Safety and Efficacy of Anti-Inflammatory Therapy in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis

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Abstract

Background

The inflammation hypothesis of atherosclerosis has been put forward more than 20 years. Although many animal experiments have suggested that anti-inflammatory therapy can inhibit the atherosclerotic process, the efficacy of anti-inflammatory therapy for patients with coronary artery disease (CAD) is still controversial. Therefore, this study aims to evaluate the safety and efficacy of anti-inflammatory drugs in patients with CAD.

Method

We conducted this systematic review and meta-analysis of randomized controlled trials about the safety and efficacy of anti-inflammatory therapy in patients with CAD. The relevant randomized controlled trials were included by searching PubMed, EMBASE, web of science and Cochrane Library database. The primary outcome was the composite outcome of cardiovascular death, myocardial infarction (MI), and stroke. The secondary outcomes included MI, coronary revascularization, cardiovascular death, all-cause death and stroke. The relative risk (RR) and 95% confidence intervals (CI) for outcome events were calculated by the fixed effects model, and trial sequential analysis was applied to assess the results.

Result

A total of ten randomized controlled trials and 61065 patients with CAD was included (32227 patients receiving the anti-inflammatory therapy, 28937 patients without receiving the anti-inflammatory therapy). Compared with patients without receiving the anti-inflammatory therapy, the anti-inflammatory therapy significantly reduced the incidence of the primary outcome in patients with CAD (RR 0.93, 0.89-0.98, *P*=0.006). In addition, the anti-inflammatory therapy can also reduce the risk of MI (RR 0.90, 0.84-0.96, *P*=0.002) and coronary revascularization (RR 0.74, 0.66-0.84, *P* <0.00001) remarkably. However, there was no significant difference in the incidence of cardiovascular death (RR 0.93, 0.85-1.02, *P*=0.12), all-cause death (RR 1.00, 0.93-1.06, *P*=0.88) and stroke (RR 0.94, 0.83-1.07, *P*=0.36) between two groups.

Conclusions

The anti-inflammatory therapy can reduce the incidence of primary outcome in patients with CAD, especially the risk of MI and coronary revascularization (Registered by PROSPERO, CRD 42020220315).

Background

Chronic low-grade inflammation plays an important role in the occurrence and development of atherosclerosis. However, the atherosclerosis is the pathological basis of coronary artery disease (CAD), which can further increase the risk of cardiovascular events, including death, myocardial infarction (MI), stroke and even cardiac arrest. Despite the use of traditional medicines and revascularization, the persistent cardiovascular risk of patient emphasizes the need for new treatment strategies [1].

Based on the central role of inflammatory process in patients with CAD, targeted anti-inflammatory therapy seems to be a promising strategy to reduce residual cardiovascular risk [2]. In fact, the anti-inflammatory effects of statins have been noticed in the early 21st century [3], and it could bring clinical benefit for patients with evidence of vascular inflammation [4–5]. In addition, the positive effect of Colchicine on patients with cardiovascular events was first reported in 2007 [6]. Subsequently, a large number of randomized trials explored the role of colchicine as an anti-inflammatory drug in patients with CAD [7–10], which suggests that low-dose Colchicine anti-inflammatory therapy has certain benefit for patients with CAD. In addition, the CANTOS trial proved that Canakinumab can reduce major cardiovascular adverse events by 15%, which provides the proof of principle for targeting pro-inflammatory cytokine pathways [11]. Meanwhile, Varespladib and Darapladib are effective drugs to reduce the levels of secretory phospholipase A_2 ($sPLA_2$) and Lipoprotein phospholipase A_2 ($Lp\text{-}PLA_2$), respectively. They are associated with active oxidized low density lipoprotein particles, leading to atherosclerosis and plaque rupture [12–13]. However, three large-scale trials of lipoprotein-coupled phospholipase A_2 inhibitors did not prove the cardiovascular benefits of anti-inflammatory therapy [14–16], but VISTA-16 trial shows that Varespladib therapy increased the risk of myocardial infraction [14]. Finally, the anti-inflammatory therapy is not recommended by the guidelines in patients with CAD.

Therefore, whether the anti-inflammatory drugs can further reduce cardiovascular risk on the basis of standard drug therapy is still controversial. This systematic review and meta-analysis aimed to analyze the safety and effectiveness of the anti-inflammatory therapy in patients with CAD. The results showed that the anti-inflammatory therapy is effective for patients with CAD, especially for the anti-inflammatory drugs that target the central interleukin-6 (IL-6) inflammatory signaling pathway.

Methods

Data Source and Quality Assessment

This systematic review and meta-analysis of randomized controlled trials was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline [17]. PubMed, web of science, EMBASE and Cochrane Library database as well as other sources were searched from

inception to 15, November 2020. The keywords were as follows: “Anti-Inflammation, Atherosclerosis, interleukin, Phospholipase A2, Methotrexate, Canakinumab, Varapladib, Darapladib, Colchicine, Coronary artery disease, Acute coronary syndrome, myocardial infarction”. There were no language restrictions for retrieval. An update reminder for PubMed was created to keep up with the latest research. The search strategy is shown (Supplementary Table 1). The inclusion criteria of this study: (a) randomized controlled trial involving patients with CAD treated with anti-inflammatory drugs; (b) follow-up for at least six month; (c) availability of complete clinical and outcome data. The study exclusion criteria included non-randomized controlled trial and anti-inflammatory drugs used in patients with myocarditis, autoimmune disease and other non-coronary artery diseases. In this meta-analysis, two investigators (Ying Niu and Nan Bai) independently screened all titles and abstracts, full-text articles of relevant trials, and then evaluated the eligibility of the trials following the inclusion and exclusion criteria. The disagreement was discussed to resolve by a third party (Ying Ma, Peng-yu Zhong and Yao-sheng Shang). The risk of bias for each trial was assessed by the Cochrane tool of collaboration, and the quality of evidence for each outcome was evaluated by the Grades of Recommendations Assessment Development and Evaluation (GRADE) [18-19]. The clinical protocols of all included trials were approved by local ethics and informed consent of patients was obtained. The meta-analysis protocol was registered in PROSPERO (CRD 42020220315).

