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Clinical outcomes of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway in coronary artery disease patients: a systemic review and meta-analysis of 37,056 individuals from 32 randomized trials

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Abstract

Background Treatment effects of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway in coronary artery disease (CAD) had conflicting results. The study aims to evaluate efficacy and safety outcomes of treatments inhibiting this pathway.

Methods Cochrane Library, Embase, Pubmed, and ClinicalTrials.gov were searched for randomized controlled trials evaluating therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway in CAD patients. Relative risks (RR) with 95% confidence intervals (CI) were calculated.

Results 32 studies and 37,056 individuals were included. Anti-inflammatory therapies inhibiting the pathway reduced the risks of myocardial infarction (MI) (RR 0.85, 95% CI 0.78–0.93) and coronary revascularization (RR 0.80, 95% CI 0.74–0.86), with no benefits in major adverse cardiovascular events (MACE), heart failure (HF), stroke, cardiovascular or all-cause mortality. Colchicine reduced the risks of MACE, MI, and coronary revascularization. IL-1 inhibitors reduced the risks of coronary revascularization, with potential benefits in MI and HF. Increased risks of infections, gastrointestinal adverse effects, and injection site reactions were found. Meta-regression analysis demonstrated that post-treatment hsCRP/CRP was correlated with MACE ($p < 0.001$) and MI ($p = 0.048$) and post-treatment IL-6 was associated with MI ($p = 0.033$).

Conclusion Anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway had satisfying safety profiles and were beneficial in preventing MI and coronary revascularization in CAD patients despite no benefits in stroke, cardiovascular, or all-cause mortality.

Keywords Anti-inflammatory therapy · Colchicine · Coronary artery disease · Interleukin-1 inhibitors · Interleukin-6 inhibitors · Methotrexate · NLRP3/IL-1 β /IL-6/CRP pathway

Abbreviations

CRP	C-reactive protein
HF	Heart failure
IL-1	Interleukin-1
IL-6	Interleukin-6
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NLRP3	NOD-like receptor protein 3
RCTs	Randomized controlled trials

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Introduction

Inflammation has been recognized as an essential part of the pathogenesis of coronary artery disease. Both innate and adaptive immune cells are involved in atherosclerosis [1]. The immune cells secrete inflammatory mediators, which promote plaque formation, progression, and rupture [2]. The central interleukin-6 (IL-6) signaling pathway is crucial for coronary artery disease. It starts with the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, which further produces interleukin-1 β (IL-1 β) and interleukin-18 (IL-18). Increased levels of IL-1 β then activate the downstream tumor necrosis factor- α (TNF- α) and IL-6 [3], which promotes hepatocytes to generate C-reactive protein (CRP) [4]. Previous observational studies have demonstrated IL-6 and high-sensitivity CRP (hsCRP) as markers to predict future cardiovascular events [5, 6], which further validated the importance of the NLRP3/IL-1 β /IL-6/CRP signaling pathway.

Multiple randomized controlled trials (RCTs) have been conducted to evaluate the treatment effects of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway, including NLRP3 inflammasome inhibitors (colchicine), IL-1 inhibitors (anakinra, canakinumab, goffikicept), IL-6 inhibitors (tocilizumab), and methotrexate. Previous studies have proven colchicine's efficacy for cardiovascular and cerebrovascular events [7, 8]. Multiple RCTs, including the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) [9], the ASSEssing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) trial [10], and the Cardiovascular Inflammation Reduction Trial (CIRT) [11], examined canakinumab, tocilizumab and methotrexate in coronary artery disease patients. However, the results of these RCTs were conflicting, and the overall effects of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway were unknown. Therefore, a systemic review examining the clinical outcomes of anti-inflammatory therapies targeting this pathway is warranted. This study aims to assess the clinical outcomes of inhibiting the central IL-6 pathway in coronary artery disease patients and summarize the efficacy and safety outcomes according to different mechanisms of treatments.

Materials and methods

Search strategy and inclusion criteria

This systemic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [12].

The original study protocol has been registered in Prospero (CRD42024527847).

A systemic search was conducted from Cochrane Library, Embase, Pubmed, and ClinicalTrials.gov, with an inception date of March 26, 2025. RCTs that evaluated the effects of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway in coronary artery disease patients were screened for inclusion. These terms were employed in the search strategy: 'coronary artery disease' and 'anti-inflammatory' or 'colchicine' or 'NLRP3 inflammasome inhibitor' or 'IL-1 inhibitor' or 'TNF- α inhibitor' or 'IL-6 Inhibitor' or 'methotrexate' and 'randomized controlled trials'. The Supplementary Methods provided details about the search strategies.

The inclusion criteria included: (1) the study population was established coronary artery disease patients; (2) RCTs compared interventions of anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway, including NLRP3 inflammasome inhibitors, IL-1 inhibitors, TNF- α inhibitors, IL-6 Inhibitors, and methotrexate, with placebo or no anti-inflammatory therapies; (3) reported any of the efficacy or safety outcomes with a minimum follow-up time of 1 month or 30 days. Studies not written in English were excluded.

Clinical outcomes and data extraction

The composite endpoint of major adverse cardiovascular events (MACE) was designated as the primary outcome. The exact definitions of MACE were different across the RCTs. Thus, the definitions were extracted from each study, including various combinations of myocardial infarction (MI), coronary revascularization, stroke, cardiac arrest, heart failure (HF), and all-cause mortality. Due to the variability in the definitions of the composite endpoints, additional efficacy outcomes were further evaluated, including MI, coronary revascularization, HF, stroke, cardiovascular, and all-cause mortality. Safety outcomes included infection, cancer, bleeding, gastrointestinal side effects, and injection site reaction. If a single study reported outcomes across multiple follow-up durations, results from the longest follow-up duration were extracted.

Two authors (YP and JJ) independently reviewed the titles, abstracts, and full texts during the study selection process, and they extracted data for eligible studies. Any disagreements were discussed with a third author (YZ). The following information of included studies was extracted: study name, trial registration number, first author of the study, year of publication, location, study design, number of trial centers, sample size, study population, intervention therapies, control groups, treatment durations, follow-up durations, age, sex, comorbidities, baseline or post-treatment

inflammatory markers, study endpoints, and the predefined efficacy or safety outcomes.

Risk of bias assessment

The study evaluated the risk of bias using version 2 of the Cochrane risk of bias tool [13]. The following 5 domains of risk of bias were analyzed, including the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The evaluation was performed independently by two authors (YP and JJ). Any disagreements were discussed with a third author (YZ).

Statistical analysis

For baseline characteristics in which only medians and interquartile ranges were reported, they were transformed into means and standard deviations [14, 15]. Dichotomous outcome variables were evaluated with relative risks (RRs) and 95% confidence intervals (CIs) using the Mantel–Haenszel method, and treatment arm continuity corrections were applied to handle the zero events [16]. Prediction intervals were calculated to demonstrate the variations of true treatment effects [17]. Higgins I^2 statistics were utilized to evaluate the heterogeneity. The random effect model was applied with $I^2 > 50\%$, indicating high heterogeneity. The common effect model was applied with $I^2 \leq 50\%$, indicating low heterogeneity. Assessment of publication bias involved the funnel plot, Egger's test, and Begg's test. The study analyzed the clinical outcomes of different treatment subgroups and compared efficacy outcomes between acute coronary syndrome (ACS) and chronic coronary syndrome (CCS), as well as different follow-up times. Due to the existing debate of whether methotrexate belongs to the anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway, a sensitivity analysis excluding methotrexate was conducted. Meta-regression analyses were performed to analyze the effects of inflammatory markers on efficacy outcomes. A two-tailed p value less than 0.05 was considered significant. Statistical analyses were conducted with R software Version 4.1.2 using the meta and metafor packages.

