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

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ABSTRACT:

Background: Inflammation plays a central role in the pathogenesis and clinical manifestations of atherosclerosis. Randomized controlled trials (RCTs) have investigated the potential benefit of colchicine in reducing cardiovascular events (CE) in patients with coronary artery disease (CAD) but produced conflicting results. The aim of this meta-analysis was to evaluate the efficacy and safety of colchicine in patients with CAD.

Methods: We systematically searched selected electronic databases from inception until 10th December 2020. Primary clinical endpoints were: major adverse cardiac events (MACE), all-cause mortality, cardio-vascular (CV) mortality, recurrent myocardial infarction (MI), stroke, hospitalization and adverse medication effects. Secondary endpoints were short-term effect of colchicine on inflammatory markers.

Results: Twelve RCTs with a total of 13,073 patients with CAD (colchicine n=6351 and placebo n=6722) were included in the meta-analysis. At mean follow-up of 22.5 months, the colchicine group had lower risk of MACE (6.20% vs. 8.87%; $p<0.001$), recurrent MI (3.41% vs. 4.41%; $p=0.005$), stroke (0.40% vs. 0.90%; $p=0.002$) and hospitalization due to CE (0.90% vs. 2.87%; $p=0.02$) compared to the control group. The two patient groups had similar risk for all-cause mortality (2.08% vs. 1.88%; $p=0.82$) and CV mortality (0.71% vs. 1.01%; $p=0.38$). Colchicine significantly reduced hs-CRP (-4.25, $p=0.001$) compared to controls but did not significantly affect IL-β1 and IL-18 levels.

Conclusions: Colchicine reduced cardiovascular events and inflammatory markers, hs-CRP and IL-6, in patients with coronary disease compared to controls. Its impact on cardiovascular and all-cause mortality requires further investigation.

Key words: Colchicine, coronary artery disease, myocardial infarction.

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of death worldwide, despite lifestyle changes, risk factors control and improvement of optimal medical therapy [1]. Lowering serum cholesterol, inhibition of platelet aggregation and control of risk factors, are the main approaches currently practiced to prevent/slow atherosclerosis progression. It is also well recognized that inflammation has a central role in the pathogenesis and clinical manifestations of atherosclerosis [2,3]. Theoretically, targeting pro-inflammatory cytokines could be a valuable therapeutic approach in the prevention and treatment of CAD. Hence this hypothesis was tested in clinical trials using a range of anti-inflammatory agents, but the results were conflicting [4-6].

Colchicine is an anti-inflammatory drug, originally extracted from the *Colchicum autumnale,* a plant used by the ancient Greeks and Egyptians. In contrast to other anti-inflammatory drugs, colchicine has broad cellular effects through inhibition of tubulin polymerization and alteration of leukocyte responsiveness [7-9]. When colchicine binds to tubulin it affects mitosis and various functions of microtubules, including leucocyte movements, exocytosis and phagocytosis. Colchicine can affect several functions of inflammatory cells, especially neutrophils, e.g. chemotaxis, adhesion and recruitment to damaged tissues [10,11]. Based on its anti-inflammatory effects, colchicine has been used for a long time for the treatment of various non-cardiac inflammatory disorders such as gout, rheumatoid arthritis, and Familial Mediterranean Fever, and in cardiac diseases such as pericarditis [12,13]. In the last decade, the safety and efficacy of colchicine in patients with CAD were tested in several randomized controlled trials (RCTs) [14-19]. The results of these trials were conflicting, and pooled analysis suggested that colchicine was not associated with a significant reduction in cardiovascular (CV) endpoints including mortality [20]. However, two majors recently published RCTs showed that

colchicine at a daily dose of 0.5mg led to a significantly lower risk of ischemic CV events compared with placebo [20, 21]. Thus, we conducted a systematic review and meta-analysis of all available RCTs [14-21] aimed to evaluate the safety and efficacy of colchicine in patients with CAD.

METHODS

We followed the PRISMA guidelines of the 2020 preferred reporting items for systematic reviews and meta-analysis statement [22]. Due to the study design (meta-analysis), neither Institutional Review Board (IRB) approval nor patient informed consent was needed.

Search strategy

We systematically searched electronic databases (PubMed-Medline, EMBASE, Scopus, Google Scholar, the Cochrane Central Registry of Controlled Trials and ClinicalTrial.gov) from inception until 10th September 2020, using the following key words: "Colchicine" AND "Coronary artery disease" OR "CAD" OR "Acute coronary syndrome" OR "Acute myocardial infarction" OR "ST elevation myocardial infarction" OR "STEMI" AND "Follow up" AND "Outcomes" OR "Inflammatory markers" OR "CRP" OR "interleukin". Additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), American College of Cardiology (ACC), National Lipid Association (NLA), and European Society of Atherosclerosis (EAS). The wild-card term ''*'' was used to increase the sensitivity of the search strategy. The literature search was limited to articles published in English and to studies in humans. Two reviewers (IB and GB)

independently evaluated each article separately. No filters were applied. The remaining articles were obtained in full-text and assessed, again, by the same two researchers who evaluated each article independently, carried out data extraction and quality assessment. Disagreements were resolved by discussion with a third party (MB).

Study selection

The inclusion criteria in this meta-analysis were: a) trials investigating CAD, reporting outcomes in two arms (colchicine and control); b) randomized controlled trials; c) follow-up trials, d) trials reporting clinical outcomes and/or inflammatory markers, e) studies enrolling adults ≥18 years.

Exclusion criteria were: a) non-randomized study design, b) studies investigating the effects of colchicine on other CV diseases such atrial fibrillation, pericarditis, heart failure etc., c) ongoing trials (unless they had reported relevant interim results).

Outcome measures

Primary clinical endpoints were major adverse cardiac events (MACE), all-cause mortality, CV mortality, recurrent MI, stroke, hospitalization, and adverse effects of treatment (gastrointestinal symptoms, myalgia, myelosuppression, discontinuation).

Secondary endpoints were short-term effects of colchicine on inflammatory markers (hs-C-reactive protein [hs-CRP] and cytokines - interleukin 6 [IL-6], IL-18, and β1). All endpoints were evaluated at the longest available follow-up according to *per* protocol definitions.

Data extraction

Eligible studies were reviewed, and the following data were abstracted: 1) first author's name; 2) year of publication; 3) name of the clinical trial; 4) country where the study was performed and number of centers; 5) study design; 6) number of participants in each studied group; 7) mean follow-up; 8) age and sex of study participants; 9) baseline level of inflammatory markers; 10) comorbidities; and 11) CV events.

Quality assessment

Assessment of risk of bias in the studies included in the analysis was performed systematically using the Cochrane quality assessment tool for RCTs [23]. The Cochrane tool has 7 criteria for quality assessment: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The risk of bias in each study was judged to be "low", "high" or "unclear" (**Table S1**).

Statistical analysis

The meta-analysis was conducted using statistical analysis, performed using the RevMan (Review Manager [RevMan] Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark), with two-tailed *p value*<0.05 considered as significant [24]. The baseline characteristics are reported as mean and standard deviation (SD). Mean and SD values were estimated using the method described by Hozo *et al.* [25]. Risk ratios (RR) with 95% confidential intervals (Cis) were presented as summary statistics for efficacy and safety. The generic inverse variance

method was used to test the mean difference of inflammatory markers baseline and after follow-up. Analysis is presented in forest plots. The meta-regression was used to test the interaction of demographic, clinic, and other important variable in clinical outcomes. Meta-analyses were performed using a random effect model. Heterogeneity between studies was assessed using Cochrane Q test and I^2 index. As a guide, I^2<25% indicated low, 25-50% moderate and >50% high heterogeneity [26]. Based on the calculated value of hazard ratio [HR] – when it is 1, above or below - we calculated the relative risk for CV events [27]. Publication bias was assessed using visual inspections of funnel plots and Egger's test. To test the possible effect of trials with a large sample size on the direction of clinical outcomes the influence analysis was performed.

RESULTS

Search results and trial flow

Of 5926 articles identified in the initial searches, 813 studies were initially considered as potentially relevant. After a stringent selection process, 12 articles met the inclusion criteria [18, 19, 21, 28-36] (**Figure S1**). Nine of the studies reported clinical outcomes [18, 19, 21, 28-30, 33, 35] whereas three of them reported only short-term effects of colchicine on inflammatory biomarkers [31, 32, 34] (**Table 1**).

Characteristics of included studies

Twelve studies, with a total of 13,073 patients met all the inclusion criteria, 6351 patients had been randomized to receive colchicine, and 6722 received placebo. The mean follow-up duration was 22.6 months (**Table 1**). The two patient groups were not different in age (62.9 ±

10.2 vs. 62.9 ± 10.1 years, p=0.93) and proportions of female participants (21 vs 18.9%, p=0.53, respectively **Table S2**).