Data Acquisition and Clinical Outcomes

The two investigators jointly extracted the characteristics of each trial included, the baseline characteristics of the patients, and the outcome of each trial. The differences should be settled by third party through consultation (Zhi-lu Wang). The primary outcome was the composite outcome of cardiovascular death, MI, and stroke. The secondary outcomes included MI, coronary revascularization, cardiovascular death, all-cause death and stroke. The MI, coronary revascularization, cardiovascular death, all-cause death and stroke was defined based on the definition used in the clinical studies included.

Statistical Analysis

ReviewManager Version 5.4 software (The Nordic Cochrane Center, Copenhagen, Denmark) and Stata version 14.0 software were used for all data analysis. The statistical significance was set to $P < 0.05$. The risk ratio (RR) and 95% confidence interval (CI) of each outcome were calculated by the fixed-effects model and Mantel-Haenszel method, and Pearson chi-square test and Higgins I^2 test were employed to assess the heterogeneity of Cochrane Q statistics. When there was significant heterogeneity ($I^2 \geq 50\%$) among studies, the random effect model was performed, and the sources of heterogeneity was found through sensitivity analysis and subgroup analysis. Meanwhile, the sensitivity analysis was used to test the impact of any individual study results on the overall results. The Cochrane Collaborative Institutional Risk Bias Assessment Tool was applied to appraise the quality of each randomized controlled trial [18]. In addition, the Egger’s and Bgger’s test, as well as visual inspection of funnel plots were employed to assess publication bias and calculate the sample size according to Trial Sequential Analysis version 0.9.5.10 software (Copenhagen Trial Unit, CTU) and evaluate the results.

Results

Search Results and Study Characteristics

A total of 1059 articles were retrieved from medical databases, American College of Cardiology 2014 and European Society of Cardiology 2020. Among them, 1018 articles were identified by reading the title and abstract, and 41 articles were identified by reading the full text. Finally, ten randomized controlled trials involving 61065 patients with CAD (32227 patients receiving anti-inflammatory therapy, and 28937 patients without receiving anti-inflammatory therapy) are included (Figure 1). The baseline characteristics of the included trials are shown (Table 1). Four trials involved Colchicine [7,9,21-22]. Three of them were Colchicine compared with placebo, and one was compared with those without Colchicine. In addition, four trials compared PLA_2 inhibitors [14-16,23], of which three compared Varespladib, one compared Darapladib. The remaining two trials compared low-dose Canakinumab and Methotrexate with placebo, respectively [11,24]. Meanwhile, seven of them included patients with acute coronary syndrome and three recruited patients with chronic coronary syndrome. The duration of follow-up in the trials ranged from six months to four years. The baseline characteristics of patients are shown (Table 2).

The Primary Outcome

Six trials reported data of the primary outcome, the result shows that the incidence of primary outcome in patients receiving anti-inflammatory therapy was significantly lower than that in patients without receiving anti-inflammatory therapy (10.66% vs 10.86%, RR 0.93, 0. 89-0.98, $P = 0.006$, $I^2 = 34\%$, $P_{\text{Heterogeneity}} = 0.18$) (Figure 2).

The Secondary Outcomes

Nine randomized controlled trials provided the risk of MI in patients with CAD. Compared with patients without receiving anti-inflammatory therapy, the anti-inflammatory therapy can significantly reduce the risk of MI (5.66% vs 6.03%, RR 0.90, 0.84-0.96, $P = 0.002$, $I^2 = 32\%$, $P_{heterogeneity} = 0.17$) (Figure 3A). Meanwhile, the meta-analysis of seven trials displays that the incidence of coronary revascularization in patients receiving anti-inflammatory therapy was significantly lower than that in patients without receiving anti-inflammatory therapy (1.94% vs.2.66%, RR 0.74, 0.66-0.84, $P < 0.00001$, $I^2 = 34\%$, $P_{heterogeneity} = 0.17$) (Figure 3B). Furthermore, the risk of cardiovascular death was reported in eight trials. The result demonstrates that the risk of cardiovascular death was similar between the two groups (3.05% vs 3.06%, RR 0.93, 0.85-1.02, $P = 0.12$, $I^2 = 0\%$, $P_{heterogeneity} = 0.72$) (Figure 3C). In addition, there is no significant difference both in the risk of all-cause death (6.13% vs 5.61%, RR 1.00, 0.93-1.06, $P = 0.88$, $I^2 = 3\%$, $P_{heterogeneity} = 0.40$) (Figure 3D) and stroke (1.58% vs 1.56%, RR 0.94, 0.83-1.07, $P=0.36$, $I^2=28\%$, $P_{heterogeneity}=0.19$) (Figure 3E) between the two groups.

