Clinical Rheumatology (2022) 41:1873–1887
https://doi.org/10.1007/s10067-022-06050-0

ORIGINAL ARTICLE

Colchicine may become a new cornerstone therapy for coronary artery disease: a meta-analysis of randomized controlled trials

Yi Chen[1] · Hongzhou Zhang[1] · Yuxin Chen[1] · Meng Li[1] · Wei Luo[1] · Yue Liu[1] · Yang Fu[1] · Huasong Xia[1] · Cong Xu[1] · Yu Jiang[2] · Yanqing Wu[1]

Received: 12 July 2021 / Revised: 14 December 2021 / Accepted: 1 January 2022 / Published online: 9 February 2022

Abstract

Purpose Colchicine is an ancient anti-inflammatory drug. In recent years, an increasing number of studies have shown that colchicine improves the prognosis of patients with coronary artery disease (CAD), while other studies have reported the opposite. The aim of this study was to evaluate the relative efficacy and safety of colchicine in treating CAD.

Methods PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were searched from inception to 20 October 2020 for randomized controlled trials (RCTs) comparing colchicine and placebo in patients with CAD. The primary outcomes were the primary composite outcomes of cardiovascular death, myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization after colchicine administration. The secondary outcomes were cardiovascular death, death from any cause, noncardiac death, MI, ischemic stroke, coronary revascularization, gastrointestinal (GI) symptoms, and the different effects of colchicine in acute and chronic CAD. We assessed the pooled odds ratio (OR) of all-cause and cardiovascular mortality for CAD in fixed-effects models, the pooled risk ratio (RR) of the primary composite outcomes, MI, ischemic stroke, and ischemia-driven coronary revascularization in fixed-effects models and the pooled RR of GI symptoms in random-effects models. The Cochrane risk of bias tool was used to assess the risk of bias in the included RCTs.

Findings Eleven of the 894 identified studies ($n = 12{,}899$ patients) were included (6501 subjects in the colchicine group; 6389 subjects in the control group). The colchicine group had significantly lower pooled RRs of the primary composite outcomes (0.73, 95% confidence interval (*CI*) 0.64–0.84, $P < 0.0001$), MI (0.77, 95% *CI* 0.64–0.92, $P = 0.004$), ischemic stroke (0.47, 95% *CI* 0.30–0.76, $P = 0.002$), and ischemia-driven coronary revascularization (0.77, 95% *CI* 0.66–0.89, $P = 0.0007$), while the pooled RR of adverse GI events (2.15 95% *CI* 1.40–3.31, $P = 0.0005$) was significantly higher. Colchicine had a lower pooled RR of ischemic stroke (0.28, 95% *CI* 0.12–0.65, $P = 0.003$) for patients with acute compared with chronic CAD.

Implications Colchicine treatment significantly decreased the risk of primary cardiovascular composite outcomes, MI, ischemic stroke, and ischemia-driven coronary revascularization in CAD patients but increased adverse GI events. There was no significant difference in all-cause mortality, cardiovascular mortality, and non-cardiovascular death between the colchicine and control groups. Colchicine performs better in acute CAD patients with ischemic stroke than chronic CAD patients. Colchicine might be a new treatment for patients with CAD.

Key points

- *Two large-scale RCTs from last year were included.*
- *The primary cardiovascular compound efficacy outcomes were reported.*
- *The risk of myocardial infarction, stroke and ischemia-driven coronary revascularization showed a downward trend after using colchicine.*
- *The effect of colchicine in acute and chronic CAD patients was analyzed.*

Keywords Colchicine · Coronary artery disease · Efficacy · Meta-analysis

Yi Chen and Hongzhou Zhang are contributed equally to this work.

✉ Yanqing Wu
wuyanqing01@sina.com

Extended author information available on the last page of the article

Introduction

Inflammation currently plays an indelible role in the pathogenesis of atherosclerosis and its acute manifestations [1–3]. Despite the best drug treatments (including antiplatelets,

statins, and anti-remodeling drugs) [4], patients with coronary artery disease (CAD) remain at risk of cardiovascular events, possibly because these treatments fail to target some of the inflammatory pathways related to the disease [5]. The established cardiovascular risk factors, which include hypertension, diabetes, dyslipidemia, and smoking, damage the vascular endothelium and trigger inflammation, leading to the influx of macrophages and lymphocytes and the secretion of cytokines and other inflammatory mediators, which promote further damage [6, 7]. At present, anti-inflammatory treatment has become an important breakthrough in the treatment of CAD.

Colchicine is a drug with potent anti-inflammatory properties [8, 9]. It has a wide range of cellular effects, including inhibition of tubulin polymerization and microtubule production, and possible effects on cell adhesion molecules, inflammatory chemokines, and inflammasomes. Moreover, colchicine has been generally used for the treatment of gout to relieve pain [10–16]. We found that colchicine has a very good effect in the treatment of pericarditis and atrial fibrillation after cardiac surgery. In recent years, studies have found that colchicine also has an effect in patients with CAD by inhibiting the NLRP3 inflammasome in various ways [17, 18]. Colchicine has emerged as a novel and promising therapeutic approach for the prevention and treatment of CAD [5, 19, 20]. However, the results of some studies have shown that colchicine did not have significantly lower rates of death from cardiovascular causes [21], death from all causes [21–23], or MI [23–25].

Hence, we conducted this meta-analysis to analyze the comprehensive outcomes of randomized clinical trials (RCTs) of CAD in which colchicine was compared with placebo.

Methods

Literature search and selection

We conducted a comprehensive systematic search using PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov from inception to 20 October 2020. We searched for studies with medical search terms and relative variants, including "Coronary Disease" or "Disease, Coronary" or "Coronary artery disease" or "Disease, Coronary Heart" or "multivessel coronary artery disease" or "Myocardial Infarction" or "Cardiovascular Stroke" or "Myocardial Infarct" or "Colchicine" or "Colchicine, (R)-Isomer" or "Colchicine, (+-)-Isomer." We searched for RCTs using search filters from the McMaster University. We also searched the corresponding references of each retrieved study to identify additional studies. All the search results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26].

The efficacy and safety results of colchicine were compared with those of placebo in all RCTs. The inclusion criteria used were as follows: (i) RCTs with a colchicine group and a control group, (ii) RCTs including chronic or acute patients with coronary disease, and (iii) RCTs analyzing primary efficacy outcomes, including cardiovascular death, death from any cause, myocardial infarction, ischemic stroke, coronary revascularization, and key adverse events, including gastrointestinal (GI) symptoms (such as diarrhea, nausea and vomiting, and GI bleeding). The exclusion criteria were as follows: (i) duplicated papers related to the same trial; (ii) systematic reviews, comments, case reports, conferences, editorials, and non-comparative studies; and (iii) incomplete RCTs or RCTs failing to report the outcomes in need.

Data extraction and quality assessment

Data extraction and quality assessments of the studies were performed independently by two investigators (C. Y. and Z. H. Z.). The data included the baseline characteristics of the trials, interventions, comparisons, sample size, medication, and follow-up duration. The outcomes included cardiovascular death, death from any cause, myocardial infarction, ischemic stroke, coronary revascularization, and GI symptoms.

The methodological quality of the 10 included RCTs was assessed by using the Cochrane Collaboration risk of bias tool (Review Manager 5.3), which included the following seven sections: selection, performance, detection, attrition, and reporting. The two investigators cross-checked the data. Any disagreement was resolved by another investigator (W. Y. Q.).

Statistical analysis

The statistical analyses were performed by using Review Manager Version 5.3.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The efficacy and safety outcomes were measured as dichotomous outcome variables and compared between the colchicine group and the control group. The pooled odds ratio (OR) or risk ratio (RR) and the corresponding 95% confidence interval (CI) were collected in the comparative analyses. We assessed heterogeneity by using the I^2 test and Cochran's χ^2 test. The total variation in the studies was described by the I^2 statistic, which reflected heterogeneity. An $I^2 \geq 50\%$ or a corresponding $P < 0.10$ indicated significant heterogeneity among the different studies. When I^2 was $< 50\%$ and P

was > 0.10, we reported the results of fixed-effects models as sensitivity analyses. All *P*-values were two-tailed, with statistical significance specified at 0.05 and *CI*s reported at the 95% level. When I^2 was > 50%, a sensitivity analysis was further performed by sequentially deleting each study and reanalyzing the datasets of all remaining studies.

