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Safety and efficacy of anti-inflammatory therapy in patients with coronary artery disease: a systematic review and meta-analysis

Ying Niu¹⁺, Nan Bai¹⁺, Ying Ma¹⁺, Peng-Yu Zhong¹⁺, Yao-Sheng Shang¹⁺ and Zhi-Lu Wang^{2*}

Abstract

Background: The inflammation hypothesis of atherosclerosis has been put forward for 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 by searching Pub-Med, EMBASE, web of science, and Cochrane Library database. The primary outcome was a composite outcome of cardiovascular death, myocardial infarction (MI), or stroke. The secondary outcomes included individual 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 60.782 patients with CAD was included. Compared with patients receiving placebo, anti-inflammatory therapy significantly reduced the incidence of the primary outcome in patients with CAD (RR 0.93, 0.89–0.98, P = 0.007). 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 0.94, 0.86–1.02, P = 0.14), all-cause death (RR 1.00, 0.94–1.07, P=0.98) and stroke (RR 0.96, 0.85–1.09, P=0.51) between two groups.

Conclusions: Anti-inflammatory therapy can reduce the incidence of the primary outcome in patients with CAD, especially the risk of MI and coronary revascularization. However, anti-inflammatory therapy increases the risk of infection. (Registered by PROSPERO, CRD 420212291032).

Keywords: Coronary artery disease, Anti-inflammatory therapy, Meta-analysis

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Background

Chronic low-grade inflammation plays an important role in the development of atherosclerosis. However, 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 have significantly improved the net clinical benifits, we still need

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Based on the central role of the inflammatory process in patients with CAD, targeted anti-inflammatory therapy seems to be a promising strategy to reduce residual cardiovascular risk [2]. The anti-inflammatory effects of statins have been noticed in the early twenty-first century [3], and it could bring clinical benefits 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, many 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 benefits 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 proinflammatory cytokine pathways [11]. Meanwhile, varespladib and darapladib are effective drugs to reduce the levels of secretory phospholipase A2 (sPLA2) and Lipoprotein phospholipase A₂ (Lp-PLA₂), 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 A2 inhibitors did not prove the cardiovascular benefits of anti-inflammatory therapy [14–16], but the VISTA-16 trial shows that varespladib therapy increased the risk of myocardial infarction [14]. Finally, anti-inflammatory therapy is not recommended by the guidelines in patients with CAD.

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

Method

Data sources and quality assessment

This systematic review and meta-analysis of randomized controlled trials were reported 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 1, January 2022. The searches strategy of PubMed as follows: "Anti-Inflammation" and "Coronary artery disease" combined text and MeSH terms. We also manually searched references for relevant meta-analyses. There were no language restrictions for retrieval. An update reminder for Pub-Med was created to keep up with the latest research. The detial search strategies of all database were shown (Additional file 2: Table S1). The inclusion criteria of this study: (a) adults aged \geq 18 years; (b) randomized controlled trial comparing anti-inflammatory drugs to placebo in patients with CAD; (c) follow-up for at least 6 months; (d) sample size > 200 patients; (e) availability of complete clinical outcome data. The exclusion criteria included: (a) nonsteroidal anti-inflammatory drugs or drugs that inhibit complement C5; (b) patients with coronary artery bypass grafting received anti-inflammatory therapy; (c) anti-inflammatory drugs for patients with myocarditis, pericarditis, 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 420212291032).

Data acquisition and clinical outcomes

Two investigators jointly extracted the characteristics of each trial including the baseline characteristics of patients, and the outcome of each trial. Differences should be settled by a third party through consultation (Zhi-lu Wang). The primary outcome was a composite outcome of cardiovascular death, MI, or stroke. The secondary outcomes included MI, coronary revascularization, cardiovascular death, all-cause death, and stroke. Meanwhile, we performed any serious adverse event, infection, and any cancer as a safety outcome. Coronary revascularization is defined as urgent or ischemiadriven coronary revascularization, MI included nonfatal myocardial infarction, ST-segment elevation myocardial infarction, or non-ST-segment elevation myocardial infarction. In addition, based on the definition of clinical studies' cardiovascular death, all-cause death, stroke, and the safety outcomes of any serious adverse event, infection, and any cancer were defined.

Statistical analysis

ReviewManager 5.4 (The Nordic Cochrane Center, Copenhagen, Denmark) and Stata version 14.0 were

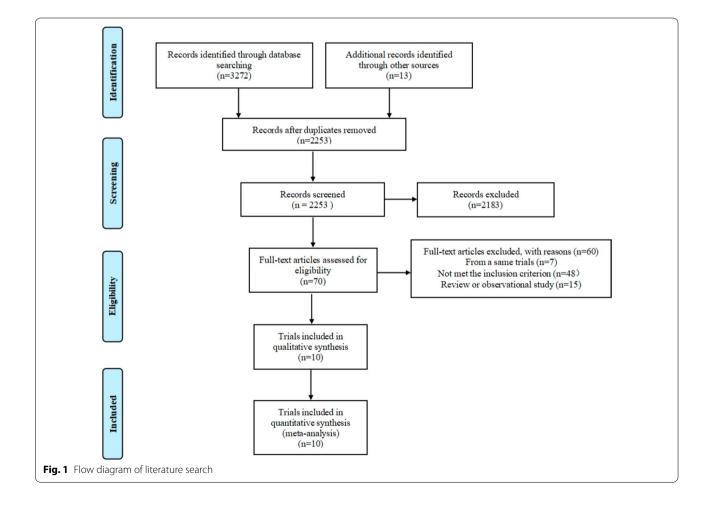
used for all data analysis. The statistical significance was set to P < 0.05. The risk ratio (RR) and 95% confidence interval (CI) of each outcome were calculated by fixed-effects model and Mantel-Haenszel method, and Pearson chi-square test and Higgins I^2 test were employed to assess the heterogeneity of Cochrane Q statistics. When there was significant heterogeneity (P-value of chi-square test was < 0.10) among studies, I^2 was used to judge the degree of heterogeneity, and the sources of heterogeneity were found through sensitivity analysis and subgroup analysis. Meanwhile, the sensitivity analysis was used to test the impacts of any individual study for 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 Bgge's tests were used to assess the publication bias. Meanwhile, Trial Sequential Analysis version 0.9.5.10 software (Copenhagen Trial Unit, CTU) was conducted to assess the results and conculate the sample size.

Results

Search results and study characteristics

A total of 2077 articles were retrieved from medical databases, and 8 articles were from references of relevant reviews. Among them, 1335 articles were identified by reading the title and abstract, and 70 articles were identified by reading the full text. Finally, ten randomized controlled trials involving 60,782 patients with CAD (32,065 patients received the anti-inflammatory therapy and 26,674 patients received placebo) are included (Fig. 1).

The characteristics of the included trials were shown (Table 1). Four trials involved colchicine [7-9, 20]. In addition, four trials compared PLA₂ inhibitors [14-16, 21], of which three compared varespladib, one compared darapladib. The remaining two trials compared low-dose canakinumab and methotrexate with placebo, respectively [11, 22]. Meanwhile, eight 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 6 to 48 months.



