Can colchicine prevent acute myocardial infarction? Systematic review and meta-analysis

¿La colchicina puede prevenir el infarto agudo de miocardio? Revisión sistemática y metaanálisis

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ABSTRACT

Objective: The association between the use of colchicine and the incidence of acute myocardial infarction (AMI) is inconsistent. The main objective of this study was to evaluate the effect of colchicine on the incidence of AMI. Assessment of the incidence of stroke and cardiovascular mortality were secondary endpoints.

Methods: A meta-analysis of randomized studies that evaluated the use of colchicine in patients with atherosclerotic disease and reported cardiovascular events was performed, after searching the PubMed/MEDLINE, Embase, Scielo and Cochrane Controlled Trials databases. A fixed or random effects model were used depending on the heterogeneity observed.

Results: Seven studies were selected for the analysis of the primary end point (5966 subjects in the colchicine arm and 5948 patients in the control arm). This meta-analysis demonstrated that colchicine therapy was associated with a lower risk of AMI (OR: 0.76, 95% CI: 0.62-0.92; $I^2 = 15\%$). Likewise, a significant reduction in the incidence of stroke was observed without a significant effect on cardiovascular mortality with pharmacological intervention.

Conclusion: The use of colchicine in patients with atherosclerotic cardiovascular disease was associated with a significant reduction in the incidence of AMI. The incorporation of colchicine into the therapeutic arsenal of cardiovascular disease should be considered by future clinical practice guidelines.

Key words: Colchicine - Acute myocardial infarction - Stroke - Cardiovascular Diseases/ mortality.

RESUMEN

Introducción: La asociación entre el uso de colchicina y la incidencia de infarto agudo de miocardio (IAM) es heterogénea.

Objetivos: El objetivo principal del presente estudio fue evaluar el efecto de la colchicina sobre la incidencia de IAM. La evaluación de la incidencia de accidente cerebrovascular (ACV) y la mortalidad cardiovascular fueron los objetivos secundarios.

Material y métodos: Se realizó un metaanálisis de estudios aleatorizados que evaluaron el uso de colchicina en pacientes con enfermedad aterosclerótica y que reportaron los eventos cardiovasculares, luego de una búsqueda en las bases de datos PubMed/MEDLINE, Embase, Scielo y Cochrane Controlled Trials. Se utilizó un modelo de efectos fijos o aleatorios según la heterogeneidad observada.

Resultados: Se seleccionaron para el análisis del punto final primario 7 estudios (con un total de 5966 sujetos en la rama colchicina y 5948 pacientes en la rama control). Este metaanálisis demostró que la terapia con colchicina se asoció a un menor riesgo de IAM (OR: 0,76, IC 95%: 0,62-0,92; $I^2=15\%$). Asimismo, se observó una reducción significativa en la incidencia de ACV, sin un efecto significativo en la mortalidad cardiovascular, con la intervención farmacológica.

Conclusión: El uso de colchicina en pacientes con enfermedad cardiovascular aterosclerótica se asoció a una reducción significativa en la incidencia de IAM. La incorporación de la colchicina dentro del arsenal terapéutico de la enfermedad cardiovascular deberá ser considerada por las futuras guías de práctica clínica.

Palabras clave: Colchicina - Infarto agudo de miocardio - Accidente cerebrovascular - Enfermedad cardiovascular/mortalidad.

INTRODUCTION

Cardiovascular disease is the leading cause of death in most countries, with considerable economic and healthcare impact. (1)

Statin therapy reduces the incidence of major coronary artery events by approximately 22% per 1.0 mmol/L ($\approx$ 39 mg/dL) reduction in low-density lipoprotein cholesterol (LDL-C). (2) However, even when patients are correctly medicated with statins and reach the lipid targets recommended by the different

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guidelines, cardiovascular events continue to occur. Once the objective of LDL-C has been achieved, the remnant cardiovascular risk is known as "residual cardiovascular risk". (3) This residual risk is largely due to lipid-related factors other than LDL-C but with potential atherogenic action, such as triglyceride-rich lipoproteins. (4, 5)

However, in addition to the residual lipid risk, other mechanisms have been proposed to explain the remnant cardiovascular risk. In this setting, inflammation is a relevant factor in the process of atherosclerosis, in the development of clinical cardiovascular events, and in residual cardiovascular risk. (6) Therefore, anti-inflammatory therapies targeting inflammation of the atherosclerotic plaque could contribute to plaque stabilization and prevention of thromboembolic events. (7, 8)

In recent years, colchicine has been proposed as a potential therapeutic option in the setting of coronary artery disease. (9) The anti-inflammatory effects of colchicine via binding to a-tubulin and b-tubulin include inhibition of microtubule polymerization, impaired leukocyte rolling and endothelial adhesion, inhibition of the NLRP inflammasome, and decreased cytokine secretion. (10)

Several meta-analyses have evaluated the association between the use of colchicine and cardiovascular events. (11-14) However, the results on the association between colchicine and the incidence of acute myocardial infarction (AMI) were heterogeneous. Moreover, in the COLCOT study, a clinical trial that included the largest number of patients, although the risk of the primary composite endpoint of cardiovascular events was significantly lower, this was mainly due to a lower incidence of stroke and urgent hospitalizations for unstable angina and not to a decrease in the risk of AMI. (15) In addition, the recent publication of two new clinical trials has made it necessary to update and clarify the information. (16, 17)

Thus, the primary aim of this meta-analysis was to evaluate the effect of colchicine on the incidence of AMI in patients with established atherosclerotic disease and the secondary aim was to analyze the impact of this drug on the incidence of stroke and cardiovascular mortality.