Clinical outcomes

Colchicine treatment was associated with lower risk of MACE (6.20% vs. 8.87%; RR=0.67, 95%CI: 0.55 to 0.83, p<0.001, I^2=37%), recurrent MI (3.41% vs. 4.41%; RR=0.78, 95%CI: 0.65 to 0.93, p=0.005, I^2=0%), stroke (0.40% vs. 0.90%; RR=0.47, 95% CI: 0.29 to 0.76, p=0.002, I^2=0%) and hospitalization due to CV causes (0.90% vs. 2.87%; RR=0.32, 95%CI: 0.12 to 0.87, p=0.02, I^2=0%) compared to the control group (**Figure 1a, Figure 2, Figure 3a**).

The two patient groups had similar risk for all-cause mortality (2.08% vs. 1.88%; RR=1.05, 95% CI: 0.71 to 1.53, p=0.82, I^2=25%) and CV mortality (0.71% vs. 1.01%; RR=0.75, 95%CI: 0.40 to 1.43, p=0.38, I^2=35%, **Figure 1b&c, Figure 3a**).

Safety outcomes

Colchicine treatment was associated with higher risk of gastrointestinal symptoms (5.79% vs. 4.52%; RR=1.49, 95%CI: 1.02 to 2.18, p=0.04, I^2=63%) but other adverse events occurred with similar frequency in the colchicine and control groups including myalgia, myelosuppression, and treatment discontinuation due to adverse events (p=0.78, p=0.71, p=0.95, p=0.95, respectively; **Figure S2, Figure 3b**).

Short-term effect of colchicine on inflammatory markers

Short-term effect of colchicine on inflammatory markers were available in 5 papers with 439 patients [28, 31, 32, 34, 35]. The two groups of patients had similar baseline hs-CRP (8.26 ± 3.3

vs. 8.53± 3.8 mg/L, *p*=0.78), IL-β1 (29.3 ± 9.3 vs. 31.19 ± 3.51, pg/ml, *p*=0.48) and IL-18 (39 ± 6.25 vs. 41.4 ± 6.50 pg/ml, *p*=0.52) but IL-6 was higher in control (8.9 ± 2.68 vs. 40.01±12, pg/ml, *p*=0.04). At short-term follow-up (mean 19 days) despite general reduction of inflammatory markers in the two groups, colchicine significantly reduced hs-CRP (mean reduction -4.25 vs. -3.25 mg/L, *p*=0.001) and IL-6 (mean reduction -5.50 vs. -1.66 pg/mL, *p*=0.001), compared to controls, whereas despite higher reduction of IL-β1 (mean reduction -66.58 vs. -34.95 pg/mL, *p*=0.16) and IL-18 (mean reduction -30.9 vs. -9.6 pg/mL; *p*=0.10) in the colchicine group, these differences proved insignificant (p=0.16, p=0.10, respectively **Figure S3, S4**).

Relationship between demographics and colchicine dose with MACE and mortality

The longer mean follow-up was associated with adverse MACE in the two patient groups, colchicine and control, (p<0.001 and p=0.02 respectively) but no relationship was found with age (p=0.13 and p=0.11 respectively), whereas the higher percent of female gender significantly interacted with MACE in the colchicine group [β=-0.015 (-0.008 to -0.023), *p*<0.001] and in controls [β=-0.005 (-0.008 to -0.002), *p*=0.002 **Figure S5**]. Similar results were found in all-cause mortality irrespective of age (p=0.53, p=0.41 respectively **Figure S6**).

In all included RCTs, colchicine was used at doses of 0.5 to 1 mg/daily and no significant interaction was found between colchicine dose with MACE [β=0.004 (-0.009 to 0.001), *p*=0.46] or all-cause mortality [β=0.016 (-0.031 to 0.063), *p*=0.23]. In addition, treatment with colchicine 0.5 mg once versus twice daily showed no interaction with all-cause mortality [β=0.006 (-0.012 to 0.023), *p*=0.53, **Figure S7**].

Influence analysis

The influence analysis showed that no single study significantly impacted the direction the effect of colchicine on clinical outcomes. Colchicine treatment was associated with lower risk of MACE in large (6.20% *vs.* 8.44%, p<0.001) and small trials (6.23% *vs.* 11.1, %, p=0.02), compared to the control. Similar to the main result, the all-cause mortality, CV mortality and recurrent MI were not statistically significant among studies, irrespective of sample sizes (**Figure S8 & S9**).

DISCUSSION

In the meta-analysis of 12 RCTs that compared the safety and efficacy of colchicine on clinical outcomes and/or inflammatory markers in patients with CAD we have shown that colchicine at a daily dose of 0.5-1.0 mg resulted in reduction of adverse clinical events compared to control. With the exception of a small increase in reported gastrointestinal symptoms in patients taking colchicine, there was no difference in the safety profile compared with controls. Short-term colchicine intake also significantly reduced all investigated inflammatory markers.

Despite the introduction of many effective drugs, CAD remains the most predominant cause of morbidity and mortality worldwide [37]. Inflammatory mediators have been shown to contribute to the pathophysiology and progression of CAD [38]. Our findings, based on the analysis of the 12 available RCTs, show that the administration of colchicine within 24 hours of unstable CAD significantly reduced the inflammatory markers (hs-CRP, IL- β1, IL-6 and IL-18). These data are supported by previous studies, which showed that colchicine acutely inhibits several effects of cytokine cascades, thereby reducing the incidence of new coronary events in acute coronary syndrome (ACS) patients [39]. Thus, our findings are of significant importance in

ACS patients, because of the inflammatory pathophysiological mechanisms in atherosclerosis. Vascular inflammation is not limited to the culprit lesion, but is likely to affect other coronary segments, hence the risk of plaque rupture, erosion and subsequent CV disease events [40]. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial showed that inflammation plays a causal role in the pathogenesis of CVD and interventions that mitigate inflammation reduce the risk of related CV events [4]. These findings were the basis for the potential benefit of using anti-inflammatory medications in reducing CV events, particularly in patients with CAD [4]. Colchicine is an anti-inflammatory agent that reduces IL-1β and IL-6 and has been used for many decades to treat gout and other inflammatory disorders [41,42]. It has been shown to reduce neutrophil-platelet aggregation, and incrementally lowers hs-CRP concentrations [43]. These properties, together with its low cost, wide availability and extensive safety data make it an attractive candidate for repurposing to treat and prevent CVD.

Over the last decade, several trials have evaluated the safety and efficacy of colchicine in treating acute myocardial infarction (MI) patients [17,18] and those with chronic CAD [14,16]. Previous meta-analyses of those trials did not report any significant difference between CAD patients treated with colchicine and those treated with placebo with respect to CV endpoints and mortality [44]. Recently, data from two major RCTs were published, comparing a daily dose of 0.5 mg colchicine and placebo, in patients with AMI [18] and in patients with chronic CAD [21], in addition to a smaller study that investigated the outcomes of ACS patients commenced on a daily colchicine dose of 1.0 mg for the first month followed with 0.5 mg daily for 11 months [36].

The LoDoCo2 trial randomized 5522 patients to receive either colchicine (0.5 mg daily) or placebo and all were followed up for a median of 28.6 months for the primary endpoint (a

composite of CV death, MI, ischemic stroke, or ischemia-driven coronary revascularization) [21]. All primary endpoints were lower with colchicine treatment (0.69; 95% CI, 0.57 to 0.83; P<0.001) but the incidence of non-CV mortality was higher in the same group of patients (0.7 vs. 0.5 events per 100 person-years; HR, 1.51; 95% CI, 0.99 to 2.31) compared to placebo [21]. The recently published time-to-treatment initiation analysis of the Colchicine Cardiovascular Outcomes Trial (COLCOT) trial [18] that included 4745 participants, compared low-dose (0.5 mg/day) colchicine, initiated within 30 days of MI with placebo. After a median follow-up of 22.6 months, the study found significant benefit of early administration of colchicine on a composite endpoint including CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization [18]. These results support what has previously been reported in Colchicine in Patients with Acute Coronary Syndrome (COPS) trial, which investigated the effect of colchicine (0.5 mg twice daily for the first month, followed by 0.5 mg daily for eleven months) in 707 patients with ACS [36]. Colchicine was well-tolerated, but did not impact the outcome events including ACS, revascularization and non-cardioembolic ischaemic stroke. Furthermore, it was associated with higher all-cause mortality [36].

These somewhat conflicting results suggest that the efficacy of colchicine in CVD might depend upon other clinical aspects of the patient population, dose of colchicine or study design. In this meta-analysis, we have addressed these questions using meta-regression. Our pooled analysis demonstrated that colchicine was well tolerated and reduced recurrent MI, stroke, and hospitalization due to CV causes, compared with placebo. Short-term colchicine application also significantly reduced circulating levels of inflammatory markers. On the other hand, colchicine did not impact all cause and CV mortality irrespective of the dose. This particular finding

suggests that the previously reported increased mortality [19, 36, 45] may be related to insufficient trial power. We also showed no significant interaction between colchicine dose and all-cause mortality. However, this result should be treated with caution, because the number of participants was relatively small in the studies that used colchicine at higher dose. Nevertheless, this issue requires further investigations.