Results

Eligible studies and quality assessments

In the review of eligible studies, a total of 32 studies were included (Fig. 1). Characteristics of these studies are shown in Table S1. A total of 37,056 individuals were involved, with 20,294 in the treatment group and 16,762 in the control

group. 10,678 patients from 20 RCTs received colchicine. 6962 patients from 6 RCTs received IL-1 antagonists. 171 patients from 3 RCTs received IL-6 antagonists, and 2483 patients from 4 trials received methotrexate. One study from Hays et al. compared colchicine to placebo and methotrexate to placebo at the same time [18], and both groups were separately included and compared to placebo in the analysis. The involved population had a mean age of 62.2, with 79.3% male. The risk of bias assessment showed low levels of bias overall (Figure S1).

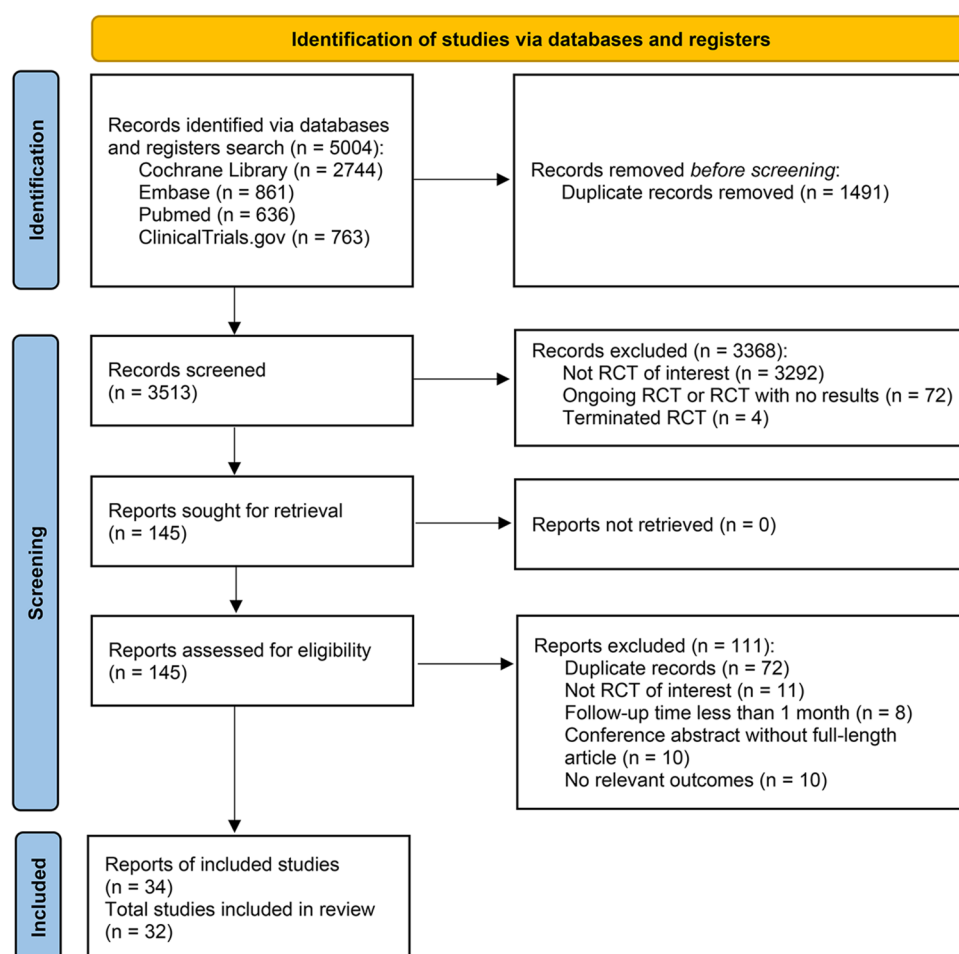
The primary outcome

The primary outcome of MACE was reported in 17 RCTs and is shown in Fig. 2. The definitions of MACE varied across included studies and were further detailed in Table S2. Overall, a nonsignificant tendency towards reducing risks of MACE was found for anti-inflammatory therapies (RR 0.83, 95% CI 0.67–1.02, prediction interval 0.40–1.74, $I^2 = 67\%$). Subgroup analyses of treatments demonstrated IL-1 inhibitors (RR 1.47, 95% CI 0.44–4.91, $I^2 = 80\%$), IL-6 inhibitors (RR 1.47, 95% CI 0.19–11.28, $I^2 = 82\%$), and methotrexate (RR 1.03, 95% CI 0.84–1.26, $I^2 = 0\%$) did not reduce the risks of MACE, while colchicine had a protection effect on MACE (RR 0.72, 95% CI 0.57–0.91, $I^2 = 67\%$).

Additional efficacy outcomes

Due to the variations in the definitions of MACE, additional efficacy outcomes were analyzed. 25 reported incidences of all-cause mortality, 23 trials reported incidences of MI, 17 reported incidences of cardiovascular death, 15 reported incidences of stroke, 13 reported incidences of revascularization, and 12 reported incidences of HF. Relative risks of the additional efficacy outcomes are shown in Figs. 3, 4, and 5, grouped by different therapies. Anti-inflammatory therapies decreased the risks of MI (RR 0.85, 95% CI 0.78–0.93, prediction interval 0.78–0.95, $I^2 = 12\%$) and coronary revascularization (RR 0.80, 95% CI 0.74–0.86, prediction interval 0.62–1.07, $I^2 = 20\%$), with neutral effects on stroke (RR 0.87, 95% CI 0.73–1.04, prediction interval 0.49–1.39, $I^2 = 0\%$) and HF (RR 0.86, 95% CI 0.74–1.01, prediction interval 0.72–1.03, $I^2 = 0\%$), cardiovascular mortality (RR 0.93, 95% CI 0.82–1.06, prediction interval 0.81–1.08, $I^2 = 0\%$), and all-cause mortality (RR 0.98, 95% CI 0.89–1.07, prediction interval 0.89–1.07, $I^2 = 0\%$). Subgroup analyses by different therapies demonstrated that colchicine decreased the risks of MI (RR 0.79, 95% CI 0.68–0.91, $I^2 = 9\%$) while IL-1 inhibitors had a nonsignificant protective tendency towards MI (RR 0.875, 95% CI 0.763–1.003, $I^2 = 31\%$). Both IL-1 inhibitors (RR 0.72, 95% CI 0.64–0.80, $I^2 = 0\%$) and colchicine (RR 0.84, 95% CI 0.74–0.94,

Fig. 1 The PRISMA flow diagram of included studies. RCT: randomized controlled trial



$I^2=15\%$) decreased the risks of coronary revascularization. IL-1 inhibitors had a nonsignificant tendency to decrease HF risks (RR 0.834, 95% CI 0.695–1.002, $I^2=28\%$). None of the anti-inflammatory therapies had benefits on stroke, cardiovascular mortality, or all-cause mortality.