METHODS
Data extraction and quality assessment: The meta-analysis was performed following the PRISMA statement for reporting systematic reviews. (18) A bibliographic search was conducted to identify clinical trials evaluating therapy with colchicine published between January 1990 and September 2020. Two independent reviewers searched the PubMed/Medline, EMBASE, Scielo, and Cochrane Clinical Trials electronic databases using the terms "colchicine", "major cardiovascular events", "myocardial infarction", "coronary heart disease", "stroke", "cardiovascular mortality", "mortality", and "cardiovascular risk". The articles selected were those randomized clinical trials that reported data on cardiovascular events and evaluated the effect of colchicine in

populations with clinical atherosclerotic disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease). In the case of studies evaluating patients undergoing cardiovascular surgery, those studies in which patients with coronary artery disease represented >50% of the total population included were selected.

The primary endpoint of the study was the impact of colchicine on the incidence of AMI, and the secondary endpoints the effect of colchicine on the incidence of stroke and cardiovascular mortality.

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the potential risk of bias of each included trial. (19) RoB 2 is structured into five distinct domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the outcome measurement and bias in selection of the reported result. Each domain was rated as "low risk of bias," "high risk of bias" or "some concerns".

The protocol design was revised and approved by the Advisory Board of the Council of Epidemiology and Cardiovascular Prevention of the Argentine Society of Cardiology.

Statistical analysis: The summary effect of the use of colchicine on the previously mentioned endpoints was estimated. Effect size measures were expressed as odds ratios (OR) and the I^2 statistic was calculated to quantify heterogeneity and inconsistency among studies. Depending on the value of I^2, a fixed effects model ($I^2 < 40\%$) or a random effects model ($I^2 > 40\%$) was chosen. The Z-test was used to compare the mean effect between subgroups. A two-tailed p value=0.05 was considered statistically significant. The analyses were performed with the R statistical software package. (20)

Analysis of publication bias: A funnel plot was created using the standard error (SE) of log OR. Harbord's test and Peters' test were performed, adjusted for the number of studies included.

Sensitivity analysis: A sensitivity analysis is a repeat of the results of the meta-analysis, excluding in each step one study included in the review. If the results obtained in the direction and magnitude of the effect are similar, the analysis is considered robust.

RESULTS
A total of 9 studies evaluating the use of colchicine were selected for the quantitative analysis. (15-17, 21-26) Seven papers including 11 914 patients were selected and considered for the primary endpoint analysis (15-17, 21, 22, 25, 26) with 5966 patients in the colchicine arm and 5948 in the placebo arm. Eight clinical trials including 12 275 patients were chosen for the analysis of stroke. (15-17, 21, 22, 24-26) For the analysis of cardiovascular mortality, 8 studies with 12 111 patients were selected. (15-17, 21-23, 25, 26) The flowchart for the selection procedure of eligible studies is shown in Figure 1.

All the studies evaluated were randomized clinical trials. The quality of the studies included in the meta-analysis is summarized in Figure 2.

Four studies included patients with stable coronary artery disease and four studies evaluated patients after an acute coronary syndrome. One study included patients with diabetes undergoing percutaneous coronary intervention and two studies evaluated patients

undergoing myocardial revascularization surgery. Mean follow-up ranged between 1 and 28.6 months.

The characteristics of the studies included is shown in Table 1.

This meta-analysis demonstrated that the use of colchicine was associated with reduced risk for AMI (OR: 0.76; 95% CI, 0.62-0.92; I^2=15%) (Figure 3), as well as a significant reduction in the incidence of stroke (OR, 0.48, 95% CI, 0.30-0.76; I^2=0%), but no significant effect on cardiovascular mortality (OR, 0.71, 95% CI, 0.49-1.05; I^2=32%) (Figure 4).

The funnel plot in Figure 5 shows absence of publication bias. The sensitivity analysis shows that the results are robust (Figure 6).

DISCUSSION

This meta-analysis demonstrated that the use of colchicine was associated with reduced risk of AMI and stroke compared with placebo, but the reduction in cardiovascular mortality was not statistically significant.