Our analysis has some obvious *strengths and limitations.* This meta-analysis assimilates the results of all trials to date that investigated the effect of colchicine on inflammatory markers and clinical outcomes in patients with CAD. However, using the pooled dataset has enabled meta-regression to be performed and to investigate interactions between demographic variables, treatment dose and outcomes. The study is limited by the fact that the meta-analysis was performed at study-level, rather than using individual patient data. Some included trials had short follow-up period, which might introduce bias into meta-analysis. The limited number of patients on higher dose of colchicine and different duration of treatment limits our finding about the impact of colchicine dose on clinical outcomes. Another limitation is the small sample data on short-term effect of colchicine on inflammatory markers and effects of co-medications used. The data obtained does not allow us to draw conclusions about the optimal time (post ACS) to initiate colchicine therapy. Future studies may be required to determine the optimal dose and timing of colchicine therapy.

In conclusion, colchicine appears to be a promising therapeutic option to effectively reduce inflammation and consequently prevent cardiovascular events. The safety profile of colchicine is acceptable, but its effect on CV- and all-cause mortality merits further investigation, and in particular long-term follow-up of clinical outcomes.

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FIGURES' LEGENDS:

Figure 1. Risk ratios of outcome with colchicine versus control; a) MACE; b) All-cause mortality; c) CV mortality.

Figure 2. Risk ratios of outcome with colchicine versus control; a) recurrent MI; b) Stroke; c) Hospitalization.

Figure 3. Summary risk ratios of outcome with colchicine versus control; a) clinical outcomes; b) safety outcomes.

TABLES' LEGENDS:

Table 1. Main characteristics of trials included in the study.

SUPPLEMENTARY DATA:

Table S1. Assessment of risk of bias in the included studies using Cochrane criteria.

Table S2. Main characteristics of patients enrolled among trials included in the study.

Figure S1. Flow chart of study section.

Figure S2. Risk ratios of safety outcome with colchicine versus control; a) Gastrointestinal symptoms; b) Myalgia; c) Myelosuppression; d) other adverse events; e) discontinuation.

Figure S3. Inflammatory markers mean change; a) hs-CRP; b) IL-B1

Figure S4. Inflammatory markers mean change; a) IL-18; b) IL-6

Figure S5. Meta-regression for interaction of follow-up, age and female gender with MACE.

Figure S6. Meta-regression for interaction of follow-up, age and female gender with all-cause mortality.

Figure S7. Meta-regression for interaction of colchicine dose with outcome – MACE and all-cause mortality.

Figure S8. Influence analysis of effect of sample size on clinical outcomes; a) MACE in large trial; b) MACE in small trial); c) All-cause mortality in large trial; d) All-cause mortality in small trial.

Figure S9. Influence analysis of effect of sample size on clinical outcomes; a) CV mortality in large trial; b) CV mortality in small trial); c) Recurrent MI; d) Recurrent MI.

Table 1. Main characteristics of trials included in the study

Study (trial) year	Study design	Center Location	Population	Sample size (Colch/Control)	Colchicine dose	Primary endpoints	Other endpoints	Follow-up
Raju 2012 (COOL)	RCTs (double blinded)	1 center (Ontario Canada)	ACS patients	80 (40/40)	1mg/daily	Inflammatory markers	All-cause mortality Stroke	1 month
Nidorf 2013 (LoDoCo)	RCTs (double blinded)	1 center Australia	CAD patients	532 (282/250)	0.5mg/daily	MACE	Death, MI, stroke	36 months
Deftereos 2013	RCTs, (double blinded)	NR Greece	CAD patients undergoing PCI	196 (100/96)	0.5mg/twice daily	MACE	Death, MI, stroke	6 months
Martinez 2015	RCTs, (double blinded)	1 center Australia	CAD patients (ACS, stable CAD)	73 (34/39)	1mg followed by 0.5 mg 1h later	Inflammatory markers		1day
Robrtson 2016	RCTs, (double blinded)	1 center Australia	ACS patients	21 (10/11)	1mg followed by 0.5 mg 1h later	Inflammatory markers		2 day
Akodad (COLIN) 2017	RCTs, (open label)	1 center France	STEMI undergoing PCI	44 (23/21)	1 mg/daily	MACE, death MI	Inflammatory markers	1 month
Kajikawa 2019	RCTs, (double blinded)	2 centers Japan	CAD patients	28 (14/14)	0.5mg/daily	Inflammatory markers		14 days
Hennessy 2019	RCTs, (double blinded)	1 center Australia	AMI	237 (119/118)	0.5mg/daily	MACE, death Hospitalization, MI	Inflammatory markers	1 month

Continued table

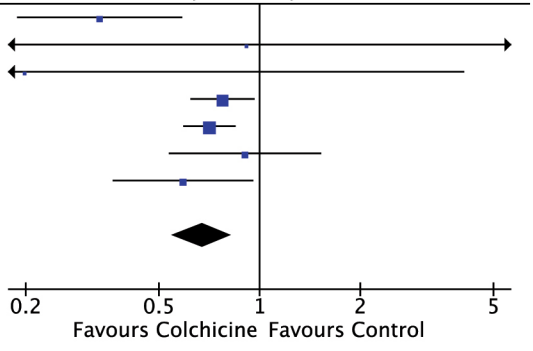
Tardif 2019 (COLCOT)	RCTs (double blinded)	167 centers 12 countries	Post MI within 30 days	4745 (2366/2379)	0.5mg/daily	MACE	Death, MI, stroke safety	22.6 months
Shah 2020 (COLCHINE-PCI)	RCTs (double blinded)	1 center New York	CAD patients undergoing PCI	400 (206/194)	1.2 mg before angio followed by 0.6 mg/daily	MACE, death Hospitalization, MI		1 month
Nidorf 2020 (LoDoCo2)	RCTs, (double blinded)	13 centers Australia	Chronic CAD patients	5522 (2762/2760)	0.5mg/daily	MACE	Death, MI, stroke safety	28.6 months
Tong 2020 (COPS trial)	RCTs, (double blinded)	17 centers Australia	ACS patients	795 (396/399)	0.5mg/twice daily (1month) than 0.5mg/ daily	MACE	Death, MI, stroke safety	12 months

Abbreviations: CAD: coronary artery disease ACS: acute coronary syndrome, CV: cardio-vascular; MI: myocardial infarction; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; NR: non-reported

a) MACE

Study or Subgroup	Colchicine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nidorf 2013	15	282	40	250	10.1%	0.33 [0.19, 0.59]	2013
Akodad 2017	1	23	1	21	0.6%	0.91 [0.06, 13.69]	2017
Hennessy 2019	0	119	2	118	0.4%	0.20 [0.01, 4.09]	2019
Tardif 2019	131	2366	170	2379	30.3%	0.77 [0.62, 0.97]	2019
Nidorf 2020	187	2762	264	2760	34.4%	0.71 [0.59, 0.85]	2020
Shah 2020	24	206	25	194	11.4%	0.90 [0.53, 1.53]	2020
Tong 2020	24	396	41	399	12.8%	0.59 [0.36, 0.96]	2020
Total (95% CI)		**6154**		**6121**	**100.0%**	**0.67 [0.55, 0.83]**	
Total events	382		543				

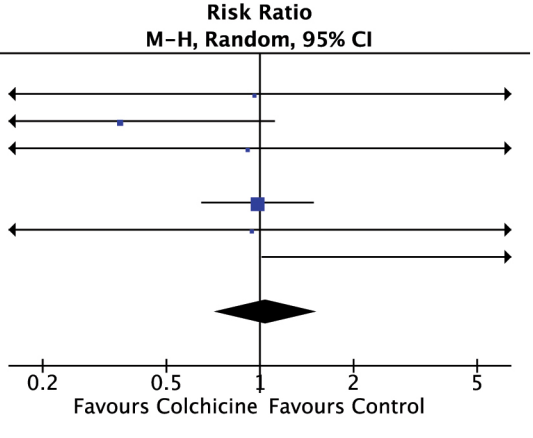
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.52$, df = 6 (P = 0.15); $I^2 = 37\%$
Test for overall effect: Z = 3.80 (P = 0.0001)



b) All cause mortality

Study or Subgroup	Colchicine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Raju 2012	0	40	0	40		Not estimable	2012
Deftereos 2013	1	100	1	96	1.9%	0.96 [0.06, 15.13]	2013
Nidorf 2013	4	282	10	250	9.5%	0.35 [0.11, 1.12]	2013
Akodad 2017	1	23	1	21	1.9%	0.91 [0.06, 13.69]	2017
Hennessy 2019	0	119	0	119		Not estimable	2019
Tardif 2019	43	2366	44	2379	37.4%	0.98 [0.65, 1.49]	2019
Shah 2020	1	206	1	194	1.9%	0.94 [0.06, 14.95]	2020
Tong 2020	8	396	1	399	3.2%	8.06 [1.01, 64.15]	2020
Nidorf 2020	73	2762	60	2760	44.1%	1.22 [0.87, 1.70]	2020
Total (95% CI)		**6294**		**6258**	**100.0%**	**1.05 [0.71, 1.53]**	
Total events	131		118				