Study	Publication year	Туре	Study cohort	Study totol size	Randomization			Follow up (month)
Mehdi Akrami et al. [7]	2021	RCT	ACS	249	Colchicine (n = 120)	VS	Placebo (n = 129)	6
LoDoCo2 [9]	2020	RCT	CCS	5522	Colchicine (n = 2762)	VS	Placebo (n = 2760)	28.6
CIRT [22]	2018	RCT	MI and MS OR T2MD	4786	Methotrexa (n = 2391)	VS	Placebo (n = 2395)	27.6
COLCOT [8]	2019	RCT	MI	4745	Colchicine (n = 2366)	VS	placebo (n = 237)	22.6
CANTOS [11]	2017	RCT	MI	10,061	Canakinumab (n=6717)	VS	placebo (n = 3344)	48
STABILITY [15]	2014	RCT	CCS	15,828	Darapladib (n = 7924)	VS	placebo (n = 7904)	44.4
SOLID-TIMI [16]	2014	RCT	ACS	13,026	Darapladib (n = 6504)	VS	placebo (n = 6522)	30
VISTA-16 [14]	2013	RCT	ACS	5145	Varespladib (n $=$ 2572)	VS	placebo (n = 2673)	6
COPS [20]	2020	RCT	ACS	795	Colchicine (n = 396)	VS	placebo (n = 399)	12
FRANCIS [21]	2010	RCT	ACS	625	Varespladib (n = 313)	VS	placebo (n = 311)	6

 Table 1
 Baseline characteristics of the included trials

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

The baseline characteristics of patients were shown (Table 2). The average age of patients in the antiinflammatory therapy group was approximately 61.8 years old and about 78.8% patients were male. In addition, 28.3% patients had diabetes, 67.6% patients accompanied hypertension, 41.8% patients suffered from PCI, and 25.5% patients had a history of current smoking. Meanwhile, the average age of patients was approximately 62.0 years old in the placebo group, of which 78.8% patients were male. Furthermore, 25.9% patients had diabetes, 68.8% patients had hypertension, 42.3% patients received PCI, and 27.8% patients had a history of current smoking approximately. Finally, in terms of optimal medical therapy, 94.6% and 95.7% the patients in the anti-inflammatory therapy group received antiplatelet and statin, respectively. Meanwhile, the antiplatelet and statin therapy rates in the placebo group were 93.5% and 95.9%. In addition, in the anti-inflammatory therapy group, 82.9% of the patients used ACEI or ARB, and 83.1% patients used beta-blockers, while 81.9% ACEI or ARB, and 83.8% beta-blockers was used in patients with receiving placebo. The duration of followed-up was 6 to 48 months.

The primary outcome

Five trials reported data of the primary outcome, the result showed that the incidence of primary outcome in patients receiving anti-inflammatory therapy was lower than that in patients receiving placebo (10.8% vs 11.0%, RR 0.93, 0. 89–0.98, P = 0.007, $I^2 = 45\%$, $P_{hetero-geneity} = 0.12$) (Fig. 2).

The secondary outcomes

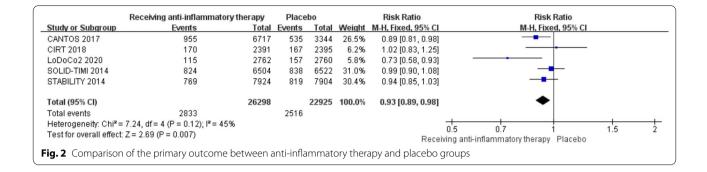
The forest map of secondary outcomes was performed (Fig. 3). Nine randomized controlled trials provided the risk of MI in patients with CAD. Compared with patients received placebo, the anti-inflammatory therapy can significantly reduced the risk of MI (5.79% vs 6.19%, RR 0.90, 0.84–0.96, P = 0.002, $I^2 = 26\%$, $P_{heterogeneity} = 0.21$). Meanwhile, the meta-analysis of seven trials displayed that the incidence of coronary revascularization in patients receiving anti-inflammatory therapy was significantly lower than that in patients receiving placebo (1.94% vs 2.66%, RR 0.74, 0.66–0.84, P < 0.00001, $I^2 = 34\%$, $P_{heteroge-}$ $_{neity} = 0.17$). Furthermore, the risk of cardiovascular death was reported in eight trials. The result demonstrated that the risk of cardiovascular death was similar between the two groups (3.32% vs 3.34%, RR 0.94, 0.86–1.02, P=0.14, $I^2 = 0\%$, $P_{heterogeneity} = 0.77$). In addition, there is no significant difference both in the risk of all-cause death (RR 1.00, 0.94–1.07, P = 0.98, $I^2 = 25\%$, $P_{heterogeneity} = 0.21$) and stroke (RR 0.96, 0.85–1.09, P=0.51, $I^2 = 30\%$, $P_{heterogene-}$ $_{itv} = 0.18$) between the two groups.

The safety outcomes

Compared placebo group, anti-inflammatory therapy increased the risk of infection in patients of CAD (RR 1.10, 1.03–1.18, P=0.007, $I^2 = 0\%$, $P_{heterogeneity}=0.42$). However, no significant difference in incidence of any serious adverse event (RR 0.98, 0.96–1.00, P=0.10, $I^2 = 0\%$, $P_{heterogeneity}=0.80$) and any cancer (RR 0.98, 0.91–1.05, P=0.56, $I^2 = 0\%$, $P_{heterogeneity}=0.78$) were observed in anti-inflammatory therapy group (Fig. 4).

Menal Akrami et al. [7]										
Patients (n) 12	120/129	2762/2760	2391/2395	2366/2379	3344/6717	7924/7904	6504/6522	2572/2573	396/399	313/311
Age (mean) 56	56.9/56.9	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	58.5/59.6
Male (%) 86	86.0/87.0	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	73.5/75.9
Smokers (%) 52	52.0/49.0	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	23.3/21.9
Hypertension (%) 52	52.0/59.0	51.4/50.3	9.06/0.06	50.1/52.0	79.1/79.9	I	73.7/73.0	74.3/76.8	50.8/49.9	86.6/88.1
Diabetes (%) 27	27.0/32.0	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	26.8/28.0
Previous ACS (%) –		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	59.0/59.0	I
Previous PCI (%) 16	16.0/20.0	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	51.0/50.0	1
Previous CABG (%) 4.(4.0/3.0	11.5/14.2	42.2/43.1	2.9/3.4	14.0/14.0	33.4/32.8	I	7.1/6.3	15.0/19.0	I
Medication use — no. (%)	(
Antiplatelet 10	100.0/100.0	90.0/80.6	87.1/85.8	98.6/98.9	91.1/92.1	100.0/100.0	96.4/96.5	91.3/91.8	99.0/98.0	92.7/91.0
ACEI or ARB 1C	100.0/100.0	72.2/71.2	72.6/72.0	/	79.6/79.8	Ι	82.7/82.4	82.5/82.3	88.0/86.0	85.9/81.7
Beta-blocker 10	100.0/100.0	61.3/62.9	78.2/79.5	89.4/88.3	I	Ι	87.2/87.4	83.9/82.9	81.0/85.0	84.0/84.6
Statins 10	1 00.0/1 00.0	93.9/94.0	86.1/85.7	98.9/99.1	91.1/91.1	1 00.0/1 00.0	94.3/94.9	98.7/99.0	98.0/99.0	I
Median lipid levels (IQR) — mg/dl	() — mg/dl									
LDL cholesterol –		I	68.0/68.0	Ι	82.8/82.0	Ι	74.9/74.9	105.1/105.0	I	61.0/60.3
HDL cholesterol –		I	41.0/41.0	I	44.5/43.7	44.4/44.8	I	43.2/43.3	I	I