Results

Study selection and quality assessment

The research selection flowchart is shown in Fig. 1. According to the previous search strategy, 894 citations were obtained after removing duplicate records from the online database from 1 January 2000 to 20 October 2020. The full texts of 72 articles were reviewed in detail, and 61 articles were further excluded because the papers were related to the same trials ($n = 13$), did not include real RCTs ($n = 24$), had unrelated topics ($n = 7$), or were conference abstracts ($n = 17$). Finally, eleven RCTs including 12,899 participants were suitable for this meta-analysis [5, 19–25, 27–29].

The characteristics, quality evaluation, and demographics of the included studies are summarized in Table 1. The follow-up durations ranged from 5 days to 3 years, and the sample sizes of the trials ranged from 44 to 5522 patients. Moreover, the risk of bias was assessed in the eleven studies and was generally found to be low in each study (Supporting Information, Fig. S1).

Primary efficacy outcomes

To assess the primary outcome, eleven trials were included in the meta-analysis. The estimated results of the primary efficacy outcomes of death from all causes, death from cardiovascular causes, and noncardiac deaths are presented in Fig. 2. There were no significant differences in all-cause mortality or cardiovascular mortality and noncardiac deaths between the colchicine group and placebo group among all the patients (Fig. 2). Surprisingly, however, the combined results of the four primary indicators (cardiovascular death, myocardial infarction, ischemic stroke, and coronary revascularization) reported by the two larger RCTs, COLCOT and LoDoCo2 [19, 20], were satisfactory. The pooled *OR* was 0.72, 95% *CI* 0.62–0.83, $P < 0.0001$ ($P = 0.51$ for heterogeneity; $I^2 = 0\%$) (Fig. 3A).

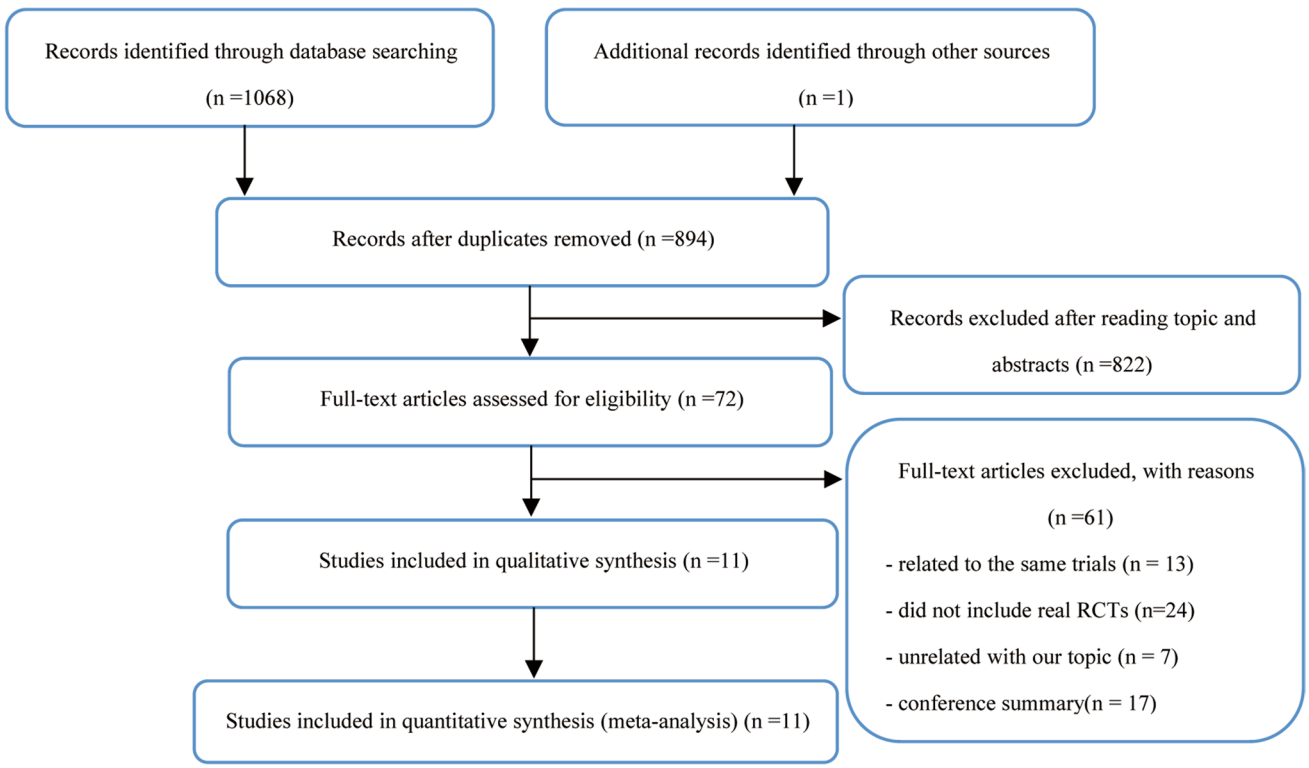


Fig. 1 Study search diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. RCTs, randomized controlled trials

Table 1 Characteristics of individual studies included in the analysis

Study	Year	Number of patients (colchicine/control)	Dose	Follow-up	Population	Mean age (year)	Sex (male%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	Smoke (%)
Akodad M. (COLIN)	2017	44 (23/21)	1 mg/qd	1 m	STEMI	60.1/59.7	82.5/76.2	39.1/47.6	13.0/14.3	34.8/38.1	73.9/66.7
Deftereos S	2013	196 (100/96)	0.5 mg/bid	6 m	DM for PCI	63.7/63.5	63/68	48/49	100/100	NA	36/40
Deftereos S	2015	151 (77/74)	1.5 mg immediately, then 0.5 mg 1 h later, then 0.5 mg/bid	5 days	STEMI	58/58	68/70	40/39	17/26	57/47	56/49
Hennessy. T (LoDoCo-MI)	2019	237 (119/118)	0.5 mg/qd	1 m	AMI	61/61	75/79	54/41	23/21	NA	65/57
Nidorf S. M. (LoDoCo)	2013	532 (282/250)	0.5 mg/qd	36 m	Stable CAD	66/67	89/89	NA	33/28	NA	4/6
Nidorf S. M (LoDoCo2)	2020	5522 (2762/2760)	0.5 mg/qd	28.6 m	Stable CAD	65.8/65.9	83.5/85.9	51.4/50.3	17.8/18.7	NA	11.5/12.0
O'Keefe	1992	197 (130/67)	1 mg/qd	6 m	Elective PCI	59/62	85/87	NA	12/12	NA	NA
Raju (COOL)	2011	80 (40/40)	1 mg/qd	1 m	ACS/ischemic stroke	57.2/57.2	85/92.5	47.5/37.5	17.5/15	47.5/47.5	45/42.5
Shah B. (COLCHICINE-PCI)	2020	400 (206/194)	1.8 mg 1–2 h before surgery	1 m	ischemic heart disease or ACS	65.9/66.6	93.7/93.3	93.2/90.2	55.3/60.3	88.3/89.2	20.9/23.7
Tardif J. C. (COLCOT)	2019	4745 (2366/2379)	0.5 mg/qd	22.6 m	MI within 1 month	60.6/60.5	80.1/81.6	50.1/52	19.5/20.9	NA	29.9/29.8
Tong (COPS)	2020	795 (396/399)	0.5 mg/bid for the first month, followed by 0.5 mg/qd	12 m	ACS	59.7/60.0	81/78	51/50	19/19	46/46	32/37

Abbreviations: *STEMI*, ST segment elevatedacute myocardial infarction; *DM*, diabetes mellitus; *PCI*, Percutaneous Coronary Intervention; *AMI*, acute myocardial infarction; *CAD*, coronary artery disease; *ACS*, acute coronary syndromes; *MI*, myocardial infarction; *qd*, quaque die; *bid*, bis in die