Subgroup Analysis

According to the Mendelian randomization data, anti-inflammatory drugs were divided into two categories [25]. Six of ten trials use anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway and the other four apply PLA_2 inhibitors (Figure 4). The subgroup analysis shows that compared with patients without receiving anti-inflammatory therapy, the anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway can reduce the risk of the primary outcome (10.7% vs 10.1%, RR 0.88 0.81-0.96, $P = 0.003$, I^2 =34%, $P_{heterogeneity}$ =0.21). Instead, there was no significant difference in the risk of the primary outcome between the two groups in patients with PLA_2 inhibitors therapy (10.2% vs 9.8%, RR 0.96 0.90-1.03, $P = 0.24$, I^2 =0%, $P_{heterogeneity}$ =0.44). However, there are not differences in the risk of the primary outcome between the two groups (I^2 = 59.8%, $P_{interaction}$ = 0.11) (Figure 4A). In addition, there is a significantly difference in the risk of MI between the two groups in the IL-6 pathway subgroup (5.6% vs 5.9%, RR 0.85, 0.77-0.94, P = 0.002, I^2 =38%, $P_{heterogeneity}$ = 0.16), but not in the PLA_2 inhibitors subgroup (6.0% vs 6.0%, RR 0.94, 0.86-1.02, $P = 0.15$, I^2 =0%, $P_{heterogeneity}$ = 0.42), and the differences between the two groups is not statistically significant (I^2 = 51.5%, $P_{interaction}$ = 0.15) (Figure 4B). The result of subgroup analysis shows that the drugs targeting the central IL-6 inflammatory signaling pathway can also reduce the incidence of coronary revascularization (2.1% vs 3.3%, RR 0.69, 0.59-0.80, $P < 0.00001$, I^2 =32%, $P_{heterogeneity}$ = 0.21). However, there is no significant difference between the two groups in patients with PLA_2 inhibitors therapy (1.6% vs 1.8%, RR 0.89, 0.71-1.13, $P=0.35$, I^2 =0%, $P_{heterogeneity}$ = 0.94), and the differences between the two groups is not statistically significant (I^2 = 70.1%, $P_{interaction}$ =0.07) (Figure 4C). Besides, there is no significant difference in the risk of cardiovascular death, all-cause death and stroke between the two groups from the use of the two anti-inflammatory drugs (Figure 4D-F). Finally, subgroup analysis of the targeting the central IL-6 inflammatory signaling pathway shows that Colchicine was more effective than Methotrexate and Canakinumab in reducing ischemic stroke (0.4% vs 0.8%, RR 0.46, 0.28-0.74, $P = 0.002$, I^2 =0%, $P_{heterogeneity}$ = 0.39), and the differences between the two groups is statistically significant (I^2 = 85.3%, $P_{interaction}$ =0.009) (Figure 5A), and both groups can significantly reduce the risk of the primary outcome, MI and coronary revascularization, but there are not statistically significant (Figure 5B-D).

Trial Sequential Analysis, Assessment of quality and Publication Bias

Trial sequential analysis is performed for each outcome (Supplementary Figure 1). The curve of the primary outcome, MI and coronary revascularization exceeded the traditional boundary and the trial sequential analysis boundary. However, the curve of cardiovascular death and stroke did not reach the traditional boundary and expected sample size. The sample size of All-cause death was too small, and the graph generation failed. The risk of bias assessment shows that there was a high risk of bias in performance and attrition (Supplementary Figure 2). The funnel plot shows that the distribution was symmetrical for each outcome, which means no publication bias (Supplementary Figure 3A-F). The P value of other outcomes are more than 0.05 except for all-cause death (Egger's = 0.04) and stroke (Egger's = 0.023) (Supplementary Figure 4A-F). The quality of GRADE evidence for the primary outcome, MI, coronary revascularization and stroke is moderate, while the quality of evidence for cardiovascular death and all-cause death outcomes is high (Supplementary Table 2).

Discussion

The findings of this meta-analysis indicate that the anti-inflammatory therapy was associated with lower incidence of the primary outcome, MI and coronary revascularization in patients with CAD. However, there is no significant difference in the risk of cardiovascular death, all-cause death and stroke. In addition, the GRADE evidence levels of outcome for cardiovascular death and all-cause death are high, other outcomes are moderate according to the certainty of the evidence.

All studies in this meta-analysis were randomized controlled trials. Among them, nine of the ten trials included were double-blind studies, and the rate of follow up loss was higher in the three trials. Therefore, there was a low risk of bias in selection, detection, and reporting, but a high risk of bias in performance and attrition. The risk of MI and coronary revascularization was reduced by 15% and 31% in the group targeting the central IL-6 inflammatory signaling pathway, respectively, based on the subsequent subgroup analysis. According to the results of trial sequential analysis, no more randomized controlled trials are needed to prove these results. The funnel plot and the Begg's and Egger's tests showed no publication bias. In addition, the small size of patients in the three trials may be the main reason for publication bias.