the patients included	
Baseline characteristics of	
Table 2	



Subgroup analysis

We performed subgroup analysis according to the population and type of drugs to explore the most benefit populations and anti-inflammatory drugs in patients with CAD. The subgroup analysis showed that compared with placebo, anti-inflammatory therapy can reduce the risk of coronary revascularization in patients with acute coronary syndrome (RR 0.63, 0.52-0.78, P < 0.0001, $I^2 = 14\%$, $P_{heterogeneity} = 0.33$) and chronic coronary syndrome (RR 0.82, 0.70–0.96, P = 0.02, $I^2 =$ 0%, $P_{heterogeneity} = 0.33$). Meanwhile, there was a significant difference between the two subgroups ($I^2 = 74.1\%$, $P_{interaction} = 0.05$). However, there was no significant difference between the two subgroups in MI ($l^2 = 7.5\%$, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %, $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), $P_{interaction} = 0.3$), cardiovascular death ($I^2 = 0$ %), $P_{interaction} = 0.3$), $P_{interaction} = 0.3$ $_{tion} = 0.61$), all-cause death ($I^2 = 0\%$, $P_{interaction} = 0.56$) and stroke ($I^2 = 0$ %, $P_{interaction} = 0.95$) (Fig. 5). In addition, another subgroup analysis was performed by the different type of anti-inflammatory drugs. According to the Mendelian randomization data, anti-inflammatory drugs were divided into two categories [23]. Six of ten trials used anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway and the other four apply PLA₂ inhibitors. The results showed that compared with placebo, the anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway can reduce the risk of coronary revascularization (RR 0.69 0.59–0.80, P < 0.00001, $I^2 = 32\%$, $P_{heterogene-}$ $_{ity} = 0.21$). While, there was no significant difference in PLA_2 inhibitors subgroup (RR 0.89 0.71–1.13, P = 0.35, $I^2 = 0\%$, $P_{heterogeneity} = 0.94$), and the differences between two groups were statistically significant ($l^2 = 70.1\%$, $P_{interaction} = 0.07$). However, there is no significant difference in the risk of primary outcome ($I^2 = 57.2\%$, $P_{interaction} = 0.13$), MI ($I^2 = 49.7\%$, $P_{interaction} = 0.16$), cardiovascular death ($I^2 = 0\%$, $P_{interaction} = 0.71$) and all-cause death ($I^2 = 0\%$, $P_{interaction} = 0.94$) between the two groups (Fig. 6). Further subgroup analysis of colchicine and other drugs targeting the central IL-6 inflammatory signaling pathway showed that colchicine can significantly reduce the incidence of ischemic stroke (RR 0.48 0.29–0.79, P=0.004, $I^2=20\%$, $P_{het-erogeneity}=0.29$) compared with other drugs. There was statistically significant observed in two subgroups ($I^2=82.5\%$, $P_{interaction}=0.02$) (Additional file 1: Figure S1).

Trial sequential analysis, assessment of quality and publication bias

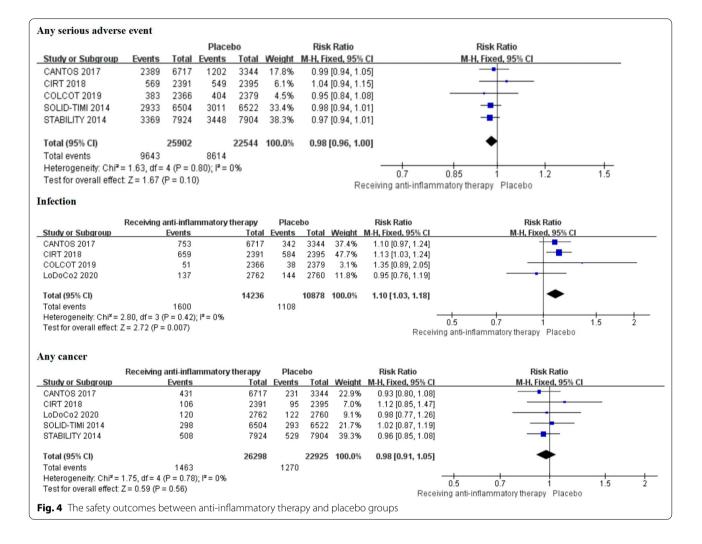
Trial sequential analysis was performed for each outcome (Additional file 1: Figure S2). The curve of the primary outcome, MI, and infection exceeded the traditional boundary and the trial sequential analysis boundary. Meanwhile, coronary revascularization exceeded the traditional boundary. However, the curve of cardiovascular death and any serious adverse event did not reach the traditional boundary and the trial sequential analysis boundary. The graph of all-cause death, stroke, and any cancer was generation failed. The risk of bias assessment showed that there was a high risk of bias in attrition (Additional file 1: Figure S3). The quality of GRADE evidence for the primary outcome, coronary revascularization, cardiovascular death, and all-cause death were moderate, while the quality of evidence for MI and stroke outcomes were low (Additional file 2: Table S2). The Egger's and Begg's tests were used to assess the publication bias (Additional file 2: Table S3). The P-value of other outcomes were more than 0.05 except for MI (Egger's = 0.04), cardiovascular death (Egger's = 0.004) and stroke (Egger's = 0.045). Furthermore, we used the trim and fill method to assessed the impact of publication bias on MI, cardiovascular death, and stroke (Additional file 1: Figure S4).

Discussion

The findings of this meta-analysis indicate that antiinflammatory therapy was associated with a lower incidence of primary outcome, MI, and coronary revascularization in patients with CAD. However, there is no significant difference in the risk of cardiovascular