There is evidence supporting and confirming the role of inflammation in the pathophysiological process of atherosclerosis. (27) Inflammasomes play an active role as one of the multiple molecular mechanisms involved in the inflammatory process. Inflammasomes are high-molecular-weight protein complexes that are formed in the cytosolic compartment in response to different triggers. (28) Among the most studied in the context of atherosclerosis development is the NLRP3 inflammasone, a cytosolic multiprotein signaling complex, which serves as a platform for caspase-1 activation leading to the synthesis of proinflammatory cytokines, as interleukin (IL)-1, IL-18 and, indirectly, IL-6. (29)

There are at least four purported mechanisms of action by which colchicine can suppress NLRP3 inflammasome activation:1) Inhibition of the MEFV gene resulting in pyrin receptor inhibition; 2) inhibition of inflammasome cytoplasmic assembly due to tubulin interference; 3) direct caspase-1 blockage; 4) inhibition of P2X7-mediated pore formation resulting in decreased K+ efflux. The final result is decreased synthesis of the active form of IL-1β. (30) A proteomic substudy of the LoDoCo2 trial demonstrated that the anti-inflammatory effect of colchicine in patients with

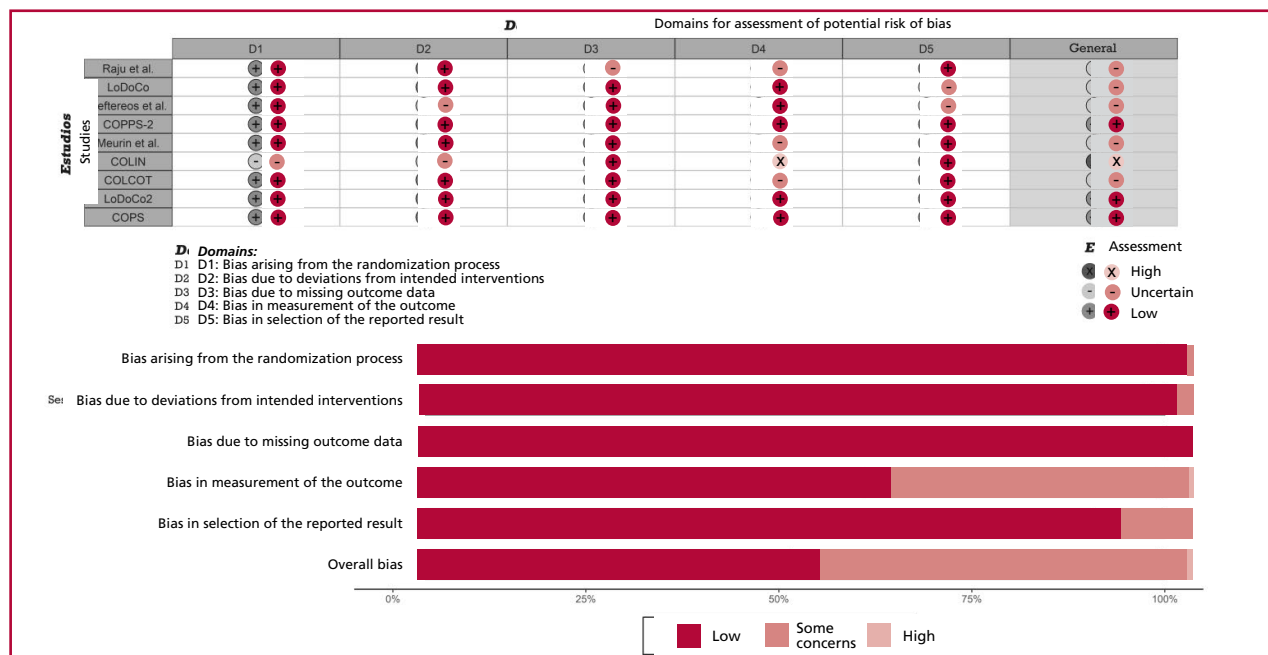**Fig. 1.** Flowchart for the selection procedure of eligible studies
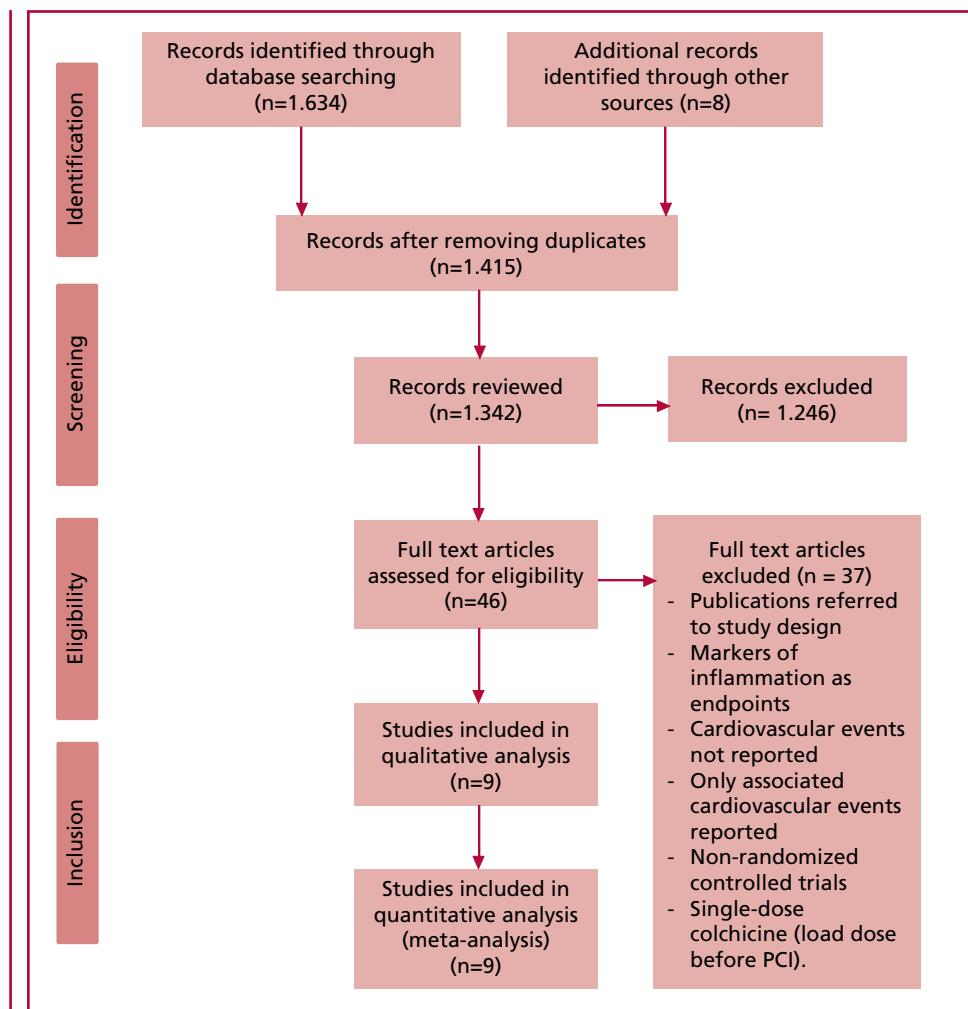
Fig. 2. Assessment of risk of bias of included studies

