchi	cine	Cont	rol		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
→ Smaller trials							
O´Keefe et al. 1992 28	41	130	8	67	9.8%	3.40 [1.49, 7.76]	
COOL trial 2012 29	14	40	7	40	8.0%	2.54 [0.89, 7.20]	
LoDoCo trial 2013 30	32	282	0	250		65.00 [3.96, 1067.34]	
Deftereos et al. 2013 31	16		7	96	8.9%	2.42 [0.95, 6.18]	
Deftereos et al. 2015 33	18	77	1	74	3.3%	22.27 [2.89, 171.74]	
Giannopoulos et al. 2015 32	5	30	1	29	2.9%	5.60 [0.61, 51.24]	
COLIN trial 2017 35	10		0	21	1.8%	33.44 [1.81, 618.57]	
LoDoCo-MI trial 2019 36	12	111	6	113	8.2%	2.16 [0.78, 5.98]	
COLCHICINE-PCI trial 2020 16 Subtotal (95% CI)	34	206 999	11	194 884	10.9% 55.9%	3.29 [1.62, 6.70] 3.88 [2.26, 6.66]	
Total events	182		41				
Heterogeneity: $Tau^2 = 0.25$;				= 0.09)	$ ^2 = 419$	6	
Test for overall effect: $Z = 4$.				0.05)	,	•	
→ Larger trials							
COLCOT trial 2019 8	408	2330	414	2346	15.6%	0.99 [0.85, 1.15]	+
COPS trial 2020 17	91	396	83	399	14.5%	1.14 [0.81, 1.59]	
LoDoCo2 trial 2020 18	53	2762	50	2760	14.0%	1.06 [0.72, 1.57]	
Subtotal (95% CI)		5488		5505	44.1%	1.02 [0.89, 1.16]	♦
Total events	552		547				
Heterogeneity: Tau ² = 0.00;	$Chi^{2} = 0.$	58, df	= 2 (P =	0.75);	$I^2 = 0\%$		
Test for overall effect: $Z = 0.1$	28 (P = 0	0.78)					
Total (95% CI)		6487		6389	100.0%	2.21 [1.45, 3.36]	◆
Total events	734		588				
Heterogeneity: Tau ² = 0.29;	$Chi^2 = 5$	0.11, d	f = 11 (P	< 0.00	0001); I ²	= 78%	0.01 0.1 1 10 100
Test for overall effect: $Z = 3$.	70 (P = 0	0.0002)				Favours colchicine Favours placebo/ control
Test for subgroup differences	s: Chi ² =	22.21,	df = 1 (I	P < 0.0	0001), I ²	= 95.5%	ravours colemente - ravours placeboy control

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

Studies	Colchi Events		Placebo/ c Events	ontrol Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
LoDoCo trial 2013 30	4	282	5	250	8.9%	0.71 [0.19, 2.66]	
COLCOT trial 2019 8	23	2366	20	2379	34.5%	1.16 [0.63, 2.11]	-
COPS trial 2020 17	5	396	0	399	2.0%	11.22 [0.62, 203.68]	
LoDoCo2 trial 2020 18	53	2762	35	2760	54.7%	1.52 [0.99, 2.34]	
Total (95% CI)		5806		5788	100.0%	1.35 [0.90, 2.02]	◆
Total events	85		60				
Heterogeneity: Tau ² =	0.03; Cl	ni ² = 3.	55, df = 3 (P = 0.31); $I^2 = 16$	%	
Test for overall effect:	Z = 1.43	B (P = 0)	0.15)				0.01 0.1 1 10 100 Favours colchicine Favours placebo/ control

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.

(A) All-	-cause mortality	with colchic	ine treatment	in ACS vs	CCS patients
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(B) All-cause mortality with short- (≤30 days) versus vs. long-term (>30 days) colchicine treatment