Safety outcomes

Safety outcomes are shown in Figs. 6 and 7. Increased risks of infection were found (RR 1.08, 95% CI 1.01–1.16, prediction interval 1.01–1.17, $I^2=0\%$), with methotrexate being the only significant contributor (RR 1.13, 95% CI 1.03–1.25, $I^2=0\%$). Risks of gastrointestinal adverse effects were increased (RR 1.51, 95% CI 1.17–1.95, prediction interval 0.64–3.54, $I^2=55\%$) in both methotrexate (RR 1.24, 95% CI 1.08–1.43, $I^2=9\%$) and colchicine (RR 1.64, 95% CI 1.18–2.28, $I^2=61\%$). IL-1 inhibitors increased the risks of injection site reaction (RR 2.69, 95% CI 1.11–6.49, prediction interval 0.18–39.49, $I^2=62\%$). All the therapies did not increase the risks of bleeding or malignancy. Funnel plots, Egger's tests, and Begg's tests showed no evidence of

publication bias (Figure S2, Table S3, and Table S4), with gastrointestinal adverse events being the only exception.

Subgroup analysis

Efficacy outcomes were compared between CCS and ACS groups, as shown in Figure S3 and Figure S4. Anti-inflammatory therapies reduced the risks of MI (RR 0.84, 95% CI 0.75–0.94) and coronary revascularization (RR 0.77, 95% CI 0.70–0.84) in the CCS groups, while the ACS groups had neutral effects on MI (RR 0.87, 95% CI 0.73–1.04) and coronary revascularization (RR 0.87, 95% CI 0.75–1.01), despite subgroup differences were insignificant for MI ($p=0.76$) and coronary revascularization ($p=0.17$). No benefits were found in either the CCS or ACS group for other efficacy outcomes.

The study also compared efficacy outcomes across different follow-up times, demonstrated in Figure S5 and Figure S6. Those studies with follow-up time longer than 1 year had proven benefits in MACE (RR 0.83, 95% CI 0.70–0.99), MI (RR 0.86, 95% CI 0.78–0.95), and coronary revascularization (RR 0.80, 95% CI 0.74–0.86), while those follow-up

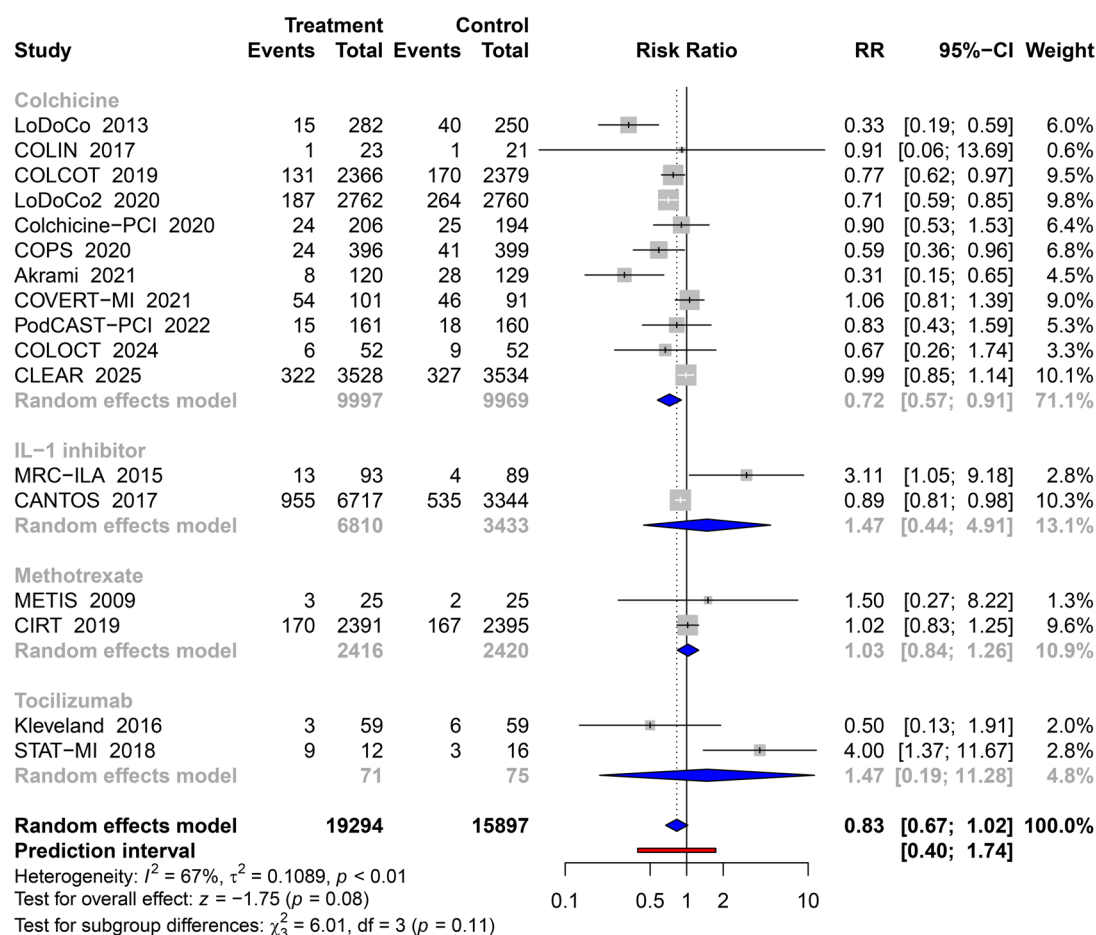


Fig. 2 Relative risks of MACE in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. MACE: major adverse cardiovascular events; IL-1: interleukin-1; IL-6: interleukin-6

time less than 1 year did not. However, subgroup differences were insignificant for these outcomes.

Sensitivity analysis

A sensitivity analysis excluding methotrexate was conducted (Figure S7, Figure S8, and Figure S9). The analysis reached similar results, with anti-inflammatory therapies reducing the risks of MI (RR 0.83, 95% CI 0.75–0.91, prediction interval 0.75–0.93, $I^2 = 15\%$) and revascularization (RR 0.77, 95% CI 0.71–0.84, prediction interval 0.60–1.04, $I^2 = 9\%$), while no proven effects on MACE, cardiovascular death, all-cause mortality, stroke, and HF. As for adverse events, the risks of infection were no longer increased by anti-inflammatory therapies (RR 1.05, 95% CI 0.95–1.15, prediction interval 0.89–1.22, $I^2 = 0\%$).

Inflammatory markers and outcomes

In the meta-regression analysis, baseline hsCRP or CRP was not associated with clinical outcomes (Figure S10).

In contrast, post-treatment hsCRP or CRP showed a linear association with MACE ($p < 0.001$) and MI ($p = 0.048$) (Fig. 8). For IL-6 levels, baseline IL-6 was linearly correlated with MACE ($p = 0.008$) and MI ($p = 0.005$) (Figure S11), while post-treatment IL-6 was linearly associated with MI ($p = 0.033$) (Figure S12).

Discussion

This is the first meta-analysis that assesses anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway in coronary artery disease patients. The study involved 37,056 pooled individuals from 32 RCTs. Overall, therapies inhibiting this pathway did not reduce the risks of MACE but had favorable effects on ischemic endpoints, including MI and coronary revascularization. The risks of serious adverse events were low, suggesting a satisfying safety profile overall. These findings bring new insights into anti-inflammatory therapies targeting this pathway.