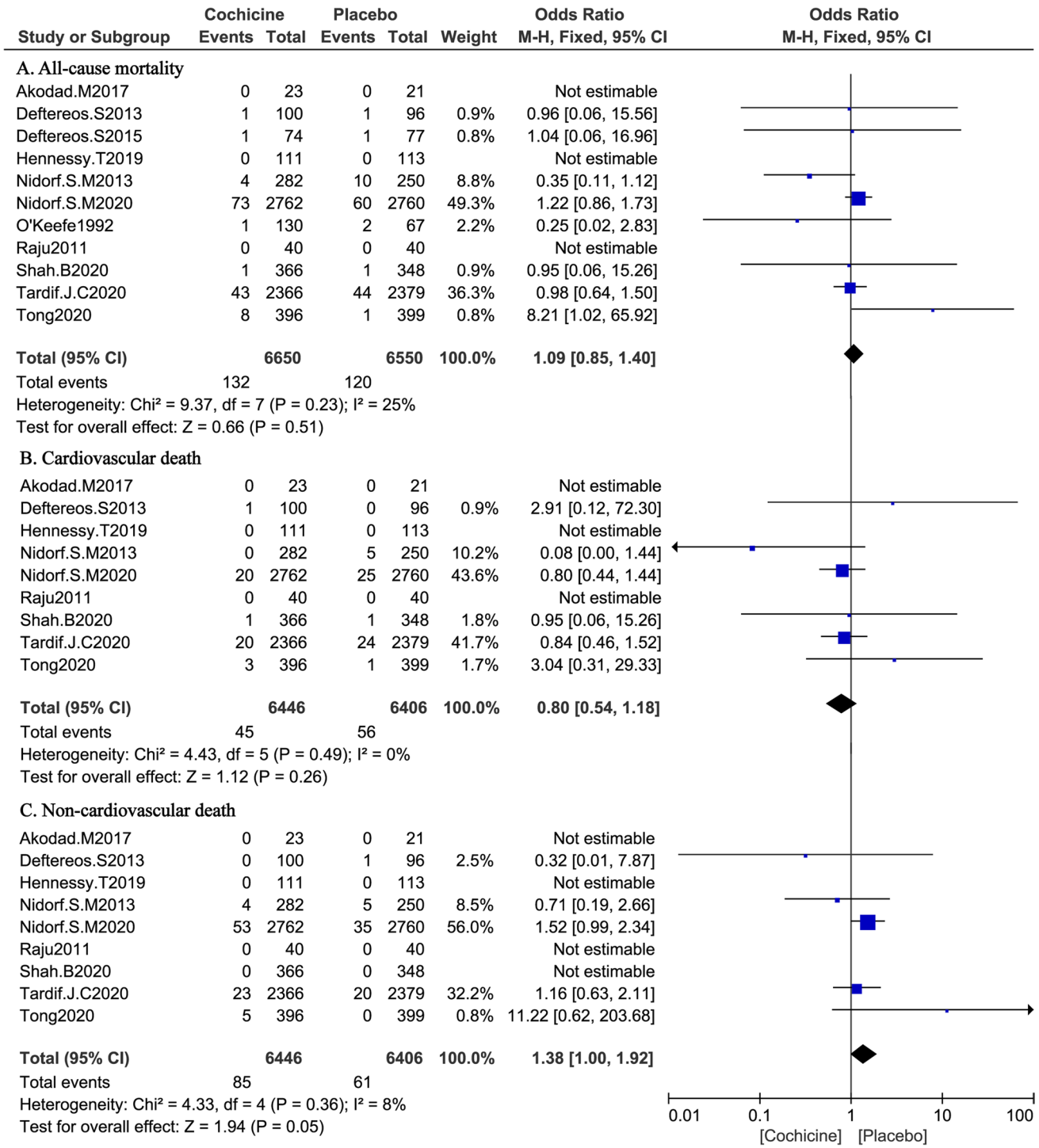


Fig. 2 Data of the comparative analysis for the effective outcomes of all-cause mortality, cardiovascular mortality, and noncardiac death in different patients with CAD (CAD, coronary artery desease)

Myocardial infarction

The composite outcome of myocardial infarction showed that the colchicine group had a lower rate than the placebo group, with a pooled *RR* of 0.77, 95% *CI* 0.64–0.92, $P = 0.004$ ($P = 0.30$ for heterogeneity; $I^2 = 17\%$) (Fig. 3B) [5, 19, 20, 23–25, 28].

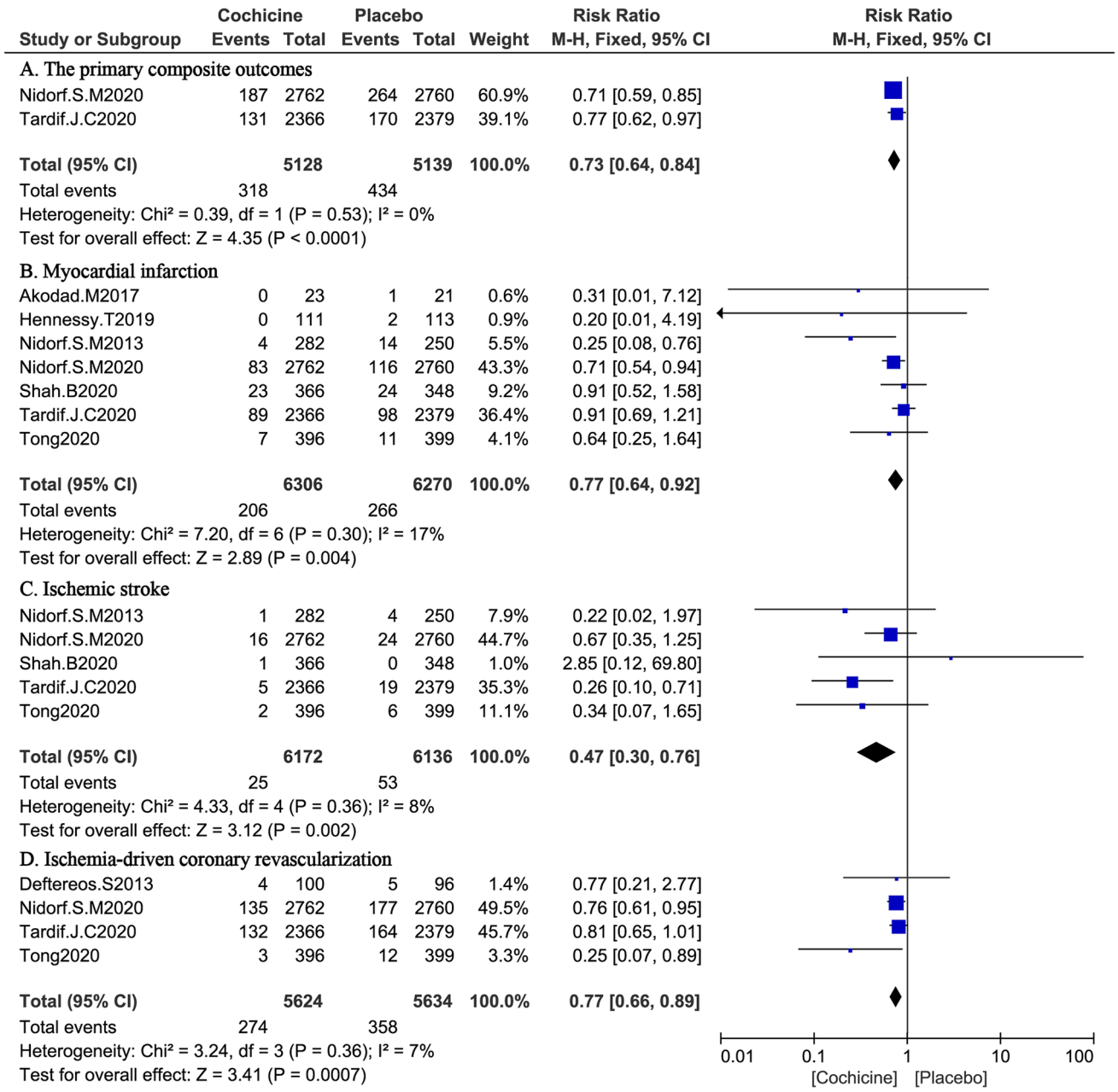


Fig. 3 Data of the comparative analysis for the effective outcomes of primary cardiovascular compound efficacy outcomes, all-cause mortality, cardiovascular mortality, MI, IS, and ischemia-driven coronary revascularization. (MI, myocardial infarction; IS, ischemic stroke)

Ischemic stroke

The risk of stroke was greatly reduced in patients treated with colchicine, with a pooled *RR* of 0.47, 95% *CI* 0.30–0.76, $P = 0.002$ ($P = 0.36$ for heterogeneity; $I^2 = 8\%$), which has been confirmed in some previous studies (Fig. 3C) [5, 19, 20, 23, 28].

