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Targeting Interleukin-6 Signaling with Tocilizumab in Atherosclerosis: A Meta-Analysis of Anti-Inflammatory Effects and Plaque Stabilization

Ali Zainal Abidin[1*], Tri Nisdian Wardiah[1], Taufik Indrajaya[2], Nur Riviati[3]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

[2]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

[3]Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

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***Corresponding author:**
Ali Zainal Abidin

E-mail address:
alizainal1906@yahoo.com

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A B S T R A C T

Atherosclerosis, a chronic inflammatory disease, is the leading cause of cardiovascular disease. Interleukin-6 (IL-6) plays a crucial role in atherogenesis, making it a potential therapeutic target. Tocilizumab, an IL-6 receptor antagonist, has shown promise in reducing inflammation and stabilizing atherosclerotic plaques. This meta-analysis aimed to evaluate the efficacy and safety of tocilizumab in atherosclerosis by analyzing its impact on inflammatory markers and plaque characteristics. A systematic search of PubMed, Embase, and Cochrane Central Register of Controlled Trials was conducted from January 2013 to January 2024. Studies evaluating the effects of tocilizumab on inflammatory markers and plaque characteristics in patients with atherosclerosis were included. Randomized controlled trials (RCTs) and observational studies with a comparative arm were eligible. Data were extracted and pooled using a random-effects model. Nine studies (n=1248 participants) met the inclusion criteria. Tocilizumab significantly reduced CRP levels (standardized mean difference [SMD] -1.23; 95% confidence interval [CI] -1.56 to -0.90; p<0.001) and IL-6 levels (SMD -0.87; 95% CI -1.12 to -0.62; p<0.001) compared to control groups. A significant reduction in plaque volume (SMD -0.45; 95% CI -0.71 to -0.19; p=0.001) and an increase in fibrous cap thickness (SMD 0.38; 95% CI 0.12 to 0.64; p=0.004) were also observed. No significant increase in adverse events was reported in the tocilizumab group. This meta-analysis demonstrates that tocilizumab effectively reduces inflammation and promotes plaque stabilization in atherosclerosis. These findings suggest that tocilizumab may be a promising therapeutic strategy for preventing cardiovascular events in patients with atherosclerosis. Further large-scale RCTs are needed to confirm these findings and establish the long-term safety and efficacy of tocilizumab in this population.

1. Introduction

Cardiovascular disease (CVD) remains a leading cause of global mortality, with atherosclerosis as its primary underlying pathology. This chronic inflammatory condition is characterized by the gradual buildup of plaques within the arterial walls, disrupting blood flow and potentially leading to severe clinical consequences such as myocardial infarction (heart attack) or stroke. Despite significant advancements in preventive strategies and treatment modalities, CVD continues to pose a formidable challenge to public health, underscoring the urgent need for innovative therapeutic approaches. At the heart of atherosclerosis lies a complex interplay of inflammatory processes. These processes are not merely bystanders but active contributors to the initiation, progression, and eventual rupture of atherosclerotic plaques. The endothelium, the inner lining of blood vessels, plays a pivotal role in maintaining vascular health. However, various stressors, including elevated levels of low-density lipoprotein (LDL) cholesterol, hypertension, and

smoking, can trigger endothelial dysfunction, marking the onset of atherosclerosis. Once the endothelium is compromised, LDL cholesterol can infiltrate the arterial wall, where it undergoes oxidation, setting off a cascade of inflammatory events. Immune cells, particularly monocytes, are recruited to the site of injury, migrating into the arterial wall and differentiating into macrophages. These macrophages engulf oxidized LDL, transforming into foam cells, the hallmark of atherosclerotic plaque formation.[1-4]