Fig. 3 Relative risks of MI (A) and coronary revascularization (B) in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. MI: myocardial infarction; IL-1: interleukin-1; IL-6: interleukin-6

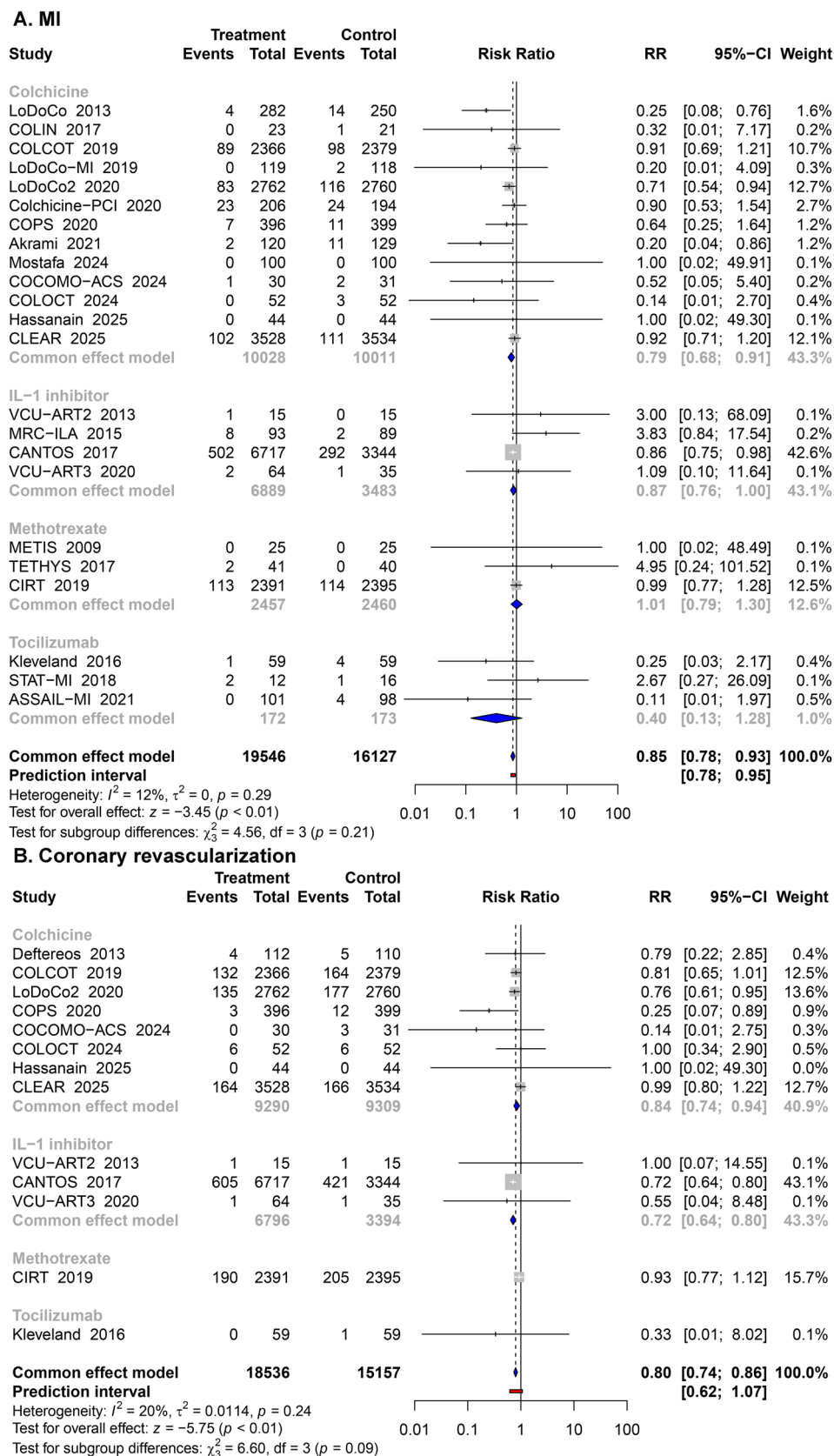
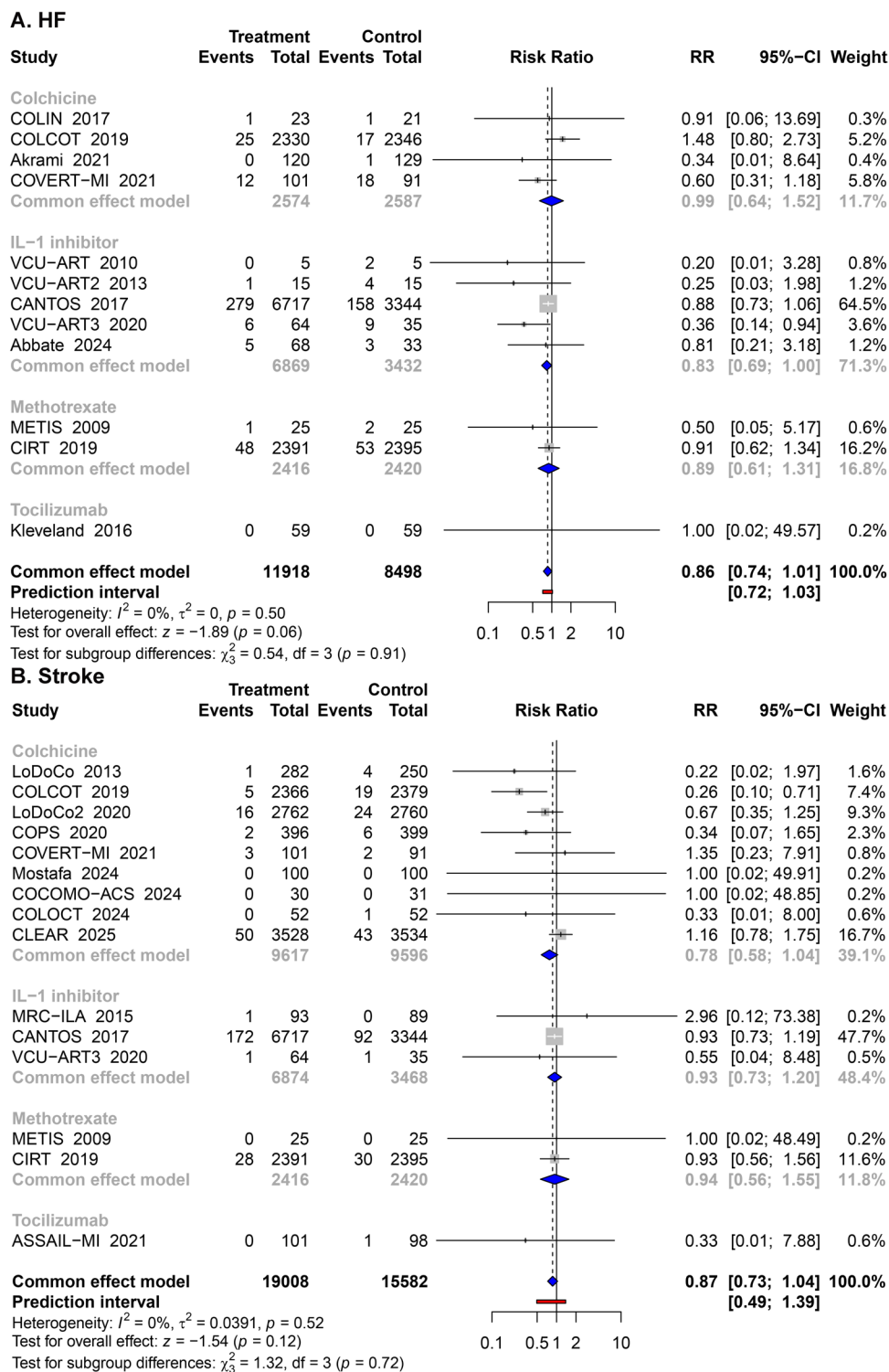


