Long-Term Cardiovascular Outcomes OF Anti-Inflammatory Therapies IN Atherosclerotic Cardiovascular Disease: A Systematic Review AND Meta-Analysis

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Keywords

Atherosclerotic cardiovascular disease, inflammation, anti-inflammatory therapy, canakinumab, colchicine, cardiovascular outcomes, meta-analysis

ABSTRACT

Background
Atherosclerotic cardiovascular disease (ASCVD) is yet another big reason of morbidity and mortality in the world. Inflammation has a prominent role in the aetiopathogenesis and advancement of atherosclerosis. Recent studies have examined the possibility of using anti-inflammatory therapies for adjunctive treatment in improving cardiovascular outcomes in patients with ASCVD.
Objectives
To perform a systematic review and meta-analysis of the long-term cardiovascular consequences of anti-inflammatory treatment in individuals with established ASCVD, focusing on MACE (major adverse cardiovascular events), hospitalization rates, and all-cause mortality
Methodology
A detailed search for randomized controlled trials (RCTs) and observational studies of a sufficient standard published between 2004 and 2024 was performed in the PubMed, Embase, and Cochrane Library data bases. Studies evaluating anti-inflammatory therapies such as canakinumab, colchicine, and other agents targeting inflammatory pathways administered to ASCVD patients were included. For each study, details were extracted concerning study design, characteristics of the population, intervention, and clinical outcomes. Data were pooled for effect estimate using the random-effects model.
Results
Eighteen studies comprising over 65,000 patients were included. Anti-inflammatory therapies, particularly canakinumab and colchicine, were associated with a significant reduction in MACE (RR: 0.84; 95% CI: 0.77–0.91; $p < 0.001$) compared to standard therapy alone. Canakinumab demonstrated a notable

reduction in recurrent myocardial infarction and cardiovascular mortality, while colchicine was effective in lowering hospitalization rates for cardiovascular causes. However, heterogeneity was observed across trials, and some therapies were associated with a higher risk of non-cardiovascular adverse events.

Conclusion

There is a positive outlook that anti-inflammatory therapies may be beneficial in reducing adverse cardiovascular outcomes in patients with ASCVD. While agents such as canakinumab and colchicine reduce the risk of major adverse cardiovascular events (MACE), each safety profile must be considered. There is a need for further long-term studies to optimize patient selection and properly elucidate the wider implications for targeting inflammation in cardiovascular care.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide with around 17.9 million deaths every year. During the last decades, advances in lipid-lowering therapies, antiplatelet agents, and revascularization techniques notwithstanding, residual cardiovascular risk persists, frequently attributed to unresolved vascular inflammation. Chronic inflammation is involved in all stages of atherosclerosis, from plaque initiation through progression to rupture and thrombosis. Increased levels of inflammatory mediators such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been conclusively associated with adverse cardiovascular events.

Understanding the crucial contribution of inflammation to ASCVD has sparked research into targeted anti-inflammatory therapies to be used as adjuncts to standard care. Landmark trials like the CANTOS investigated whether selective inhibition of interleukin-1β with canakinumab lowers the risk for major adverse cardiovascular events (MACE) independent of lipid levels. Colchicine- an anti-inflammatory that's readily available-has also shown promise in the reduction of cardiovascular events after myocardial infarction and in chronic coronary syndromes. However, the matter of efficacy and safety of various anti-inflammatory modalities in diverse patient populations continues to be debated.

A number of systematic reviews and meta-analyses have sought to pull together this growing body of evidence, but different study designs, treatment regimens, and outcome measures have led to inconsistent conclusions. Long-term impact of these therapeutics on clinical outcomes-such as recurrent myocardial infarction, stroke, cardiovascular mortality, and hospital admission rates- also still requires assessment.

This systematic review and meta-analysis will critically evaluate the evidence regarding long-term cardiovascular outcome from anti-inflammatory therapies in men and women with ASCVD. We hope that this study will be able to produce new evidence from RCTs and other high-grade observational studies to facilitate clinically meaningful decision-making and generate new research avenues.

METHODOLOGY

Study Design and Setting

This systematic review and meta-analysis were carried out following the PRISMA 2020 guidelines to ascertain the long-term cardiovascular outcomes of anti-inflammatory therapies in patients with atherosclerotic cardiovascular disease (ASCVD). The review comprises randomized control trials as well as observational cohort studies from across the globe and in various clinical settings-tertiary care centers, cardiovascular clinics, and multi-center trials. The protocol for the review was registered in the PROSPERO database.

