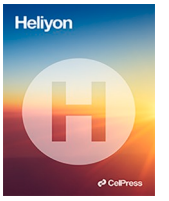
Heliyon 10 (2024) e30408

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Time to benefit of colchicine in patients with cardiovascular disease: A pooled analysis of randomized controlled trials

Haonan Sun [a,1], Chuanyi Huang [a,1], Linjie Li [a,1], Wenjun Zhu [a], Jingge Li [a], Pengfei Sun [a], Geru A [a], Gregg C. Fonarow [b], Qing Yang [a,**], Xin Zhou [a,*]

[a] Department of Cardiology, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, China
[b] Division of Cardiology, David Geffen School of Medicine at University of California, Geffen Hall 885 Tiverton Drive Los Angeles, CA 90095, USA

ARTICLE INFO

Keywords:
Colchicine
Major adverse cardiovascular event
Time to benefit
Meta-analysis

ABSTRACT

Background: Low-dose colchicine has been shown to lower major adverse cardiovascular events (MACE) among those with cardiovascular disease (CVD). It remains unclear how long a CVD patient needs to live to potentially benefit from colchicine. Our study aimed to determine the time to benefit (TTB) of colchicine in individuals with CVD.
Methods: Literature searches were performed in PubMed for the cardiovascular outcome trial of colchicine in patients with CVD until October 12, 2023. The primary outcome measured was MACE. Reconstructed individual participant data (IPD) and the stratified Cox proportional hazards model were used to calculate the hazard ratio (HR) and 95 % confidence interval (CI) to estimate the efficacy of colchicine, and Weibull survival curves were fitted to estimate TTB for specific absolute risk reduction (ARR) thresholds (0.002, 0.005, and 0.01).
Results: Four trials randomizing 11,594 adults aged between 59.8 and 66.5 years were included (follow-up duration: 12–28.6 months). Compared with placebo, colchicine reduced the risk of MACE (HR 0.68, 95 % CI: 0.60 to 0.78) but had no impact on cardiovascular and all-cause mortality. A TTB of 11.0 months (95 % CI: 0.59 to 21.3) was estimated to be needed to prevent 1 MACE in 100-colchicine-treated patients. The TTB for acute coronary syndrome was similar compared to stable coronary artery disease (10.7 vs. 11.2 months for ARR = 0.010).
Conclusions: By using reconstructed IPD, this pooled analysis demonstrated that colchicine was associated with reduced nonfatal MACE, and the TTB was approximately 11.0 months to prevent 1 MACE per 100 patients.

1. Introduction

Atherosclerotic cardiovascular disease (CVD) is a major global health issue, causing significant mortality and morbidity. The cholesterol hypothesis, which posits atherosclerosis as lipid accumulation in vessels [1], underpins the use of lipid-lowering therapy as a primary preventive strategy for CVD. However, recurrent CVD events indicate residual risk, despite advancements in therapies targeting low-density lipoprotein cholesterol (LDL-C) [2]. Recently, inflammation has been recognized as a key therapeutic target in

* Corresponding author.
** Corresponding author.
E-mail addresses: cardio-yq@tmu.edu.cn (Q. Yang), xinzhou@tmu.edu.cn (X. Zhou).
[1] These authors contributed equally to this study.

https://doi.org/10.1016/j.heliyon.2024.e30408
Received 15 April 2024; Accepted 25 April 2024
Available online 29 April 2024

atherosclerosis [3]. Colchicine is a commonly used oral anti-inflammatory drug with a long history, which plays an anti-inflammatory role by inhibiting the aggregation of microtubules [4]. Four independent randomized controlled trials (RCTs) [Low-Dose Colchicine (LoDoCo), LoDoCo2, Colchicine Cardiovascular Outcomes Trial (COLCOT), and Colchicine in Patients With Acute Coronary Syndromes (COPS)] evaluating the effect of colchicine in a broad spectrum of >11,000 patients with acute and chronic coronary artery disease (CAD) followed for up to 5 years, demonstrated that colchicine may reduce the risk of cardiovascular death, myocardial infarction, ischemic stroke and ischemia-driven revascularization by >30 % [5]. The 2021 European Society of Cardiology guidelines recommended that low-dose colchicine (0.5 mg/d orally) be considered for secondary prevention (IIb Class, A Level) [6]. In 2023, colchicine was approved by the US Food and Drug Administration (FDA) as the first anti-inflammatory therapy in patients with established CVD or with multiple risk factors.