Studies	Colchie Events		Placebo/ o Events		Weight	Odds Ratio M-H. Random, 95% Cl	Odds Ratio M–H, Random, 95% CI
Therapy duration≤							
COOL trial 2012 29	0	40	0	40		Not estimable	
Deftereos et al. 2015 33	1	77	1	74	3.8%	0.96 [0.06, 15.64]	
Giannopoulos et al. 2015 32	0	30	0	29		Not estimable	
Zarpelon et al. 2016 34	4	71	7	69	14.8%	0.53 [0.15, 1.89]	
COLIN trial 2017 35	0	23	0	21		Not estimable	
LoDoCo-MI trial 2019 36	0	119	0	118		Not estimable	
COLCHICINE-PCI trial 2020 ¹⁶ Subtotal (95% CI)	1	206 566	1	194 545	3.8% 22.4%	0.94 [0.06, 15.16] 0.63 [0.22, 1.84]	
Total events	6		9				
Heterogeneity: $Tau^2 = 0.00$;	$Chi^2 = 0.$	24. df	= 2 (P = 0.1)	$(89): ^2 = ($	0%		
Test for overall effect: $Z = 0.1$							
Therapy duration >	30 days						
O'Keefe et al. 1992 28	1	130	2	67	5.0%	0.25 [0.02, 2.83]	
LoDoCo trial 2013 30	4	282	10	250	16.7%	0.35 [0.11, 1.12]	
Deftereos et al. 2013 31	1	100	1	96	3.8%	0.96 [0.06, 15.56]	
COLCOT trial 2019 *	43	2366	44	2379	45.5%	0.98 [0.64, 1.50]	
COPS trial 2020 17 Subtotal (95% CI)	8	396 3274	1	399 3191	6.5% 77.6%	8.21 [1.02, 65.92] 0.86 [0.34, 2.16]	
Total events	57		58				
Heterogeneity: $Tau^2 = 0.50$;	$Chi^2 = 8.$	17. df	= 4 (P = 0.0)	$(09): ^2 = 1$	51%		
Test for overall effect: $Z = 0.3$							
Total (95% CI)		3840		3736	100.0%	0.80 [0.46, 1.41]	•
Total events	63		67				
Heterogeneity: $Tau^2 = 0.13$;	$Chi^2 = 8.$	82. df	= 7 (P = 0.3)	(27) ; $I^2 = 3$	21%		terre als de la se
Test for overall effect: $Z = 0.1$							
Test for subgroup differences			f = 1 (P = 0)	$(0.66), 1^2 =$	= 0%		Favours colchicine Favours placebo/ control

(C) All-cause mortality with low- vs. high-dose colchicine treatment

Studies	Colchi Events		Placebo/ c Events		Weight	Odds Ratio M-H. Random, 95% Cl		Odds Ratio M-H. Random, 95% Cl
Single dose or ≤0.			Events	Total	weight	m-n, Kandom, 95% Ci		M-H, Kandom, 95% Cl
LoDoCo trial 2013 30	4	282	10	250	9.0%	0.35 [0.11, 1.12]		
COLCOT trial 2019	43		44	2379		0.98 [0.64, 1.50]		
LoDoCo-MI trial 2019 36	0	119	0	118	33.470	Not estimable		T
COPS trial 2020 17	8	396	1	399	3.2%	8.21 [1.02, 65.92]		
LoDoCo2 trial 2020 "	-	2762	60	2760	38.8%	1.22 [0.86, 1.73]		
COLCHICINE-PCI trial 2020 Subtotal (95% CI)			1	194 6100	1.8%	0.94 [0.06, 15.16] 1.04 [0.63, 1.71]		
Total events	129	0151	116	0100	00.270	1.04 [0.05, 1.71]		
Heterogeneity: $Tau^2 = 0.13$;		0.0 46		101 12 -	E 0.9/			
Test for overall effect: $Z = 0$			= 4 (F = 0.0	/9), 1 =	50%			
Test for overall effect. 2 = 0	.10 (r = (5.67)						
>0.5mg daily								
O'Keefe et al. 1992 28	1	130	2	67	2.4%	0.25 [0.02, 2.83]		
COOL trial 2012 29	0	40	0	40		Not estimable		
Deftereos et al. 2013 31	1	100	1	96	1.8%	0.96 [0.06, 15.56]		
Deftereos et al. 2015 33	1	77	1	74	1.8%	0.96 [0.06, 15.64]		
Giannopoulos et al. 2015 32	0	30	0	29		Not estimable		
Zarpelon et al. 2016 34	4	71	7	69	7.8%	0.53 [0.15, 1.89]		
COLIN trial 2017 35	0	23	0	21		Not estimable		
Subtotal (95% CI)		471		396	13.8%	0.54 [0.20, 1.44]		
Total events	7		11					
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 0.$	71, df	= 3 (P = 0.8)	$(37); I^2 = 0$	0%			
Test for \overline{o} verall effect: Z = 1	.22 ($P = 0$	0.22)						
Total (95% CI)		6602		6496	100.0%	0.96 [0.65, 1.41]		+
Total events	136		127					
Heterogeneity: $Tau^2 = 0.07$;	$Chi^{2} = 10$	0.50, d	f = 8 (P = 0)	.23); I ² =	24%		0.01	
Test for overall effect: $Z = 0$							0.01	0.1 i 10 10 Favours colchicine Favours placebo/ control
Test for subgroup difference	s: Chi ² =	1.35. 0	f = 1 (P = 0)	.24), I ² =	= 26.0%			ravours continente ravours placebo/ control

Figure S6.