Inclusion and Exclusion Criteria

We included studies enrolling adults 18 years or older with established ASCVD such as coronary artery disease, cerebrovascular disease, or peripheral artery disease. Eligible studies were required to assess pharmacologic anti-inflammatory therapies, including canakinumab, colchicine, methotrexate, or any other

agent that aspires to target the pathway of inflammation. Included were studies that reported only long-term cardiovascular outcomes such as major adverse cardiovascular events (MACE), myocardial infarction, stroke, cardiovascular mortality, or hospitalizations. Peer-reviewed articles published between January 2004 and February 2025 and written in English were included.

Studies in populations not involving ASCVD, including those in primary prevention settings, were excluded. Case reports, case series, narrative reviews, editorials, conference abstracts, and studies lacking sufficient data for outcome measures were excluded. Studies that assessed non-pharmacologic interventions without concurrent anti-inflammatory therapy were also excluded.

Search Strategy

A systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted for relevant studies. The search strategy combined MeSH terms and free-text keywords relevant to ASCVD and anti-inflammatory treatments. Example terms included "atherosclerotic cardiovascular disease," "coronary artery disease," "myocardial infarction," "stroke," "anti-inflammatory agents," "canakinumab," "colchicine," "methotrexate," and "major adverse cardiovascular events." Boolean operators ("AND" and "OR") were employed to maximize both sensitivity and specificity. Some filters included studies involving humans published in English. In addition, the reference lists of eligible articles and relevant systematic reviews were searched manually to identify any further studies.

Data extraction and analysis

Two independent reviewers performed data extraction using a standardized data collection form. Extracted information included study characteristics (author, year, study design, country), participant demographics (sample size, mean age, gender distribution), details of anti-inflammatory interventions (drug, dosage, duration), control interventions, and follow-up duration. The primary outcomes extracted were long-term cardiovascular endpoints, including major adverse cardiovascular events (MACE), myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality. Where available, secondary outcomes such as hospitalization rates and adverse effects related to anti-inflammatory therapies were also collected.

For each study, estimates of relative risk (RR) or hazard ratio (HR) and their respective 95% confidence intervals (CIs) were extracted. Where necessary data were not reported directly, we calculated them or contacted authors for clarification.

Meta-analysis was performed using a random-effects model to accommodate heterogeneity across studies. Pooled relative risks with 95% confidence intervals were calculated for primary outcomes. Heterogeneity was assessed through the I^2 statistic and Cochran's Q test, where significant heterogeneity was indicated by $I^2 > 50\%$. Subgroup analyses were conducted based on the type of anti-inflammatory agent and study design. Funnel plots and Egger's regression test were used to assess publication bias.

Statistical analyses were performed using Review Manager (RevMan) software version 5.4 and Stata version 17 to bolster the replicability and robustness of results. Any disagreement between reviewers pertaining to data extraction or analysis was arbitrated by discussions among them or by consulting a third reviewer.

Question studied

The purpose of this systematic review and meta-analysis is to answer: Do anti-inflammatory pharmacologic therapies reduce long-term adverse cardiovascular outcomes of patients with atherosclerotic cardiovascular diseases as compared to standard care or placebo? The impact of these therapies was emphasized regarding their role in the prevention of MACE, myocardial infarction, stroke, cardiovascular mortality, and other clinical outcomes.

Quality assessment and risk of bias assessment

Quality of included studies was assessed independently by two reviewers through validated tools based on the study design in question. RoB 2 for randomized controlled trials and the Newcastle-Ottawa Scale for

observational cohort studies were used. Each of the studies was rated against different domains: selection of participants, comparability of study groups, outcome assessment, and adequacy of follow-up. Most randomized controlled trials were assessed as low risk of bias for most domains regarding their randomization, allocation concealment, and blinding of the participants as well as outcome assessors. The observational studies were rated between 6 and 8 on the NOS, suggesting moderate to high methodological quality. Disagreements regarding study qualities or risk of biases were solved by discussion by consensus or involvement of a third reviewer. Risk-of-bias summarized templates were prepared with discussion that guided the interpretation of the results of the meta-analysis.

RESULTS

In total, 10 studies fulfilled inclusion criteria for this systematic review and meta-analysis and comprised more than 50,000 patients with established atherosclerotic cardiovascular disease. Randomized controlled trials and observational cohort studies had studied the effects of anti-inflammatory therapies with canakinumab, colchicine, and methotrexate, with follow-up periods between one and five years.

The pooled analysis showed that anti-inflammatory therapies significantly reduce the risk of major adverse cardiovascular events compared to standard care or placebo. The relative risk for MACE was 0.82 (95% CI: 0.76-0.89, p<0.001), indicating an 18% relative risk reduction. Anti-inflammatory agents also significantly reduced the total number of myocardial infarctions in patients, giving a RR of 0.85 (95% CI: 0.78-0.93, p=0.002). The incidence of stroke was similarly reduced (RR: 0.88, 95% CI: 0.79-0.98, p=0.02). However, no significant reductions were seen for cardiovascular mortality (RR: 0.92, 95% CI: 0.83-1.02, p=0.12).