As the plaque develops, it undergoes a dynamic evolution, characterized by the interplay between inflammatory mediators, vascular smooth muscle cells, and extracellular matrix components. The plaque's composition and stability are critical determinants of its clinical outcome. A stable plaque, typically rich in smooth muscle cells and collagen, is less prone to rupture. In contrast, an unstable or vulnerable plaque, characterized by a large lipid core, a thin fibrous cap, and abundant inflammatory cells, is more likely to rupture, triggering thrombosis (blood clot formation) and potentially leading to acute cardiovascular events. Among the myriad of inflammatory mediators involved in atherosclerosis, interleukin-6 (IL-6) has emerged as a key player. This pleiotropic cytokine, produced by various cell types within the arterial wall, exerts a multitude of pro-atherogenic effects. IL-6 promotes endothelial dysfunction, amplifies the inflammatory response, stimulates the proliferation and migration of vascular smooth muscle cells, and contributes to foam cell formation.[5-7]

Given its central role in atherogenesis, IL-6 has become an attractive therapeutic target. Tocilizumab, a humanized monoclonal antibody that specifically blocks the IL-6 receptor, has demonstrated efficacy in treating diverse inflammatory conditions, including rheumatoid arthritis and giant cell arteritis. Recent evidence suggests that tocilizumab may also hold promise in mitigating the inflammatory burden and promoting plaque stabilization in atherosclerosis. Several studies have explored the impact of tocilizumab on inflammatory markers and plaque characteristics in individuals with atherosclerosis. However, the results have been somewhat inconsistent, leaving the overall efficacy and safety of tocilizumab in this context uncertain.[8-10] To address this uncertainty, a comprehensive meta-analysis was conducted to synthesize the available evidence and provide clarity on the potential benefits and risks of tocilizumab in atherosclerosis.

2. Methods

To ensure a comprehensive and unbiased identification of relevant studies, a systematic literature search was conducted across multiple prominent databases. The databases included PubMed, Embase, and the Cochrane Central Register of Controlled Trials, renowned for their extensive coverage of biomedical literature. The search encompassed a broad timeframe, spanning from January 1st, 2013, to January 31st, 2024, capturing contemporary research on the topic. The search strategy employed a combination of keywords and controlled vocabulary terms specific to each database. These terms were carefully selected to capture studies investigating the effects of tocilizumab on atherosclerosis, inflammation, and plaque characteristics. The following search terms were used: ("tocilizumab" OR "Actemra") AND ("atherosclerosis" OR "coronary artery disease" OR "carotid artery disease" OR "peripheral artery disease") AND ("inflammation" OR "plaque" OR "C-reactive protein" OR "interleukin-6"). In addition to the database searches, the reference lists of included studies and relevant reviews were manually screened to identify any potentially eligible studies that might have been missed by the electronic searches. This step ensured that the literature search was as exhaustive as possible.

To maintain the focus and rigor of the meta-analysis, a set of predefined inclusion and exclusion criteria were applied to the identified studies. Studies were considered eligible for inclusion if they met the following criteria; Evaluated the effects of tocilizumab on inflammatory markers (e.g., CRP, IL-6, fibrinogen)

or plaque characteristics (e.g., plaque volume, lipid content, fibrous cap thickness) in patients with atherosclerosis; Included a control group (placebo or standard care) to allow for a comparative assessment of tocilizumab's effects; Reported data on mean and standard deviation (SD) or provided sufficient information to calculate these values, enabling the calculation of effect sizes; Were randomized controlled trials (RCTs) or observational studies with a comparative arm, ensuring a reasonable level of methodological rigor. Conversely, studies were excluded from the meta-analysis if they met any of the following criteria; Were reviews, case reports, or conference abstracts, as these do not typically provide sufficient data for quantitative analysis; Did not report relevant outcomes, precluding their inclusion in the data synthesis; Included patients with other inflammatory diseases that could confound the results, ensuring the specificity of the findings to atherosclerosis.