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

(A) Cardiovascular mortality with colchicine treatment in ACS vs. CCS patients

Studies	Colchie		Placebo/ c			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
ACS patients							
COOL trial 2012 29	0	40	0	40		Not estimable	
Deftereos et al. 2015 30	1	77	1	74	2.1%	0.96 [0.06, 15.64]	
COLIN trial 2017 ³⁵	0	23	0	21		Not estimable	
COLCOT trial 2019 *	20	2366	24	2379	45.9%	0.84 [0.46, 1.52]	
LoDoCo-MI trial 2019 3	6 0	119	0	118		Not estimable	
COPS trial 2020 17	3	396	1	399	3.2%	3.04 [0.31, 29.33]	
Subtotal (95% CI)		3021		3031	51.2%	0.91 [0.52, 1.60]	•
Total events	24		26				
Heterogeneity: $Tau^2 = 0$).00: Chi ²	= 1.17	7. $df = 2$ (P	= 0.56):	$I^2 = 0\%$		
Test for overall effect: Z							
CCS patients							
LoDoCo trial 2013 ³⁰	0	282	5	250	1.9%	0.08 [0.00, 1.44]	·
LoDoCo2 trial 2020 ¹⁸	20	2762	25	2760	46.8%	0.80 [0.44, 1.44]	
Subtotal (95% CI)		3044		3010	48.8%	Text 0.39 [0.05, 3.32]	
Total events	20		30				
I otal events				0.1.01	12 5000		
	65; Chi ²	= 2.4	5, $df = 1$ (P	= 0.12);	1 = 59%		
Heterogeneity: Tau ² = 1 Test for overall effect: Z				= 0.12);	1 = 59%		
Heterogeneity: Tau ² = 1 Test for overall effect: Z					100.0%		•
Heterogeneity: Tau ² = 1 Test for overall effect: Z Total (95% CI)	2 = 0.87 (P = 0.3	39)			0.82 [0.55, 1.22]	•
Heterogeneity: Tau ² = 1 Test for overall effect: Z Total (95% CI) Total events	44	P = 0.3	56	6041	100.0%		•
Heterogeneity: Tau ² = 1	44 2.00; Chi ²	P = 0.3 6065 = 3.85	56 5, df = 4 (P	6041	100.0%		0.01 0.1 1 10 10 Favours colchicine Favours placebo/ control

(B) Cardiovascular mortality with short- (≤30 days) versus vs. long-term (>30 days) colchicine treatment

Studies	Colchi Events		Placebo/ co Events		Wei-he	Odds Ratio M-H, Random, 95% CI	Odds Ratio M–H, Random, 95% CI
Therapy durat			Events	TOLAI	weight	M-H, Kandolli, 95% Cl	M-H, Kanuolii, 95% Ci
COOL trial 2012	012301	40	0	40		Not estimable	
	0		0	40	2.10/		
Deftereos et al. 2015		77	1	74	2.1%	0.96 [0.06, 15.64]	
COLIN trial 2017 35	0	23	0	21		Not estimable	
LoDoCo-MI trial 2019 [∞] Subtotal (95% CI)	0	119 259	0	118 253	2.1%	Not estimable 0.96 [0.06, 15.64]	
Total events	1		1				
Heterogeneity: Not appl	icable						
Test for overall effect: Z	= 0.03	(P = 0.9)	98)				
Therapy durat	ion > 30	days					
LoDoCo trial 2013 30	0	282	5	250	1.9%	0.08 [0.00, 1.44]	· · · · · · · · · · · · · · · · · · ·
Deftereos et al. 2013 31	1	100	1	96	2.1%	0.96 [0.06, 15.56]	
COLCOT trial 2019 *	20	2366	24	2379	45.0%	0.84 [0.46, 1.52]	_
LoDoCo2 trial 2020 18	20	2762	25	2760	45.9%	0.80 [0.44, 1.44]	
COPS trial 2020 17	3	396	1	399	3.1%	3.04 [0.31, 29.33]	
Subtotal (95% CI)		5906		5884	97.9%	0.82 [0.55, 1.22]	◆
Total events	44		56				
Heterogeneity: $Tau^2 = 0$	0.00; Chi ²	2 = 3.8	5, $df = 4 (P =$	= 0.43);	$I^2 = 0\%$		
Test for overall effect: Z	= 0.98	(P = 0.3)	33)				
Total (95% CI)		6165		6137	100.0%	0.82 [0.55, 1.22]	•
Total events	45		57				
Heterogeneity: $Tau^2 = 0$	0.00: Chi	2 = 3.8	6. df = 5 (P =	= 0.57);	$I^2 = 0\%$		
Test for overall effect: Z							0.01 0.1 i 10 100
Test for subgroup differ				= 0.91), $I^2 = 0\%$		Favours colchicine Favours placebo/ control
5							