A recently published meta-analysis of the efficacy of Colchicine demonstrated that compared with the placebo group, the Colchicine reduced the risk of major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) [26]. The subgroup analysis of this meta-analysis also showed that Colchicine can significantly reduce the incidence of the composite outcome of myocardial infarction, stroke, coronary revascularization or cardiovascular death in patients with acute coronary syndrome. Meanwhile, Colchicine was not associated with an increased risk for hospitalization, infection risk of common pneumonia, gastrointestinal disorders and new cancer. In fact, Colchicine is a drug targeting the central IL-6 inflammatory signaling pathway. The subgroup analysis of this study showed that the anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway can reduce the incidence of the composite outcome of the cardiovascular death, MI and stroke, as well as the risk of MI and coronary revascularization. Further subgroup analysis of inflammatory signaling pathway targeting the central IL-6 showed that all three drugs can reduce the risk of the primary outcome, MI, coronary revascularization and stroke. However, Colchicine can reduce the incidence of ischemic stroke to more extent.

The results of this meta-analysis need to be applied with caution. Firstly, according to the subgroup analysis of this study, drugs targeting the central IL-6 inflammatory signaling pathway, such as Colchicine, Canakinumab and Methotrexate, can reduce cardiovascular events in patients with CAD, while PLA_2 inhibitors cannot. Therefore, it is recommended that patients with CAD should use the anti-inflammatory drugs that inhibit central IL-6 inflammatory signaling pathway. Meanwhile, Colchicine is easy to obtain and economical compared with Canakinumab and Methotrexate, which improves compliance of patients. Secondly, patients with chronic coronary syndrome and acute coronary syndrome were included in this study. The results support the effectiveness of anti-inflammatory therapy in these cohorts. Finally, other factors need to be considered in clinical practice. The characteristics of race are essential factor influencing the effect of anti-inflammatory therapy. The trial by Irena tepanikova et al. showed that the concentrations of inflammation markers in black

patients was higher than that in white patients, which led to that black patients may benefit more from anti-inflammatory therapy [26]. However, it should be noted that white people are the majority of participants in this study, and the efficacy of anti-inflammatory therapy in non-white patient needs further study.

Limitations

This systematic review and meta-analysis of randomized clinical trials may have some limitations. Firstly, the subjects of this trial included patients with acute coronary syndrome and chronic coronary syndrome, which may be the cause of heterogeneity. Secondly, the three small sample size trials had a low incidence of positive events and a wide confidence interval, which reduced the quality of evidence [7, 22, 23]. Finally, the lost follow-up rate of three trials was more than 20%, which reduced the reliability of the analysis results [16, 23, 24].

Conclusions

On the basis of standard medical therapy, the anti-inflammatory therapy can significantly reduce the incidence of MI and coronary revascularization in patients with CAD, which proves that anti-inflammatory drugs have clinical benefit. In addition, compared with other anti-inflammatory drugs mentioned in this article, Colchicine is more effective in reducing the risk of ischemic stroke. Furthermore, Colchicine is cheap and available all over the world, which enables patients to have better compliance.

Declarations

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Authors' contributions

Ying Niu: Study design, Data collection, Data analysis, Manuscript. Nan Bai: Data collection, Data analysis, Validation. Ying Ma: Data collection, Validation. Peng-yu Zhong: Data collection, Validation. Yao-sheng Shang: Data collection, Validation. Zhi-Lu Wang: Scientific revision of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests regarding the publication of this article.

References

1. Golia E, Limongelli G, Natale F, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep. 2014 Sep. doi: 10.1007/s11883-014-0435-z.
2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002 Mar 5. doi: 10.1161/hc0902.104353.
3. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA. 2001 Jul 4. doi: 10.1001/jama.286.1.64.
4. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20. doi: 10.1056/NEJMoa0807646.
5. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009 Apr 4. doi: 10.1016/S0140-6736(09)60447-5.
6. Crittenden DB, Lehmann RA, Schneck L, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol. 2012 Jul. doi: 10.3899/jrheum.111533.
7. Nidorf SM, Eikelboom JW, Budgeon CA, et al. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013 Jan 29. doi: 10.1016/j.jacc.2012.10.027.

8. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019 Dec 26. doi: 10.1056/NEJMoa1912388.
9. Nidorf SM, Fiolet ATL, Mosterd A. et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020 Nov 5. doi: 10.1056/NEJMoa2021372.
10. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome: A CT Coronary Angiography Study. JACC Cardiovasc Imaging. 2018 Feb. doi: 10.1016/j.jcmg.2017.08.013.
11. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 Sep 21. doi: 10.1056/NEJMoa1707914.
12. Rosenson RS. Phospholipase A2 inhibition and atherosclerotic vascular disease: prospects for targeting secretory and lipoprotein-associated phospholipase A2 enzymes. Curr Opin Lipidol. 2010 Dec. doi: 10.1097/MOL.0b013e32833eb581.
13. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010 May 1. doi: 10.1016/S0140-6736(10)60319-4.
14. Nicholls SJ, Kastelein JJ, Schwartz GG, et al. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. JAMA. 2014 Jan 15. doi: 10.1001/jama.2013.282836.
15. White HD, Held C, Stewart R, et al. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med. 2014 May 1. doi: 10.1056/NEJMoa1315878.
16. O'Donoghue ML, Braunwald E, White HD, et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA. 2014 Sep 10. doi: 10.1001/jama.2014.11061.
17. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2. doi: 10.1136/bmj.g7647.
18. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18. doi: 10.1136/bmj.d5928.
19. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26. doi: 10.1136/bmj.39489.470347.AD.
20. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019 Dec 26. doi: 10.1056/NEJMoa1912388.
21. Tong DC, Quinn S, Nasis A, et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. Circulation. 2020 Nov 17. doi: 10.1161/CIRCULATIONAHA.120.050771.
22. Rosenson RS, Hislop C, Elliott M, et al. Effects of varespladib methyl on biomarkers and major cardiovascular events in acute coronary syndrome patients. J Am Coll Cardiol. 2010 Sep 28. doi: 10.1016/j.jacc.2010.06.015.
23. Ridker PM, Everett BM, Pradhan A, et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med. 2019 Feb 21. doi: 10.1056/NEJMoa1809798.
24. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J. 2014 Jul 14. doi: 10.1093/eurheartj/ehu203.
25. Fiolet ATL, Opstal TSJ, Mosterd A, et al. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. Eur Heart J. 2021 Mar 26. doi: 10.1093/eurheartj/ehab115.
26. Stepanikova I, Bateman LB, Oates GR. Systemic Inflammation in Midlife: Race, Socioeconomic Status, and Perceived Discrimination. Am J Prev Med. 2017 Jan. doi: 10.1016/j.amepre.2016.09.026