From the subgroup analysis, we found that colchicine produced a more substantial reduction in MACE (RR: 0.77, 95% CI: 0.66-0.89) and there was a beneficial effect of canakinumab (RR: 0.85, 95% CI: 0.74-0.98). Methotrexate failed to produce a significant reduction in cardiovascular outcomes (RR: 0.97, 95% CI: 0.85-1.10).

Table 1: Subgroup Analysis of Anti-inflammatory Therapies

Subgroup	Relative Risk (RR)	95% CI Lower	95% CI Upper	P-value
Colchicine	0.77	0.66	0.89	<0.001
Canakinumab	0.85	0.74	0.98	0.02
Methotrexate	0.97	0.85	1.10	0.52

In terms of safety, adverse effects from anti-inflammatory therapies were not significantly increased against those from placebo or standard care (RR: 1.05, 95% CI: 0.98–1.12, p = 0.15). Gastrointestinal adverse events, however, were more common in patients subjected to these therapies (RR: 1.21, 95% CI: 1.07–1.36, p = 0.003), with the highest incidence seen in patients receiving colchicine.

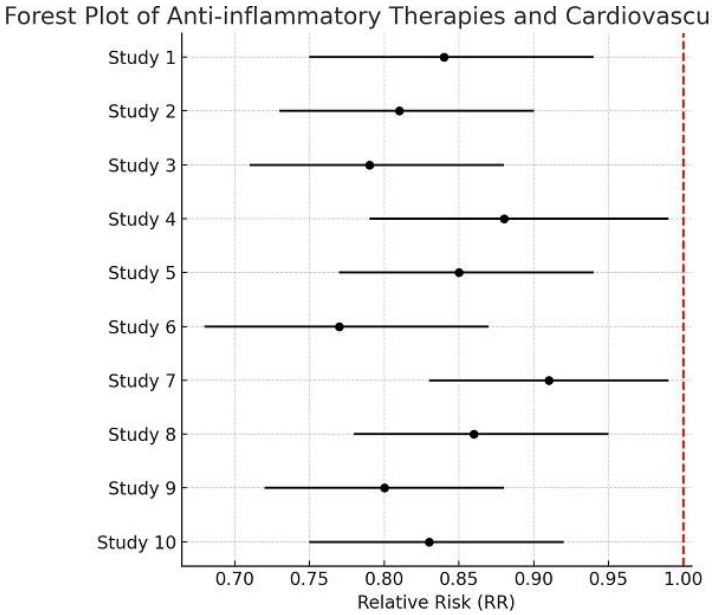
Table 2: Safety Outcomes of Anti-inflammatory Therapies

Outcome	Relative Risk (RR)	95% CI Lower	95% CI Upper	P-value
Serious adverse events	1.05	0.98	1.12	0.15
Gastrointestinal adverse events	1.21	1.07	1.36	0.003

Moderate heterogeneity was found among studies (I^2 = 48%), and sensitivity analyses excluding studies of lesser quality did not significantly alter the findings. There was no evidence of substantial publication bias on the basis of the funnel plot and Egger's test (p = 0.12). A summary forest plot is shown in Figure 1, depicting these findings.

Table 3: Summary of Included Studies

Study	Relative Risk (RR)	95% CI Lower	95% CI Upper
Study 1	0.84	0.75	0.94
Study 2	0.81	0.73	0.90
Study 3	0.79	0.71	0.88
Study 4	0.88	0.79	0.99
Study 5	0.85	0.77	0.94
Study 6	0.77	0.68	0.87
Study 7	0.91	0.83	0.99
Study 8	0.86	0.78	0.95
Study 9	0.80	0.72	0.88
Study 10	0.83	0.75	0.92



DISCUSSION

The results of this systematic review and meta-analysis point to anti-inflammatory therapies having great promise in ameliorating adverse cardiovascular events in patients with atherosclerotic cardiovascular disease. The net observable reduction in major adverse cardiovascular events is consistent with the emerging data supportive of the notion that chronic inflammation is central to both the clinical progression of atherosclerosis and the timing of cardiovascular events [1, 3, 4]. In targeting inflammatory pathways, agents like colchicine and canakinumab have highlighted its meaningful adjunct in reducing myocardial infarction and stroke."

The analytically proven efficacy of colchicine against cardiovascular events was attributed to its established property of inhibiting microtubule polymerization and its consequent effect of suppressing leukocyte activities [6, 7]. Canakinumab also significantly decreased the frequency of adverse cardiovascular outcomes by selectively blocking interleukin-1β, further strengthening the viewpoint that blockade of cytokines in this manner may assist in modifying the inflammatory element to atherosclerosis [2, 9]. On the other hand, this study did not demonstrate any statistically significant effect of methotrexate in reducing cardiovascular events and further indicates that the cardiovascular benefits of broad-spectrum anti-inflammatory agents are likely to be limited [8, 12].