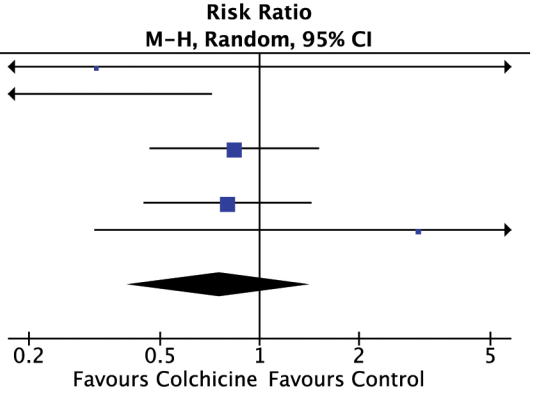
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.95$, df = 6 (P = 0.24); $I^2 = 25\%$
Test for overall effect: Z = 0.23 (P = 0.82)



c) CV mortality

Study or Subgroup	Colchicine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Deftereos 2013	0	100	1	96	3.8%	0.32 [0.01, 7.76]	2013
Nidorf 2013	0	282	10	250	4.7%	0.04 [0.00, 0.72]	2013
Akodad 2017	0	23	0	21		Not estimable	2017
Tardif 2019	20	2366	24	2379	42.1%	0.84 [0.46, 1.51]	2019
Hennessy 2019	0	119	0	118		Not estimable	2019
Nidorf 2020	20	2762	25	2760	42.4%	0.80 [0.45, 1.44]	2020
Tong 2020	3	396	1	399	7.1%	3.02 [0.32, 28.94]	2020
Total (95% CI)		**6048**		**6023**	**100.0%**	**0.75 [0.40, 1.43]**	
Total events	43		61				

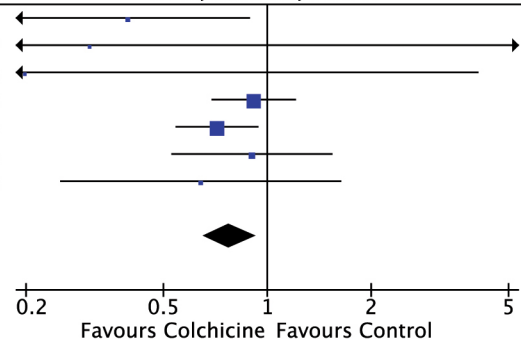
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 6.15$, df = 4 (P = 0.19); $I^2 = 35\%$
Test for overall effect: Z = 0.87 (P = 0.38)



a) Recurrent MI

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nidorf 2013	8	282	18	250	4.7%	0.39 [0.17, 0.89]	2013
Akodad 2017	0	23	1	21	0.3%	0.31 [0.01, 7.12]	2017
Hennessy 2019	0	119	2	118	0.3%	0.20 [0.01, 4.09]	2019
Tardif 2019	89	2366	98	2379	39.5%	0.91 [0.69, 1.21]	2019
Nidorf 2020	83	2762	116	2760	40.8%	0.71 [0.54, 0.94]	2020
Shah 2020	23	206	24	194	10.8%	0.90 [0.53, 1.54]	2020
Tong 2020	7	396	11	399	3.6%	0.64 [0.25, 1.64]	2020
Total (95% CI)		**6154**		**6121**	**100.0%**	**0.78 [0.65, 0.93]**	
Total events	210		270				

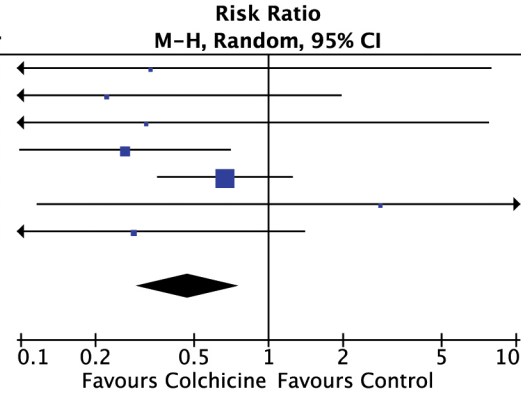
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.87$, df = 6 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 2.80 (P = 0.005)



b) Stroke

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Raju 2012	0	40	1	40	2.2%	0.33 [0.01, 7.95]	2012
Nidorf 2013	1	282	4	250	4.7%	0.22 [0.02, 1.97]	2013
Deftereos 2013	0	100	1	96	2.2%	0.32 [0.01, 7.76]	2013
Tardif 2019	5	2379	19	2379	23.2%	0.26 [0.10, 0.70]	2019
Nidorf 2020	16	2762	24	2760	56.6%	0.67 [0.35, 1.25]	2020
Shah 2020	1	206	0	194	2.2%	2.83 [0.12, 68.96]	2020
Tong 2020	2	396	6	339	8.8%	0.29 [0.06, 1.40]	2020
Total (95% CI)		**6165**		**6058**	**100.0%**	**0.47 [0.29, 0.76]**	
Total events	25		55				

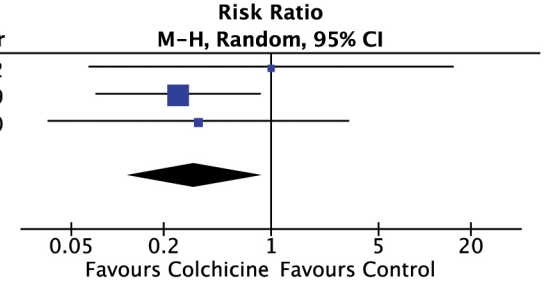
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.67$, df = 6 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 3.10 (P = 0.002)



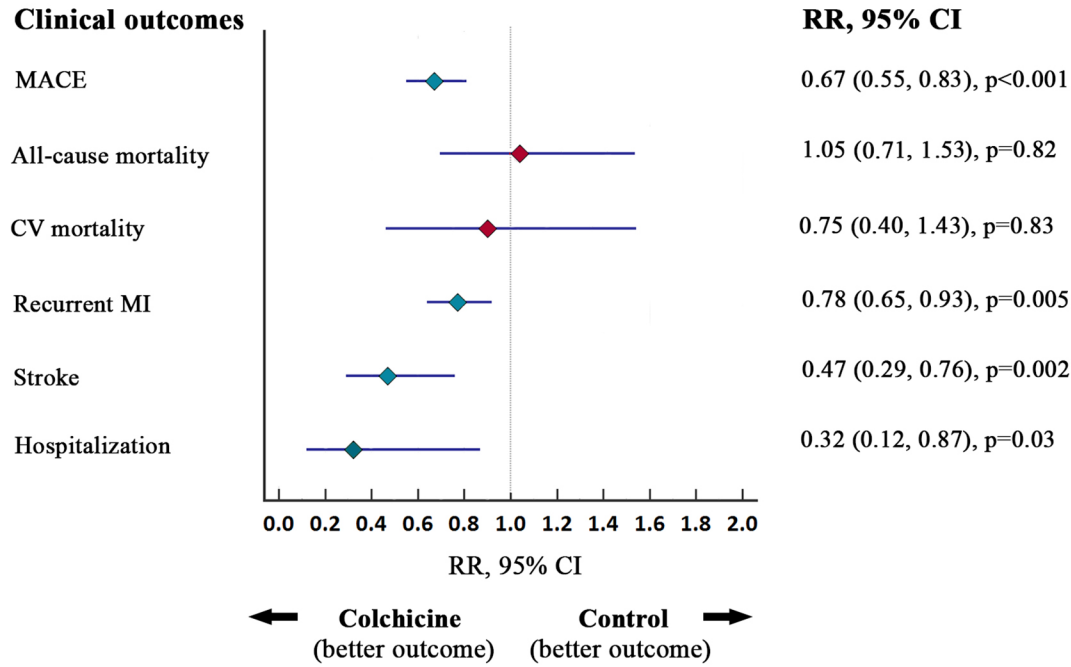
c) Hospitalization

Study or Subgroup	Cholchicine Events	Cholchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Raju 2012	1	40	1	40	13.6%	1.00 [0.06, 15.44]	2012
Hennessy 2019	3	119	12	118	66.4%	0.25 [0.07, 0.86]	2019
Tong 2020	1	396	3	399	20.0%	0.34 [0.04, 3.22]	2020
Total (95% CI)		**555**		**557**	**100.0%**	**0.32 [0.12, 0.87]**	
Total events	5		16				