Table 1. Characteristics of the studies included in the analysis

Article	Colchicine arm (daily doses)	n	Control arm	n	Colchicine arm (daily doses)	Follow-up (months)
Raju et al. (21)	1 mg	40	Placebo	40	ACS or ischemic stroke	1
LoDoCo (31)	0.5 mg	282	Usual care	250	Stable coronary artery disease	24
Defteros et al. (23)	1 mg	100	Placebo	96	Diabetics with need for percutaneous coronary intervention	6
COPPS-2 (24)	0.5 a 1 mg (according to body weight)	180	Placebo	180	Post-cardiovascular surgery	3
Meurin et al. (25)	1 mg	98	Placebo	99	Post-cardiovascular surgery with pericardial effusion	6
COLIN (26)	1 mg	23	Placebo	21	ACS	1
COLCOT (35)	0.5 mg	2366	Placebo	2379	ACS	22.6
LoDoCo-2 (22)	0.5 mg	2762	Placebo	2760	Stable coronary artery disease	28.6
COPS (17)	1 mg for 1 month, then 0.5 mg	396	Placebo	399	ACS	12

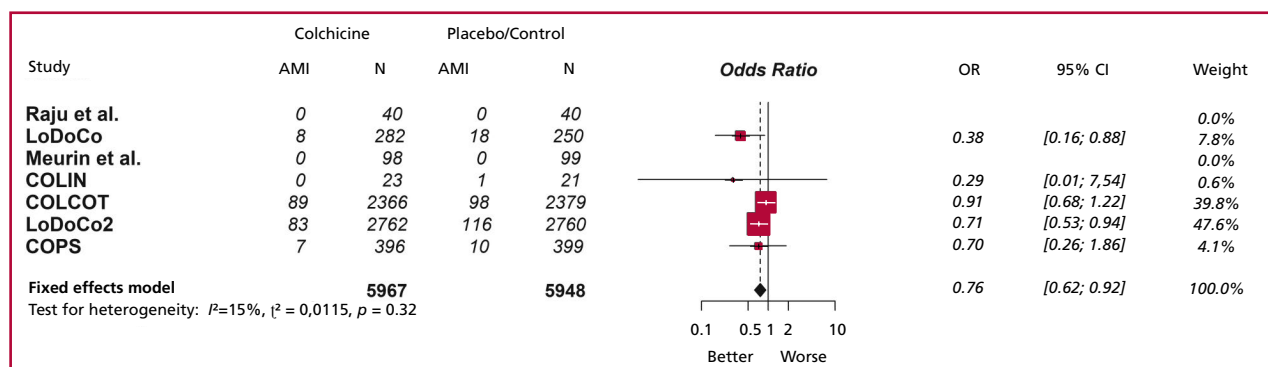ACS: Acute coronary syndrome.