Tables

Table 1
Baseline characteristics of the included trials.

Study	Publication year	Type	Study cohort	Study totol size	Randomization			Follow up(month)
LoDoCo[7]	2013	RCT	CCS	532	Colchicine (n=282)	VS	non-colchicine (n=250)	24
LoDoCo2[9]	2020	RCT	CCS	5522	Colchicine (n=2762)	VS	placebo (n=2760)	28.6
CIRT[23]	2018	RCT	MI and MS OR T2MD	4786	Methotrexa (n=2391)	VS	placebo (n=2395)	27.6
COLCOT[20]	2019	RCT	MI	4745	Colchicine (n=2366)	VS	placebo (n=237)	22.6
CANTOS[11]	2017	RCT	MI	10061	Canakinumab(n=6717)	VS	placebo (n=3344)	48
STABILITY[15]	2014	RCT	CCS	15828	Darapladib (n=7924)	VS	placebo (n=7904)	44.4
SOLID-TIMI[16]	2014	RCT	ACS	13026	Darapladib (n=6504)	VS	placebo (n=6522)	30
VISTA-16[14]	2013	RCT	ACS	5145	Varespladib (n=2572)	VS	placebo (n=2673)	6
COPS[21]	2020	RCT	ACS	795	Colchicine (n=396)	VS	placebo (n=399)	12
FRANCIS[22]	2010	RCT	ACS	625	Varespladib (n=313)	VS	placebo (n=311)	6

Abbreviations: RCT, randomized controlled trial; CCS, chronic coronary syndrome; MI, myocardial infarction; MS, metabolic syndrome; T2MD, Type 2 diabetes mellitus; ACS, acute coronary syndrome.

Table 2
Baseline characteristics of the patients included.

	LoDoCO[7]	LoDoCO2[9]	CIRT[23]	COLCOT[20]	CANTOS[11]	STABILITY[15]	SOLID-TIMI[16]	VISTA-16[14]	COPS[21]	FR
Patients (n)	282/250	2762/2760	2391/2395	2366/2379	3344/6717	7924/7904	6504/6522	2572/2573	396/399	31
Age(mean)	66.0/67.0	65.8/65.9	65.6 /66.0	60.6/60.5	61.1/61.1	65.0/65.0	64.0/64.0	61.0/60.7	59.7/60.0	58
Male (%)	89.0/88.8	83.5/85.9	80.7/81.8	80.1/81.6	74.1/74.4	81.5/81.0	74.6/74.5	73.1/74.4	81.3/77.7	73
Smokers(%)	4.0/6.0	11.5/12.0	11.2/11.3	29.9/29.8	22.9/43.1	19.8/21.0	18.9/19.1	33.2/33.4	32.3/37.3	23
Hypertension(%)	/	51.4/50.3	90.0 /90.6	50.1/52.0	79.1/79.9	/	73.7/73.0	74.3/76.8	50.8/49.9	86
Diabetes(%)	33.0/28.0	17.8/18.7	33.0/34.4	19.5/20.9	39.9/40.1	33.6/34.0	35.0/34.1	31.1/31.2	18.9/19.8	26
Previous ACS(%)	23/24	84.1/84.6	60.7/60.9	15.6/16.7	87.9/88.2	59.1/69.1	31.0/31.2	29.6/30.2	59/59	/
Previous PCI(%)	60/55	76.0/75.3	58.4/59.3	16.6/17.0	65.6/67.3	50.3/50.3	23.6/24.2	18.6/17.7	51/50	/
Previous CABG(%)	22/16	11.5/14.2	42.2/43.1	2.9/3.4	14.0/14.0	33.4/32.8	/	7.1/6.3	15/19	/
Medication use — no. (%)										
Antiplatelet	94.0/93.0	90.0/80.6	87.1/85.8	98.6/98.9	/	/	96.4/96.5	91.3/91.8	99.0/98.0	92
ACEI or ARB	60.0/55.0	72.2/71.2	72.6/72.0	/	/	/	82.7/82.4	82.5/82.3	88.0/86.0	85
Beta-blocker	71.0/62.0	61.3/62.9	78.2/79.5	89.4/88.3	/	/	87.2/87.4	83.9/82.9	81.0/85.0	84
Statins	94.0/96.0	93.9/94.0	86.1/85.7	98.9/99.1	/	/	94.3/94.9	98.7/99.0	98.0/99.0	/
Median lipid levels (IQR) — mg/dl										
LDL cholesterol	/	/	68.0/68.0	/	82.8/82.0	/	74.9/74.9	105.1/105.0	/	61
HDL cholesterol	/	/	41.0/41.0	/	44.5/43.7	44.4/44.8	/	43.2/43.3	/	/

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI, angiotensin-converting e inhibitors; ARB, angiotensin receptor blockers; IQR, inter quartile range.

