Meta-analysis Evaluating the Utility of Colchicine in Secondary Prevention of Coronary Artery Disease

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Colchicine has shown potential therapeutic benefits in cardiovascular conditions owing to its broad anti-inflammatory properties. Here, we performed a meta-analysis to determine the efficacy and safety of colchicine in patients with coronary artery disease (CAD). A systematical search in electronic databases of PubMed, The Cochrane Library, and Scopus were carried out to identify eligible studies. Only randomized controlled trials evaluating the cardiovascular effects of colchicine in CAD patients were included. Study-level data of cardiovascular outcomes or adverse events were pooled using random-effect models. We finally included 5 randomized controlled trials with follow-up duration ≥6 months, comprising a total of 11,790 patients with CAD. Compared with placebo or no treatment, colchicine administration was associated with a significantly lower incidence of major adverse cardiovascular events (relative risk [RR] 0.65, 95% confidence interval [CI] 0.52 to 0.82). Such a benefit was not modified by the clinical phenotype of CAD (p for interaction = 0.34). Colchicine treatment also decreased the risk of myocardial infarction (RR 0.73, 95% CI 0.55 to 0.98), coronary revascularization (RR 0.61, 95% CI 0.42 to 0.89) and stroke (RR 0.47, 95% CI 0.28 to 0.81) in CAD patients, but with no impact on cardiovascular mortality. In addition, the rates of common adverse events were generally similar between colchicine and control groups, including noncardiovascular deaths (RR 1.50, 95% CI 0.93 to 2.40) and gastrointestinal symptoms (RR 1.05, 95% CI 0.91 to 1.22). In conclusion, the results of our meta-analysis demonstrated that colchicine treatment may reduce the risk of future cardiovascular events in CAD patients. **(Am J Cardiol 2021;140:33−38)**

Coronary artery disease (CAD) is a prevalent and progressive atherosclerotic illness, accounting for nearly 8.93 million deaths worldwide in the year 2017.[1] During the past several decades, great advances have been achieved in the management of CAD, including lifestyle modification, medications, and interventional therapy. However, even with these treatments, patients with CAD are still at high risk for cardiovascular events.[2] The pivotal role of inflammation in atherosclerosis has been well characterized, from initiation through deterioration and finally may contribute to the ongoing complications of CAD.[3] Targeting proinflammatory elements is thus becoming a theoretically therapeutic option for the risk reduction in CAD patients. Colchicine is a decades-old drug that has been traditionally used in a variety of inflammatory conditions such as gouty attacks, rheumatoid arthritis, familial Mediterranean fever, and pericarditis.[4] Owing to its potent anti-inflammatory effects, colchicine has emerged with salutary cardiovascular findings in individuals with high cardiovascular risk.[5] However, for patients with established CAD, the therapeutic benefits and harms of colchicine remains inconclusive in relative clinical trials. We therefore conducted a meta-analysis to determine the clinical utility of colchicine treatment in patients with CAD.

Methods

This study was performed in accordance with the preferred reporting Items for systematic reviews and meta-analyses statement.[6] To obtain the potentially eligible studies, we systematically searched the databases of PubMed, The Cochrane Library, and Scopus from inception to August 2020. The terms used in the search process were as follows: ("colchicine") AND ("coronary artery disease" OR "coronary heart disease" OR "angina" OR "myocardial infarction" OR "acute coronary syndrome [ACS]" OR "ischemic heart disease" OR "percutaneous coronary intervention"). The citation lists of relevant publications were also checked to get further suitable studies. To be included in this meta-analysis, the retrieved reports must meet each of the following conditions: (1) randomized controlled trials (RCTs) comparing the effects of colchicine versus placebo or no treatment in CAD patients; (2) have reported the efficacy outcomes data we focused on in the present study; (3) with at least 6-month follow-up duration. Review articles, editorials, duplicates, and post hoc analyses of original RCTs were excluded.

In general, the baseline characteristics of studies and patients were abstracted by 2 independent reviewers. We also documented the end points data in each study for the

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subsequent pooling analyses. The Cochrane collaborations tool for assessing the risk of bias[7] was applied to evaluate the methodological quality of each study, which included the following 6 aspects: generation of random sequence, allocation concealment, binding of participants and personnel, binding of outcomes evaluator, incomplete outcome data, and selective reports. Any discordance in data collection and quality assessment between the 2 reviews were handled by consultation with a third reviewer.