Fig. 3. Effect of colchicine on the incidence of acute myocardial infarction. Fixed effects model, odds ratio, 95% confidence interval and I² statistics

A

	Colchicine		Placebo			OR	95% CI	Weight
Study	Stroke	N	Stroke	N				
Raju et al.	0	40	1	40		0.33	[0.01; 8.22]	2.6%
LoDoCo	1	282	4	250		0.22	[0.02; 1,97]	7.6%
COPPS-2	2	180	1	180		2.01	[0.18; 22.38]	1.8%
Meurin et al.	0	98	1	99		0.33	[0.01; 8.28]	2.7%
COLIN	0	23	0	21				0.0%
COLCOT	5	2366	19	2379		0.26	[0.10; 0.71]	33.8%
LoDoCo-2	12	2762	24	2760		0.66	[0.35; 1.25]	42.7%
COPS	2	396	5	399		0.40	[0.08; 2.07]	8.9
Fixed effects model		**6147**		**6128**		0.48	[0.30; 0.76]	100.0%

Test for heterogeneity: $I^2=0\%$, $t^2 = 0$, $p = 0.62$

B

	Colchicine		Placebo			OR	95% CI	Weight
Study	Cardiovascular mortality	N	Cardiovascular mortality	N				
Raju et al.	0	40	0	40				0.0%
LoDoCo	0	282	10	250		0.04	[0.00; 0,70]	18.0%
Deftereos et al.	1	100	1	96		2.96	[0.06; 15.56]	1.6%
Meurin et al.	0	98	0	99				0.0%
COLIN	0	23	0	21				0.0%
COLCOT	20	2366	24	2379		0.84	[0.46; 1.52]	38.5%
LoDoCo-2	20	2762	25	2760		0.80	[0.44; 1.44]	40.3%
COPS	3	396	1	399		0.04	[0.31; 29.33]	1.6%
Fixed effects model		**6067**		**6044**		0.71	[0.49; 1.05]	100.0%

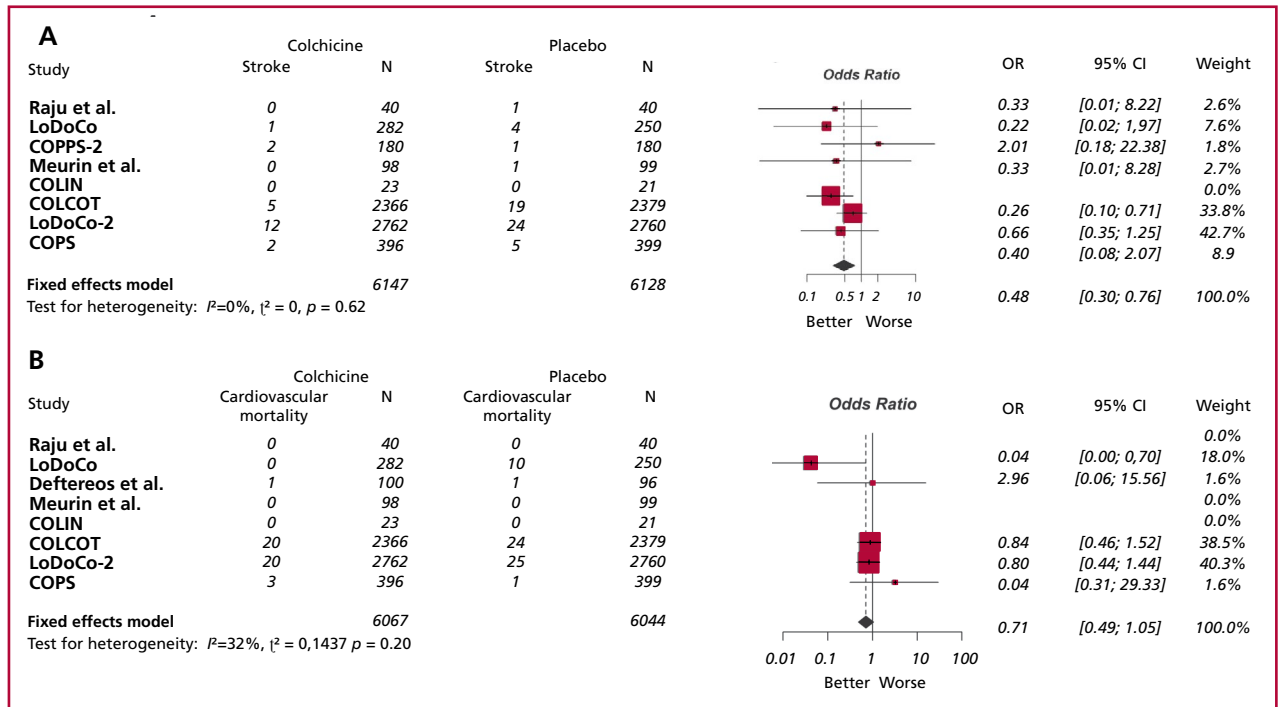Test for heterogeneity: $I^2=32\%$, $t^2 = 0,1437$ $p = 0.20$