As colchicine's utilization expands, concerns about its potential long-term adverse effects are on the rise. The most common is gastrointestinal intolerance, including symptoms like diarrhea, nausea, vomiting, and abdominal pain. Additionally, colchicine can interact with statins, leading to myotoxicity [7], and prolonged high doses may cause bone marrow inhibition and neuromuscular toxicity [8]. These potential risks, often preceding the drug's benefits, are particularly pertinent in older adults with multiple comorbidities.

Considering these risks highlights the need to determine the time course for colchicine's benefits. Recently, the framework developed by Lee et al. provides a customized approach to preventive strategies for older adults, evaluating the equilibrium between a patient's life expectancy and the time needed for the intervention to demonstrate benefits (time to benefit, TTB) [9]. This approach provides potential insights into interventions with prolonged TTB which may not produce net benefit for those with limited life expectancy, as they might endure early intervention harms without living long enough to experience its benefits. Prior studies, particularly those focusing on individuals aged 50–75 years without known CVD, have contributed vital perspectives, indicating the preventive potential of statins over 2.5 years [10]. However, there's still a significant knowledge gap regarding the specific TTB for colchicine in CVD patients.

In the present study, we aimed to assess the TTB of colchicine in patients with CVD, providing clinicians with decision-making references on whether to implement colchicine therapy.

2. Methods

2.1. Data sources and searches

We conducted this pooled analysis in accordance with PRISMA guidelines [11]. We performed a literature search in PubMed for the cardiovascular outcome trial of colchicine using in patients with CVD until October 12, 2023 (searching strategy is shown in the **Supplemental Material**).

2.2. Study selection

Investigators independently dual reviewed abstracts and full-text articles to identify studies meeting prespecified eligibility criteria. Discrepancies were resolved by discussion and consensus. The inclusion criteria include: 1) population with CVD, 2) intervention with colchicine, 3) the primary outcome measured as MACE, 4) availability of Kaplan-Meier (KM) curves for the primary outcome.

2.3. Outcomes of interest

The primary outcome measured is the first MACE, initially defined by individual trials as a composite of cardiovascular outcomes, typically including cardiovascular/all-cause mortality, stroke, myocardial infarction/acute coronary syndrome (ACS), and coronary revascularization. In cases where trials modified the definition of MACE components, we performed analyses based on the established composite outcome definitions for each trial. The cardiovascular or all-cause mortality as secondary outcome could be analyzed if it was reduced significantly and shown by KM curve in each trial.

2.4. Data extraction

One investigator abstracted data into standardized collection tables including study characteristics (first author's name, date of publication, study population, total number of participants, duration of follow-up), participants' characteristics (age, sex, previous history [hypertension and diabetes], and lipid lowering drugs), intervention dose, incidence and estimates of risk along with 95 % confidence interval (CI). A second investigator verified the entries.

2.5. Data reconstructing process

Individual participant data (IPD) were reconstructed from the numbers of patients at risk and the KM graph when original study data were not available. The steps of reconstructing each survival analysis included: (1) locating and retrieving the graphical representation of the KM curves from the published literature. High-resolution images are preferred, as they allow for more precise data extraction in subsequent steps. (2) digitizing these graphs to estimate the survival percentage over time. We accurately extracted data from the curves using DataGrabber software. Before data extraction, the axes on the KM plot need to be calibrated within the software

to match the scale of time and survival probability accurately. Then, we could select and extract of survival probability at specified time intervals along the curve. (3) reconstructing IPD through the 'IPDfromKM' package written in R [12].

2.6. Certainty of evidence

The quality of the evidence for each outcome was rated as per the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [13]. Certainty of the overall evidence was rated as high, moderate, low, or very low based on the assessment of the domains for study limitations, inconsistency, indirectness of evidence, imprecision and publication bias.

2.7. Statistical analysis

After reconstructing individual data of each curve, the cumulative rates of primary outcome at each time point in the colchicine and placebo group from the pooled trials were estimated using the KM curve. The hazard ratio (HR) and 95 % CI were calculated using the stratified Cox proportional hazards model to adjust for the clustering of patients from the same trial. Then, like the method implemented by Yourman et al. [10], we fitted Weibull survival curves using the event data for the control and intervention groups. We obtained estimates of time to specific absolute risk reduction (ARR) thresholds (0.002, 0.005, and 0.010) for each study. We performed Markov chain Monte Carlo computations using the R function "brm" in the "brms" package. The 95 % CI of TTB was calculated based on the simulated sampling distribution of TTB by 100,000 Markov chain Monte Carlo simulations.