Coronary revascularization

Colchicine treatment was associated with a significant reduction in the incidence of ischemia-driven coronary revascularization with a pooled *RR* of 0.77, 95% *CI* 0.66–0.89, $P = 0.0007$ ($P = 0.36$ for heterogeneity; $I^2 = 7\%$) (Fig. 3D) [19–21, 23, 28].

Sub-group analysis

Compared with patients with chronic coronary heart disease, colchicine significantly reduced the risk of ischemic stroke in patients with acute coronary heart disease with a pooled *RR* of 0.28, 95% *CI* 0.12–0.65, $P=0.003$ ($P=0.80$ for heterogeneity; $I^2=0\%$). However, there was no difference in all-cause mortality, cardiovascular mortality, noncardiac deaths, and myocardial infarction between the two (Figs. 4 and 5) [5, 19, 20, 28].

Safety outcomes

Regarding adverse GI events, compared with placebo, colchicine led to a numerically higher risk of GI symptoms with a pooled *RR* of 2.15, 95% *CI* 1.40–3.31, $P=0.0005$ ($P<0.00001$ for heterogeneity; $I^2=81\%$) [5, 20–25, 27–29] (Fig. 6). There was no significant difference in the risk of pneumonia, infection, cancer, myalgia, neutropenia, or paraesthesia between the colchicine group and the control group (Supporting Information, Figs. S2–S7).

Discussion

A meta-analysis of RCTs may provide additional evidence for clinical practice guidelines beyond that provided by individual studies. Most of the studies included in this meta-analysis were multicenter, randomized, double-blind, active-controlled trials with a low risk of bias. All the RCTs included patients with acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). The present study was the first to provide composite evidence of primary cardiovascular compound efficacy outcomes among RCTs comparing colchicine with placebo, and it was also the first study to compare the effects of colchicine in stable and acute CAD. We also added 2 large-scale RCT studies newly published last year. These data suggest that colchicine is superior to placebo in reducing the primary composite outcomes of cardiovascular death, myocardial infarction, ischemic stroke, and ischemia-driven coronary revascularization but does not result in a significant difference in all-cause mortality, cardiovascular mortality, and non-cardiac deaths. Furthermore, after treatment with colchicine, the patient's risk of myocardial infarction, stroke, and ischemia-driven coronary revascularization showed a downward trend. Not surprisingly, the colchicine group had a higher incidence of GI symptoms than the placebo group.

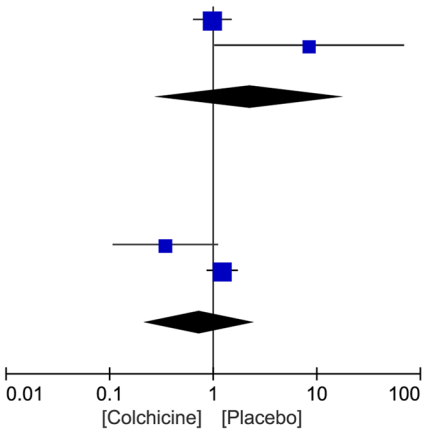
Colchicine showed superiority over placebo in terms of the pooled primary efficacy outcomes. The LoDoCo2 trial [19], which had a large number of participants, showed that colchicine reduced the risks of the primary composite outcomes of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. The COLCOT trial [20], another study with a large number of participants, obtained a similar result. Although Tardif JC [20] added resuscitated cardiac arrest to the composite outcome, the number of patients with this incident was not large enough to affect the overall results. The effect of adding colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease. These results are important because they suggest that colchicine may have a role in the prevention of cardiovascular events caused by instability of native atherosclerotic plaques in patients with stable coronary disease, possibly by inhibiting an inflammatory pathway that has been identified in unstable native coronary plaques [30]. Among the included studies, only three completely reported the above outcome indicators [19, 20, 28], and LoDoCo2 and COLCOT [19, 20] included the primary composite results. When analyzing these results separately, we found that the risks of myocardial infarction, ischemic stroke, and ischemia-driven coronary revascularization in the colchicine group were reduced, while there was no significant difference in cardiovascular death between the two groups, which led to the overall composite result showing the benefits of colchicine.

Tong et al. [28] showed that colchicine did not affect the rate of the primary composite outcome of death, ACS, ischemia-driven urgent revascularization, or stroke compared to standard medical therapy alone at the 365-day follow-up. However, in fact, the prevalence of stroke and revascularization in the colchicine group was better than that in the control group. The reason for this consequence is the high all-cause mortality in the colchicine group. Interestingly, the outcomes including 400-day follow-up as well as using only cardiovascular death rather than total death demonstrated that there was a significant reduction in the primary outcome between groups in favor of colchicine. It also suggests that there is an early sustained effect from colchicine that increases throughout treatment. This may be a result of both the anti-inflammatory properties and plaque-modulating effects of colchicine [31] and may potentially explain the impact on the rates of urgent revascularization [28].

Interestingly, when we sub-analyzed the four largest studies (LoDoCo, LoDoCo2, COLCOT, and COPS) of chronic MI and acute MI, we made new discoveries. We found that death from all causes, death from cardiovascular causes and noncardiac deaths in patients with acute MI and chronic MI, was not statistically significant (Fig. 4). Notably, although the results for non-cardiovascular deaths were not statistically significant, colchicine seemed to increase non-cardiovascular deaths. Although the number of studies is insufficient for statistics, colchicine has shown significant benefits for the primary composite outcomes of cardiovascular death,

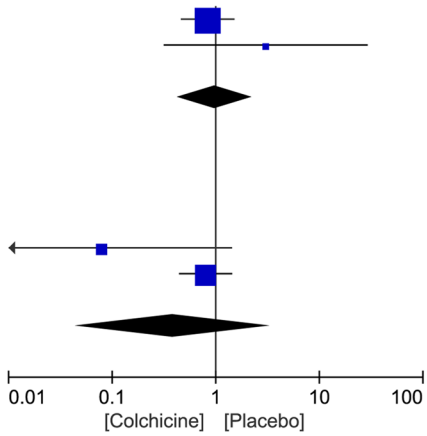
A All-cause mortality

Study or Subgroup	Cochicine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1. Acute coronary artery desease						
Tardif.J.C2020	43	2366	44	2379	61.7%	0.98 [0.64, 1.50]
Tong2020	8	396	1	399	38.3%	8.21 [1.02, 65.92]
Total (95% CI)		**2762**		**2778**	**100.0%**	**2.21 [0.29, 17.16]**
Total events	51		45			
Heterogeneity: Tau² = 1.72; Chi² = 3.93, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 0.76 (P = 0.45)						
2. Stable coronary artery desease						
Nidorf.S.M2013	4	282	10	250	39.8%	0.35 [0.11, 1.12]
Nidorf.S.M2020	73	2762	60	2760	60.2%	1.22 [0.86, 1.73]
Total (95% CI)		**3044**		**3010**	**100.0%**	**0.74 [0.22, 2.49]**
Total events	77		70			
Heterogeneity: Tau² = 0.61; Chi² = 4.11, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.49 (P = 0.63)						



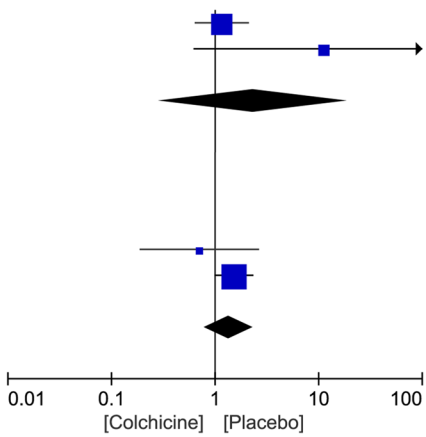
B Cardiovascular mortality

Study or Subgroup	Cochicine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1. Acute coronary artery desease						
Tardif.J.C2020	20	2366	24	2379	87.3%	0.84 [0.46, 1.52]
Tong2020	3	396	1	399	12.7%	3.04 [0.31, 29.33]
Total (95% CI)		**2762**		**2778**	**100.0%**	**0.98 [0.42, 2.28]**
Total events	23		25			
Heterogeneity: Tau² = 0.12; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 0.04 (P = 0.97)						
2. Stable coronary artery desease						
Nidorf.S.M2013	0	282	5	250	31.2%	0.08 [0.00, 1.44]
Nidorf.S.M2020	20	2762	25	2760	68.8%	0.80 [0.44, 1.44]
Total (95% CI)		**3044**		**3010**	**100.0%**	**0.39 [0.05, 3.32]**
Total events	20		30			
Heterogeneity: Tau² = 1.65; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.87 (P = 0.39)						