Fig. 4 Relative risks of HF (A) and stroke (B) in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. HF: heart failure; IL-1: interleukin-1; IL-6: interleukin-6

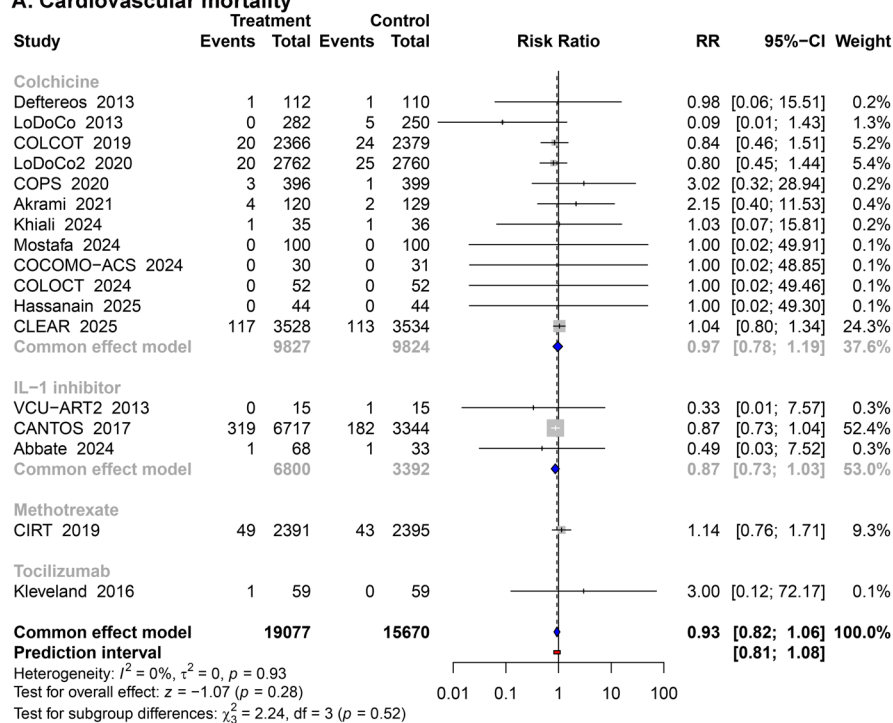


In recent years, inflammation has been gradually recognized as an essential part of the pathogenesis of cardiovascular diseases. NLRP3 inflammasome initiates the central IL-6 pathway and its activation increases downstream production of IL-1 and IL-18 [2], contributing to plaque instability and the progression of atherosclerotic plaques [19,

20]. Therefore, NLRP3 inflammasome inhibitors were the most studied anti-inflammatory therapies in the cardiovascular disorders population, and multiple large-scale RCTs were conducted [21–25]. Despite conflicting results, existing meta-analyses proved that colchicine could decrease inflammatory markers [26], lower the risks of major adverse

Fig. 5 Relative risks of cardiovascular (A) and all-cause mortality (B) in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. IL-1: interleukin-1; IL-6: interleukin-6

A. Cardiovascular mortality



B. All-cause mortality

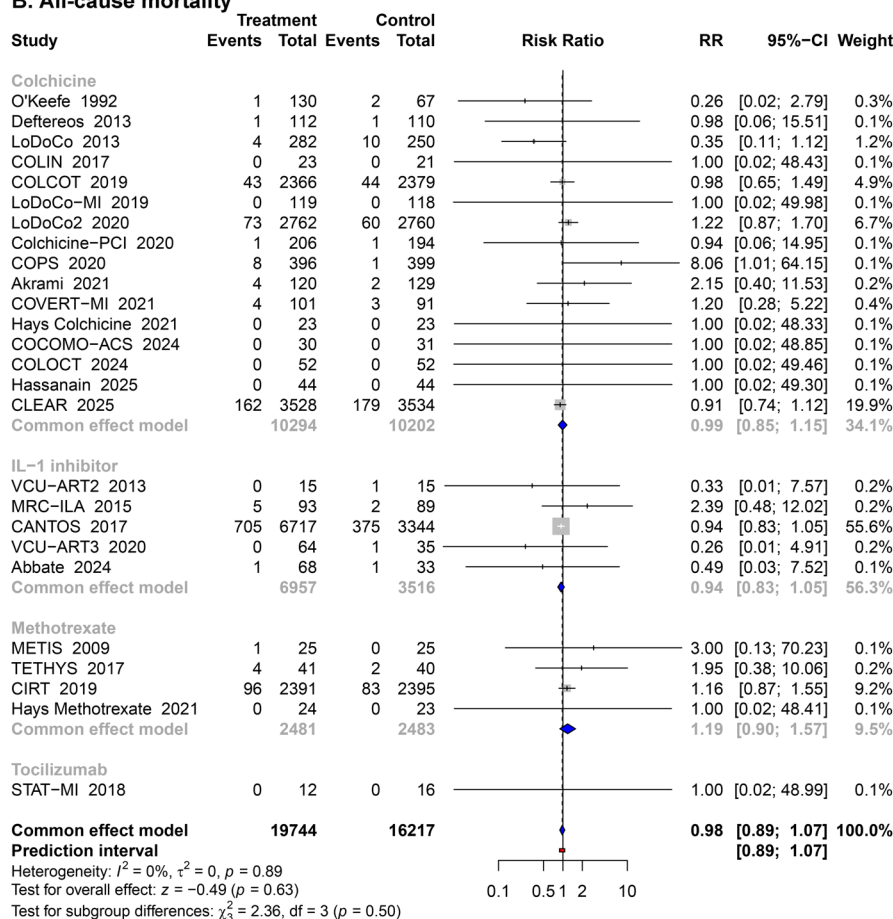
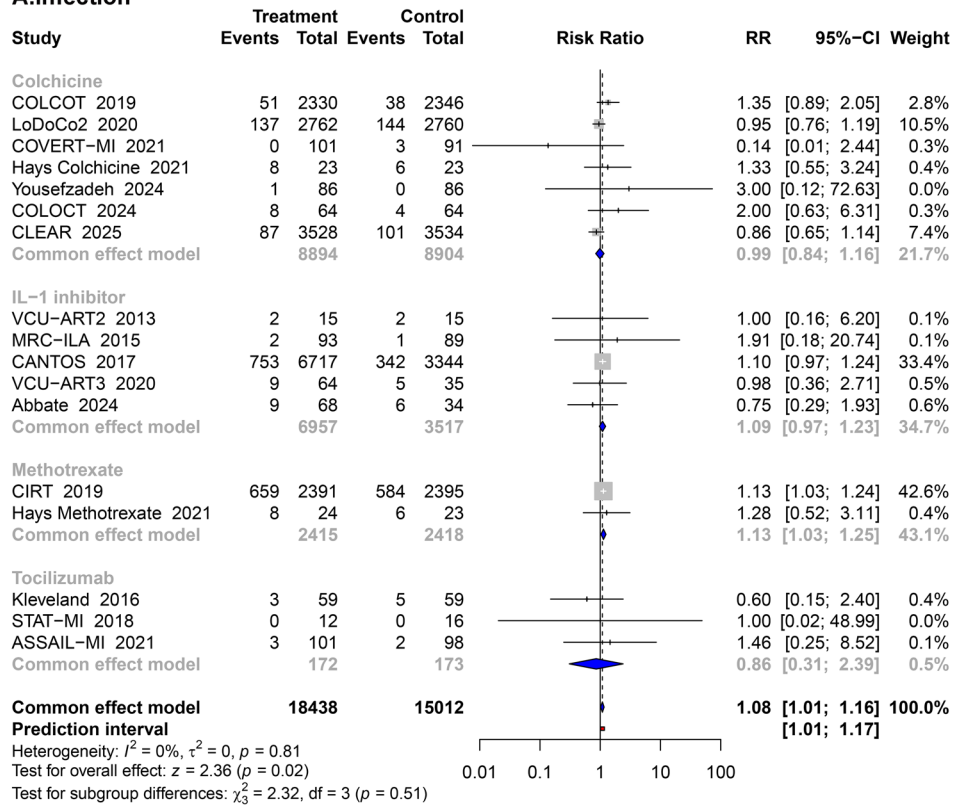