The primary efficacy outcome of the present meta-analysis was major adverse cardiovascular events (MACE). Since the components of MACE were not completely uniform across the included trials, we used the study-specific definitions. The secondary efficacy outcomes included cardiovascular mortality, myocardial infarction, coronary revascularization, and stroke. For the safety outcomes, we focused on incidence of noncardiovascular deaths, gastrointestinal events, infection, pneumonia, and cancer. All end points data were assessed at the longest available follow-up time.

The aggregated effect size for each outcome was presented as relative risk (RR) and corresponding 95% percentage interval (CI), which was calculated based on random-effect models with Mantel-Haenszel method. The heterogeneity across RCTs was examined by using the Cochrane Q test with a significance threshold of $p < 0.1$. We also described the heterogeneity as low, moderate, and high with I^2 statistic values of <25%, 25% to 75%, and >75%, respectively. Subgroup analysis for the primary end point was performed according to the clinical phenotype of CAD (stable CAD vs ACS). The difference between subsets was confirmed by conducting a heterogeneity test across subgroups rather than across studies.[8] To assess the stability of results, we also conducted sensitivity analyses by excluding each study in sequence. Publication bias of the meta-analytic result was investigated by Egger's test. All statistical analyses were implemented with Review Manager 5.3 (RevMan, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and STATA 12.0 software (STATA Corp, College Station, TX), and p values <0.05 were regarded as significant.

Results

The search strategy initially documented a total of 516 articles. After scanning the titles and/or abstracts, 482 reports were considered as irrelevant and were excluded. In the remaining 34 records, 29 were further removed according to the eligibility and exclusion criteria. As a consequence, 5 RCTs[9–13] published between 2013 and 2020 were included into the final analysis (Figure 1).

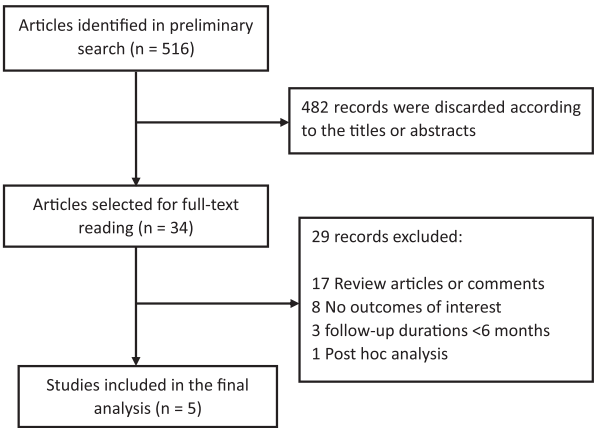

Figure 1. The flow diagram for study search process.

The main features of the included studies and patients are summarized in Table 1. The 5 trials comprised 11,790 patients with CAD, of whom 5,906 were assigned to the colchicine group and 5,884 to the control group (placebo or no treatment). The used dosages of colchicine were 0.5 mg once or twice daily, and the follow-up duration varied from 6 to 29 months. The average age of patients ranged from 60 to 66 years, and men accounted for 83% of the population. With regard to methodological quality, most of the studies have reported random sequence generation and allocation concealment. Four trials were double-blinded, and 4 had performed blinded assessment of outcomes. The concomitant treatments were well balanced between colchicine and control groups in the included studies, as shown in Supplementary Table 1. Neither incomplete end points data nor selective outcome reporting was seen in the included RCTs (Supplementary Figure 1).

The meta-analytic result of primary end point is shown in Figure 2. All of the included trials have provided the data about MACE, with moderate heterogeneity observed across

Table 1
Baseline characteristics of the included studies

Study	Year	Country	Population	No. of participants*	Colchicine dose	Age (yr)	Male	DM	HTN	Smoker	Follow-up (months)
COLCOT[9]	2019	12 countries	Within 30 days post MI	2366/2379	0.5 mg once daily	61	81%	20%	51%	30%	22.6
COPS[10]	2020	Australia	Presenting with ACS	396/399	0.5 mg twice daily for 1 month, followed by 0.5 mg once daily for 11 months	60	79%	19%	50%	35%	13.3
Deftereos et al.[11]	2013	Greece	Diabetic patients with BMS	100/96	0.5 mg twice daily	64	65%	100%	49%	74%	6
LoDoCo[12]	2013	Australia	Stable coronary disease	282/250	0.5 mg once daily	66	89%	30%	NA	5%	36
LoDoCo2[13]	2020	Australia and Netherlands	Chronic coronary disease	2762/2760	0.5 mg once daily	66	85%	18%	51%	12%	28.6

ACS = acute coronary syndrome; BMS = bare mental stent; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; NA = not available.
* Data were reported as colchicine control group.