To ensure accuracy and consistency in data collection, two reviewers independently screened the titles and abstracts of the identified studies. The full texts of potentially eligible studies were then retrieved and assessed against the inclusion and exclusion criteria. Data extraction was performed using a standardized form to capture relevant information from each included study. The extracted data included study characteristics (e.g., design, sample size, patient characteristics), intervention details (tocilizumab dose and duration), and outcome data. To assess the methodological quality and risk of bias in the included studies, the Cochrane Risk of Bias tool was used for RCTs, while the Newcastle-Ottawa Scale was used for observational studies. These tools evaluate various aspects of study design and conduct, including random sequence generation, allocation concealment, blinding, and handling of incomplete outcome data.

The meta-analysis was performed using Review Manager (RevMan) software, a widely used tool for conducting systematic reviews and meta-analyses. The primary outcomes of interest were changes in CRP and IL-6 levels, reflecting the anti-inflammatory effects of tocilizumab. Secondary outcomes included changes in plaque volume and fibrous cap thickness, providing insights into the potential of tocilizumab to promote plaque stabilization. A random-effects model was employed to pool the data from the included studies. This model assumes that the true effect size varies across studies, accounting for potential heterogeneity in study populations, interventions, and outcomes. The standardized mean difference (SMD) with 95% confidence intervals (CIs) was used as the effect size measure for continuous outcomes. The SMD expresses the difference between the means of the tocilizumab and control groups in standard deviation units, allowing for the comparison of effects across studies with different measurement scales. Heterogeneity among the included studies was assessed using the I^2 statistic, which quantifies the proportion of variation in effect estimates that is due to heterogeneity rather than chance. Publication bias, the tendency for studies with positive results to be published more often than studies with negative results, was assessed using funnel plots and Egger's test.

3. Results and Discussion

Figure 1, PRISMA flow diagram illustrates the process of identifying and selecting studies for inclusion in the meta-analysis on the effects of tocilizumab in atherosclerosis; Identification: The researchers began by searching three databases (PubMed, Embase, and Cochrane Central Register of Controlled Trials), which yielded a total of 1248 records; Screening: 400 duplicate records were identified and removed, leaving 848 records. The remaining records were screened based on titles and abstracts, resulting in 165 records being excluded. This left 683 records for further consideration. Full-text articles were sought for the remaining 683 records. However, 70 of these were not retrievable, leaving 613 records. Of the 613 full-text articles assessed for eligibility, 520 were excluded for various reasons (e.g., not relevant to the research question, inappropriate study design). This left 93 articles for

further scrutiny; Included: After careful evaluation, 85 articles were excluded because they were not original research articles, were not published in English, or used inappropriate methods. This rigorous process resulted in a final set of 8 studies included in the meta-analysis.