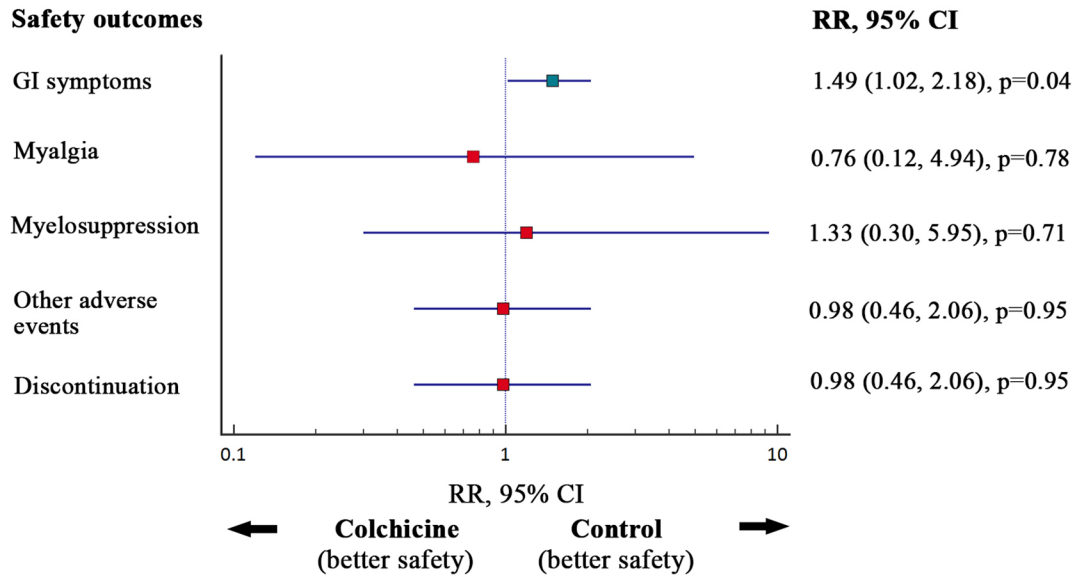
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 2.22 (P = 0.03)



a) Risk ratios of clinical outcomes with colchicine vs. control



b) Risk ratios of safety outcomes with colchicine vs. control



SUPPLEMENTARY DATA:

Table S1. Assessment of risk of bias in the included studies using Cochrane criteria.

Study (trial) year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Raju (COOL) 2012	L	L	L	H	L	L	L
Nidorf (LoDoCo) 2013	L	L	L	U	L	L	L
Deftereos 2013	L	L	L	U	L	U	L
Martinez 2015	L	U	U	U	L	U	L
Robrtson 2016	L	U	U	U	L	L	L
Akodad (COLIN) 2017	L	L	L	L	L	L	L
Kajikawa 2019	L	L	L	L	L	L	L
Hennessy 2019	L	L	L	L	L	L	L
Tardif (COLCOT) 2019	L	L	L	L	L	L	L
Shah (COLCHINE-PCI) 2020	L	L	L	L	L	L	L
Nidorf (LoDoCo2) 2020	L	L	L	L	L	L	L
Tong (COPS trial) 2020	L	L	L	L	L	L	L

Legend: L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

Table S2. Main characteristics of patients enrolled among trials included in the study.

Study (trial) year	Groups	Age year	Female %	HTN %	DM %	Dyslipidemia %	Smoking %	Prior MI	Prior PCI	Prior CABG
Raju (COOL) 2012	Colchicine	57±11	15	47.5	17.5	47.5	45	20	NR	NR
	Control	58±8.7	8.0	37.5	15	47.5	42.5	15	NR	NR
Nidorf (LoDoCo) 2013	Colchicine	66±9.6	11	NR	33	NR	4	23	65	22
	Control	67±9.2	11	NR	28	NR	6	24	50	16
Deftereos 2013	Colchicine	64 ±6.9	38	48	100	NR	36	NR	NR	NR
	Control	63 ± 7.2	32	49	100	NR	40	NR	NR	NR
Martinez 2015	Colchicine	63 ±9.2	22	62	55	73	18.5	28	18	5
	Control	63 ±10	10	64.5	20.5	67	23	23	41	12.5
Robertson 2016	Colchicine	69.8±12	22	67	22	78	44	11	11	11
	Control	67.5±14	27	91	36	73	27	55	27	27
Akodad (COLIN)	Colchicine	60±13	17.5	39	13	34.8	74	NR	4.3	0
2017	Control	59.7±11	34.8	47	14	38.1	67	NR	4.8	4.8
Kajikawa 2019	Colchicine	68±7*	3.7*	89*	35*	NR*	28*	57*	71*	3.6*
	Control									
Hennessy 2019	Colchicine	61±13	23	54	23	NR	65	15	11	NR
	Control	61±12	25	41	21	NR	57	15	12	NR
Tardif 2019	Colchicine	60.6±10.7	19	50	19	NR	29.9	15.6	16.5	2.8
(COLCOT)	Control	60.5±10.6	19.9	52	21	NR	29.8	16.7	17.1	3.4
Shah 2020	Colchicine	65.9 ± 9.9	6.3	93	56	88	72	24.8	36	NR
(COLCHINE-PCI)	Control	66.6 ± 10	6.7	90	60	89	69	26.8	38	NR
Nidorf 2020	Colchicine	65.8±8.4	16.5	17.8	51	NR	11.5	84	76	11
(CoLoCo2)	Control	65.9±8.7	14.1	18.7	50	NR	12	84	75	14
Tong 2020	Colchicine	59.7±10	19	51	19	46	32	15	13	4
(COPS)	Control	60±10	22	50	19	46	37	15	13	3

Abbreviations: HTN: hypertension; DM: diabetes mellitus; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass grafting; NR: non-reported. (*) whole group

Figure S1. Flow chart of study section.

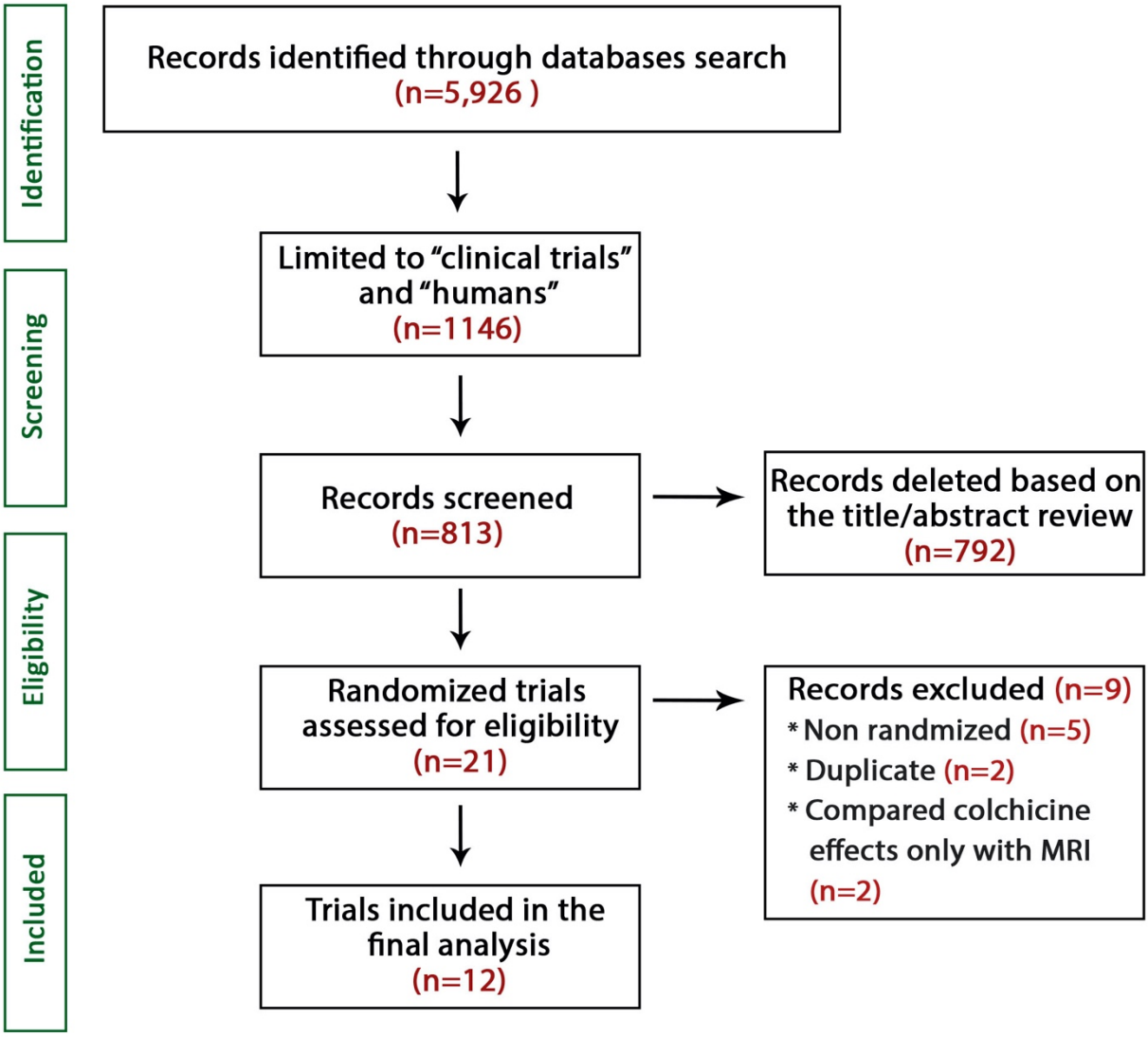
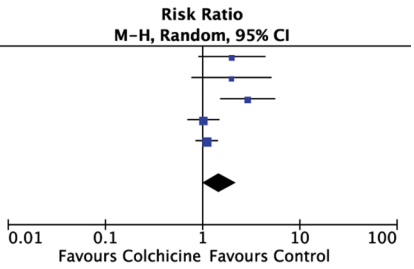