Figures

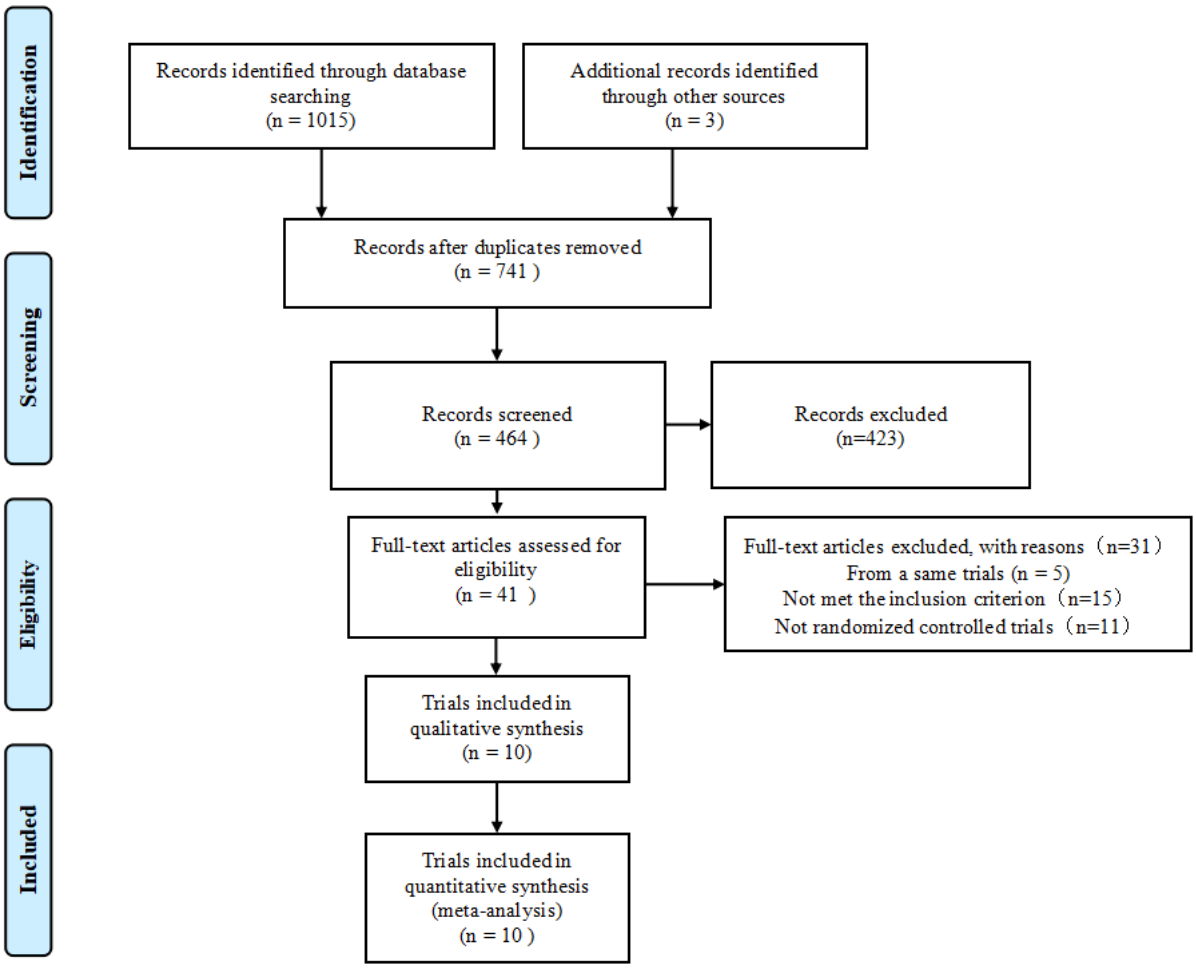

Figure 1

A total of 1059 articles were retrieved from medical databases, American College of Cardiology 2014 and European Society of Cardiology 2020. Among them, 1018 articles were identified by reading the title and abstract, and 41 articles were identified by reading the full text. Finally, ten randomized controlled trials involving 61065 patients with CAD (32227 patients receiving anti-inflammatory therapy, and 28937 patients without receiving anti-inflammatory therapy) are included (Figure 1).