Fig. 6 Relative risks of infection (A) and gastrointestinal adverse effect (B) in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. IL-1: interleukin-1; IL-6: interleukin-6

A. Infection



B. Gastrointestinal adverse event

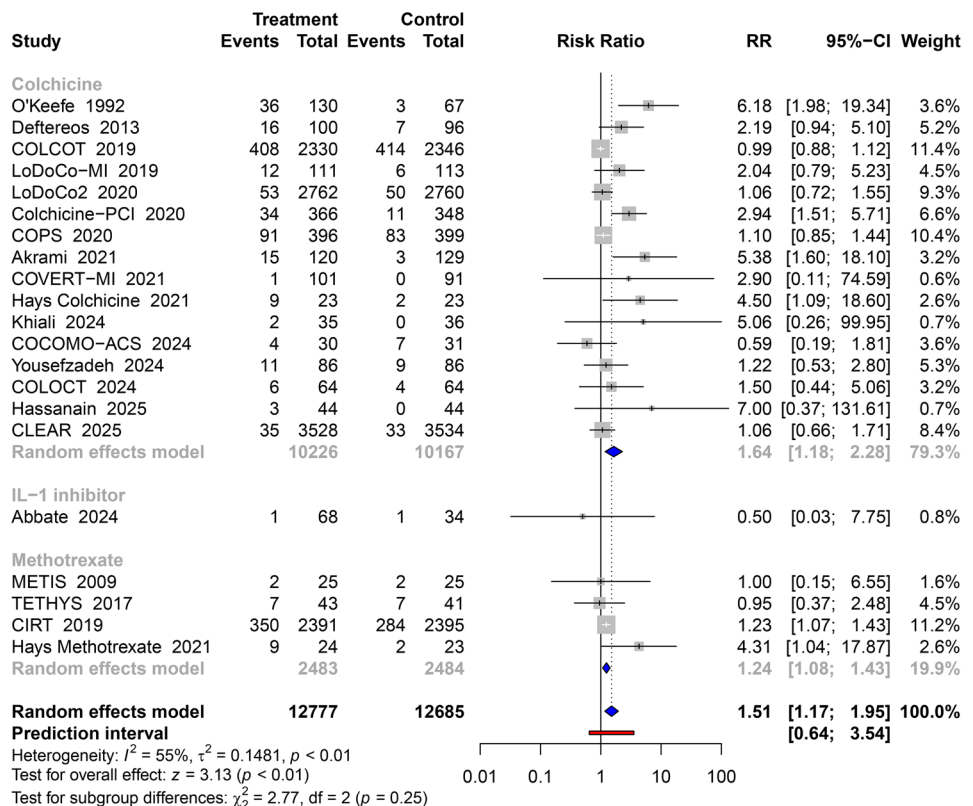
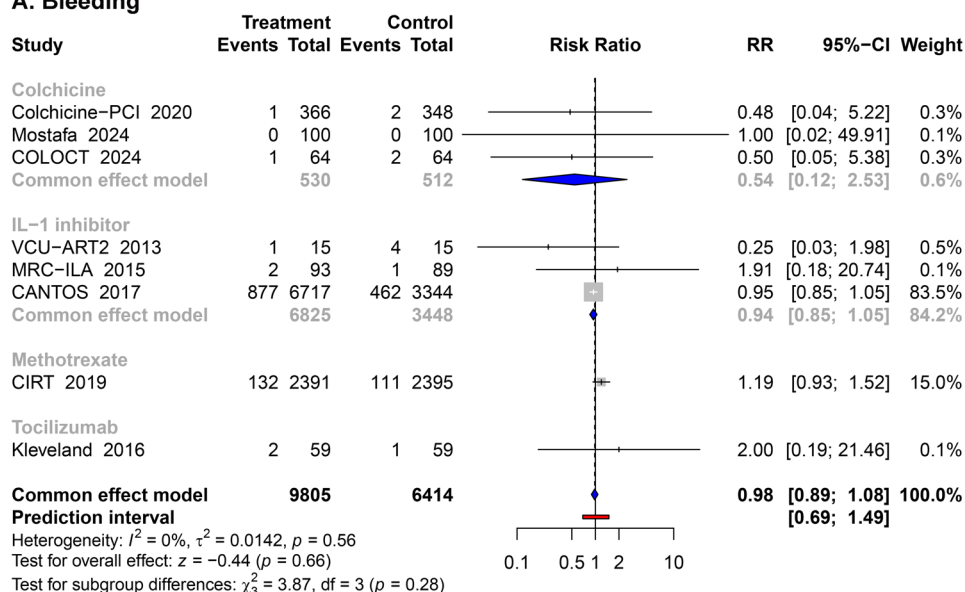
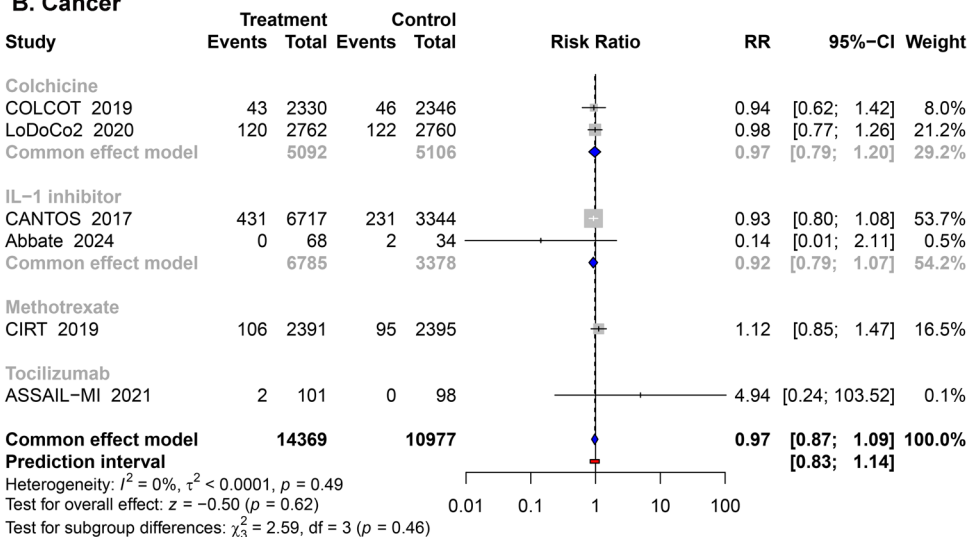