Fig. 4. Effect of colchicine on the incidence of stroke (A) and cardiovascular mortality (B). Fixed effects model, odds ratio, 95% confidence interval and I2 statistics
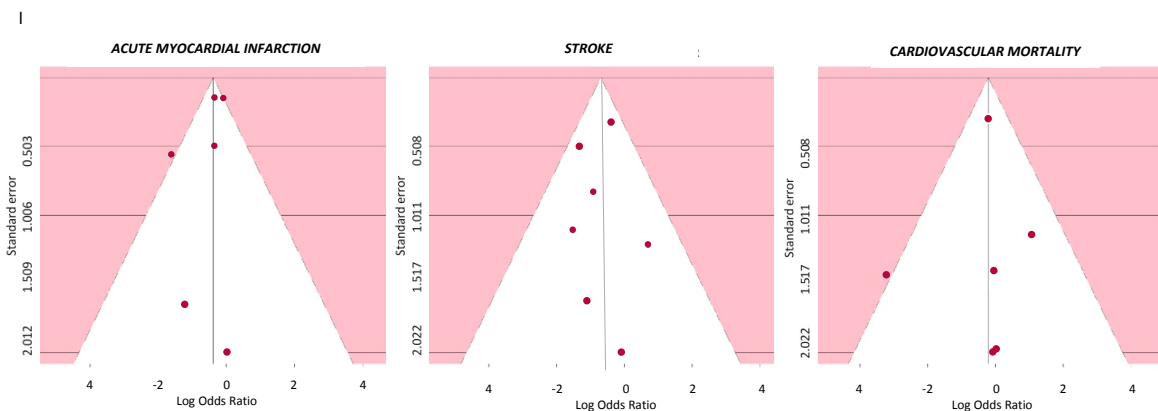

Fig. 5. Funnel plot for analysis of publication bias

chronic coronary artery disease could be explained not only by its action on the inflammasome, but by its role on neutrophil inhibition. (31)

Colchicine is not the only drug with anti-inflammatory effect that has been evaluated for cardiovascular prevention. The CANTOS trial reported that anti-inflammatory therapy targeting the IL-1 innate immunity pathway with canakinumab in patients with previous myocardial infarction led to a significantly lower rate of cardiovascular events than placebo. (32) However, in the CIRT trial, the use of lower-dose methotrexate in patients with stable atherosclerotic disease did not reduce levels of IL-1, IL-6, or C-reactive pro-

tein and did not result in fewer cardiovascular events than placebo. (33)

Despite all the evidence available on the pathophysiologic issues that would explain the potential benefit of colchicine on the incidence of AMI, previously published clinical trials have shown contradictory results. Perhaps the reduction in the incidence of stroke is the most robust benefit observed. (14) Although cerebrovascular and coronary events share the pathophysiological basis, the potential beneficial impact of colchicine on the development of atrial fibrillation could be an additional mechanism in the protection of ischemic cerebrovascular events. (34)
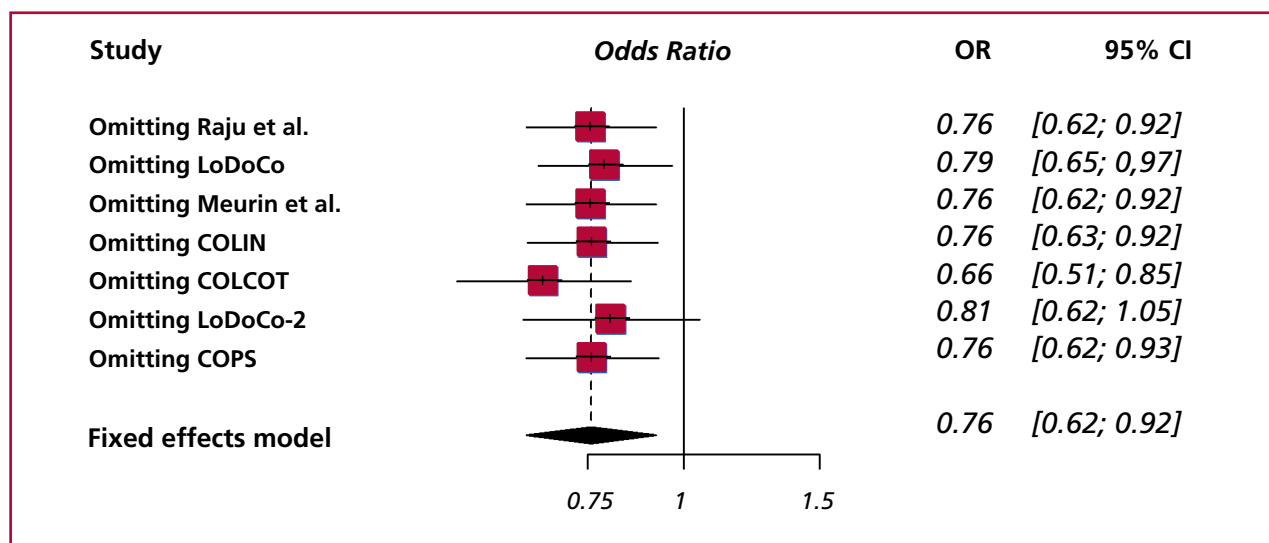
Study	Odds Ratio	OR	95% CI
Omitting Raju et al.		0.76	[0.62; 0.92]
Omitting LoDoCo		0.79	[0.65; 0,97]
Omitting Meurin et al.		0.76	[0.62; 0.92]
Omitting COLIN		0.76	[0.63; 0.92]
Omitting COLCOT		0.66	[0.51; 0.85]
Omitting LoDoCo-2		0.81	[0.62; 1.05]
Omitting COPS		0.76	[0.62; 0.93]
Fixed effects model		0.76	[0.62; 0.92]

0.75   1   1.5

Fig. 6. Sensitivity analysis

The main goal of our meta-analysis was to determine the association between the use of colchicine and the incidence of AMI, incorporating the most recently published clinical trials.