C Non-cardiac mortality

Study or Subgroup	Cochicine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1. Acute coronary artery desease						
Tardif.J.C2020	23	2366	20	2379	69.4%	1.16 [0.63, 2.11]
Tong2020	5	396	0	399	30.6%	11.22 [0.62, 203.68]
Total (95% CI)		**2762**		**2778**	**100.0%**	**2.32 [0.28, 18.94]**
Total events	28		20			
Heterogeneity: Tau² = 1.56; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.79 (P = 0.43)						
2. Stable coronary artery desease						
Nidorf.S.M2013	4	282	5	250	15.5%	0.71 [0.19, 2.66]
Nidorf.S.M2020	53	2762	35	2760	84.5%	1.52 [0.99, 2.34]
Total (95% CI)		**3044**		**3010**	**100.0%**	**1.35 [0.78, 2.33]**
Total events	57		40			
Heterogeneity: Tau² = 0.04; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%						
Test for overall effect: Z = 1.08 (P = 0.28)						



◂**Fig. 4** Data of the comparative analysis with stable CAD and acute MI for all-cause mortality, cardiovascular mortality, and noncardiac mortality

MI, ischemic stroke, and ischemia-driven coronary revascularization in acute and chronic CAD patients. Although the incidence of MI in patients with chronic MI and acute MI is not statistically significant, colchicine seems to show certain benefits in patients with chronic MI (Fig. 5A), and more RCT tests are needed in the future to prove this result. This may be due to irreversible damage to the hearts of patients with MI, which makes them more likely to have MI. However, patients with acute MI have a lower incidence of ischemic stroke (Fig. 5B). In fact, the ischemic stroke rate of patients with chronic MI in the colchicine group was also lower than that in the placebo group, but the effect was not significant enough to reach statistical significance. In the future, we may be more focused on the application of colchicine for chronic MI.

The essence of CAD is actually the inflammation caused by atherosclerosis. The activation of inflammasomes may be caused by many irritating stimuli (such as hypertension, dyslipidemia, smoking, metabolic syndrome) leading to vascular endothelial dysfunction and LDL particle intimal aggregation, forming asymmetric atherosclerotic plaques on the artery wall. After lipid macrophages are deposited on the arterial wall, the inflammatory response leads to the formation of free crystalline cholesterol in the interstitium (Fig. 7). Cholesterol crystal embolization can cause remote ischemia and tissue inflammation or stimulate direct inflammation. This stimulus is then recognized by innate immune receptors on the cell surface (TLRs) or inside the cell (NLRs). The TLR signaling pathway activates NF-kb through reactive oxygen species and produces IL-1β, and NLrRs are integrated into the structure of the inflammasome. At the same time, colchicine also inhibits the production of interleukin 18 (IL-18), which is closely related to IL-1β, and requires the cleavage of caspase-1 mediated by the NLRP3 inflammasome to produce the active form [32, 33]. Colchicine blocks the intracellular assembly of inflammasomes, and inflammasomes are the key to activating pro-IL-1β and pro-IL-18 to IL-1β and IL-18, respectively (Fig. 4). Currently, the specific mechanism by which colchicine interferes with CAD is less well understood. It inhibits the synthesis of TNF-α, leukotriene B4, prostaglandin E2, and TxA2 as well as the activity of COX − 2. Even at low doses, it impairs adhesion of polymorphonuclear leukocytes (PMNs) to the endothelium by reducing both E- and P-selectin expression, inhibiting neutrophil migration and thus inflammation [11, 13]. More recently, a novel mechanism of action by blocking the activity of the NLRP3 inflammasome was described, thereby reducing the crystal-mediated production of IL-1β and IL-18 and neutrophil migration [32–36]. A study by Otani K et al. of a mouse model of small intestine injury showed that colchicine inhibited the protein expression of cleaved caspase-1 and mature IL-1β [36]. Likewise, in the study by Misawa et al., colchicine inhibition of intracellular transport of ASC was described, thus blocking colocalization of NLRP3 inflammasome proteins and their function [33]. Marques-da-Silva et al. recently demonstrated that pore formation (and the resulting intracellular K + reduction) is a key step in the NLRP3 inflammasome response to ATP, and colchicine produces potent inhibition of P2X7- and P2X2-induced pore formation, resulting in lower levels of ROS and IL-1β [37]. The formation of P2X7 pores is a necessary step in the innate immune response for triggering ATP-induced NLRP3 inflammasome activation [38]. This event is upstream of microtubule depolymerization and may represent a new therapeutic target for the treatment of chronic inflammation [39]. The most promising targets for the control of inflammation appear to lie within the IL-1β pathway. The CANTOS trial [40] with canakinumab provided proof of principle that inhibition of IL-1β can improve outcomes. However, canakinumab, which is a monoclonal antibody and hence expensive, is unlikely to be widely adopted for long-term treatment. Of the available alternatives, repurposing colchicine shows the best potential for affordable and accessible anti-inflammatory treatment of atherosclerosis. Ongoing trials are needed to establish their efficacy and safety.

A retrospective study found a reduced prevalence of myocardial infarction among gout patients who used colchicine (1.2%) versus those who did not (2.6%, $P = 0.03$), and patients taking colchicine also demonstrated trends towards reduced mortality and lower CRP levels [41]. We found that the risk of myocardial infarction was reduced, and the most likely reason was that the rate of nonfatal events decreased with no reduction in fatal infarctions. Raju et al. found no difference in hsCRP or platelet aggregation in the colchicine group compared with the placebo group [27]. However, this study did not specify how soon after the ACS diagnosis colchicine was administered, and by 30 days after the index event, acute inflammatory processes would have subsided even in the control group, rendering these findings difficult to interpret. There were no significant differences between the colchicine group and the placebo group in several main endpoints in the study of Akodad et al. [24]. The lack of an effect of colchicine in this study may be explained by the late administration of colchicine in the intensive care unit after reperfusion and without a loading dose. Another reason is that the two study groups were not balanced with regard to areas at risk, such as infarct area and infarct size, which is a major bias. These negative results may suggest that treatment should be given at the onset of reperfusion as soon as possible to optimize its action and reduce reperfusion injuries associated with inflammation burden.