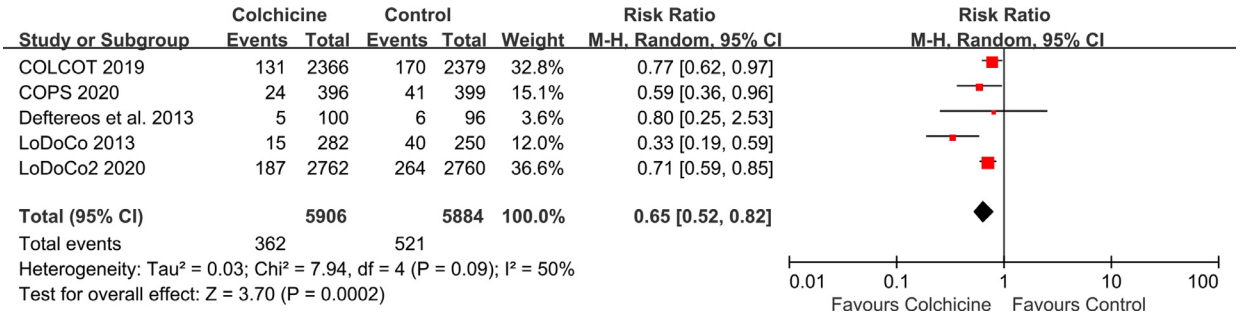

Figure 2. Meta-analysis for the risk of major adverse cardiovascular events (MACE). CI = confidence interval.

them ($I^2 = 50\%$, p = 0.09). Compared with placebo or no treatment, additional colchicine use was associated with a remarkably reduced risk of experiencing MACE (RR 0.65, 95% CI 0.52 to 0.82; p <0.001). The reduction in MACE rate were consistent between subsets of trials recruiting only stable CAD or ACS patients (p for interaction = 0.34; Supplementary Figure 2). Omitting each trial 1 at a time did not neutralize the pooled RR of MACE. The p value of Egger's test was 0.344, indicating the absence of publication bias (Supplementary Figure 3).

There were low to moderate heterogeneity across the trials reporting cardiovascular death (I^2= 32%), myocardial infarction (I^2 = 40%), coronary revascularization (I^2= 40%), and stroke (I^2 = 8%). Pooling analysis indicated that the incidence of cardiovascular death in the colchicine group was similar to those in the control group (RR 0.79, 95% CI 0.43 to 1.45; p = 0.45; Figure 3). The risk of myocardial infarction (RR 0.73, 95% CI 0.55 to 0.98; p = 0.04), coronary revascularization (RR 0.61, 95% CI 0.42 to 0.89; p = 0.01) and stroke (RR 0.47, 95% CI 0.28 to 0.81; p = 0.007) were, however, significantly lowered after treatment with colchicine in CAD patients.

The pooled estimates of safety end points are exhibited in Figure 4. There were low heterogeneity across the studies regarding common adverse events such as noncardiovascular death (I^2= 23%) and gastrointestinal discomforts (I^2 = 20%). The aggregated RR for noncardiovascular death was 1.50 (95% CI 0.93 to 2.40, p = 0.09) in the colchicine group as compared with the control group. In addition, colchicine administration was not correlated with an increased incidence of gastrointestinal disturbance (RR 1.05, 95% CI 0.91 to 1.22, p = 0.51). Other adverse events, such as infection, pneumonia, cancer, and myalgia were also comparable between the 2 groups (Supplementary Figure 4).

Discussion

In the present study of patients with a history of CAD, colchicine treatment led to a significant risk reduction in MACE, myocardial infarction, coronary revascularization, and stroke as compared with placebo or no treatment. Moreover, colchicine did not increase the rate of adverse clinical events, including noncardiovascular death and gastrointestinal events.