We pooled the estimates from each study using the sample size of each study as weights. Heterogeneity and its effects were evaluated by using the I^2 statistic. Furthermore, subgroup analysis was conducted based on study population [acute coronary syndrome (ACS), stable CAD]. Furthermore, Considering the differences in the components of the composite outcomes, we conducted sensitivity analysis after excluding trials with significant differences in components or with no beneficial outcome. The risk of bias was assessed according to the Cochrane tool used to assess bias [14]. Stata (version 15.1, StataCorp, College Station, TX, USA) and R (version 4.18) were used for the meta-analysis. The two-tailed level of statistical significance was set at $P < 0.05$.

3. Results

After screening 310 records, we included four RCTs (LoDoCo [15], LoDoCo2 [16], COLCOT [17], and COPS [18]) with 11,594 participants. The baseline characteristics of each publication are shown in Table 1. The years of publication range from 2013 to 2020. The mean age was from 59.8 to 66.5 years, indicating all trials were conducted based on relatively elderly populations. The follow-up duration ranged between 12 and 28.6 months. Of these trials, LoDoCo and LoDoCo2 trial focused on populations with stable CAD, COLCOT and COPS trial focused on ACS. Only the COPS trial had an intervention group of 0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months, and all the other studies had intervention groups of 0.5 mg daily. The primary composite endpoints for the LoDoCo2, COPS, and COLCOT trials all included cardiovascular/all-cause mortality, stroke, myocardial infarction/ACS, and coronary revascularization. In contrast, the primary composite endpoint for the LoDoCo trial was ACS, out-of-hospital cardiac arrest, and ischemic stroke. Detailed components and event rates of MACE in each trial are shown in Table S1 in the **Supplemental Material**. After reconstructing IPD of all trials, we presented the side-by-side comparisons of original curves taken from the original articles and reconstructed curves and visually found that the algorithm recovered IPD from published trials with a high degree of accuracy (Figs. S1 and S2 in the **Supplemental Material**).

The KM curve of pooled trial data indicated a consistently lower cumulative incidence of the MACE in the colchicine vs control group (HR 0.68, 95 % CI: 0.60–0.78; $P < 0.001$) (Fig. 1). Then, we calculated the time needed to prevent 1 MACE per 100, 200, or 500

Table 1
Study baseline characteristics.

Study	LoDoCo, 2013	COLCOT, 2019	COPS, 2020	LoDoCo2, 2020
Study design	Randomized, observer-blinded	Randomized, controlled, double-blind	Randomized, controlled, double-blind	Randomized, controlled, double-blind
Study population	Stable CAD	Recent MI (<30 days)	ACS	Stable CAD
Sample size	532	4745	795	5522
Colchicine dose	0.5 mg once daily	0.5 mg once daily	0.5 mg twice daily first month, once daily 11 months	0.5 mg once daily
Mean age, year	66.5	60.6	59.8	65.9
Male, %	89.0	80.9	79.5	84.7
Mean Follow time, m	24	22.6	12	28.6
Hypertension, %	N.A.	51	50.3	50.9
Diabetes, %	30.3	20.2	19	18.24
Lipid lowering drugs, %	95	99	98.9	96.6
Incidence, %[a]	10.3	6.34	7.80	8.17
Effect size[a]	0.33 (0.18–0.59)	0.77 (0.61–0.96)	0.65 (0.38–1.09)	0.69 (0.57–0.83)

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, MI = myocardial infarction, N.A. = not applicable.
[a] Refers to the incidence and effect size of the primary composite outcome.