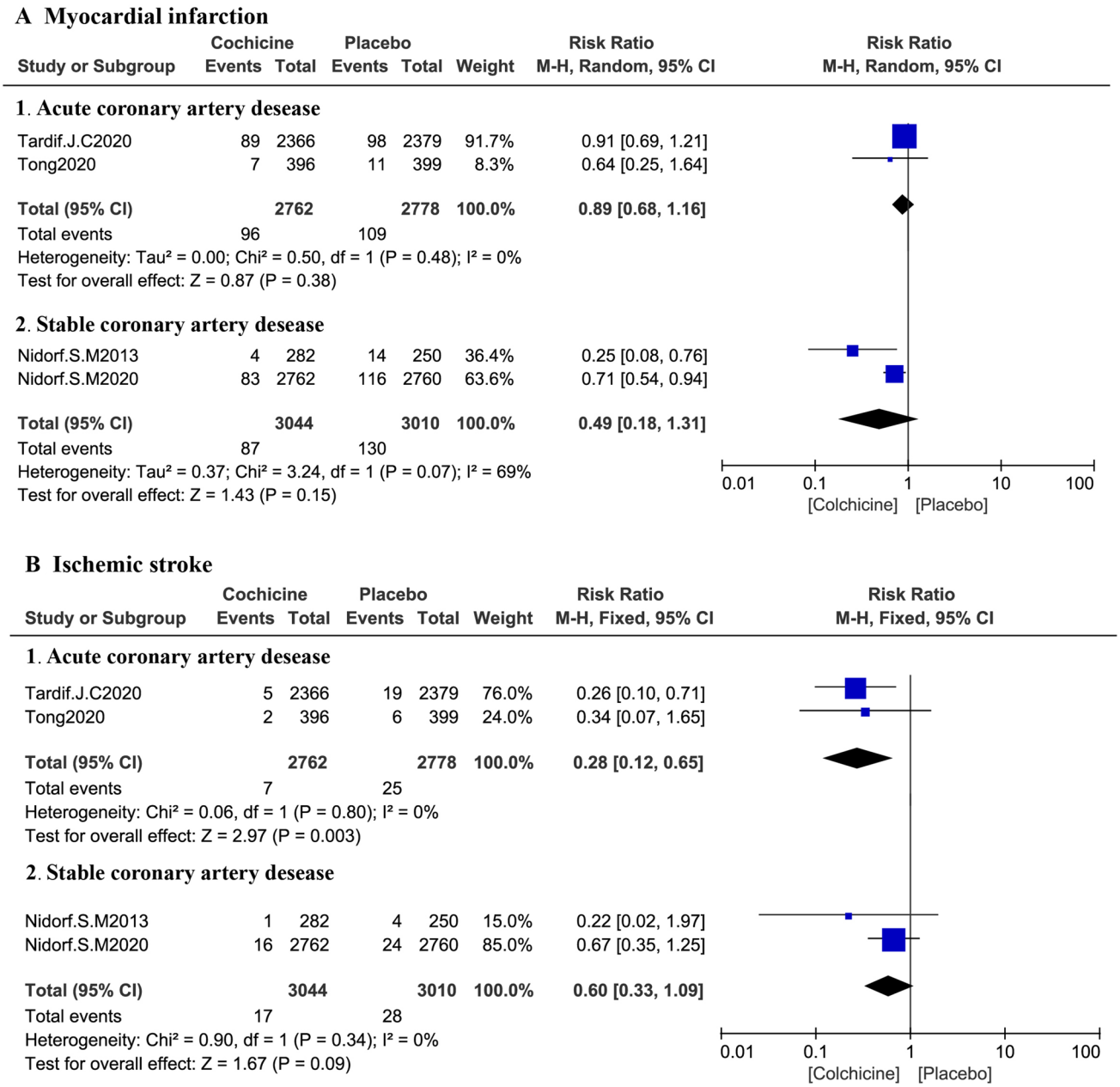


Fig. 5 Data of the comparative analysis with stable CAD and acute MI for myocardial infarction and ischemic stroke

Deftereos et al. [22] obtained the opposite result, which showed that administration of oral colchicine reduced the infarct size, with a reduction in creatine kinase area under the curve and a reduction in infarct size on cardiac MRI in patients admitted for STEMI. However, it seems difficult to compare these two studies [22, 27] because of the different populations and reperfusion results. In the LoDoCo-MI trial [25], readmission rates were significantly lower in the colchicine-treated patients, but the numbers were small, the events were diverse, and the majority was for relatively benign reasons and/or events that seem unlikely to be related to the trial medication. Thus, the observed differences seem likely to be due to chance. Shah B et al. [23] found that acute preprocedural administration of colchicine attenuated the increase in hs-CRP and IL-6 but did not reduce the risk of death, nonfatal myocardial infarction, or target vessel revascularization at 30 days or the outcome of PCI-related myocardial infarction. It attenuated the intracardiac production of many cytokines and chemokines, but there is no evidence that this dosing scheme improves cardiovascular outcomes [42].

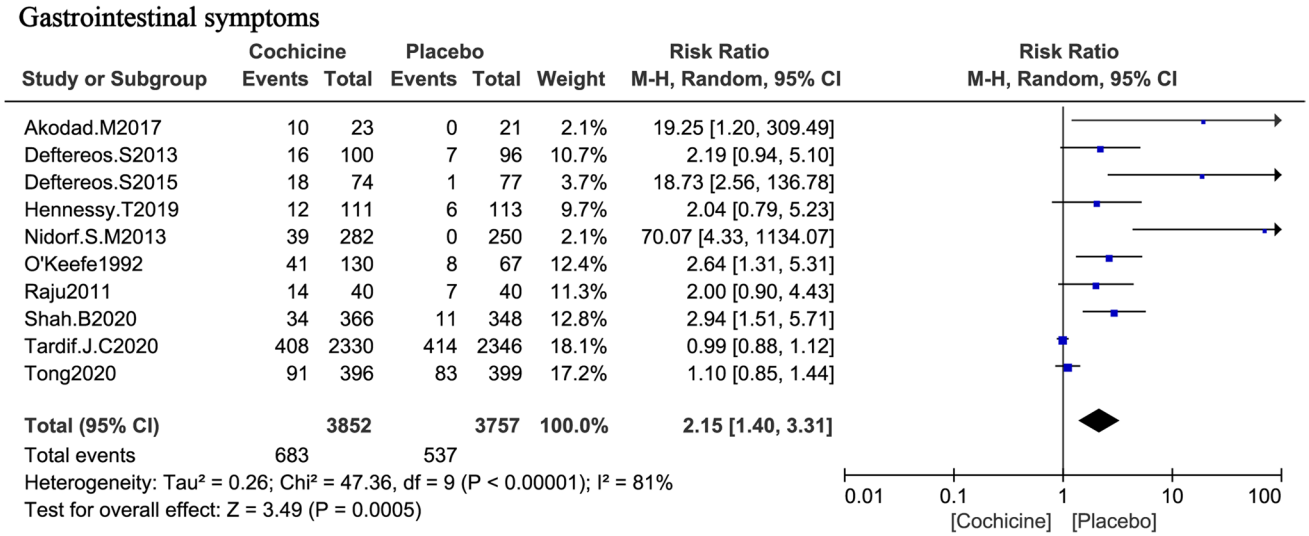


Fig. 6 Data of the comparative analysis for the effective outcomes of GI symptoms. (GI, gastrointestinal)

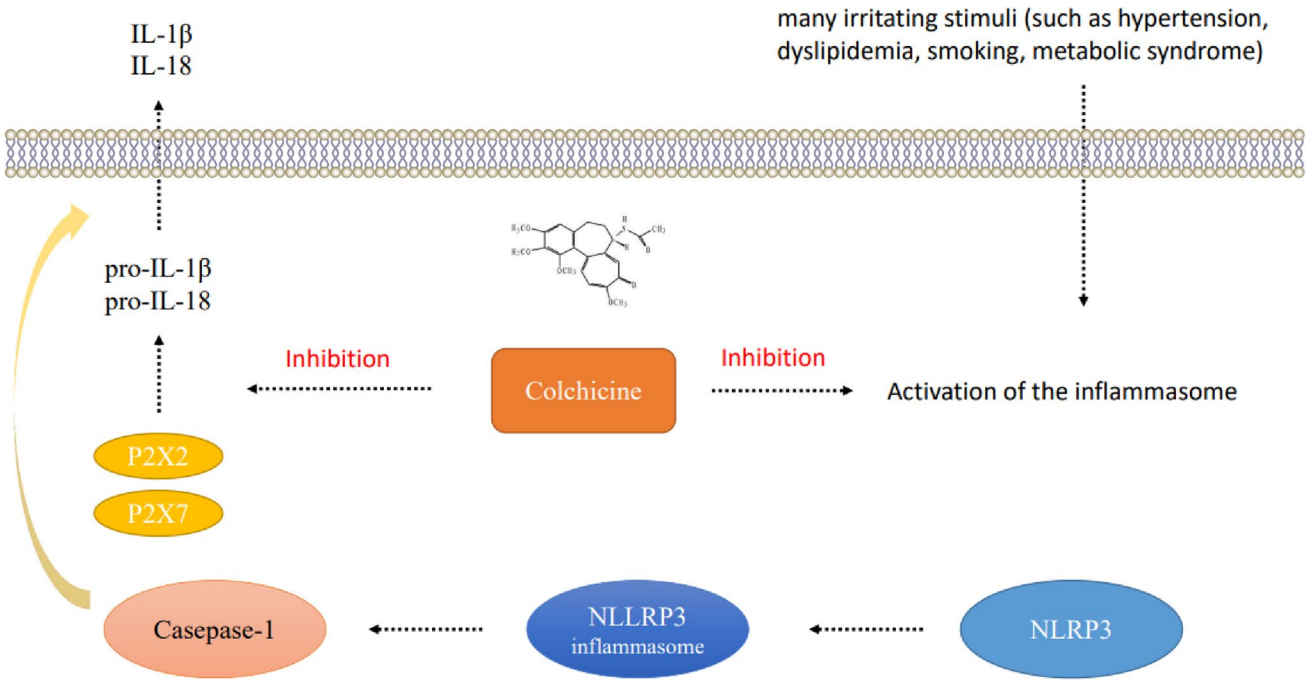


Fig. 7 The pathway of inflammasome activation and the mechanism of action of colchicine. The initial stimulation may be atherosclerosis caused by high fat. This stimulus is then recognized by innate immune receptors on the cell surface (TLRs) or inside the cell (NLRs). The TLR signaling pathway activates NF-kb through reactive oxygen species and produces IL-1β, and NLrRs are integrated into the structure of the inflammasome. Colchicine blocks the intracellular assembly of inflammasomes, and inflammasomes are the key to activating pro-IL-1β and pro-IL-18 to IL-1β and IL-18, respectively. And colchicine can effectively inhibit the formation of pores induced by P2X7 and P2X2, thereby reducing the levels of ROS and IL-1β. The formation of P2X7 stomata is a necessary step in the innate immune response to trigger ATP-induced NLRP3 inflammasome activation