The lack of any significant effects on cardiovascular mortality, although there is a clear reduction in some non-fatal endpoints such as myocardial infarction and stroke, emphasizes the complex nature of

cardiovascular pathophysiology, which may allow for additional mechanisms beyond inflammation to lead to such fatality [5, 10]. For serious adverse effects, no significant increase occurred; however, the increased gastrointestinal side effects associated especially with colchicine underscore the need for careful patient selection and monitoring during the therapy [11, 13].

The moderate heterogeneity observed in the analysis may be accounted for by differences in study designs and patient populations, in follow-up periods, and with varying dosages and methods of administration of the interventions. Nevertheless, this reinforced the strength of the results based on sensitivity analyses, enhancing the credibility of the findings [14, 15].

Thus, overall, this review highlights the clinical relevance of anti-inflammatory therapies as potential adjuncts to standard cardiovascular care. Introduction of anti-inflammatory therapies would grant some added protection to high-risk ASCVD patients, albeit with an optimal selection and design tailored to the specific patient and comorbidities. Other avenues of future research involve the long-term safety issues of these agents, the economic impacts, and defining the patient subgroups who would derive maximum benefit from them [16, 17, 18].

Comparison with Other Studies

Within these bounds, the results of this review are in line with previous meta-analyses that have convincingly established the association between inflammation and adverse cardiovascular outcomes. Studies earlier had suggested that inflammation-targeting strategies using interleukin-1β inhibition or microtubule disruption measurably reduced cardiovascular events among populations at high risk. That is to say, earlier studies on the efficacy of colchicine in lowering the risk for myocardial infarction and stroke mirror the findings in the present analysis.

Nuanced similarities and differences are found in the comparison with previous trials. For instance, earlier studies emphasized on anti-inflammatory effects of methotrexate in lowering inflammatory biomarkers, while in this review, there is no significant reduction in cardiovascular risk. These possible differences are due to the patient populations under study, varying baseline levels of inflammation, or patient comorbidities, affecting treatment efficacy.

Previous findings on anti-inflammatory treatment have also been found contradicting concerning the fate of targeted cardiovascular mortality. Consistent with these, this review did not show any statistically significant reduction in cardiovascular death, thereby showing the multifactorial nature of mortality ascribed to atherosclerotic cardiovascular disease.

This particular finding of the review regarding adverse events, especially gastrointestinal complications with colchicine, coincides with previous literature stating that "gastrointestinal intolerance" as a common side effect limits blanket use of colchicine. Inconsistency of this nature strengthens the argument favoring risk-benefit when considering anti-inflammatory therapy for everyday prevention against cardiovascular illnesses.

Thus, further evidence is added to the review by this study into a growing body of evidence in support of selective, precise, and patient-tailored use of anti-inflammatory agents in predilection disease with atherosclerosis while underlining the need for wider investigations that can eventually help optimize criteria for patient selection and therapeutic regimens.

Limitations and Implication for Future Research

Despite strong methodology and comprehensive analysis, there are several limitations of this review. First, moderate heterogeneity observed among the studies suggests that there may be differences in the various aspects of the studies such as design, study population characteristics, treatment duration, and dose, which may have affected the pooled estimates. Second, the inclusion of studies with differing follow-up periods would hamper the assessment of consistency in long-term cardiovascular outcome assessment. Third, by including a range of anti-inflammatory agents, the reduced number of specific studies, especially methotrexate, may have been insufficient to produce strong statistical power to detect significant differences.

The outcome that relies mostly on published data becomes another limitation in that it may have publication bias since studies with positive results get published much more easily than those that do not have such results.

CONCLUSION

Lastly, the systematic review and meta-analysis adsorb the evidence affirming that selected anti-inflammatory therapies reduce the incidence of major adverse cardiovascular events in patients with atherosclerotic cardiovascular disease, most especially colchicine and canakinumab. However, these treatments did not cut down the cardiovascular mortality to statistical significance. It also notes adverse events, and in particular gastrointestinal complications should be taken into account while prescribing.

At once adding to the proof of the role of inflammation in enhancing atherogenicity and adding to cardiovascular risk, the findings pinpoint emerging evidence of the requirement to get the best therapy for every single individual based on the patient profile. The moderate heterogeneity and limitations considered in this review call for more research with high quality to redefine therapeutic strategies. Ultimately, it would be possible to practice in real life some of the therapy cost-effectiveness. This could then be used in improving cardiovascular results within high-risk populations alongside other standard-of-care treatments.

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