When we analyzed the two largest clinical studies, the results were different. In the COLCOT study, which included 4,745 patients after an acute coronary syndrome, there was no significant difference in the incidence of AMI with the use of colchicine 0.5 mg per day. (15) However, a sub-analysis of the COLCOT study showed a greater benefit in patients who received colchicine within the first three days after AMI compared with subjects who received the drug between days 4 and 30. (35) On the other hand, the recently published LoDoCo-2 trial, which included 5,522 subjects with stable coronary artery disease, reported a significant decrease of 30% in the incidence of AMI after the administration of the same dose of colchicine. (16) Similarly, the results of the LoDoCo study, which included patients with stable coronary artery disease, showed a significant reduction in the incidence of acute coronary events with the use of colchicine (22), whereas the COPS study, which was developed in patients with a recent acute coronary syndrome and used a higher dose of colchicine during the first month (1 mg), did not demonstrate a clinical benefit in the incidence of AMI. (17)

A priori, one could intuitively assume that patients after an acute coronary syndrome have increased inflammation, so they should benefit the most from the pharmacological intervention. However, the inconsistency between the hypotheses based on pathophysiology and the results observed in clinical trials has not been fully clarified. In general, most patients were taking statins in all the clinical trials, but the use of dual antiplatelet therapy (aspirin with another antiplatelet agent) was higher in the studies including pa-

tients with acute coronary syndromes.

Is the efficacy of colchicine greater in steady, low-level of inflammation? In the acute phase of the disease, in the presence of a major prothrombotic state, could antiplatelet drugs or anticoagulants attenuate the effect of colchicine? Clearly, we do not have definitive answers to these questions, considering that the differences could also be explained by statistical issues (lack of power in smaller studies) or simply by chance. Our meta-analysis was not designed to determine whether colchicine has different effects in different populations, and this impact should be analyzed in future research.

After analyzing all the pooled data available to date, the main result of our meta-analysis showed that the use of colchicine was associated with a 24% reduction in the incidence of AMI. Furthermore, the beneficial effect on the incidence of stroke was also reconfirmed. Finally, we did not find an association between the use of colchicine and lower cardiovascular mortality, although there was a nonsignificant favorable trend. The low incidence of cardiovascular mortality compared with the incidence of AMI (105 vs 430 events) could explain the absence of statistical significance.

This meta-analysis has some limitations. Firstly, there was clinical heterogeneity due to the characteristics of the populations, different doses of colchicine and different follow-up. However, in the analysis of the primary endpoint, statistical heterogeneity was low, and the sensitivity analysis showed robust results. Secondly, the analysis included only overall data from each trial without considering individual data. Thirdly, few studies were included in our analysis and many of them had few events. Finally, data on the inflammatory status during follow-up were scarcely reported. Consequently, we were unable to determine if the association between the use of colchicine and the

lower incidence of AMI would change when considering the level of inflammatory markers achieved with pharmacological therapy.

CONCLUSION

Our analysis demonstrated that the use of colchicine in patients with atherosclerotic cardiovascular disease was associated with reduced risk of AMI. The incidence of cerebrovascular events was significantly lower in patients treated with colchicine compared with placebo. Yet, colchicine did not reduce cardiovascular mortality significantly. The incorporation of colchicine into the cardiovascular disease therapeutic toolkit should be discussed and considered in future clinical practice guidelines.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carsonet AP, et al. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. Circulation 2020;141:e139–e596. https://doi.org/10.1161/CIR.0000000000000757.

2. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81. https://doi.org/10.1016/S0140-6736(10)61350-5.

3. Hernández-Mijares A, Ascaso JF, Blasco M, Brea A, Díaz A, Mantilla T, et al. Residual cardiovascular risk of lipid origin. Components and pathophysiological aspects. Clin Investig Arterioscler 2019;31:75-88. https://doi.org/10.1016/j.arteri.2018.06.007.

4. Varbo A, Nordestgaard BG. Remnant cholesterol and triglyceride-rich lipoproteins in atherosclerosis progression and cardiovascular disease. Arterioscler Thromb Vasc Biol 2016;36:2133-2135. https://doi.org/10.1161/ATVBAHA.116.308305.

5. Lawler PR, Akinkuolie AO, Harada P, Glynn RJ, Chasman DI, Ridker PM, et al. Residual risk of atherosclerotic cardiovascular events in relation to reductions in very low-density lipoproteins. J Am Heart Assoc 2017;6:e007402. http://dx.doi.org/10.1161/JAHA.117.007402.

6. Prati F, Marco V, Paoletti G, Albertucci M. Coronary inflammation: why searching, how to identify and treat it. Eur Heart J Suppl 2020;22(Suppl E):E121-24. https://doi.org/10.1093/eurheartj/suaa076.