To date, this is the first meta-analysis demonstrating the cardiovascular benefit of colchicine in CAD patients, regardless of their clinical phenotypes. Two previous meta-analyses have also investigated the effects of colchicine therapy in CAD patients, and the results showed that this drug was not associated a significant decrease in cardiovascular risk.[14,15] The discrepancy with our findings may be explained by the insufficient number of patients and short follow-up intervals in those 2 meta-analyses. Besides, in a recent analysis by Katsanos et al,[16] the authors also suggested that colchicine treatment decreases stroke risk of CAD patients, but with no evaluation on other cardiovascular outcomes. The total sample size of our study has nearly doubled (from 6,154 to 11,790) due to the addition of 2 recent published RCTs.[10,13] Thus, our results may provide more reliable and complete evidence for the use of colchicine in secondary prevention of CAD. Of note, the inclusion of LoDoCo (low-dose colchicine for secondary prevention of cardiovascular disease)[12] trial may introduce randomization bias due to its prospective randomized open blinded end point[17] design. However, these bias have been largely avoided because at all times, the LoDoCo investigators were unaware of the subsequent allocation of a newly recruited patient; and more importantly, excluding this trial did not alter our final results as shown in the sensitivity analysis.

Ongoing inflammation was deemed as a potential dominator for the residual cardiovascular risk in CAD patients who have already received the guideline-based therapy.[18] The hypothesis that anti-inflammation agents may attenuate this risk has also been tested in recent clinical researches. The cardiovascular inflammation reduction trial found a null effect of methotrexate on either inflammatory marker levels or future cardiovascular events in stable atherosclerotic patients.[19] The Canakinumab anti-inflammatory thrombosis outcome study indicated that IL-1β antagonist canakinumab could lower the rate of recurrent cardiovascular events in patients with previous myocardial infarction and elevated high-sensitivity C-reactive protein levels.[20] Despite these findings, the clinical use of canakinumab was limited by cost-effectiveness, inconvenience administration (subcutaneous injection), and concerns of fatal infections.[21,22]

In contrast to canakinumab, colchicine is an inexpensive drug available worldwide with known efficacy and side effect profiles for a range of inflammatory diseases. By affecting the mitosis and microtubules assembly, colchicine is able to disrupt several functions of inflammatory cells, such as chemotaxis, adhesion, and recruitment to injured tissues.[23] More importantly, colchicine could target the