МІ

Study or Subgroup	Receiving anti-inflammato Events	Tot	al Even			Risk Ratio ight M-H, Fixed, 95	
CANTOS 2017	502	671				.7% 0.86 [0.75, 0	
CIRT 2018	113	239		14 23		.6% 0.99 [0.77, 1	
COLCOT 2019	89	236		38 23		.7% 0.91 [0.69, 1	
COPS 2020	7					0.6% 0.64 [0.25, 1	
FRANCIS 2010	3 83	31 276	13 82 11			0.50 (0.13, 1 0.8% 0.71 (0.54, 0	
LoDoCo2 2020 Mehdi Akram et al 2021	83	2/0				i.8% 0.71 [0.54, 0 i.6% 0.20 [0.04, 0	
SOLID-TIMI 2014	547	650				.9% 0.97 [0.87, 1	
STABILITY 2014	361	79:		05 79		.7% 0.89 [0.77, 1	
					12 10		
Total (95% CI) Total events	1707	2949	93 161		43 100	0.0% 0.90 [0.84, 0	.96]
	8, df = 8 (P = 0.21); I ² = 26%		10				+ + + + + + + + + + + + + + + + + + + +
Test for overall effect: Z = 3						F	0.1 0.2 0.5 1 2 5 Receiving anti-inflammatory therapy Placebo
Coronawy royacoularizati							
Coronary revascularizatio	eiving anti-inflammatory the	ramu	Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total Ev			Veight I	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CANTOS 2017	110	6717			20.8%	0.64 [0.49, 0.85]	
CIRT 2018	41	2391			9.1%	0.82 [0.55, 1.24]	
COLCOT 2019	25 3	2366 396		2379 399	9.1% 2.2%	0.50 [0.31, 0.81]	
COPS 2020 FRANCIS 2010	3	396	12		0.2%	0.25 [0.07, 0.89] 0.99 [0.06, 15.81]	
LoDoCo2 2020	135	2762			32.4%	0.76 [0.61, 0.95]	
STABILITY 2014	128	7924			26.2%	0.89 [0.70, 1.13]	
Total (95% CI)		22869	10	492 1	00.0%	0.74 [0.66, 0.84]	•
Total events	443	22009	518	-132 T	00.070	0.14 [0.00, 0.04]	•
Heterogeneity: Chi ² = 9.06,						-	
Test for overall effect: Z = 4	.64 (P < 0.00001)					Receivi	ng anti-inflammatory therapy Placebo
Cardiovascular death							
I	Receiving anti-inflammatory		Place			Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events			M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CANTOS 2017 CIRT 2018	319 49	6717 2391	182	3344	24.0%		
COLCOT 2019	49	2391 2366	43 24	2395 2379	4.2% 2.4%		
COPS 2020	3	396	24	399	0.1%		
LoDoCo2 2020	20	2762	25	2760	2.5%		
Mehdi Akram et al 2021	4	120	2	129	0.2%		
SOLID-TIMI 2014	243	6504	268	6522	26.5%		1
STABILITY 2014 VISTA-16 2013	359 37	7924 2572	373 32	7904 2573	36.9% 3.2%		
1011102010			01			1.10 [0.12, 1.00]	
Total (95% CI)		31752		28405	100.0%	0.94 [0.86, 1.02]	•
Total events Heterogeneity: Chi ² = 4.93,	1054 df = 8 (P = 0.77): P = 0%		950				
Test for overall effect: Z = 1.						Recei	0.1 0.2 0.5 1 2 5 10 ving anti-inflammatory therapy Placebo
All-cause death							
	Receiving anti-inflammatory	therany	Place	ho		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total		M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CANTOS 2017	705	6717	375	3344	29.3%		•
CIRT 2018	96 43	2391 2366	83 44	2395 2379	4.9% 2.6%		
COLCOT 2019 COPS 2020	43	2366	44	2379	2.6%		······
FRANCIS 2010	10	396	6	399	0.1%		
LoDoCo2 2020	73	2762	60	2760	3.5%		+
Mehdi Akram et al 2021	4	120	2	129	0.1%		
SOLID-TIMI 2014	371	6504	395	6522	23.1%		1
STABILITY 2014 VISTA-16 2013	582 55	7924 2572	577 41	7904 2573	33.8% 2.4%		T
VIG17410 2013	22	2572	41	2073	∠.4%	1.34 [0.90, 2.00]	
Total (95% CI)		32065		28716	100.0%	1.00 [0.94, 1.07]	•
Total events	1947		1584				
Heterogeneity: Chi ² = 11.98 Test for overall effect: Z = 0.							0.1 0.2 0.5 1 2 5 10
reaction over all effect. Z = 0.	02 (1 = 0.30)					Recei	ving anti-inflammatory therapy Placebo
Stroke							
	ceiving anti-inflammatory th		Placeb			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total I				M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
CANTOS 2017 CIRT 2018	172 28	6717 2391	92 30	3344 2395	24.9% 6.1%		
COLCOT 2019	28	2391	30 19	2395	3.8%		
COPS 2020	2	396	6	399	1.2%		
FRANCIS 2010	1	313	1	311	0.2%		
LoDoCo2 2020	16	2762	24	2760	4.9%		
SOLID-TIMI 2014	145	6504	130	6522	26.3%	1.12 [0.88, 1.41]	- -
STABILITY 2014	154	7924	152	7904	30.8%		
VISTA-16 2013	8	2572	9	2573	1.8%		
Total (95% CI) Total events	501	31945		28587	100.0 %	0.96 [0.85, 1.09]	•
Lotal events	531 0.46-0.00-0.400-18-000		463				
							0.1 0.2 0.5 1 2 5 10
Heterogeneity: Chi ² = 11.4							
						Rece	iving anti-inflammatory therapy Placebo



death, all-cause death, and stroke. However, antiinflammatory therapy increased the risk of infection in patients with CAD. Meanwhile, there did not significantly increase the incidence of any serious adverse events and any cancer. In addition, the GRADE evidence levels of outcome for primary outcome, coronary revascularization, infection are moderate, and MI is low according to the certainty of the evidence.

Based on the subgroup analysis, the risk of coronary revascularization was reduced by 31% in the group of targeting the central IL-6 inflammatory signaling pathway and decreased by 37% in patients with acute coronary syndrome group. According to the results of the trial sequential analysis, false-positive results were obtained for coronary revascularization, therefore, more randomized controlled trials are needed to prove these results. In addition, anti-inflammatory therapy can also reduce the incidence of the primary outcome and MI in patients with CAD and the conclusion was reliable. The Egger's test showed that MI, cardiovascular death, and stroke have publication bias. While the funnel plot has no obvious asymmetry after the trim and fill method.

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 and was not associated with an increased risk for hospitalization, infection risk of common pneumonia, gastrointestinal disorders, and new cancer [24]. Colch icine is a drug targeting the central IL-6 inflammatory signaling pathway. The subgroup analysis of our study showed that the anti-inflammatory drugs targeting the central IL-6 inflammatory signaling pathway can reduce the incidence of primary outcome (composite outcome of cardiovascular death, MI, or stroke), as well as the risk of MI and coronary revascularization. Further subgroup analysis of the drugs targeting the central IL-6 inflammatory signaling pathways showed that colchicine can reduce the incidence of isc hemic