patients treated with colchicine for each study (ARR = 0.010, ARR = 0.005, or ARR = 0.002; respectively) (Table 2). Through IPD reconstructed from the LoDoCo2 trial, for instance, 11.6, 5.92, and 2.46 months were needed to prevent 1 MACE per 100, 200, and 500 patients with stable CAD treated with colchicine, respectively. Similarly, COLCOT trial indicated that 12.2, 5.06, and 1.60 months were needed to prevent 1 MACE per 100, 200, and 500 patients with ACS treated with colchicine, respectively. The meta-analysis further revealed that, a TTB of 11.0 months (95 % CI: 0.59 to 21.3), 5.12 months (95 % CI: 0.48 to 9.75), and 1.93 months (95 % CI: 0.30 to 3.56) was needed to prevent 1 MACE for 100, 200, and 500 patients treated with colchicine, respectively. We observed that the all-cause mortality did not decrease significantly across four trials, and there was even a trend towards increased mortality in the COPS trial (Table S2 in the **Supplemental Material**). Additionally, KM curves regarding mortality were not shown, hence we did not further analyze secondary outcomes.

The subgroup analysis based on the patient population were conducted (Table 2). The TTB for ACS patients was similar compared to stable CAD patients (10.7 vs. 11.2 months for ARR = 0.010). There was moderate heterogeneity among the studies. Especially in LoDoCo and COPS trials, TTB is lower than the other two trials. First, LoDoCo and COPS trials had a small sample size. In addition, the primary endpoints of LoDoCo trial are ACS, out-of-hospital cardiac arrest, and ischemic stroke, which were different from the primary endpoints of other studies. And the COPS trial did not achieve statistical differences in primary outcomes. Therefore, we conducted the sensitivity analysis excluding LoDoCo and COPS trials, respectively. We found that it would need 11.2 months (95 % CI: 0.31 to 22.0) and 11.5 months (95 % CI: 0.51 to 22.6), respectively, to prevent one MACE among 100 patients treated with colchicine (Table 3).

The risk of bias of all the trials included was low according to the Cochrane tool for assessing risk of bias in RCTs (Table S3 in the **Supplemental Material**). The main bias was due to open-label of intervention measures in LoDoCo trial. The GRADE assessment for quality of evidence of studies for MACE was summarized (Table S4 in the **Supplemental Material**). The analysis was based on moderate certainty of evidence, primarily due to inconsistent results.

4. Discussion

In this pooled analysis involving over 11,000 reconstructed IPD from four cardiovascular outcome RCTs on colchicine use in patients with CVD, a significant clinical benefit of colchicine was observed. This benefit, reflected in a reduced incidence of nonfatal MACE, highlighted that the TTB for colchicine use was approximately 11.0 months to prevent one nonfatal MACE per 100 patients with CVD. These results suggest colchicine's utility for patients with an expected lifespan beyond 11.0 months, whereas it may be less advantageous for those with shorter life expectancies. Our findings provide insights for clinicians in making informed decisions about employing colchicine in CVD management.

Colchicine, a well-tolerated and cost-effective drug, has been traditionally used to treat various conditions such as gout, pericarditis, primary biliary cirrhosis, Behcet's disease, and familial Mediterranean fever [19]. With evolving understanding of atherosclerosis, targeting inflammation has become a pivotal therapeutic strategy in patients with atherosclerosis. In a combined analysis of trials of low-dose colchicine for CVD, a highly statistically significant more than 30 % reduction in myocardial infarction, stroke, coronary revascularization, or cardiovascular death was reported [5]. These magnitudes of benefit are larger than those seen in contemporary secondary prevention trials of adjunctive lipid-lowering medication [20]. Consistent with previous findings, our analysis using reconstructed IPD reaffirms the efficacy of colchicine in CVD treatment, especially noting a 32 % reduction in MACE risk.

Nonetheless, long-term colchicine use raises potential safety concerns, including gastrointestinal intolerance and an elevated risk of infections, such as pneumonia [17,21], which might be linked to colchicine-induced bone marrow inhibition [8]. Notably, while colchicine decreased MACE risk, there was no significant difference in all-cause mortality, with even a trend toward increased

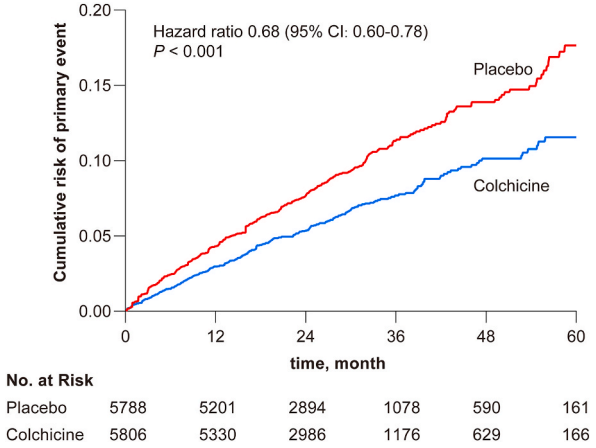


Fig. 1. Cumulative Risk and HR of Primary Outcome for Colchicine vs Placebo at 60 months.
Based on reconstructed individual patient-level data, the cumulative rates of primary outcome at each time point in the colchicine and placebo group from the pooled trials were estimated using the KM curve. The HR and 95 % CI were calculated using the stratified Cox proportional hazards model.