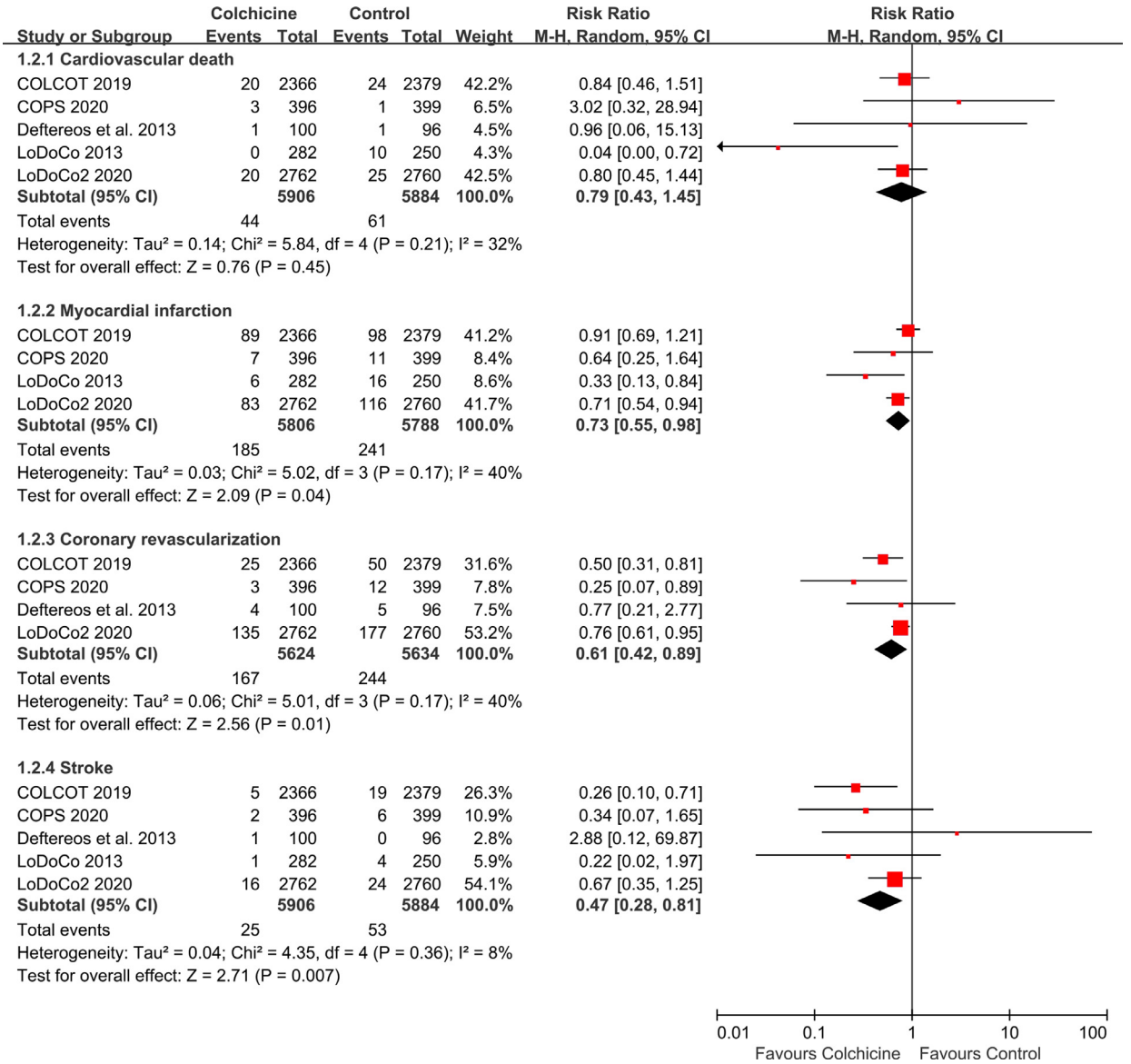

Figure 3. Meta-analysis for the risk of cardiovascular death, myocardial infarction, coronary revascularization and stroke. CI = confidence interval.

upregulated NLRP3 inflammasome activity in atheroma, thereby inhibiting the production of IL-1β and IL-18 and the downstream IL-6 signaling.[24] It has been proven that in patients with ACS, oral colchicine administration before cardiac catheterization significantly decreases the local levels of proinflammatory cytokines.[25] The unresolved inflammation is believed to make atherosclerotic plaques vulnerable to erosion or rupture, leading to acute events including thrombosis and myocardial infarction.[26] Accordingly, a recent study based on computed tomography angiography revealed that colchicine therapy induces favorable plaque modification and stabilizes the coronary lesion.[27] In addition, colchicine was shown in vitro to reduce platelet aggregation by interfering with the key proteins involved in cytoskeleton rearrangement.[28]

In the included trials, the concomitant treatments were well balanced between colchicine and control groups, including antithrombotic agents, statins, β-blockers, and renin-angiotensin inhibitors. The cardiovascular benefit was observed in patients who have already received these guideline-recommended therapies, suggesting the utility of low-dose colchicine in routine clinical practice of CAD. Although we observed a lower risk of developing ischemic cardiovascular events in colchicine treated patients, this did not translate to improved cardiovascular survivals. It should be mentioned that even with 11,790 patients in sample size, our study may be underpowered to detect the potential difference in rare events such as cardiovascular mortality. Indeed, the incidence rate of cardiovascular death was only 1% (61 of 5,884) in the control group of this meta-analysis. Future large-scale, rigorous RCTs are required to clarify the impact of colchicine on cardiovascular deaths.