In two prospective, randomized placebo-controlled trials examined the effects of colchicine on restenosis after coronary angioplasty. O'Keefe et al. [29] found that colchicine (0.6 mg BID) failed to reduce the incidence of restenosis in 6-month-old patients undergoing balloon angioplasty, while Deftereos S et al. [21] obtained the opposite result in patients with diabetes treated with bare-metal stents. These results might suggest that colchicine has no effect on early restenosis related to elastic

recoil after balloon angioplasty but that it may prevent neointimal hyperplasia that causes early in-stent stenosis, as has been described in animal models [43].

In our results, we found that the incidence of atrial fibrillation in patients with CAD did not change significantly after the use of colchicine (Fig. S3) [19, 20]. A meta-analysis of 5 RCTs on atrial fibrillation after open heart surgery that involved 1412 patients found that the colchicine group had a lower risk of atrial fibrillation than the placebo group [44]. A study in patients undergoing CABG found the benefit of taking colchicine the night before surgery and continued for 5 days in the prevention of postoperative AF (14.8 vs. 30.6%; $P=0.006$. [45]. Unfortunately, the subsequent trials COPPS-2, AF-POMR, and END-AF [46–48] that initiated colchicine before the surgery and settled for all episodes of postoperative AF failed to demonstrate a benefit of colchicine in preventing postoperative AF. The main postulated explanation for these results, which contrasted with those of the COPPS trial [49], was the high rate of medication discontinuation (20%) in COPPS-2 and lack of power in the END-AF and AF-POMR trials [50]. Although the data are conflicting, current clinical guidelines support the use of adjunctive colchicine in the postoperative setting to decrease the risk of AF after cardiac surgery [51]. We need larger randomized studies before a more definitive recommendation can be made.

The main adverse reactions of colchicine that we know are GI symptoms, including nausea, vomiting, diarrhea, and GI bleeding. In our research, most of the discontinuations in the colchicine group were due to GI intolerance. But the results are highly heterogeneous because the results of the occurrence of GI symptoms were mainly derived from studies with short follow-up periods. This may be related to the patient's disease type, medication time, and dose, and there are many factors that cannot be generalized. In addition, patients with chronic coronary heart disease generally take drugs, such as aspirin, that cause GI discomfort for a long time, so they will also take drugs that protect the GI tract, which may be one of the reasons why there is no obvious discomfort in the GI tract during long-term follow-up. Therefore, we can only assume that short-term colchicine use can cause GI symptoms, and more clinical trials of long-term colchicine use are needed to determine whether long-term colchicine use will also cause GI symptoms.

In the COLCOT trial [20], it was found that the incidence of pneumonia increased slightly and was statistically significant. However, the infection rate of patients after using colchicine was not significantly higher than that of the placebo group, which led us to consider whether long-term colchicine treatment impairs the patient's immune response to infection. The results we obtained show that the probability of myopathy after the use of colchicine in coronary heart patients has not increased [19, 21, 28]; however, in the ACS setting, colchicine would be prescribed with concomitant high-intensity statin therapy but may increase the serum concentrations and myopathic effects of many statins. This may be a barrier to colchicine treatment in some patients at risk for myalgias, although risk could be mitigated with statin dose adjustments [42].

The new data show the potential of colchicine as a new treatment option for cardiovascular disease. Among myriad anti-inflammatory agents currently being tested, such as canakinumab (IL-1β monoclonal antibody), tocilizumab (IL-6 receptor blockade), etanercept (tumor necrosis factor inhibitor), and methotrexate, colchicine stands out as a promising therapy for cardiovascular disease [52]. Colchicine may have an enormous impact on patients with atherosclerosis worldwide because of its wide availability, low cost, and convenient administration if clinically proven to be beneficial. While biological and other immunomodulatory agents carry the risk of unintended adverse consequences, colchicine has been shown to be a relatively safe drug for long-term use in patients with ischemic heart disease [5]. Over the next few years, we need additional large-scale clinical trials to clarify the role of colchicine in cardiovascular disease to continue to solve this puzzle.

Our study has some potential limitations. First, the dosage of the medicine is different for patients, and the effect of low dosage on the disease remains to be studied. Second, confounding factors, such as heart function, types of coronary artery disease, age, and sex, were difficult to control. Third, unpublished data or articles published in other languages were not included. Fourth, different sample sizes and different control drugs (some studies used only the best drug treatment, rather than a placebo) may have led to confounding bias and affected the composite outcomes. Finally, this meta-analysis may be underpowered for a long-term adverse event comparison between colchicine and placebo due to the different durations of the included RCTs.

Conclusion

In conclusion, the pooled estimates showed that compared with placebo, colchicine significantly decreased the risk of primary cardiovascular composite outcomes, MI, ischemic stroke, and ischemia-driven coronary revascularization but failed to improve all-cause mortality and cardiovascular mortality in patients with CAD. Colchicine improved the risk of ischemic stroke in patients with acute CAD more than in patients with chronic CAD. Short-term colchicine use increased the risk of adverse GI effects compared with placebo. There was no significant difference in the risk of pneumonia, infection, cancer, myalgia, neutropenia, or paraesthesia between the colchicine group and the control group.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06050-0.

Author contribution YC and HZ reviewed the articles, performed the meta-analysis, and wrote the manuscript. YC, ML, WL, and YF were responsible for the statistical analysis. CX, HX, and YL provided editing assistance, and YJ and YW designed and revised the manuscript. All authors reviewed and agreed on this information before submission.

Funding This work was supported by the National Key Research and Development Plan of China (20212BBG71004), the National Natural Science Foundation of China (82160085), Beijing Health Promotion Association (20181BCB24013), special funds for guiding local scientific and technological development by the central government of China (S2019CXSFG0016) and the Natural science funding (20202BAB206005).

Declarations

Disclosures None.