Table 2
TTB for the major adverse cardiovascular events in patients with colchicine.

Study name and publication year	TTB (95 % CI), month		
	ARR = 0.002	ARR = 0.005	ARR = 0.01
Stable CAD patients			
LoDoCo, 2013	1.97 (0.74–4.45)	3.87 (1.71–7.74)	6.43 (3.23–11.9)
LoDoCo2, 2020	2.46 (1.41–4.53)	5.92 (3.48–10.8)	11.6 (6.86–21.1)
Subgroup	2.42 (0.98–3.85)	5.74 (2.39–9.09)	11.2 (4.64–17.7)
ACS patients			
COPS, 2020	0.20 (0.03–1.90)	0.70 (0.10–6.37)	1.97 (0.32–15.4)
COLCOT, 2019	1.60 (0.44–7.51)	5.06 (1.46–22.4)	12.2 (3.66–51.4)
Subgroup	1.40 (−1.63 to 4.43)	4.43 (−4.54 to 13.4)	10.7 (−9.74 to 31.2)
Summary TTB, month	**1.93 (0.30 to 3.56)**	**5.12 (0.48 to 9.75)**	**11.0 (0.59 to 21.3)**
Test of heterogeneity			
I^2, %	78.0	64.6	69.0
P value	0.003	0.037	0.022

Abbreviations: ACS = acute coronary syndrome, ARR = absolute risk reduction, CAD = coronary artery disease, CI = confidence interval, TTB = time to benefit.

Table 3
Sensitivity analysis.

Study name and publication year	TTB (95 % CI), month		
	ARR = 0.002	ARR = 0.005	ARR = 0.01
Excluding LoDoCo trial			
COPS, 2020	0.20 (0.03–1.90)	0.70 (0.10–6.37)	1.97 (0.32–15.4)
LoDoCo2, 2020	2.46 (1.41–4.53)	5.92 (3.48–10.8)	11.6 (6.86–21.1)
COLCOT, 2019	1.60 (0.44–7.51)	5.06 (1.46–22.4)	12.2 (3.66–51.4)
Summary TTB, month	**1.93 (0.22 to 3.63)**	**5.18 (0.32 to 10.0)**	**11.2 (0.31 to 22.0)**
Excluding COPS trial			
LoDoCo, 2013	1.97 (0.74–4.45)	3.87 (1.71–7.74)	6.43 (3.23-11.9)
LoDoCo2, 2020	2.46 (1.41–4.53)	5.92 (3.48–10.8)	11.6 (6.86–21.1)
COLCOT, 2019	1.60 (0.44–7.51)	5.06 (1.46–22.4)	12.2 (3.66–51.4)
Summary TTB, month	**2.06 (0.31 to 3.81)**	**5.44 (0.47 to 10.4)**	**11.5 (0.51 to 22.6)**

Abbreviations: ARR = absolute risk reduction, TTB = time to benefit.

mortality observed in the COPS trial. Previous meta-analyses have found that the reduction in cardiovascular mortality with colchicine was offset by an increase in non-cardiovascular mortality [22]. This finding further indicates possible non-cardiovascular risks associated with prolonged colchicine use, underscoring the need to identify an optimal treatment duration that balances benefits and risks effectively.

TTB, defined as the time between preventive intervention and improved health outcomes [9], is vital for individualized therapy, especially for the elderly individuals [23]. Previous studies assessed the TTB of common CVD prevention medication and emphasized its significance. For instance, Chen et al.'s work on sodium-glucose cotransporter 2 (SGLT2) inhibitors indicated that treating 100 heart failure (HF) patients with these inhibitors for just 1.74 months prevented one cardiovascular death or worsening HF [24]. In parallel, our study quantified TTB at specific absolute risk difference thresholds using reconstructed IPD from KM curves and focused on the timing of benefit from colchicine therapy in patients with CVD. The novel approach demonstrated that treating 100 patients with colchicine for 11.0 months is required to prevent one MACE, providing a reference for optimizing treatment duration.

