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; I² = 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.
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 α-tubulin and β-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 I2 statistic was calculated to quantify heterogeneity and inconsistency among studies. Depending on the value of I2, a fixed effects model (I2 <40%) or a random effects model (I2 >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; I²=15%) (Figure 3), as well as a significant reduction in the incidence of stroke (OR, 0.48, 95% CI, 0.30-0.76; I²=0%), but no significant effect on cardiovascular mortality (OR, 0.71, 95% CI, 0.49-1.05; I²=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
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**Table 1.** Characteristics of the studies included in the analysis

<table>
<thead>
<tr>
<th>Article</th>
<th>Colchicine arm (daily doses)</th>
<th>n</th>
<th>Control arm</th>
<th>n</th>
<th>Colchicine arm (daily doses)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raju et al. (21)</td>
<td>1 mg</td>
<td>40</td>
<td>Placebo</td>
<td>40</td>
<td>ACS or ischemic stroke</td>
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<tr>
<td>LoDoCo (31)</td>
<td>0.5 mg</td>
<td>282</td>
<td>Usual care</td>
<td>250</td>
<td>Stable coronary artery disease</td>
<td>24</td>
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<tr>
<td>Deftereos et al. (23)</td>
<td>1 mg</td>
<td>100</td>
<td>Placebo</td>
<td>96</td>
<td>Diabetics with need for percutaneous coronary intervention</td>
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</tr>
<tr>
<td>COPPS-2 (24)</td>
<td>0.5 a 1 mg (according to body weight)</td>
<td>180</td>
<td>Placebo</td>
<td>180</td>
<td>Post-cardiovascular surgery</td>
<td>3</td>
</tr>
<tr>
<td>Meurin et al. (29)</td>
<td>1 mg</td>
<td>98</td>
<td>Placebo</td>
<td>99</td>
<td>Post-cardiovascular surgery with pericardial effusion</td>
<td>6</td>
</tr>
<tr>
<td>COLIN (26)</td>
<td>1 mg</td>
<td>23</td>
<td>Placebo</td>
<td>21</td>
<td>ACS</td>
<td>1</td>
</tr>
<tr>
<td>COLCOT (25)</td>
<td>0.5 mg</td>
<td>2366</td>
<td>Placebo</td>
<td>2379</td>
<td>ACS</td>
<td>22.6</td>
</tr>
<tr>
<td>LoDoCo2 (22)</td>
<td>0.5 mg</td>
<td>2762</td>
<td>Placebo</td>
<td>2760</td>
<td>Stable coronary artery disease</td>
<td>28.6</td>
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<tr>
<td>COPS (17)</td>
<td>1 mg for 1 month, then 0.5 mg</td>
<td>396</td>
<td>Placebo</td>
<td>399</td>
<td>ACS</td>
<td>12</td>
</tr>
</tbody>
</table>

ACS: Acute coronary syndrome.

**Fig. 2.** Assessment of risk of bias of included studies

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
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<td>0.65</td>
<td>0.97</td>
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<td>0.62</td>
<td>0.92</td>
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<tr>
<td>Omitting COLIN</td>
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<td>Omitting COPS</td>
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Fixed effects model

<table>
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<th>Odds Ratio</th>
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<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.76</td>
<td>0.62</td>
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</tbody>
</table>

Fig. 6. Sensitivity analysis
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.

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None.

REFERENCES