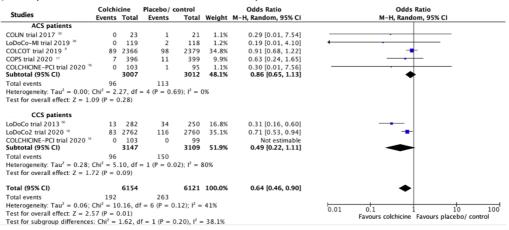
	Colchi	cine	Placebo/ co	ontrol		Odds Ratio	Odds Ratio
Studies	Events		Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Single dose or	≤0.5mg	daily					
LoDoCo trial 2013 [∞]	0	282	5	250	1.9%	0.08 [0.00, 1.44]	·
COLCOT trial 2019		2366	24	2379	45.0%	0.84 [0.46, 1.52]	_
LoDoCo-MI trial 2019 3	0	119	0	118		Not estimable	
COPS trial 2020 17	3	396	1	399	3.1%	3.04 [0.31, 29.33]	
LoDoCo2 trial 2020 18	20	2762	25	2760	45.9%	0.80 [0.44, 1.44]	
Subtotal (95% CI)		5925		5906	95.9%	0.81 [0.48, 1.37]	◆
Total events	43		55				
Heterogeneity: Tau ² = 0	.07; Chi ²	= 3.84	4, df = 3 (P =	= 0.28);	$I^2 = 22\%$		
Test for overall effect: Z	= 0.78 (P = 0.4	14)				
>0.5mg daily							
COOL trial 2012 29	0	40	0	40		Not estimable	
Deftereos et al. 2013 31	1	100	1	96	2.1%	0.96 [0.06, 15.56]	
Deftereos et al. 2015 33	1	77	1	74	2.1%	0.96 [0.06, 15.64]	
COLIN trial 2017 ³⁵	0	23	0	21		Not estimable	
Subtotal (95% CI)		240		231	4.1%	0.96 [0.13, 6.90]	
Total events	2		2				
Heterogeneity: Tau ² = 0	.00; Chi ²	= 0.00	0, df = 1 (P =	= 1.00);	$I^2 = 0\%$		
Test for overall effect: Z	= 0.04 (P = 0.9	97)				
Total (95% CI)		6165		6137	100.0%	0.82 [0.55, 1.22]	•
Total events	45		57				
Heterogeneity: $Tau^2 = 0$	00 Chi ²	= 3.86	df = 5 (P)	= 0 5 7).	$I^2 = 0\%$		0.01 0.1 1 10

Figure S7.

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

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(A) New myocardial infarction with colchicine treatment in ACS vs. CCS patients



(B) New myocardial infarction with short- (≤30 days) versus vs. long-term (>30 days) colchicine treatment