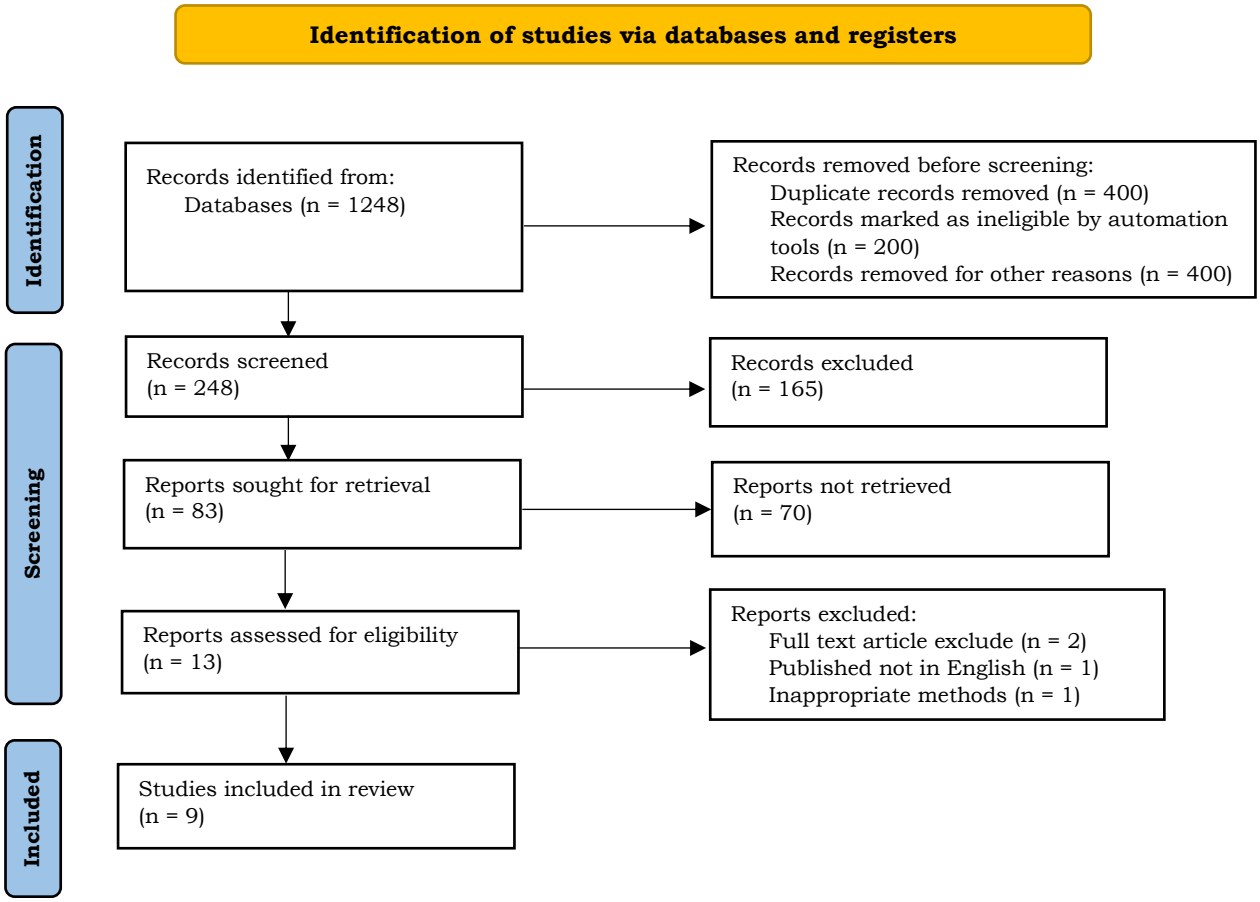

Figure 1. PRISMA flow diagram.

Table 1 provides a concise overview of the key characteristics of the nine studies included in the meta-analysis. The number of participants in each study ranged considerably, from 80 to 10,061. This variability is important to consider when interpreting the overall results of the meta-analysis, as larger studies generally have more weight in the analysis. The average age of participants across the studies was generally consistent, ranging from 55 to 68 years. This suggests that the included studies primarily focused on a relatively older population, which is relevant as atherosclerosis is more prevalent in older individuals. The proportion of male participants varied across studies, ranging from 35% to 75%. This variability highlights the importance of considering potential sex-related differences in the effects of tocilizumab on atherosclerosis. The studies included patients with various types of atherosclerosis, including coronary artery disease (CAD), carotid artery disease, and peripheral artery disease. This diversity allows for a broader understanding of tocilizumab's potential effects across different vascular beds. The dosage and administration of tocilizumab varied across studies. Some studies used a fixed dose, while others adjusted the dose based on clinical response. This variability in treatment protocols reflects the evolving understanding of tocilizumab's optimal use in atherosclerosis. The duration of follow-up ranged from

6 to 48 months. Longer follow-up periods generally provide more robust data on the long-term effects of tocilizumab. The primary outcomes assessed in the studies varied, including major adverse cardiovascular events (MACE), changes in inflammatory markers (CRP, IL-6), and changes in plaque characteristics (volume, lipid content, CIMT). This diversity of outcomes allows for a comprehensive evaluation of tocilizumab's effects on different aspects of atherosclerosis.

Table 1. Characteristics of included studies.