Heterogeneities among the RCTs led to varied TTBs. Considering the distinct pathological mechanisms between stable CAD and ACS, we performed a subgroup analysis based on the study population, revealing that both groups required a similar TTB to prevent one MACE. Among the included trials, the LoDoCo and COPS trials presented some biases. The LoDoCo trial, with its open-label design and small sample size, reported up to a 67 % reduction in the primary outcome, possibly influenced by its study design and size. The primary outcomes of this trial, i.e., ACS, out-of-hospital cardiac arrest, and ischemic stroke, also differed from conventional composite cardiovascular outcomes. The COPS trial, with its small sample size and short follow-up duration, showed no statistical difference in the primary composite endpoint, possibly due to a higher proportion of all-cause mortality in the colchicine group. Considering these factors, we conducted sensitivity analyses excluding the LoDoCo and COPS trials, which yielded similar results: treating 100 patients with colchicine required 11.2 and 11.5 months, respectively, to prevent one MACE, aligning with the main findings.

Although colchicine is recommended for secondary prevention in patients with CVD [6,25], current guidelines offer limited detailed guidance on colchicine treatment. The study evaluated the TTB for colchicine, which can improve the decision-making process for clinicians by balancing risks and benefits, especially when initiating colchicine treatment in patients who have just experienced CVD. Its relatively short TTB may lead to increased use of colchicine in patients with a longer life expectancy. Detailed communication with patients about medications can also increase patient adherence. Conversely, it may lead to decreased use in patients with a life expectancy of less than 11 months. In summary, the TTB for colchicine could provide further information for

clinical practice and guideline recommendations.

4.1. Strengths and limitations

A major strength of our study is that this is the use quantitative methods to determine the TTB for the prevention of cardiovascular events with colchicine therapy in patients with CAD and fills a critical gap for the timing of clinical benefits about colchicine therapy, especially for those patients with a limited life expectancy. The study has the following limitations that need to be noted. First, although we reconstructed the IPD based on KM graph, baseline characteristics of individual trial participants are not known, we could not look at important patient subgroups (e.g diabetes, heart failure, older). Second, although the recalculated HR is similar to original HR, there still are some minor differences between Weibull curve and KM curve by visual inspection. Third, the heterogeneity in the composition of composite outcomes among the included trials may introduce potential bias into the results. Fourth, the limited number of trials restricts our ability to perform subgroup analyses. Future research should include more RCTs to enable more comprehensive subgroup analyses. Finally, trials rarely included very old participants (with limited life expectancy), further studies are needed to evaluate the efficacy of colchicine in patients with limited life expectancy.

5. Conclusions

By using reconstructed IPD data from 4 RCTs, this meta-analysis demonstrated the clinical benefit of colchicine associated with reduced nonfatal MACE and showed that the TTB of colchicine was approximately 11.0 months to prevent 1 MACE per 100 patients with established CVD.

Sources of funding

This work was supported by National Natural Science Foundation of China (82321001, 82320108001, 72274133 and 82270349) and Tianjin Key Medical Discipline (Specialty) Construction Project (Grant No. TJYXZDXK-069C).

Role of the funder/sponsor

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

CRediT authorship contribution statement

Haonan Sun: Writing – original draft, Formal analysis, Data curation. **Chuanyi Huang:** Software, Methodology, Formal analysis. **Linjie Li:** Data curation, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Wenjun Zhu:** Supervision, Investigation, Data curation. **Jingge Li:** Visualization, Supervision. **Pengfei Sun:** Writing – original draft, Supervision. **Geru A:** Visualization, Validation, Supervision. **Gregg C. Fonarow:** Writing – review & editing. **Qing Yang:** Writing – review & editing, Conceptualization. **Xin Zhou:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not Applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30408.