Charling	Colchi	cine	Placebo/ c	ontrol		Odds Ratio	Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Therapy duration≤	30 days						
COLIN trial 2017 35	0	23	1	21	1.1%	0.29 [0.01, 7.54]	
LoDoCo-MI trial 2019 [™]	0	119	2	118	1.2%	0.19 [0.01, 4.10]	
COLCHICINE-PCI trial 2020 16	0	206	1	194	1.1%	0.31 [0.01, 7.71]	
Subtotal (95% CI)		348		333	3.4%	0.26 [0.04, 1.60]	
Total events	0		4				
Heterogeneity: $Tau^2 = 0.00$;	$Chi^{2} = 0.$	05, df	= 2 (P = 0.9)	$(77); I^2 = 1$	0%		
Test for overall effect: $Z = 1$.	45 (P = 0	0.15)					
Therapy duration >	30 days						
LoDoCo trial 2013 30	13	282	34	250	16.8%	0.31 [0.16, 0.60]	_ _
COLCOT trial 2019 8	89	2366	98	2379	34.8%	0.91 [0.68, 1.22]	
LoDoCo2 trial 2020 18	83	2762	116	2760	35.2%	0.71 [0.53, 0.94]	
COPS trial 2020 17	7	396	11	399	9.9%	0.63 [0.24, 1.65]	
Subtotal (95% CI)		5806		5788	96.6%	0.65 [0.44, 0.96]	•
Total events	192		259				
Heterogeneity: $Tau^2 = 0.09$;	$Chi^2 = 8.$	85, df	= 3 (P = 0.0)	()(); $I^2 = 1$	66%		
Test for overall effect: $Z = 2$.							
Total (95% CI)		6154		6121	100.0%	0.64 [0.46, 0.90]	•
Total events	192		263				
Heterogeneity: $Tau^2 = 0.06$;	$Chi^2 = 10$	0.15. d	f = 6 (P = 0)	.12): I ² =	41%		
Test for overall effect: $Z = 2$.			(· -		-		0.01 0.1 i 10 100
Test for subgroup differences			f = 1 (P = 0)).33), l ² =	= 0%		Favours colchicine Favours placebo/ control

(C) New myocardial infarction with low- vs. high-dose colchicine treatment

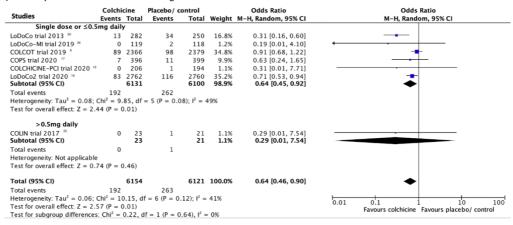
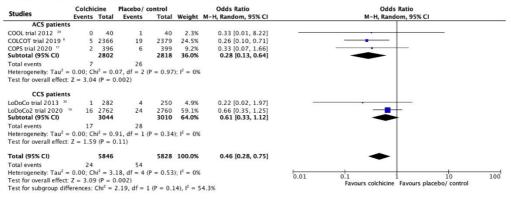


Figure S8

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

(A) Stroke / TIA with colchicine treatment in ACS vs. CCS patients



(B) Stroke / TIA with short- (<30 days) versus vs. long-term (>30 days) colchicine treatment

a	Colchi	cine	Placebo/ c	ontrol		Odds Ratio		Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
Therapy duration≤	30 days							
COOL trial 2012 29	0	40	1	40	2.2%	0.33 [0.01, 8.22]		
Deftereos et al. 2013 31	1	100	0	96	2.2%	2.91 [0.12, 72.30]		
COLCHICINE-PCI trial 2020 ³¹ Subtotal (95% CI)	6 1	366 506	0	348 484	2.2% 6.6%	2.86 [0.12, 70.45] 1.40 [0.22, 8.98]		
Total events	2		1					
Heterogeneity: $Tau^2 = 0.00$;	$Chi^2 = 1$	18, df	= 2 (P = 0.5)	56): $I^2 = 0$	0%			
Test for overall effect: $Z = 0$.	36 (P = 0)	0.72)						
Therapy duration >	30 days							
LoDoCo trial 2013 30	1	282	4	250	4.7%	0.22 [0.02, 1.97]	_	
COLCOT trial 2019 *	5	2366	19	2379	23.4%	0.26 [0.10, 0.71]		
LoDoCo2 trial 2020 18	16	2762	24	2760	56.5%	0.66 [0.35, 1.25]		
COPS trial 2020 17	2	396	6	399	8.8%	0.33 [0.07, 1.66]		
Subtotal (95% CI)		5806		5788	93.4%	0.46 [0.27, 0.77]		•
Total events	24		53					
Heterogeneity: $Tau^2 = 0.02$;	$Chi^2 = 3$	14. df	= 3 (P = 0.3)	$(37): ^2 = -$	4%			
Test for overall effect: $Z = 2$.								
Total (95% CI)		6312		6272	100.0%	0.50 [0.31, 0.81]		•
Total events	26		54					
Heterogeneity: $Tau^2 = 0.00$;	$Chi^2 = 5$	56. df	= 6 (P = 0.4)	$(7); ^2 = 1$	0%			
Test for overall effect: $Z = 2$.							0.01	
Test for subgroup differences			if = 1 (P = 0)).25), l ² =	= 23.0%			Favours colchicine Favours placebo/ control
· ·····								