								Coronary 1	revascularizatio					
Study or Subgroup	Receiving anti-inflammatory Events		Placebo Events Tot	tal Weight	Risk Ratio M-H, Fixed, 95% Cl		k Ratio xed, 95% Cl	Study or Subgroup	Receiving anti-inflammatory t Events		Placebo	al WoinH	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
1.18.1 ACS								1.19.1 ACS	Lycins	Total Et		a weight	m-n, nxeu, 55% ci	m-n, rixed, 35% Cl
CANTOS 2017 CIRT 2018	502 113	6717 2391	292 334 114 239	44 22.7%	0.86 (0.75, 0.98) 0.99 (0.77, 1.28)	-	►	CANTOS 2017	110	6717		44 20.8%	0.64 [0.49, 0.85]	
COLCOT 2019	89	2366	98 237		0.91 [0.69, 1.21]	_	+	CIRT 2018 COLCOT 2019	41 25	2391 2366	50 23 50 23		0.82 [0.55, 1.24] 0.50 [0.31, 0.81]	
COPS 2020	7	396	11 39		0.64 [0.25, 1.64]			COPS 2020	25	396		9 9.1% 99 2.2%	0.25 [0.07, 0.89]	
RANCIS 2010 Aehdi Akram et al 2021	3	313 120	6 31 11 12		0.50 [0.13, 1.97]			FRANCIS 2010	ů 1	313			0.99 [0.06, 15.81]	
SOLID-TIMI 2014	547	6504		23 0.0%	0.97 [0.87, 1.09]		+	Subtotal (95% CI)		12183		28 41.4%	0.63 [0.52, 0.78]	◆
Subtotal (95% CI)		18807	1547		0.92 [0.85, 0.99]	•	◆	Total events	180		198			
Fotal events	1263 85, df= 6 (P = 0.25); I ² = 24%		1096					Heterogeneity: Chi* = Test for overall effect :	4.64, df = 4 (P = 0.33); P = 14%					
Heterogeneity: Chi# = 7.8 Test for overall effect: Z =								restion overall effect.	2 = 4.40 (F < 0.0001)					
								1.19.2 CCS						
1.18.2 CCS oDoCo2 2020	83	2762	110 27	60 6.8%	0.71 (0.54, 0.94)		_	LoDoCo2 2020	135	2762		60 32.4%		
STABILITY 2014	361	7924		04 23.7%	0.89 [0.77, 1.02]	-	•	STABILITY 2014 Subtotal (95% CI)	128	7924 10686	143 79 106		0.89 [0.70, 1.13] 0.82 [0.70, 0.96]	▲
Subtotal (95% CI)		10686	1066	64 30.4%	0.85 [0.75, 0.96]	4	►	Total events	263	10000	320	N 3000 A	0.02 [0.10, 0.00]	•
Total events	444 91, df = 1 (P = 0.17); I ² = 48%		521					Heterogeneity: Chi ² =	0.93, df = 1 (P = 0.33); I ^e = 0%					
Test for overall effect: Z =	= 2.57 (P = 0.01)							Test for overall effect.	Z = 2.42 (P = 0.02)					
								Total (95% CI)		22869	10.4	100.0%	0.74 [0.66, 0.84]	•
Fotal (95% CI) Fotal events	1707	29493	2614 1617	43 100.0%	0.90 [0.84, 0.96]	•	•	Total events	443	22003	518	52 100.0 M	0.74 [0.00, 0.04]	•
	1707 1.88, df = 8 (P = 0.21); P = 26%		1617		-		+ + + + + + + + + + + + + + + + + + + +		9.06, df = 6 (P = 0.17); I ² = 34%		510			0,1 0,2 0,5 1 2 5 10
Test for overall effect Z =	= 3.17 (P = 0.002)				Receivi	0.2 0.5 ng anti-inflammatory therap	1 2 5 w Placeho	Test for overall effect.	Z = 4.64 (P < 0.00001)				Receiv	0.1 0.2 0.5 1 2 5 10 ing anti-inflammatory therapy Placebo
Test for subaroup differe	ences: Chi ^a = 1.08. df = 1 (P = 0.	30), I ² = 7.5%	,			ing and initial initial of y drot up	1 10000	Test for subaroup diffe	erences: Chi ² = 3.86. df = 1 (P =	0.05). I ² = 74	.1%			
Cardiovascu	ılar death							All-cause d	eath					
	Receiving anti-inflammatory	therappe	Placebo		Risk Ratio	Dia	k Ratio		Receiving anti-inflammator	therapy	Placebo		Risk Ratio	Risk Ratio
tudy or Subgroup	Events			tal Weight	M-H, Fixed, 95% CI		xed, 95% Cl	Study or Subgroup	Events	y therapy Total			t M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.20.1 ACS								1.21.1 ACS						
CANTOS 2017 CIRT 2018	319 49	6717 2391	182 334 43 239	44 26.2%	0.87 [0.73, 1.04]	-	<u>† </u>	CANTOS 2017 CIRT 2018	705 96	6717 2391		3344 29.39 2395 4.99		
CIRT 2018 COLCOT 2019	49	2391 2366	43 235 24 237		1.14 (0.76, 1.71) 0.84 (0.46, 1.51)			COLCOT 2019	43	2391	44	2395 4.97		
COPS 2020	3	396	1 39		3.02 [0.32, 28.94]			→ COPS 2020	8	396	1	399 0.19	6 8.06 [1.01, 64.15]	
Mehdi Akram et al 2021	4	120	2 12		2.15 [0.40, 11.53]			 FRANCIS 2010 Mehdi Akram et al 202 	10 1 4	313 120	6	311 0.49 129 0.19		
SOLID-TIMI 2014 //STA-16 2013	211	6504 2572	241 652 32 257	22 26.0% 73 3.5%	0.88 (0.73, 1.05) 1.16 (0.72, 1.85)	_		SOLID-TIMI 2014	371	6504	395	522 23.19		
Subtotal (95% CI)	57	21066		41 63.2%	0.92 [0.82, 1.03]			VISTA-16 2013	55	2572		2573 2.49		
Total events	643		525					Subtotal (95% CI) Total events	1292	21379	947 1	62.7	0.99 [0.91, 1.07]	Ţ
Heterogeneity: Chi ² = 4.7 Test for overall effect: Z =	73, df = 6 (P = 0.58); P = 0%							Heterogeneity: Chi ^a = 1	0.45, df = 7 (P = 0.16); I ² = 33%		047			
rest for overall effect. Z =	= 1.49 (P = 0.14)							Test for overall effect 2	(= 0.35 (P = 0.73)					
1.20.2 CCS								1.21.2 CCS						
LoDoCo2 2020 STABILITY 2014	20 308	2762 7924	25 276 315 790	60 2.7% 04 34.1%	0.80 [0.45, 1.44] 0.98 [0.84, 1.14]		-	LoDoCo2 2020	73	2762		2760 3.59		
Subtotal (95% CI)	308	10686	315 /90		0.96 [0.84, 1.14]	-	•	STABILITY 2014 Subtotal (95% CI)	582	7924 10686		7904 33.89 1664 37.31		1
Total events	328		340					Total events	655	10080	637	1004 37.3	1.05 [0.92, 1.14]	Ť
Heterogeneity: Chi ² = 0.4 Test for overall effect: Z =	41, df = 1 (P = 0.52); I ² = 0%							Heterogeneity: Chi ^a = 1	.09, df = 1 (P = 0.30); I ^e = 8%					
rescior overall ellect. 2 =	= 0.50 (P = 0.61)							Test for overall effect 2	(P = 0.63)					
Total (95% CI)		31752	2846	J5 100.0%	0.93 [0.85, 1.02]	•		Total (95% CI)		32065		8716 100.05	6 1.00 [0.94, 1.07]	•
		31/52						Total events	1947 1.98. df = 9 (P = 0.21); P = 25%		1584			
	971	31/52	865				1 1.5 2	Heterogeneity: Chi* = 1 Test for overall effect. 2					_	0.1 0.2 0.5 1 2 5
Heterogeneity: Chi# = 5.4	44, df = 8 (P = 0.71); P = 0%	51752	865			0.5 0.7				FE) 18 - 016			Rece	iving anti-inflammatory therapy Placebo
Heterogeneity: Chi ² = 5.4 Test for overall effect: Z =	44, df = 8 (P = 0.71); P = 0%		865		Receivi	0.5 0.7 ng anti-inflammatory therap	.,	Test for subaroup diffe	rences: Chi ² = 0.35. df = 1 (P = 0					
Heterogeneity: Chi² = 5.4 Fest for overall effect: Z = Fest for subaroup differe	44, df = 8 (P = 0.71); P = 0% = 1.49 (P = 0.14)		865		Receivi		,	Test for subaroup diffe	rences: Chi ² = 0.35. df = 1 (P = 0	50). F = 036				
Heterogeneity: Chi ^a = 5.4 Fest for overall effect: Z = Fest for subaroux differe troke	44, df = 8 (P = 0.71); ² = 0% = 1.49 (P = 0.14) ences: Chi ² = 0.26. df = 1 (P = 0.1	61). I ^a = 0%				ng anti-inflammatory therap		Test for subaroup diffe	rences: Chi# = 0.35. df = 1 (P = 0	50). F = 0%				
Heterogeneity: Chi ^z = 5.4 Fest for overall effect Z = Fest for subaroux differe Stroke	44, df = 8 (P = 0.71); ² = 0% = 1.49 (P = 0.14) ences: Chi ² = 0.26. df = 1 (P = 0.) Receiving anti-inflammatory th	61). I ^a = 0% ierapy	Placebo		Risk Ratio	ng anti-inflammatory therap Risk	k Ratio	Test for subaroup diffe	rences: Chi ² = 0.35. df = 1 (P = 0	50). F = 0%				
Heterogeneity: Chi ^z = 5.4 Test for overall effect. Z = Test for subaroux differe Stroke Study or Subgroup	44, df = 8 (P = 0.71); ² = 0% = 1.49 (P = 0.14) ences: Chi ² = 0.26. df = 1 (P = 0.1	61). I ^a = 0% ierapy	Placebo	_Weight_M		ng anti-inflammatory therap Risk		Test for subaroup diffe	rences: Chi ² = 0.35. df = 1 (P = 0	50), 1 = 0 %				
leterogeneity. Chi ² = 5.4 rest for overall effect Z = rest for subarous differe troke F Study or Subgroup CANTOS 2017	44, df = 8 (P = 0.71); P = 0% = 1.49 (P = 0.14) ences: ChiP = 0.26, df = 1 (P = 0.) Receiving anti-inflammatory th Events 172	61). P= 0% Herapy Total Ev 6717	Placebo rents Total 92 3344	24.9%	Risk Ratio M-H, Fixed, 95% Cl 0.93 (0.73, 1.19)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroup diffe	rences: Chi ^a = 0.35. df= 1 (P = 0	50). 1 = 0 %				
Heterogeneity: Chi ^a = 5.4 Fest for overall effect 2 = Fest for subaroux differe itroke Study or Subgroup L22.1 ACS CANTOS 2017 CIRT 2018	44, df = 8 (P = 0.71), P = 0% = 1.48 (P = 0.14) nnces: ChiP = 0.26. df = 1 (P = 0.) Receiving anti-inflammatory th Events 172 28	61). ² = 0% erapy Total Ev 6717 2391	Placebo rents Total 92 3344 30 2395	24.9% 6.1%	Risk Ratio <u>A.H., Fixed, 95% Cl</u> 0.93 (0.73, 1.19) 0.93 (0.56, 1.56)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroup diffe	rences: Chi ^p = 0.35. df= 1 dP = 0	50.1 - 0%				