7. Ridker PM. From CRP to IL-6 to IL-1: moving upstream to identify novel targets for atheroprotection. Circ Res 2016;118:145-56. <https://doi.org/10.1161/CIRCRESAHA.115.306656>.

8. Li B, Li W, Li X, Zhou H. Inflammation: a novel therapeutic target/direction in atherosclerosis. Curr Pharm Des. 2017;23:1216-27. https://doi.org/10.2174/1381612822666161230142931.

9. Akodad M, Sicard P, Fauconnier J, Roubille F. Colchicine and myocardial infarction: A review. Arch Cardiovasc Dis 2020 Jul 22:S1875-2136(20)30143-1. https://doi.org/10.1016/j.acvd.2020.04.007.

10. Leung YY, Hui LLY, Kraus VB. Colchicine: Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45:341-350. https://doi.org/10.1016/j.semarthrit.2015.06.013.

11. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, et al. Cardiovascular effects and safety of long-term colchicine

treatment: cochrane review and meta-analysis. Heart 2016;102:590-6. https://doi.org/10.1136/heartjnl-2015-308542.

12. Verma S, Eikelboom JW, Nidorf SM, Al-Omran M, Gupta N, Teoh H, et al. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2015;15:96. https://doi.org/10.1186/s12872-015-0068-3.

13. Al-Abdouh A, Barbarawi M, Khan SU, Osman M, Upadhrasta S, Solipuram V, et al. Colchicine therapy in patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Coron Artery Dis. 2020 Jul 23. https://doi.org/10.1097/MCA.0000000000000931.

14. Masson W, Lobo M, Molinero G, Masson G, Lavalle-Cobo A. Role of Colchicine in Stroke Prevention: An Updated Meta-Analysis. J Stroke Cerebrovasc Dis 2020;29:104756. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104756.

15. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 2019;381:2497-2505. https://doi.org/10.1056/NEJMoa1912388.

16. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020 383:1838-47.https://doi.org/10.1056/NEJMoa2021372.

17. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in Patients with Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. Circulation 142:1890-900 https://doi.org/10.1161/CIRCULATIONAHA.120.050771.

18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidiset JP, al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

19. Sterne JAC, Savovi J, Page MJ, Elbers RG, Blencowe NS, Boutronet I, al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.

20. Conducting meta-analyses in R with the metaphor package. J Stat Softw 2010;36:1-48.

21. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. J Thromb Thrombolysis 2012;33:88-94. https://doi.org/10.1007/s11239-011-0637-y.

22. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013;61:404-410. https://doi.org/10.1016/j.jacc.2012.10.027.

23. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol 2013;61:1679-1685. https://doi.org/10.1016/j.jacc.2013.01.055.

24. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosiet A, et al. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. JAMA 2014;312:1016-1023. https://doi.org/10.1001/jama.2014.11026.

25. Meurin P, Lelay-Kubas S, Pierre B, Pereira H, Pavy B, Iliou MC, et al. Colchicine for postoperative pericardial effusion: a multicentre, double-blind, randomised controlled trial. Heart 2015;101:1711-6. https://doi.org/10.1136/heartjnl-2015-307827.

26. Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, et al. COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. Arch Cardiovasc Dis 2017;110:395-402. https://doi.org/10.1016/j.acvd.2016.10.004.

27. Libby P, Hansson GK. Inflammation and immunity in diseases of the arterial tree: players and layers. Circ Res 2015;116:307-11. https://doi.org/10.1161/CIRCRESAHA.116.301313.

28. Próchnicki T, Mangan MS, Latz E. Recent insights into the molecular mechanisms of the NLRP3 inflammasome activation. F1000Res. 2016 Jun 22;5:F1000 Faculty Rev-1469. https://doi.org/10.12688/f1000research.8614.1.

29. Wang L, Hauenstein AV. The NLRP3 inflammasome: Mechanism of action, role in disease and therapies. Mol Aspects Med 2020;26:100889. https://doi.org/10.1016/j.mam.2020.100889.

30. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis 2018;269:262-71. https://doi.org/10.1016/j.atherosclerosis.2017.12.027.

31. Opstal TSJ, Hoogeveen RM, Fiolet ATL, Silvis MJM, The SHK, Bax WA, et al. Colchicine Attenuates Inflammation Beyond the Inflammasome in Chronic Coronary Artery Disease: A LoDoCo2 Proteomic Substudy. Circulation Circulation 2020;142:1996-8. https://doi.org10.1161/CIRCULATIONAHA.120.050560

32. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119-31. https://doi.org/10.1056/NEJMoa1707914.

33. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med 2019;380:752-62. https://doi.org/10.1056/NEJMoa1809798.

34. Lennerz C, Barman M, Tantawy M, Sopher M, Whittaker P. Colchicine for primary prevention of atrial fibrillation after open-heart surgery: Systematic review and meta-analysis. Int J Cardiol 2017;249:127-37. https://doi.org/10.1016/j.ijcard.2017.08.039.

35. Bouabdallaoui N, Tardif J, Waters D, Pinto F, Maggioni AP, Rafael D, et al. Time to treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020;41:4092-9 https://doi.org/10.1093/euroheartj/ehaa659