(C) Stroke / TIA with with low- vs. high-dose colchicine treatment

	Colchi	cine	Placebo/ c	ontrol		Odds Ratio	Odds Ratio
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
. Single dose or ≤0.	5mg dail	У					
LoDoCo trial 2013 30	1	282	4	250	4.7%	0.22 [0.02, 1.97]	
COLCOT trial 2019	5	2366	19	2379	23.4%	0.26 [0.10, 0.71]	
COPS trial 2020 17	2	396	6	399	8.8%	0.33 [0.07, 1.66]	
COLCHICINE-PCI trial 2020	16 1	366	0	348	2.2%	2.86 [0.12, 70.45]	
LoDoCo2 trial 2020 ¹⁸ Subtotal (95% CI)	16	2762 6172	24	2760 6136	56.5% 95.6%	0.66 [0.35, 1.25] 0.47 [0.27, 0.81]	•
Total events	25		53				
Heterogeneity: $Tau^2 = 0.04$;	$Chi^2 = 4$	33. df	= 4 (P = 0.3)	(6): $I^2 = 3$	8%		
Test for overall effect: $Z = 2$							
>0.5mg daily							
COOL trial 2012 29	0	40	1	40	2.2%	0.33 [0.01, 8.22]	
Deftereos et al. 2013 ³¹ Subtotal (95% CI)	1	100 140	0	96 136	2.2%	2.91 [0.12, 72.30] 0.98 [0.10, 9.55]	
Total events	1		1				
Heterogeneity: $Tau^2 = 0.00$;	$Chi^2 = 0$	89. df	= 1 (P = 0.3)	$(5) \cdot l^2 = l$	0%		
Test for overall effect: $Z = 0$			10.000	37,1			
Total (95% CI)		6312		6272	100.0%	0.50 [0.31, 0.81]	•
Total events	26		54				
Heterogeneity: $Tau^2 = 0.00$;	$Chi^2 = 5.$	56, df	= 6 (P = 0.4)	(7); $I^2 = 1$	0%		0.01 0.1 1 10 10
Test for overall effect: $Z = 2$.							0.01 0.1 1 10 10 Favours colchicine Favours placebo/ control
Test for subaroup difference			f - 1 /P - 0	EA) 12	- 0%		ravours colonicine Favours placebo/ control

Figure S9.

Ischemia driven or urgent revascularization with colchicine compared to placebo/ standard therapy

	Colchi	cine	Placebo/ o	ontrol		Odds Ratio		Odds Ratio	
Studies	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Deftereos et al. 2013 31	4	112	5	110	6.9%	0.78 [0.20, 2.98]			
COLCOT trial 2019 8	25	2366	50	2379	31.6%	0.50 [0.31, 0.81]			
COPS trial 2020 17	3	396	12	399	7.6%	0.25 [0.07, 0.88]			
LoDoCo2 trial 2020 18	135	2762	177	2760	54.0%	0.75 [0.60, 0.94]			
COLCHICINE-PCI trial 2020 16	0	206	0	194		Not estimable			
Total (95% CI)		5842		5842	100.0%	0.61 [0.42, 0.88]		•	
Total events	167		244						
Heterogeneity: $Tau^2 = 0.05$;	$Chi^{2} = 4.$	79, df	= 3 (P = 0.1)	9); $I^2 = 3$	37%		0.01		100
Test for overall effect: $Z = 2.0$	64 (P = 0	0.008)					0.01	0.1 1 10 Favours colchicine Favours placebo/	100 control

Figure S10.

Infectious complications with colchicine compared to placebo/ standard therapy

Studies	Colchi Events		Placebo/ c Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M–H, Random, 95% Cl
Zarpelon et al. 2016 ³⁴	19	71	6	69	19.1%	3.84 [1.43, 10.31]	
COLCOT trial 2019 *	51	2330	38	2346	37.3%	1.36 [0.89, 2.08]	+=-
LoDoCo2 trial 2020 18	137	2762	144	2760	43.7%	0.95 [0.75, 1.21]	+
Total (95% CI)		5163		5175	100.0%	1.42 [0.81, 2.47]	•
Total events	207		188				
Heterogeneity: Tau ² =	0.17; Ch	$i^2 = 8.5$	57, df = 2 (F	P = 0.01)	$I^2 = 779$	%	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.22	(P = 0	.22)				Favours colchicine Favours placebo/ control