Heterogeneity: Chi [#] = 5.4 Fest for overall effect Z = Fest for subaroux differe it roke Study or Subgroup 1.22.1 ACS CANTOS 2017 CIRT 2018 COLCOT 2019	44, df = 8 (P = 0, 71), P = 0% = 1.49 (P = 0, 14) nnces: ChiP = 0.26. df = 1 (P = 0) Receiving anti-inflammatory th Events 172 28 5	61). ² = 0% herapy Total Ev 6717 2391 2366	Placebo ents Total 92 3344 30 2395 19 2379	24.9% 6.1% 3.8%	Risk Ratio A.H. Fixed, 95% CI 0.93 [0.73, 1.19] 0.93 [0.56, 1.56] 0.26 [0.10, 0.71] ←	ng anti-inflammatory therap Risk	k Ratio	Test for suborouo diffe	rences: Chi ^p = 0.35. df= 1 dP = 0	50.1 - 0%				
Heterogeneily: Chi [®] = 5.4 Fest for overall effect 2 = fest for subaroub differe troke F Study or Subaroup Suby or Subaroup CANTOS 2017 CIRT 2018 COLCOT 2019 COLCOT 2019 COPS 2020	44, df = 8 (P = 0.71), P = 0% = 1.48 (P = 0.14) nnces: ChiP = 0.26. df = 1 (P = 0.) Receiving anti-inflammatory th Events 172 28	61). ² = 0% erapy Total Ev 6717 2391	Placebo rents Total 92 3344 30 2395	24.9% 6.1% 3.8% 3.1.2%	Risk Ratio <u>A.H., Fixed, 95% Cl</u> 0.93 (0.73, 1.19) 0.93 (0.56, 1.56)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroua diffe	rences: Chi ^r = 0.35. df= 1 rP = 0	50.1 - 0%				
Heterogeneily. Chill = 6. Fest for subcround leffect Z = fest for subcround leffect Z = troke troke Festive vs. Subgroup L22.1 ACS SANTOS 2017 DICT 2018 SOLCOT 2019 SOLCOT 2019 SOLCOT 2019 SOLCOT 2019 SOLCOT 2019 SOLCOT 2010 SOLCOT 2010	4, df = 8 (P = 0.7); P = 3%, 1.48 (P = 0.14) inces: Ch ^a = 0.26, df = 1 (P = 0.) Receiving anti-inflammatory th <u>Events</u> 172 28 5 2 1 145	61). P= 0% terapy <u>Total Ev</u> 6717 2391 2366 396 313 6504	Placebo eents Total 92 3344 30 2395 19 2379 6 399 1 311 130 6522	24.9% 6.1% 3.8% 1.2% 0.2% 26.3%	Risk Ratio <u>AH. Fixed, 95% CI</u> 0.93 (0.56, 1.56) 0.26 (0.10, 0.71) ← 0.39 (0.06, 15.81) ← 1.12 (0.88, 1.41)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroue diffe	rences: Chi ^p = 0.35. df= 1 dP = 0	50.1 - 0%				
Heterogeneilty: Chi# = 5.4 fest for subcroux different fest for subcroux different troke troke study of Subcroux juit 24 ACS cxArtOs 2017 juit 2018 c0Cord 2019 c0Cord 2019 c0Cord 2019 c0Cord 2019 Scolub 2010 FRANCIS 2010 SIGLA-TMI 2014 SIGLA-TMI 2013	44, df = 8 (P = 0, 71); P = 0% = 1.49 (P = 0.14) nnces: Chil ² = 0.26, df = 1 (P = 0.) Receiving anti-inflammatory th Events 172 28 5 2 1	61). P = 0% total Ev 6717 2396 396 313 6504 2572	Placebo rents Total 92 3344 30 2395 19 2379 6 399 1 311 130 6522 9 2573	24.9% 6.1% 3.8% 1.2% 0.2% 26.3% 8 1.8%	Risk Ratio 0.41, Fixed, 95% Cl 0.93 [0.73, 1.19] 0.93 [0.56, 1.56] ← 0.94 [0.07, 1.65] ← 0.99 [0.06, 15.81] ← 1.12 [0.88, 1.41] 0.89 [0.34, 2.30]	ng anti-inflammatory therap Risk	k Ratio	Test for subaroux diffe	rences: Chi ^a = 0.35. df = 1 (P = 0	50.1 - 0%				
eletropenelly chief 2 determined that the set of subaroux different and the set of subaroux different that the set of the	44, dr = 8 (P = 0.7); P = 0%, = 1.48 (P = 0.14); ences: Chi ^a = 0.26, df = 1 (P = 0. Receiving anti-inflammatory th Events 172 28 5 5 2 1 145 8 301	61). P= 0% Total Ew 6717 2366 396 313 6504 2572 21259	Placebo eents Total 92 3344 30 2395 19 2379 6 399 1 311 130 6522	24.9% 6.1% 3.8% 1.2% 0.2% 26.3% 8 1.8%	Risk Ratio <u>AH. Fixed, 95% CI</u> 0.93 (0.56, 1.56) 0.26 (0.10, 0.71) ← 0.39 (0.06, 15.81) ← 1.12 (0.88, 1.41)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroue diffe	rences: Chi ^a = 0.35, df = 1 (P = 0	30), 1 = 030				
eletrogeneity ChP= 5.4 fest for overall effect 2 fest for subnox differe trocke <u>Budy of Subgroup</u> <u>1221 ACS</u> ANTOS 2017 JRT 2018 2024 OT 2019 2079 2020 FRANCIS 2010 BOLLD-TIMI 2014 MISTA-16 2013 Mixtotal (95% CD) Total events telerogeneity. ChP= 11	44, dr = 8 (P = 0.71; Y = 0%) nnces: Chi ^a = 0.26, df = 1 (P = 0) Receiving anti-inflammatory th Fourts 172 28 5 2 2 145 361 001, df = 0(P = 0.12;) ^a = 40%	61). P= 0% Total Ew 6717 2366 396 313 6504 2572 21259	Placebo ents Total 92 3344 30 2395 19 2379 6 3399 1 311 130 6522 9 2573 17923	24.9% 6.1% 3.8% 1.2% 0.2% 26.3% 8 1.8%	Risk Ratio 0.41, Fixed, 95% Cl 0.93 [0.73, 1.19] 0.93 [0.56, 1.56] ← 0.94 [0.07, 1.65] ← 0.99 [0.06, 15.81] ← 1.12 [0.88, 1.41] 0.89 [0.34, 2.30]	ng anti-inflammatory therap Risk	k Ratio	Test for suboroue diffe	rences: Chi ^a = 0.35, df = 1 (P = 0	30), 1 = 030				
Heteropeneity Chill = 2.5 Fest for svalberoux differe Erstor overal effect. Z = Fest for subbroux differe L22.1 ACS DAUTOS 2017 SUIT 2018 DOLC-DT 2019 DOLDS 2010 SOLD-TMI 2014 AISTA-16 2013 Subtotal (95% CD) Total events	44, dr = 8 (P = 0.71; Y = 0%) nnces: Chi ^a = 0.26, df = 1 (P = 0) Receiving anti-inflammatory th Fourts 172 28 5 2 2 145 361 001, df = 0(P = 0.12;) ^a = 40%	61). P= 0% Total Ew 6717 2366 396 313 6504 2572 21259	Placebo ents Total 92 3344 30 2395 19 2379 6 3399 1 311 130 6522 9 2573 17923	24.9% 6.1% 3.8% 1.2% 0.2% 26.3% 8 1.8%	Risk Ratio 0.41, Fixed, 95% Cl 0.93 [0.73, 1.19] 0.93 [0.56, 1.56] ← 0.94 [0.07, 1.65] ← 0.99 [0.06, 15.81] ← 1.12 [0.88, 1.41] 0.89 [0.34, 2.30]	ng anti-inflammatory therap Risk	k Ratio	Test for subaroue diffe	rences: Chi ^a = 0.35, df = 1 (P = 0	301.1 = 0.36				
telerogeneity Chill = 3.5 restfor overall effect. Z = restfor subbroub differe trocke restfor volution of the restformer o	44, dr = 8 (P = 0.71; Y = 0%) nnces: Chi ^a = 0.26, df = 1 (P = 0) Receiving anti-inflammatory th Fourts 172 28 5 2 2 145 361 001, df = 0(P = 0.12;) ^a = 40%	61). P= 0% Total Ew 6717 2366 396 313 6504 2572 21259	Placebo ents Total 92 3344 30 2395 19 2379 6 3399 1 311 130 6522 9 2573 17923	24.9% 6.1% 3.8% 1.2% 0.2% 26.3% 8 1.8%	Risk Ratio 0.41, Fixed, 95% Cl 0.93 [0.73, 1.19] 0.93 [0.56, 1.56] ← 0.94 [0.07, 1.65] ← 0.99 [0.06, 15.81] ← 1.12 [0.88, 1.41] 0.89 [0.34, 2.30]	ng anti-inflammatory therap Risk	k Ratio	Test for suboroue diffe	rences: Chi ^a = 0.35, df = 1 (P = 0	301.1 - 036				
eletrogeneity Chill® - 5 estfor subaroux differe trocker 221 ACS 221 A	4, d = 0 = 0 - 71; r = 0% 1 = 40 = 0 = 10 Receive a set of the - 0.28. d = 1 (P = 0) Receive a set of the - 0.28. d = 1 (P = 0) Receive a set of the - 0.28. d = 1 (P = 0) 172 28 5 2 172 28 5 2 1 172 5 2 1 172 38 30 10 10 10 10 10 10 10 10 10 1	61). P= 0% Total Ev 6717 2386 386 383 5504 2572 21259 2762	Placebo ents Total 92 3344 30 2395 19 2379 6 399 1 311 130 6522 9 2573 17923 287 24 2760	 24.9% 6.1% 3.8% 1.2% 0.2% 2.26.3% 1.8% 64.3% 4.9% 	Risk Ratio 0.93 (0.73, 1.19) 0.93 (0.55, 1.56) 0.26 (0.10, 0.71) 0.94 (0.07, 1.65) 0.94 (0.06, 1.58, 11) 1.12 (0.88, 1.41) 0.89 (0.84, 2.30) 0.96 (0.82, 1.12) 0.967 (0.35, 1.25)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroue diffe	ences: Ch ² = 0 35, df = 1 (P = 0	30), F = 036				
eletrogenergy, Chi# - 5, 2 els for ovalia effect Z - els for subaroux differe trocke	$\label{eq:constraint} \begin{array}{l} 4, d'=0 \in \mathcal{P} = 0.71; p^{+}=0.8; \\ 1.80 = 0.10; \\ 1$	61). P= 0% Total Ev 6717 2391 2366 396 313 6504 21259 2762 7924	Placebo ents Total 92 3344 30 2395 19 2379 6 399 1 311 130 6522 9 2573 17923 287 24 2760	 24.9% 6.1% 3.8% 1.2% 0.2% 2.26.3% 1.8% 64.3% 64.3% 3.0.8% 	Risk Ratio 4.H. Fixed, 95% CI 0.93 (0.73, 1.19) 0.93 (0.56, 1.56) 0.26 (0.10, 0.71) ↔ 0.93 (0.06, 15.81) ↔ 0.93 (0.06, 15.81) ↔ 1.12 (0.88, 1.41) 0.96 (0.82, 1.12) 0.96 (0.82, 1.12) 0.96 (0.85, 1.25) 1.01 (0.81, 1.26)	ng anti-inflammatory therap Risk	k Ratio	Test for subaroue diffe	ences: Ch ² = 0 35, df = 1 dP = 0	301.1 = 0.36				
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stroke to more extent. Another meta-analysis by Haiming Wang, et al. of anti-inflammatory therapy in patients with CAD showed that anti-inflammatory therapy appears to have a beneficial effect on reducing the risk of recurrent myocardial infarction in patients with stable coronary heart disease at the cost of increasing infection [25]. Different from Haiming Wang's study, we investigated the effect of anti-inflammatory therapy on longterm outcomes in patients with CAD. Our study showed that anti-inflammatory therapy can reduce the incidence of primary outcome, MI, and coronary revascularization in patients with CAD after at least 6 months of follow up, and our study also shows that anti-inflammatory therapy can significantly reduce the incidence of coronary revascularization in patients with acute coronary syndrome.