A nominal higher rate of noncardiovascular death was seen in the colchicine group than the control group. The pooled effect size for this outcome was dominated by the result of LoDoCo2 trial (hazard ratio: 1.51, 95% CI: 0.99 to

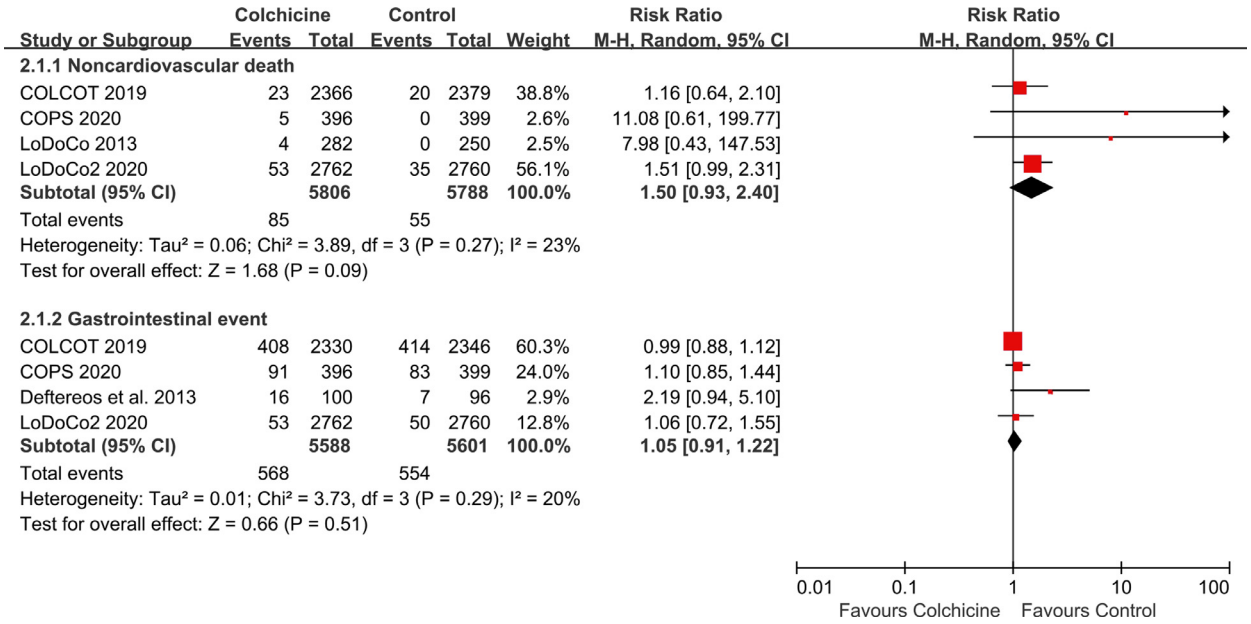

Figure 4. Meta-analysis for the risk of noncardiovascular death and gastrointestinal events. CI = confidence interval.

2.31), where the increased trend of noncardiovascular death was explained by chance.[13] Also in our study, the incidence of potential causes for noncardiovascular death, such as infection, pneumonia and cancer, were not increased after colchicine treatment. Due to the lack of patient-level data, we cannot make a clear interpretation for this finding. Additionally, attentions should be put into the gastrointestinal events related to colchicine, although we observed a similar rate of this side effect between colchicine and control groups. Gastrointestinal intolerances were common during colchicine use (up to 18%), especially diarrhoea and nausea, both at high and at low dosages.[29,30] More serious complications including myopathy, liver injury, and infectious events, were very infrequent in clinical trials.[29] In general, colchicine is well tolerated when used in therapeutic doses and adjusted for hepatic and/or renal dysfunction.[30]

Some weakness should be addressed. First of all, as with any meta-analysis, our report shared the flaws of original studies and was limited by the heterogeneity across trials and possibility of publications bias. However, we have tried our best to minimize the influence of these limitations, including methodological quality assessment, application of random-effect models and subgroup analysis, and examination of potential publication bias. Secondly, the definitions of MACE were not completely uniform across the trials, potentially introducing some reporting and detection bias. Thirdly, the follow-up times in the included trials were all ≤3 years, and the very long-term benefits and risks of colchicine treatment remained yet unknown. Finally, the doses of colchicine reported in this study are not the doses approved or available in the United States.

Authors' Contributions

Meng Xia: Investigation, Data curation, Writing - Original draft preparation; Xueying Yang: Investigation, Data curation, Visualization, Supervision; Cheng Qian: Conceptualization, Methodology, Software, Writing - Review & Editing, Funding acquisition.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.043.

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