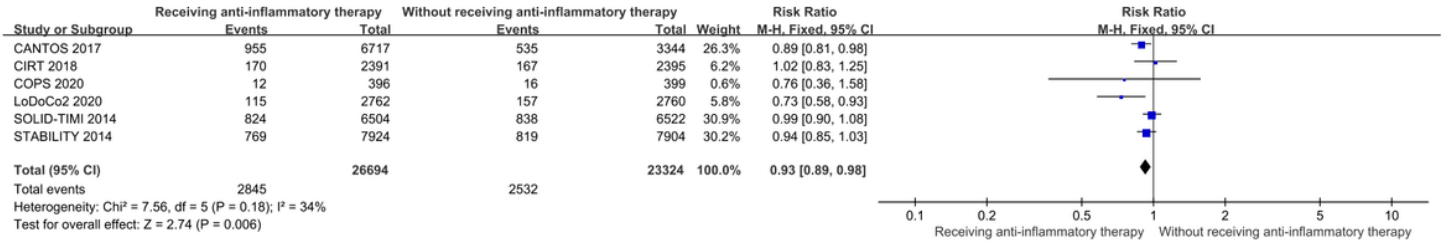

Figure 2

Six trials reported data of the primary outcome, the result shows that the incidence of primary outcome in patients receiving anti-inflammatory therapy was significantly lower than that in patients without receiving anti-inflammatory therapy (10.66% vs 10.86%, RR 0.93, 0. 89-0.98, P = 0.006, I2 = 34%, P Heterogeneity = 0.18) (Figure 2).

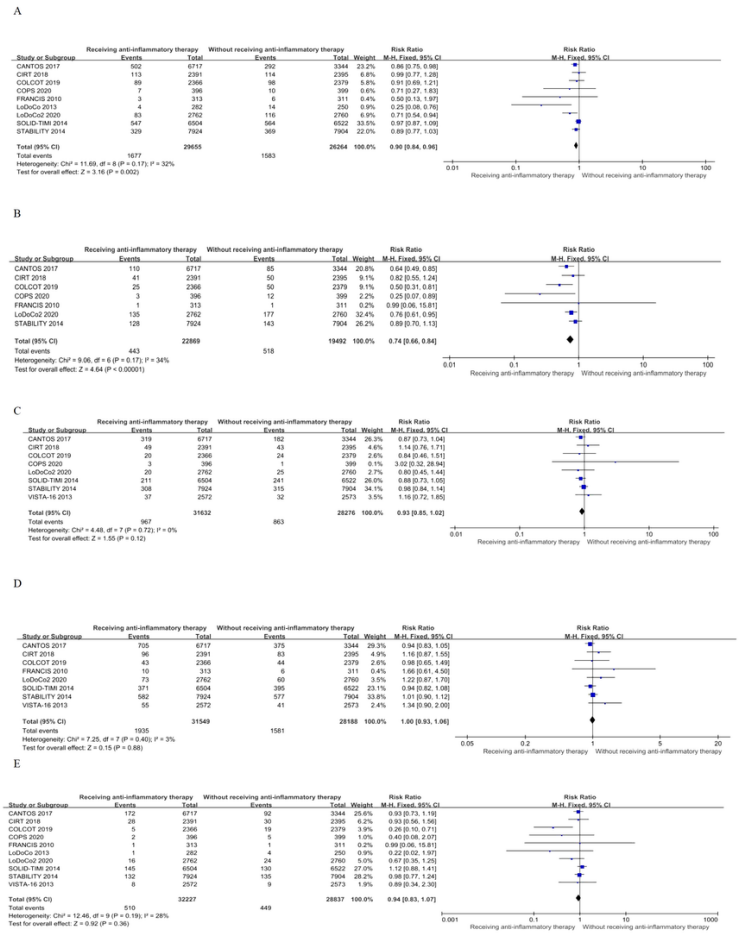

Figure 3

Nine randomized controlled trials provided the risk of MI in patients with CAD. Compared with patients without receiving anti-inflammatory therapy, the anti-inflammatory therapy can significantly reduce the risk of MI (5.66% vs 6.03%, RR 0.90, 0.84-0.96, P = 0.002, I2 = 32%, P heterogeneity = 0.17) (Figure 3A). Meanwhile, the meta-analysis of seven trials displays that the incidence of coronary revascularization in patients receiving anti-inflammatory therapy was significantly lower than that in patients without receiving anti-inflammatory therapy (1.94% vs.2.66%, RR 0.74, 0.66-0.84, P < 0.00001, I2 = 34%, Pheterogeneity = 0.17) (Figure 3B). Furthermore, the risk of cardiovascular death was reported in eight trials. The result demonstrates that the risk of cardiovascular death was similar between the two groups (3.05% vs 3.06%, RR 0.93, 0.85-1.02, P= 0.12, I2 = 0%, Pheterogeneity = 0.72) (Figure 3C). In addition, there is no significant difference both in the risk of all-cause death (6.13% vs 5.61%, RR 1.00, 0.93-1.06, P = 0.88, I2 = 3%, Pheterogeneity = 0.40) (Figure 3D) and stroke (1.58% vs 1.56%, RR 0.94, 0.83-1.07, P=0.36, I2=28%, Pheterogeneity=0.19) (Figure 3E) between the two groups.