Fig. 7 Relative risks of bleeding (A), cancer (B), and injection site reaction (C) in coronary artery disease patients treated with anti-inflammatory therapies targeting the NLRP3/IL-1 β /IL-6/CRP pathway. IL-1: interleukin-1; IL-6: interleukin-6

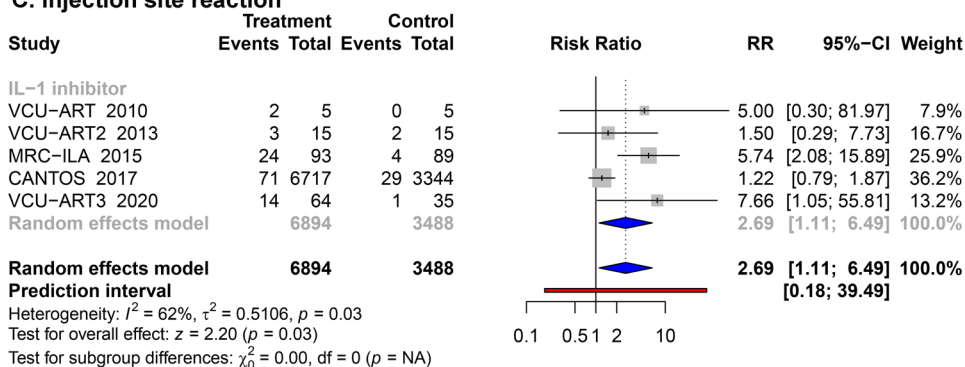
A. Bleeding



B. Cancer



C. Injection site reaction



cardiovascular and cerebrovascular events in CAD patients [7], and reduce AF recurrence after catheter ablation [27]. With the advent of the CANTOS trial [9], canakinumab, an IL-1 β inhibitor, showed the benefits of decreasing hsCRP and IL-6 levels to reduce the risks of recurrent

cardiovascular events, which brought attention to anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway. A previous meta-analysis was conducted on inhibition of the NLRP3/IL-1 β /IL-6 pathway in ST-elevation MI (STEMI) patients [28]. However, the involved

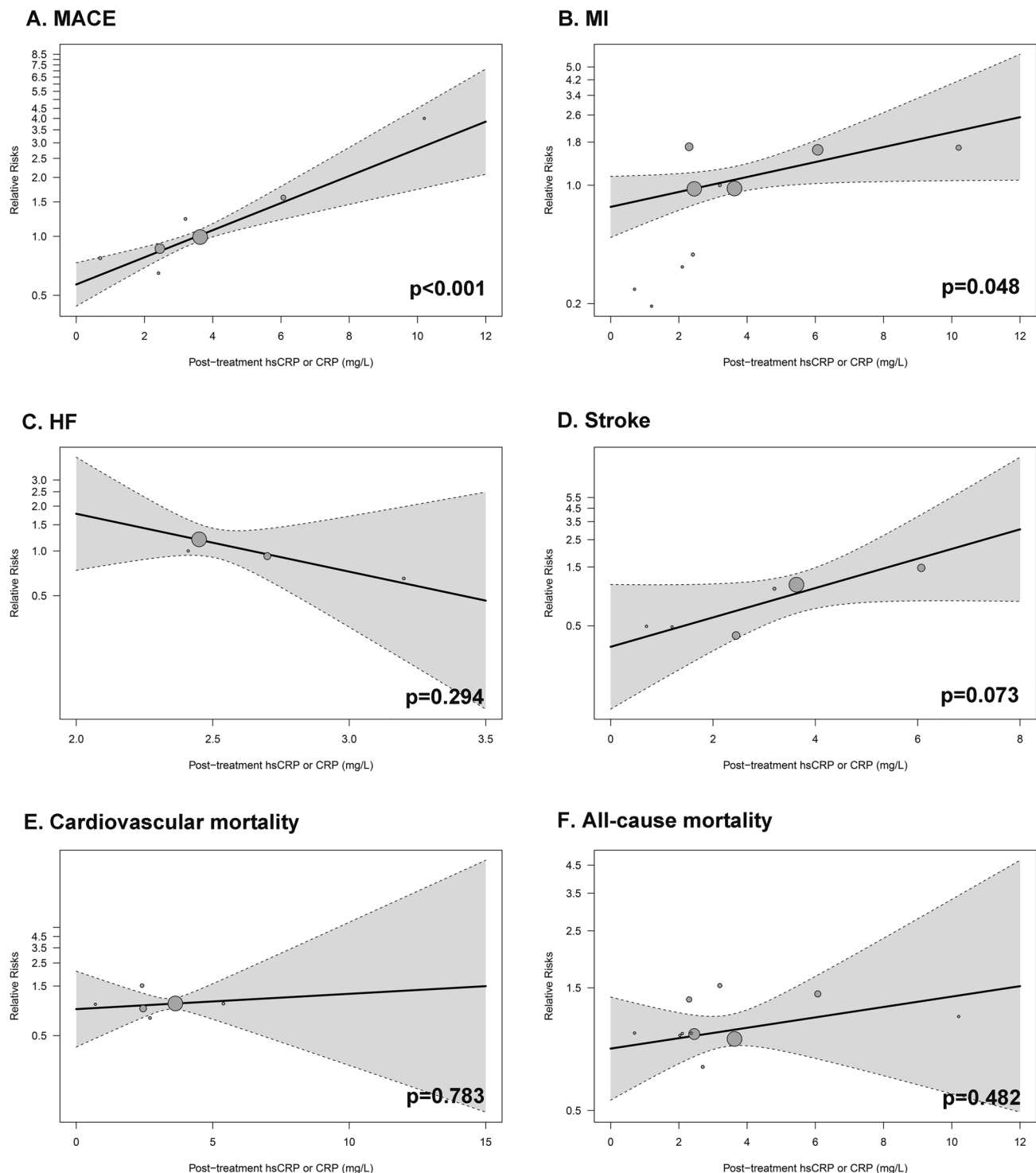


Fig. 8 Bubble plots of post-treatment hsCRP or CRP levels and relative risks of MACE (**A**), MI (**B**), HF (**C**), stroke (**D**), cardiovascular mortality (**E**), and all-cause mortality (**F**). The meta-regression line

is in black, with the shaded area indicating 95% confidence intervals. CRP: C-reactive protein; HF: heart failure; MACE: major adverse cardiovascular events; MI: myocardial infarction

RCTs were small to medium scales, and only preliminary findings could be found. This study analyzed the NLRP3/IL-1 β /IL-6/CRP pathway while extending the study population to coronary artery disease patients. With the inclusion

of multiple large-scale RCTs, more solid results have been arrived.

In this meta-analysis, similar to previous studies [7, 29], the benefits of colchicine are well-proven for MACE, MI,

and coronary revascularization, with homogeneous results across the majority of studies. However, with the results from the landmark CLEAR trial [25], this meta-analysis did not identify any benefits of colchicine in reducing stroke risk, which was contrary to prior studies. Despite the proven benefits, colchicine failed to decrease the risks of either cardiovascular or all-cause mortality. For mortality endpoints, the mortality rates were low, which made it challenging to prove significant benefits. Moreover, it is notable that one of the large-scale RCTs, the Low-Dose Colchicine-2 (LoDoCo2) trial [24], showed that colchicine increased the risks of non-cardiovascular death despite not increasing the risks of cancer or infection. The exact causes of non-cardiovascular mortality were not available. In the future, large-scale RCTs are warranted to find out colchicine's effect on mortality events, and detailed causes of death, especially non-cardiovascular mortality, should be documented.