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 PLA2 inhibitors cannot. Therefore, it is recommended that patients with CAD should use anti-inflammatory drugs that inhibit the central IL-6 inflammatory signaling pathway. Meanwhile, colchicine is easy to obtain and

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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$ \begin{array}{c} \text{Col-COT 2019} & \text{B9} & \text{2266} & \text{B9} & \text{2279} & \text{556} & \text{G91} [\text{B91}, 121] \\ \text{LGO-C2} 2020 & \text{C211} & \text{277} & \text{216} & \text{113} & \text{20} & \text{C17} & \text{641} & \text{25,164} \\ \text{LGO-C2} 2020 & \text{2211} & \text{277} & \text{216} & \text{116} & \text{276} & \text{656} & \text{0.71} [\text{B-5,0.94}] \\ \text{LGO-C2} 2020 & \text{2211} & \text{277} & \text{116} & \text{276} & \text{656} & \text{0.71} [\text{B-5,0.94}] \\ \text{Total events} & \text{766} & \text{C20} (\text{P-276}) \\ \text{Testor constant stets} 2 = 312 \sigma = 0.0021 \\ Testor constant st$
ball (95): (1) 11970 649 38.5% 0.89 (0.82, 0.96) openetic, (1) 12.0 659 659 openetic, (1) 12.0 659 openetic, (1) 2.24 650.4 638 openetic, (1) 12.0 659 openetic, (1) 12.0 659 openetic, (1) 12.0 659 openetic, (1) 12.0 659 openetic, (1) 12.0 116.7 openetic, (1) 12.0 11.2 openetic, (1) 12.0 12.0	$ \begin{array}{c} Lobolog 20200 & 83 & 27/2 & 116 & 2706 & 656 & 071 (554, 0.64) \\ \hline which drawn at 2021 & 2 & 110 & 172 & 0.65 & 0.21 (55, 0.64) \\ \hline which drawn at 2021 & 2 & 112 & 100 & 0.21 (55, 0.64) \\ \hline which drawn at 2021 & 2 & 1122 & 1140 & 44.1% & 0.85 (0.77, 0.84) \\ \hline which weres & -7.20, of c.5 (9 = 0.002) \\ \hline which weres & -7.2$
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and dividing 150 1657 product 01 157 1657 product 01 157 157 product 01 157 12 product 01 157 12 product 01 10 12 product 01	STABLITY 2014 229 7024 309 7004 2205 0.898 (077,100) Total events 0 70 24 20 5 0.498 (0.871,100) Total events 0 70 24 20 5 0.498 (0.871,00) Textor owned effect 2 - 1 44 9 - 0.15 Textor owned effect 2 - 1 44 9 - 0.15 Textor owned effect 2 - 1 44 9 - 0.15 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 1 30 9 - 0.002 Textor owned effect 2 - 0.002 Textor owne
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.6 Subgroup analysis of targeting the central IL-6 inflammatory signaling	