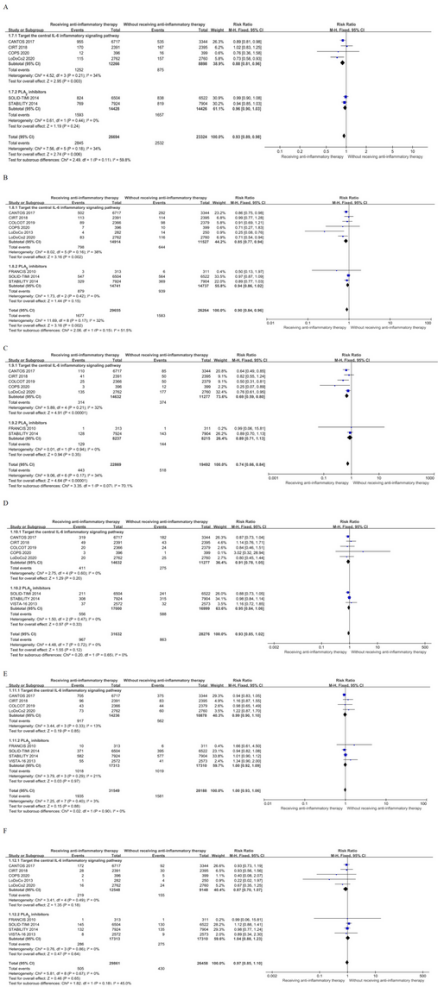

Figure 4

The subgroup analysis shows that compared with patients without receiving anti-inflammatory therapy, the anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway can reduce the risk of the primary outcome (10.7% vs 10.1%, RR 0.88 0.81-0.96, P = 0.003, I2 =34%, Pheterogeneity =0.21). Instead, there was no significant difference in the risk of the primary outcome between the two groups in patients with PLA2 inhibitors therapy (10.2% vs 9.8%, RR 0.96 0.90-1.03, P = 0.24, I2 =0%, Pheterogeneity =0.44). However, there are not differences in the risk of the primary outcome between the two groups (I2 = 59.8%, P interaction = 0.11) (Figure 4A). In addition, there is a significantly difference in the risk of MI between the two groups in the IL-6 pathway subgroup (5.6% vs 5.9%, RR 0.85, 0.77-0.94, P = 0.002, I2 =38%, Pheterogeneity = 0.16), but not in the PLA2 inhibitors subgroup (6.0% vs 6.0%, RR 0.94, 0.86-1.02, P = 0.15, I2 =0%, Pheterogeneity = 0.42), and the differences between the two groups is not statistically significant (I2 = 51.5%, P interaction = 0.15) (Figure 4B). The result of subgroup analysis shows that the drugs targeting the central IL-6 inflammatory signaling pathway can also reduce the incidence of coronary revascularization (2.1% vs 3.3%, RR 0.69, 0.59-0.80, P < 0.00001, I2 =32%, Pheterogeneity = 0.21). However, there is no significant difference between the two groups in patients with PLA2 inhibitors therapy (1.6% vs 1.8%, RR 0.89, 0.71-1.13, P=0.35, I2 =0%, Pheterogeneity = 0.94), and the differences between the two groups is not statistically significant (I2 = 70.1%, P interaction =0.07) (Figure 4C). Besides, there is no significant difference in the risk of cardiovascular death, all-cause death and stroke between the two groups from the use of the two anti-inflammatory drugs (Figure 4D-F).

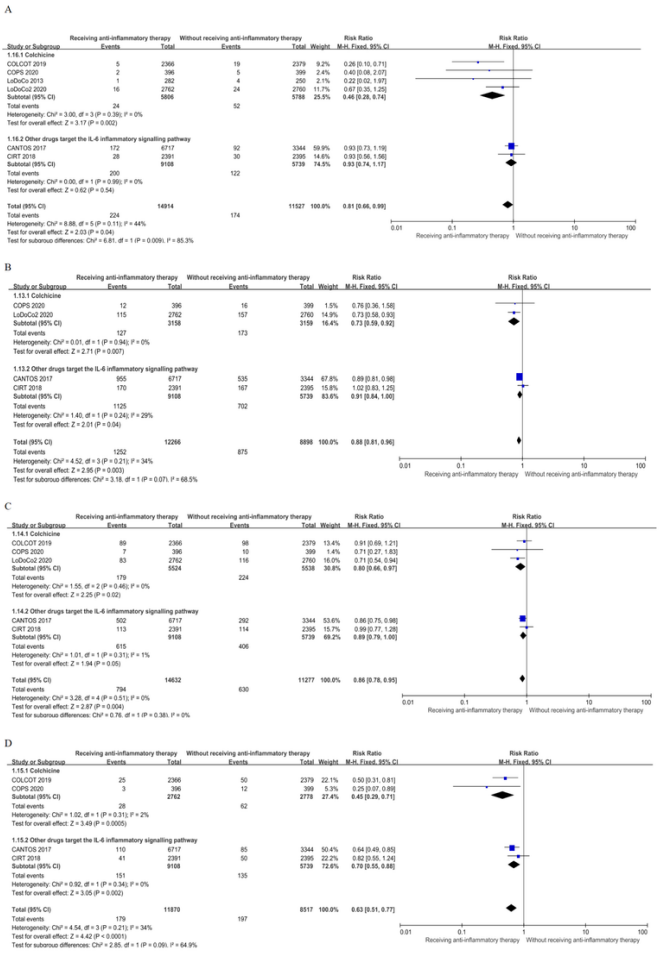

Figure 5

Finally, subgroup analysis of the targeting the central IL-6 inflammatory signaling pathway shows that Colchicine was more effective than Methotrexate and Canakinumab in reducing ischemic stroke (0.4% vs 0.8%, RR 0.46, 0.28-0.74, P = 0.002, I2 =0%, Pheterogeneity = 0.39), and the differences between the two groups is statistically significant (I2 = 85.3%, P interaction =0.009) (Figure 5A), and both groups can significantly reduce the risk of the primary outcome, MI and coronary revascularization, but there are not statistically significant (Figure 5B-D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementary.docx