Figure S2. Risk ratios of safety outcome with colchicine versus control; a) Gastrointestinal symptoms; b) Myalgia; c) Myelosuppression; d) other adverse events; e) discontinuation.

a) Gastrointestinal symptoms

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Raju 2012	14	40	7	40	14.1%	2.00 [0.90, 4.43]	2012
Hennessy 2019	12	119	6	118	11.2%	1.98 [0.77, 5.11]	2019
Shah 2020	34	206	11	194	17.6%	2.91 [1.52, 5.58]	2020
Nidorf 2020	53	2760	52	2762	26.5%	1.02 [0.70, 1.49]	2020
Tong 2020	91	396	83	399	30.6%	1.10 [0.85, 1.44]	2020
Total (95% CI)		**3521**		**3513**	**100.0%**	**1.49 [1.02, 2.18]**	
Total events	204		159				

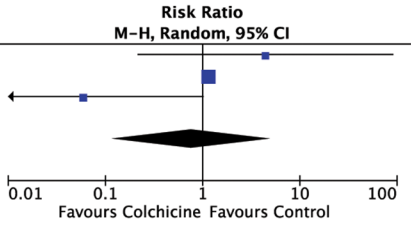
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.73$, df = 4 (P = 0.03); $I^2 = 63\%$
Test for overall effect: Z = 2.04 (P = 0.04)



b) Myalgia

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nidorf 2013	2	282	0	250	22.2%	4.43 [0.21, 91.93]	2013
Nidorf 2020	384	3762	334	3760	53.9%	1.15 [1.00, 1.32]	2020
Tong 2020	0	396	8	399	23.9%	0.06 [0.00, 1.02]	2020
Total (95% CI)		**4440**		**4409**	**100.0%**	**0.76 [0.12, 4.92]**	
Total events	386		342				

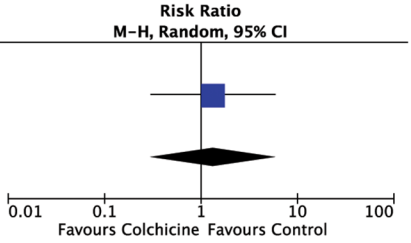
Heterogeneity: $Tau^2 = 1.67$; $Chi^2 = 4.96$, df = 2 (P = 0.08); $I^2 = 60\%$
Test for overall effect: Z = 0.28 (P = 0.78)



c) Myelosuppression

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Raju 2012	0	40	0	40		Not estimable	2012
Akodad 2017	0	23	0	21		Not estimable	2017
Nidorf 2020	4	2762	3	2760	100.0%	1.33 [0.30, 5.95]	2020
Tong 2020	0	396	0	399		Not estimable	2020
Total (95% CI)		**3221**		**3220**	**100.0%**	**1.33 [0.30, 5.95]**	
Total events	4		3				

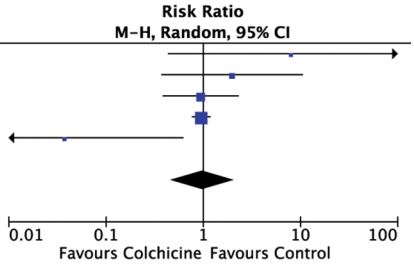
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



d) Other adverse events

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nidorf 2013	4	282	0	250	5.8%	7.98 [0.43, 147.53]	2013
Hennessy 2019	4	119	2	118	14.0%	1.98 [0.37, 10.62]	2019
Shah 2020	9	206	9	194	28.2%	0.94 [0.38, 2.32]	2020
Nidorf 2020	146	2762	153	2760	45.9%	0.95 [0.76, 1.19]	2020
Tong 2020	0	396	13	399	6.1%	0.04 [0.00, 0.63]	2020
Total (95% CI)		**3765**		**3721**	**100.0%**	**0.98 [0.46, 2.06]**	
Total events	163		177				

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 8.01$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: Z = 0.06 (P = 0.95)



e) discontinuation due to adverse events

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nidorf 2013	4	282	0	250	5.8%	7.98 [0.43, 147.53]	2013
Hennessy 2019	4	119	2	118	14.0%	1.98 [0.37, 10.62]	2019
Shah 2020	9	206	9	194	28.2%	0.94 [0.38, 2.32]	2020
Nidorf 2020	146	2762	153	2760	45.9%	0.95 [0.76, 1.19]	2020
Tong 2020	0	396	13	399	6.1%	0.04 [0.00, 0.63]	2020
Total (95% CI)		**3765**		**3721**	**100.0%**	**0.98 [0.46, 2.06]**	
Total events	163		177				

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 8.01$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: Z = 0.06 (P = 0.95)

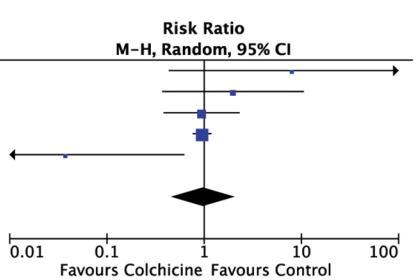
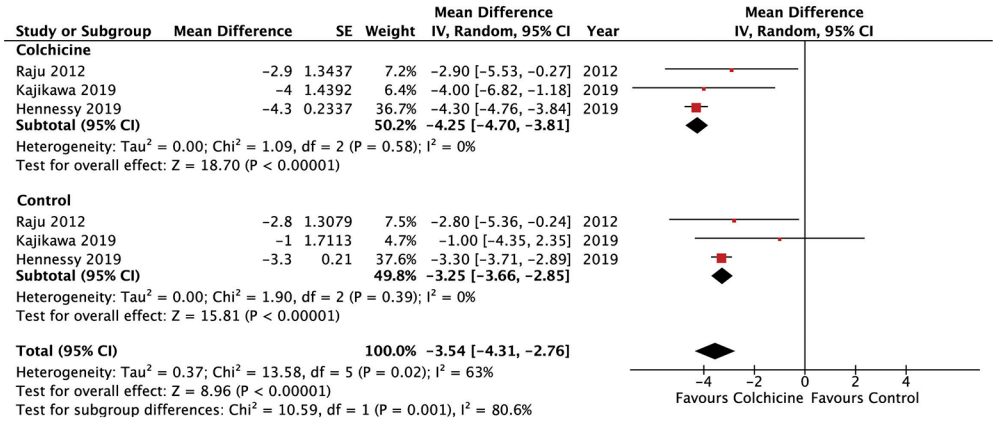