New insights were gained for the other therapies. As for IL-1 inhibitors, they reduced the risks of revascularization, with a nonsignificant tendency of reduction in MI and HF risks. Despite less evidence being found for IL-1 inhibitors, compared with colchicine, the CANTOS trial showed the breakthrough findings of canakinumab and brought new targets for anti-inflammatory interventions [9]. Notably, there were 3 different doses of canakinumab analyzed in the CANTOS trial, and higher doses were associated with more significant beneficial effects. However, the effects of different doses were combined into one group in this study, which might weaken the protective effects of the higher dosages. Apart from the CANTOS trial, other RCTs evaluated anakinra and goflikcept in small-to-medium-size populations [30–34]. In these trials, the event number for most endpoints was less than 10, which made the relative risks more susceptible to random errors. Therefore, despite conflicting results between the CANTOS trial and other trials, the overall analyses showed that IL-1 inhibitors had potential benefits in ischemic endpoints. Interestingly, all the trials demonstrated a lower incidence of HF events. The CANTOS trial indicated that IL-6 level was in association with HF events [35], further validating the hypothesis that NLRP3/IL-1 β /IL-6/CRP pathway inhibition might be crucial for preventing HF. The CANTOS trial did not compare left ventricular structural changes between the groups, while a pooled analysis of the three Virginia Commonwealth University Anakinra Response Trial (VCU-ART) studies did not find any significant changes in left ventricular ejection fraction, left ventricular end-systolic volume, or left ventricular end-diastolic volume [36]. Therefore, the pathological process behind this beneficial tendency toward HF still needs to be studied.

Interleukin-6, a downstream inflammatory marker of the NLRP3/IL-1 β /IL-6/CRP pathway, is associated with worse

outcomes in MI patients [37]. Tocilizumab binds to the IL-6 receptor and has been hypothesized as a therapy for MI patients. Multiple RCTs analyzed the effects of tocilizumab in coronary artery disease patients [10, 38, 39]. The sample sizes ranged from 28 to 199, and no significant benefits were found for any prespecified efficacy outcomes. Among the trials, Kleveland et al. focused on non-ST-elevation myocardial infarction (NSTEMI) patients [38], while the ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) trial focused on STEMI patients [10]. Both trials showed a decreased inflammatory response in the tocilizumab group. Kleveland found decreased troponin T release, and the ASSAIL-MI trial showed protective myocardial salvage in the tocilizumab group. Additional evidence is necessary to determine whether tocilizumab is effective in clinical outcomes. The third trial, the short-term application of tocilizumab during myocardial infarction (STAT-MI) trial [39], did not reach the target sample size due to interim futility analysis, making the study results less convincing. However, the study reported 2 cases (18.2%) of cardiac tamponade, which suggested a potential impediment to myocardial healing. Therefore, the safety of tocilizumab in MI patients still needs to be tested in large-scale studies.

Methotrexate, one of the disease-modifying antirheumatic drugs (DMARDs), decreased the risks of cardiovascular diseases in rheumatic arthritis patients [40]. It lowered various proinflammatory cytokines, including IL-1 β and IL-6 [41]. However, it was uncertain whether the beneficial effects of methotrexate in autoimmune disease patients applied in the CAD population. After the success of the CANTOS trial, it was hypothesized that methotrexate could lead to lower cardiovascular event risks, and the large-scale Cardiovascular Inflammation Reduction Trial (CIRT) was conducted [11]. Unfortunately, no single RCT of methotrexate has shown any beneficial effects on cardiovascular events, while solid evidence of increasing risks of infection and gastrointestinal adverse effects was found. In CIRT, low-dose methotrexate failed to lower IL-1 β , IL-6, or hsCRP in CAD patients. Moreover, no differences in CRP or hsCRP between the methotrexate group and the control group were found in all the involved RCTs. This suggested that apart from the classical NLRP3/IL-1 β /IL-6/CRP pathway, methotrexate might have other pathway targets as well, such as the adenosine receptor [42]. Therefore, a sensitivity analysis was conducted in this study.

Lastly, meta-regression analysis showed that lower post-treatment hsCRP or CRP was correlated with lower risks of clinical outcomes, including MACE and MI. It has been recognized that hsCRP is a biomarker of residual inflammatory risk and predicts cardiovascular disease events [43]. A secondary analysis of the CANTOS trial revealed that participants who reached hsCRP under 2 mg/L after canakinumab

treatment had reductions in MACE, cardiovascular mortality, and all-cause mortality, whereas no benefits were found in patients with hsCRP over 2 mg/L after anti-inflammatory therapies [44]. Therefore, minimizing residual inflammatory risk is essential, and post-treatment hsCRP might be able to identify those who would benefit from anti-inflammatory treatments. Moreover, the study found that baseline and post-treatment IL-6 were correlated with MACE or MI, suggesting IL-6 as another potential inflammatory marker to select patients for anti-inflammatory therapies.

Limitations

This study has several limitations. MACE was chosen as the primary outcome. However, the definitions of MACE were highly variable in the included RCTs. Moreover, the effects of anti-inflammatory treatments on MACE endpoints were heterogeneous, which might cause potential bias to the primary outcome. Thus, the components of MACE were further evaluated. In most RCTs, clinical outcomes were not the primary endpoints, which might weaken the power of the results. Several RCTs used log-rank tests and Cox proportional-hazards models to conduct the time-to-event analysis [9, 11, 21, 22, 24]. In this meta-analysis, we used the number of patients with targeted events to calculate relative risks instead of hazard ratios. This might lead to bias despite a previous study finding that analyzing time-to-event outcomes as binary is adequate for low event probabilities [45]. The meta-regression analysis of inflammatory markers and clinical outcomes included CRP and hsCRP, whichever the involved study measured. In total, 17 studies reported baseline hsCRP levels, while 6 reported baseline CRP levels. However, hsCRP was more sensitive than CRP [46], which might cause potential bias in the meta-regression analysis. Besides, most study outcomes in the IL-1 inhibitor, methotrexate, and tocilizumab groups were based on less than 5 RCTs. Therefore, the overall results in these groups might be underpowered, and more large-scale studies are still warranted. Lastly, whether methotrexate belongs to anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway is still in debate, and we conducted a sensitivity analysis excluding methotrexate to further testify to the study results.

Conclusions

Anti-inflammatory therapies inhibiting the NLRP3/IL-1 β /IL-6/CRP pathway were beneficial in preventing MI and coronary revascularization in coronary artery disease patients, while no reductions in MACE, stroke, HF,

cardiovascular mortality, or all-cause mortality were found. Colchicine could reduce the risks of MI and coronary revascularization and was the only therapy that reduced the risks of MACE. IL-1 inhibitors could reduce the risks of coronary revascularization, with potential benefits in MI and HF. Anti-inflammatory therapies had satisfying safety profiles overall, with increased risks of infection (methotrexate), gastrointestinal adverse effects (colchicine and methotrexate), and injection site reactions (IL-1 inhibitors).

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00011-025-02058-9>.

Author contribution YZ conceived the study. YP and JJ searched the database. Disagreements were discussed with YZ. YP analyzed the data and wrote the manuscript. JJ, FF, and YZ revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability All data are available upon reasonable request to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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