References

[1] P. Libby, J.E. Buring, L. Badimon, et al., Atherosclerosis, Nat. Rev. Dis. Prim. 5 (1) (2019) 56.
[2] F. Gomez-Delgado, M. Raya-Cruz, N. Katsiki, J. Delgado-Lista, P. Perez-Martinez, Residual cardiovascular risk: when should we treat it? Eur. J. Intern. Med. 120 (2024) 17–24.
[3] P.M. Ridker, The time to initiate anti-inflammatory therapy for patients with chronic coronary atherosclerosis has arrived, Circulation 148 (14) (2023) 1071–1073.
[4] F.S. Zhang, Q.Z. He, C.H. Qin, P.J. Little, J.P. Weng, S.W. Xu, Therapeutic potential of colchicine in cardiovascular medicine: a pharmacological review, Acta Pharmacol. Sin. 43 (9) (2022) 2173–2190.

[5] M. Imazio, M. Nidorf, Colchicine and the heart, Eur. Heart J. 42 (28) (2021) 2745–2760.
[6] F.L.J. Visseren, F. Mach, Y.M. Smulders, et al., 2021ESC Guidelines on cardiovascular disease prevention in clinical practice, Eur. Heart J. 42 (34) (2021) 3227–3337.
[7] S. Stewart, K.C.K. Yang, K. Atkins, N. Dalbeth, P.C. Robinson, Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials, Arthritis Res. Ther. 22 (1) (2020) 28.
[8] S.G. Deftereos, F.J. Beerkens, B. Shah, et al., Colchicine in cardiovascular disease: in-depth review, Circulation 145 (1) (2022) 61–78.
[9] S.J. Lee, R.M. Leipzig, L.C. Walter, Incorporating lag time to benefit into prevention decisions for older adults, JAMA 310 (24) (2013) 2609–2610.
[10] L.C. Yourman, I.S. Cenzer, W.J. Boscardin, et al., Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 Years A meta-analysis, JAMA Intern. Med. 181 (2) (2021) 179–185.
[11] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Grp, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269.
[12] N. Liu, Y.H. Zhou, J.J. Lee, IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves, BMC Med. Res. Methodol. 21 (1) (2021) 111.
[13] G.H. Guyatt, A.D. Oxman, G.E. Vist, et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 336 (7650) (2008) 924–926.
[14] J.A.C. Sterne, J. Savovic, M.J. Page, et al., RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019).
[15] S.M. Nidorf, J.W. Eikelboom, C.A. Budgeon, P.L. Thompson, Low-dose colchicine for secondary prevention of cardiovascular disease, J. Am. Coll. Cardiol. 61 (4) (2013) 404–410.
[16] S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, et al., Colchicine in patients with chronic coronary disease, N. Engl. J. Med. 383 (19) (2020) 1838–1847.
[17] J.C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, N. Engl. J. Med. 381 (26) (2019) 2497–2505.
[18] D.C. Tong, S. Quinn, A. Nasis, et al., Colchicine in patients with acute coronary syndrome the Australian COPS randomized clinical trial, Circulation 142 (20) (2020) 1890–1900.
[19] L. Sattar, R.A. Memon, F. Ashfaq, et al., Efficacy and safety of colchicine in prevention of secondary cardiovascular outcomes among patients with coronary vessel disease: a meta-analysis, Cureus 14 (7) (2022) e26680.
[20] K. Nelson, V. Fuster, P.M. Ridker, Low-dose colchicine for secondary prevention of coronary artery disease: review topic of the week, J. Am. Coll. Cardiol. 82 (7) (2023) 648–660.
[21] J. Siak, N. Flint, H.G. Shmueli, R.J. Siegel, F. Rader, The use of colchicine in cardiovascular diseases: a systematic review, Am. J. Med. 134 (6) (2021) 735–744. e731.
[22] A.T.L. Fiolet, T.S.J. Opstal, A. Mosterd, et al., Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials, Eur. Heart J. 42 (28) (2021) 2765–2775.
[23] H.M. Holmes, L.C. Min, M. Yee, et al., Rationalizing prescribing for older patients with multimorbidity: considering time to benefit, Drugs Aging 30 (9) (2013) 655–666.
[24] K.Y. Chen, Z.Q. Nie, R. Shi, et al., Time to benefit of sodium-glucose cotransporter-2 inhibitors among patients with heart failure, JAMA Netw. Open 6 (8) (2023) e2330754.
[25] R.A. Byrne, X. Rossello, J.J. Coughlan, et al., 2023 ESC Guidelines for the management of acute coronary syndromes, Eur. Heart J. 44 (38) (2023) 3720–3826.