Figure S3. Inflammatory markers mean change; a) hs-CRP; b) IL-B1

a) hs-CRP



b) IL-β1

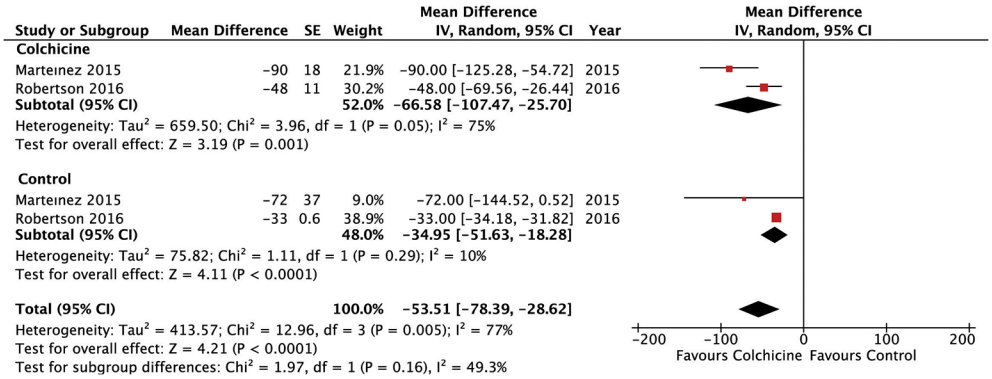


Figure S4. Inflammatory markers mean change; a) IL-18; b) IL-6

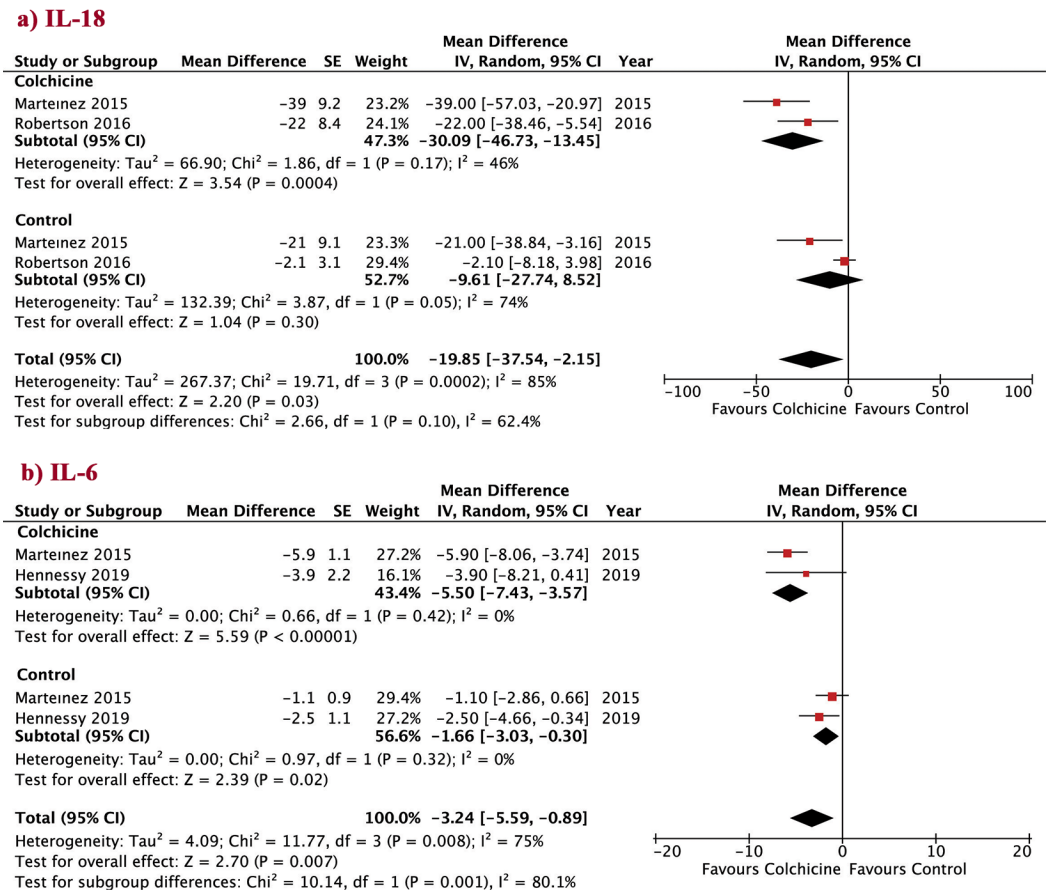
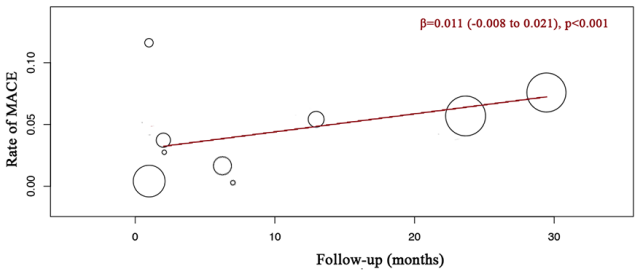


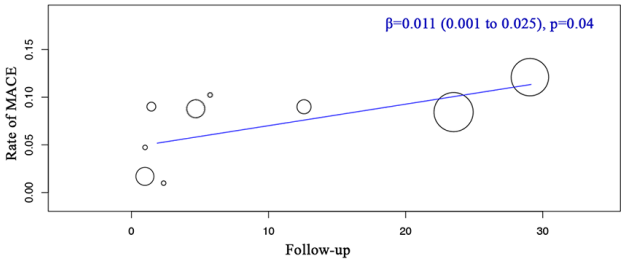
Figure S5. Meta-regression for interaction of follow-up, age and female gender with MACE.

A) Interaction of follow-up with MACE

a) Colchicine

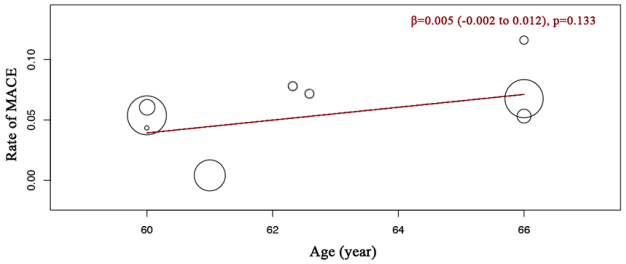


b) Control

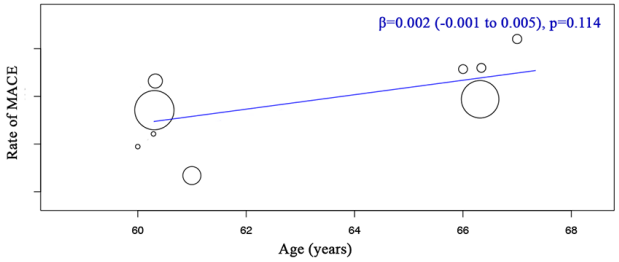


B) Interaction of age with MACE

a) Colchicine

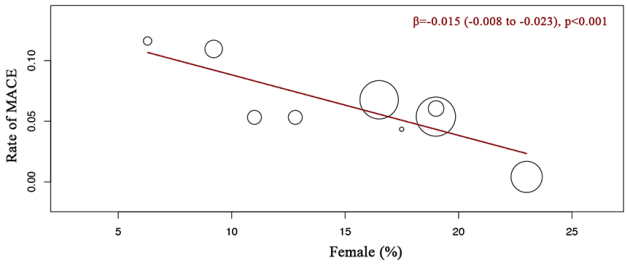


b) Control



C) Interaction of gender with MACE

a) Colchicine



b) Control

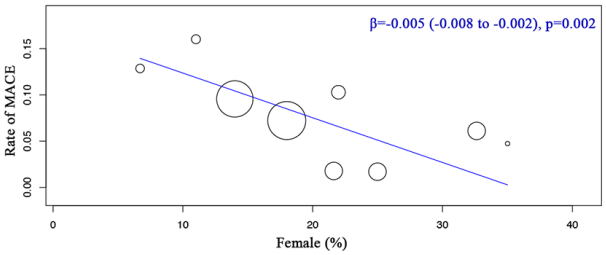
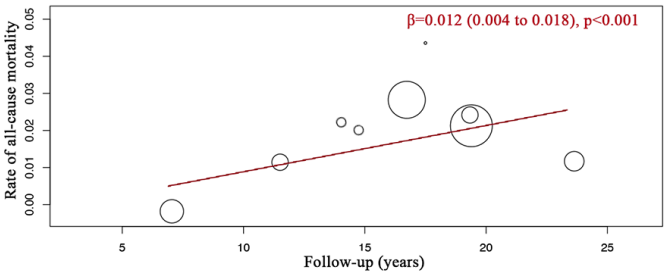


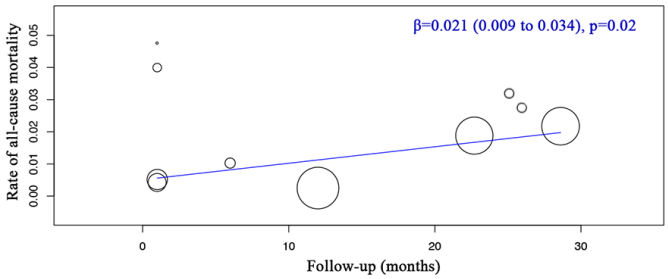
Figure S6. Meta-regression for interaction of follow-up, age and female gender with all-cause mortality.