economical compared with canakinumab and methotrexate, which improves the compliance of patients. Secondly, patients with chronic coronary syndrome and acute coronary syndrome were included in this study. The results support lower coronary revascularization rates after anti-inflammatory therapy in patients with the acute coronary syndrome. In addition, anti-inflammatory therapy can increase the incidence of infection in patients with CAD. Therefore, it should be used with caution in patients with CAD at high risk of infection. Finally, other factors need to be considered in clinical practice. The characteristics of race are essential factors influencing the effect of anti-inflammatory therapy. The trial by Irena tepanikova et al. showed that the concentrations of inflammation markers in black patients were 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 patients needs further studied.

Limitations

This systematic review and meta-analysis of randomized clinical trials may have some limitations. Firstly, the follow-up duration of all included trials was at least 6 months, the short-term clinical benifts of anti-inflammatory therapy needs further exploration. 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, 20, 21]. Thirdly, the lost follow-up rate of three trials was more than 20%, which reduced the reliability of the analysis results [16, 21, 22]. In addition, we cannot obtain the optimal medical therapy, including antiplatelet, statins, betablockers, and renin–angiotensin–aldosterone system receptor inhibitor cannot be further analyzed. Finally, the composite outcome of cardiovascular death, MI, and stroke favored the anti-inflammatory group. However, given that the incidence of serious adverse events in the two groups is almost the same, the clinical importance is debatable. Therefore, more randomized trials are needed to prove this.

Conclusions

Based on standard medical therapy, anti-inflammatory therapy can significantly reduce the incidence of a composite outcome of cardiovascular death, MI, or stroke, MI, and coronary revascularization in patients with CAD, which proves that anti-inflammatory drugs have clinical benefits. However, anti-inflammatory therapy increases the risk of infection, which limited use in patients at high risk of infection. 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.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12872-022-02525-9.

Additional file 1. Supplementary Figure 1. Subgroup analysis of colchicine and other drugs targeting the central IL-6 inflammatory signaling pathway. **Supplementary Figure 2.** Size of information required for each outcome. **Supplementary Figure 3.** Assessment for the risk of bias in each randomized controlled trial included. **Supplementary Figure 4.** The trim and fill method of MI, cardiovascular death, and stroke.

Additional file 2. Supplementary Table 1. Search strategy of this metaanalysis. Supplementary Table 2. Summary of GRADE evidence quality for each outcome. Supplementary Table 3. The P-value of Begg's and Egger's for each outcome.

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Authors' contributions

YN: Study design, data collection, data analysis, manuscript. NB: data collection, data analysis, validation. YM: data collection, validation. PYZ: data collection, validation. YSS: data collection, validation. ZLW: scientific revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing inter ests regarding the publication of this article.

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