References

1. Ross R (1999) Atherosclerosis–an inflammatory disease. N Engl J Med 340(2):115–126
2. Libby P, Ridker PM, Maseri A (2002) Inflammation and atherosclerosis. Circulation 105(9):1135–1143
3. Libby P (2013) Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 368(21):2004–2013
4. Zhang H, Huang T, Shen W, Xu X, Yang P, Zhu D, Fang H, Wan H, Wu T, Wu Y, Wu Q. Efficacy and safety of sacubitril-valsartan in heart failure: a meta-analysis of randomized controlled trials. *ESC Heart Fail*. 2020 Sep 25.
5. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL (2013) Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 61(4):404–410
6. Libby P (2001) What have we learned about the biology of atherosclerosis? The role of inflammation. Am J Cardiol 88(7B):3J-6J
7. Virmani R, Burke AP, Farb A, Kolodgie FD (2006) Pathology of the vulnerable plaque. J Am Coll Cardiol 47(8 Suppl):C13-18
8. Niel E, Scherrmann JM (2006) Colchicine today. Joint Bone Spine 73(6):672–678
9. Terkeltaub RA (2009) Colchicine update: 2008. Semin Arthritis Rheum 38(6):411–419
10. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, Okunogbe A, Han D, Shanman R (2017) Management of gout: a systematic review in support of an American College of Physicians clinical practice guideline. Ann Intern Med 166(1):37–51
11. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G (1995) Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 96(2):994–1002
12. Dalbeth N, Lauterio TJ, Wolfe HR (2014) Mechanism of action of colchicine in the treatment of gout. Clin Ther 36(10):1465–1479
13. Leung YY, Yao Hui LL, Kraus VB (2015) Colchicine–update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 45(3):341–350
14. Pope RM, Tschopp J (2007) The role of interleukin-1 and the inflammasome in gout: implications for therapy. Arthritis Rheum 56(10):3183–3188
15. Perico N, Ostermann D, Bontempeill M, Morigi M, Amuchastegui CS, Zoja C, Akalin E, Sayegh MH, Remuzzi G (1996) Colchicine interferes with L-selectin and leukocyte function-associated antigen-1 expression on human T lymphocytes and inhibits T cell activation. J Am Soc Nephrol 7(4):594–601
16. Ravelli RB, Gigant B, Curmi PA, Jourdain I, Lachkar S, Sobel A, Knossow M (2004) Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. Nature 428(6979):198–202
17. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E (2010) NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 464(7293):1357–1361
18. Rajamaki K, Lappalainen J, Oorni K, Valimaki E, Matikainen S, Kovanen PT, Eklund KK (2010) Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. PloS one 5(7):e11765
19. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings MMW, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL. Colchicine in patients with chronic coronary disease. *The New England journal of medicine*. [Article in Press]. 2020.
20. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS et al (2019) Efficacy and safety of low-dose colchicine after myocardial infarction. N Eng J Med 381(26):2497–2505
21. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, Driva M, Hahalis G, Pyrgakis V, Alexopoulos D et al (2013) Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardio 61(16):1679–1685
22. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G, Goudevenos J, Alexopoulos D, Pyrgakis V et al (2015) Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation 132(15):1395–1403
23. 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. *Cir: Cardiovasc Interv*. [Journal: Article in Press]. 2020.
24. Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, Leclercq F, Macia JC, Gervasoni R, Cung TT et al (2017) COLIN trial: value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. Arch Cardiovasc Dis 110(6–7):395–402
25. Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, Hillis GS (2019) 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 215:62–69
26. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
27. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW (2012) 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 33(1):88–94

28. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong AS, Bhindi R, Whitbourn R, Lee A, Hengel C, Asrress K, Freeman M, Amerena J, Wilson A, Layland J. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. *Circulation*. [Article in Press]. 2020.
29. O'Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO (1992) Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. J Am Coll Cardiol 19(7):1597–1600
30. Naruko T, Ueda M, Haze K, van der Wal AC, van der Loos CM, Itoh A, Komatsu R, Ikura Y, Ogami M, Shimada Y, Ehara S, Yoshiyama M, Takeuchi K, Yoshikawa J, Becker AE (2002) Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation 106(23):2894–2900
31. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, Glinz D, Nordmann AJ, Briel M (2016) Colchicine for prevention of cardiovascular events. Cochrane Database Syst Rev 27(1):CD011047
32. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440(7081):237–241
33. Misawa T, Takahama M, Kozaki T, Lee H, Zou J, Saitoh T, Akira S (2013) Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. Nat Immunol 14(5):454–460
34. Van Gorp H, Saavedra PH, de Vasconcelos NM, Van Opdenbosch N, Vande Walle L, Matusiak M, Prencipe G, Insalaco A, Van Hauwermeiren F, Demon D, Bogaert DJ, Dullaers M, De Baere E, Hochepied T, Dehoorne J, Vermaelen KY, Haerynck F, De Benedetti F, Lamkanfi M (2016) Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in pyrin inflammasome activation. Proc Natl Acad Sci U S A 113(50):14384–14389
35. Park YH, Wood G, Kastner DL, Chae JJ (2016) Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat Immunol 17(8):914–921
36. Otani K, Watanabe T, Shimada S, Takeda S, Itani S, Higashimori A, Nadatani Y, Nagami Y, Tanaka F, Kamata N, Yamagami H, Tanigawa T, Shiba M, Tominaga K, Fujiwara Y, Arakawa T (2016) Colchicine prevents NSAID-induced small intestinal injury by inhibiting activation of the NLRP3 inflammasome. Sci Rep 2(6):32587
37. Marques-da-Silva C, Chaves MM, Castro NG, Coutinho-Silva R, Guimaraes MZ (2011) Colchicine inhibits cationic dye uptake induced by ATP in P2X2 and P2X7 receptor-expressing cells: implications for its therapeutic action. Br J Pharmacol 163(5):912–926
38. Mangold A, Alias S, Scherz T, Hofbauer T, Jakowitsch J, Panzenbock A, Simon D, Laimer D, Bangert C, Kammerlander A, Mascherbauer J, Winter MP, Distelmaier K, Adlbrecht C, Preissner KT, Lang IM (2015) Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circ Res 116(7):1182–1192
39. Kobayashi Y (2015) Neutrophil biology: an update. EXCLI J 14:220–227
40. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, Group CT (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Eng J Med 377(12):1119–1131
41. Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, Cronstein BN, Sedlis SP, Pillinger MH (2012) Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol 39(7):1458–1464
42. McKnight AH, Katzenberger DR, Britnell SR. Colchicine in acute coronary syndrome: a systematic review. *Ann Pharmacother*. [Article in Press]. 2020.
43. Muller DW, Ellis SG, Topol EJ (1991) Colchicine and antineoplastic therapy for the prevention of restenosis after percutaneous coronary interventions. J Am Coll Cardiol 17(6 Suppl B):126B-131B
44. Lennerz C, Barman M, Tantawy M, Sopher M, Whittaker P (2017) Colchicine for primary prevention of atrial fibrillation after open-heart surgery: systematic review and meta-analysis. Int J Cardiol 15(249):127–137
45. Sarzaeem M, Shayan N, Bagheri J, Jebelli M, Mandegar M (2014) Low dose colchicine in prevention of atrial fibrillation after coronary artery bypass graft: a double blind clinical trial. Tehran Univ Med J 72(3):147–154
46. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, Caforio AL, Cemin R, Chirillo F, Comoglio C, Cugola D, Cumetti D, Dyrda O, Ferrua S, Finkelstein Y, Flocco R, Gandino A, Hoit B, Innocente F, Maestroni S, Musumeci F, Oh J, Pergolini A, Polizzi V, Ristic A, Simon C, Spodick DH, Tarzia V, Trimboli S, Valenti A, Belli R, Gaita F, Investigators C- (2014) Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. Jama 312(10):1016–1023
47. Tabbalat RA, Hamad NM, Alhaddad IA, Hammoudeh A, Akasheh BF, Khader Y (2016) Effect of colchicine on the incidence of atrial fibrillation in open heart surgery patients: END-AF trial. Am Heart J 178:102–107
48. Zarpelon CS, Netto MC, Jorge JC, Fabris CC, Desengrini D, Jardim Mda S, Silva DG (2016) Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization. Arq Bras Cardiol 107(1):4–9
49. Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, Maestroni S, Zingarelli E, Barosi A, Simon C, Sansone F, Patrini D, Vitali E, Ferrazzi P, Spodick DH, Adler Y, Investigators C (2010) Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS): a multicenter, randomized, double-blind, placebo-controlled trial. Eur Heart J 31(22):2749–2754
50. Chen K, Schenone AL, Borges N, Militello M, Menon V (2017) Teaching an old dog new tricks: colchicine in cardiovascular medicine. Am J Cardiovasc Drugs 17(5):347–360
51. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G. (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 64(21):e1-76
52. Tong DC, Wilson AM, Layland J (2016) Colchicine in cardiovascular disease: an ancient drug with modern tricks. Heart (British Cardiac Society) 102(13):995–1002

Authors and Affiliations

Yi Chen[1] · Hongzhou Zhang[1] · Yuxin Chen[1] · Meng Li[1] · Wei Luo[1] · Yue Liu[1] · Yang Fu[1] · Huasong Xia[1] · Cong Xu[1] · Yu Jiang[2] · Yanqing Wu[1]

[1] Department of Cardiovascular Medicine, Donghu District, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Nanchang 330006, Jiangxi, China

[2] Department of Cardiovascular Medicine, Donghu District, The First Affiliated Hospital of Nanchang University, No. 17, Yongzhengwai Road, Nanchang 330006, Jiangxi, China