A) Interaction of follow-up with all-cause mortality

a) Colchicine

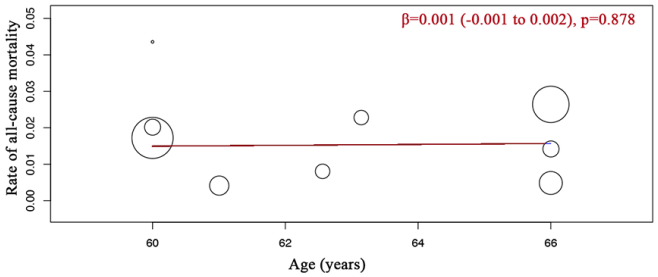


b) Control

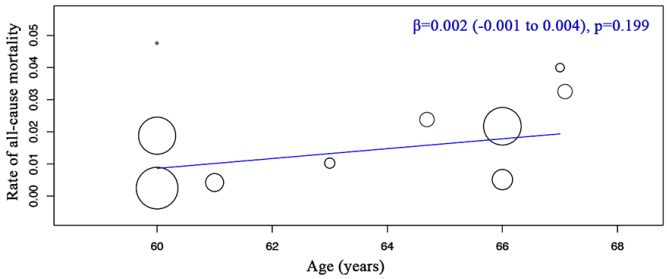


B) Interaction of age with all-cause mortality

a) Colchicine

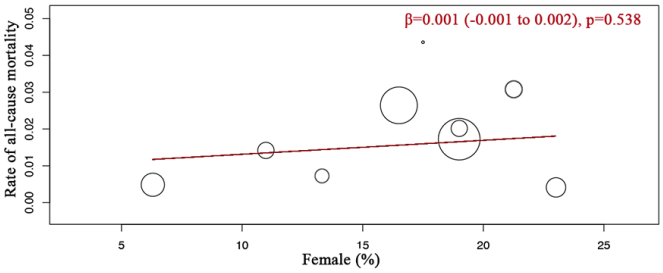


b) Control



C) Interaction of gender with all-cause mortality

a) Colchicine



b) Control

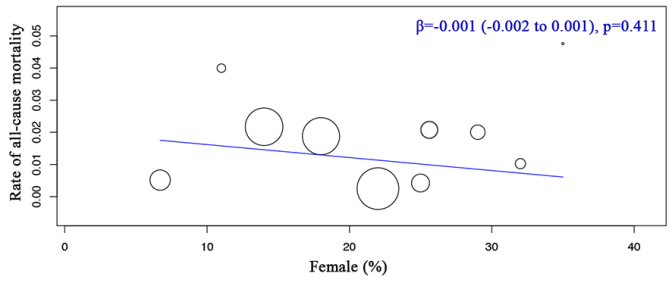
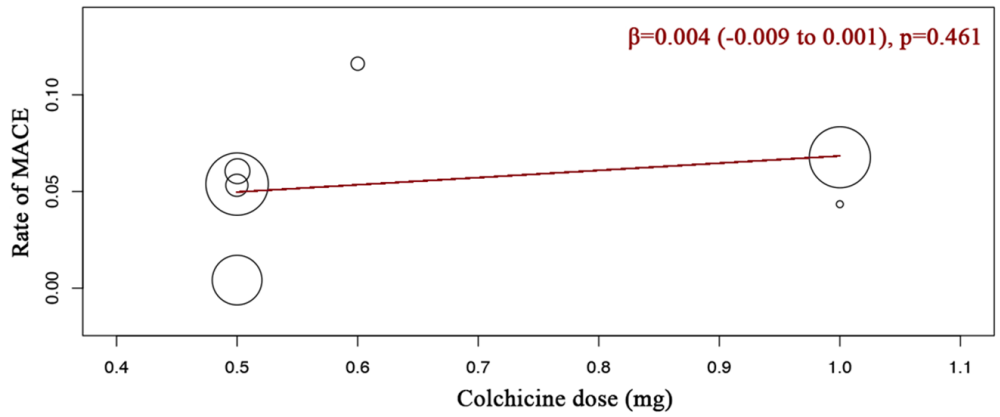
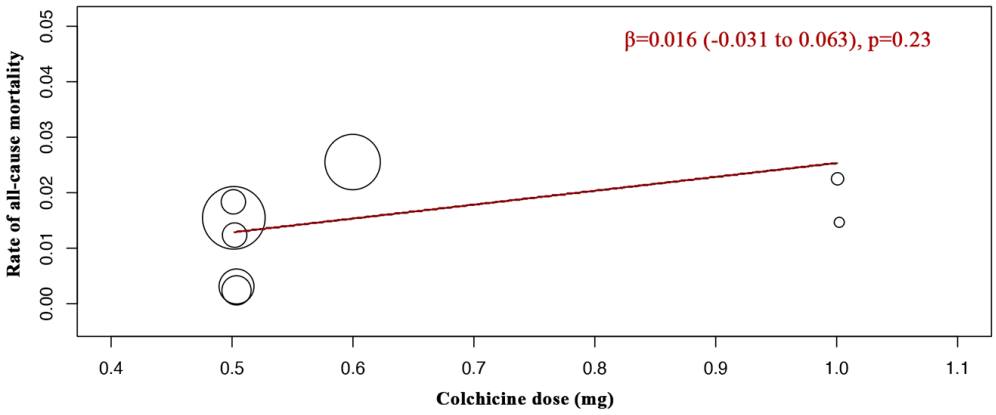


Figure S7. Meta-regression for interaction of colchicine dose with outcome – MACE and all-cause mortality.

a) MACE



b) All-cause mortality



b) All-cause mortality with 0.5 mg colchicine (mono vs. twice daily)

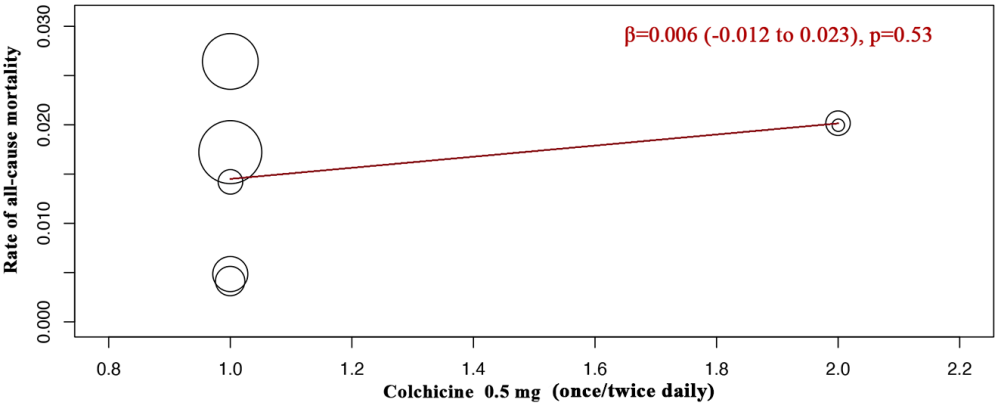


Figure S8. Influence analysis of effect of sample size on clinical outcomes; a) MACE in large trial; b) MACE in small trial); c) All-cause mortality in large trial; d) All-cause mortality in small trial.

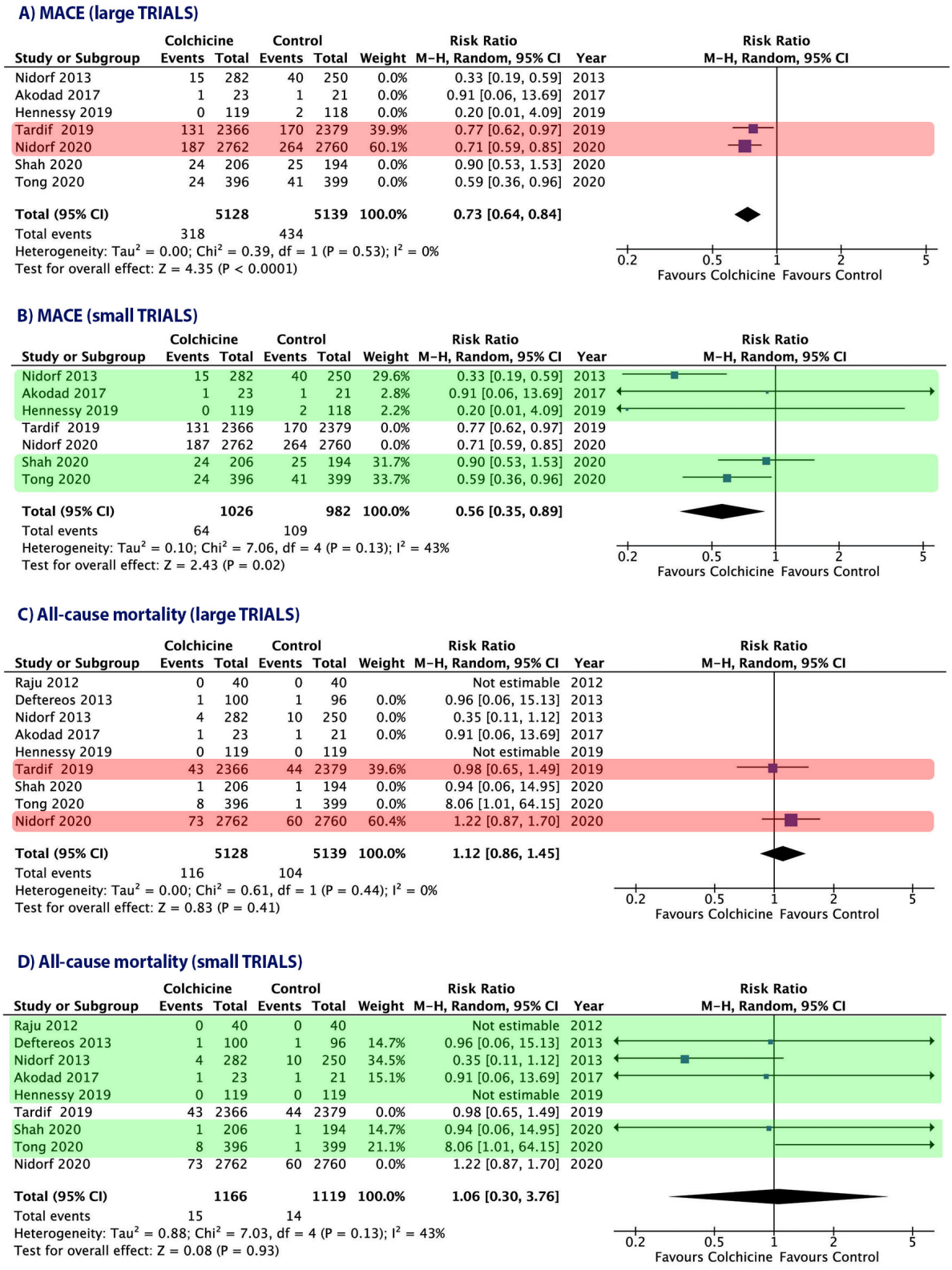


Figure S9. Influence analysis of effect of sample size on clinical outcomes; a) CV mortality in large trial; b) CV mortality in small trial); c) Recurrent MI; d) Recurrent MI.