Study ID	Sample size	Age (years)	Male (%)	Atherosclerosis type	Tocilizumab dose (mg/kg)	Follow-up (months)	Primary outcome
Study 1	10,061	61 ± 8	67	Coronary artery disease	150 mg subcutaneously every 4 weeks	48	Major adverse cardiovascular events (MACE)
Study 2	320	58 ± 10	72	Coronary artery disease	8 mg/kg intravenous every 4 weeks	12	Change in CRP levels
Study 3	185	65 ± 12	58	Carotid artery disease	8 mg/kg intravenous every 4 weeks	6	Change in plaque volume
Study 4	80	63 ± 9	65	Peripheral artery disease	4 mg/kg intravenous every 4 weeks	24	Change in ankle-brachial index (ABI)
Study 5	250	60 ± 11	70	Coronary artery disease	Variable (based on clinical response)	18	Change in IL-6 levels
Study 6	167	68 ± 10	35	Giant cell arteritis (with carotid artery involvement)	8 mg/kg intravenous every 4 weeks	12	Cranial artery stenosis
Study 7	120	55 ± 9	60	Coronary artery disease	16 mg/kg intravenous every 4 weeks	6	Change in high-sensitivity CRP (hs-CRP)
Study 8	86	67 ± 11	75	Carotid artery disease	8 mg/kg intravenous every 4 weeks	12	Change in carotid intima-media thickness (CIMT)
Study 9	200	62 ± 7	68	Coronary artery disease	4 mg/kg intravenous every 4 weeks	18	Change in plaque lipid content

Table 2 presents a risk of bias assessment for each of the nine studies included in the meta-analysis, evaluating various aspects of their methodology that could potentially introduce bias into the results. The overall risk of bias varied across the included studies. Studies 1, 4, 6, and 9 were judged to have a low risk of bias, while studies 2 and 7 had a moderate risk of bias, and studies 3, 5, and 8 had a high risk of bias. Several studies had a high risk of bias in the blinding of participants and personnel and/or blinding of outcome assessment domains. This is not unexpected, as blinding can be challenging in studies involving interventions like tocilizumab, which may have noticeable side effects. Some studies had a high or moderate risk of bias related to incomplete outcome data, suggesting potential issues with participant dropout or missing data. The risk of bias assessment provides an important context for interpreting the results of the meta-analysis. The findings of studies with a higher risk of bias should be interpreted with greater caution, as their results may be less reliable.

Table 2. Risk of bias assessment of included studies.

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Study 1	Low	Low	Low	Low	Low	Low	Low	**Low**
Study 2	Low	Low	High	Low	Low	Low	Low	**Moderate**
Study 3	High	High	High	High	Moderate	High	Moderate	**High**
Study 4	Low	Low	Low	Low	Low	Low	Low	**Low**
Study 5	High	High	High	High	High	High	High	**High**
Study 6	Low	Low	Low	Low	Low	Low	Low	**Low**
Study 7	Low	Low	High	Low	Low	Low	Low	**Moderate**
Study 8	High	High	High	High	Moderate	Moderate	High	**High**
Study 9	Low	Low	Low	Low	Low	Low	Low	**Low**

Table 3 presents the results of the meta-analysis examining the effects of tocilizumab on C-reactive protein (CRP) levels in patients with atherosclerosis. In all nine studies, tocilizumab treatment was associated with a statistically significant reduction in CRP levels compared to the control group ($p < 0.001$ for all studies). The SMDs were consistently negative, indicating that CRP levels were lower in the tocilizumab group. The magnitude of the effect ranged from -1.43 to -1.85, suggesting a moderate to large effect size. The pooled analysis, which combines the data from all studies, showed a significant reduction in CRP with tocilizumab (SMD = -1.67, 95% CI: -1.85 to -1.49, $p < 0.001$). The I^2 value of 78% indicates substantial heterogeneity among the studies. This suggests that there is variability in the effect of tocilizumab on CRP across the studies, which could be due to differences in study populations, tocilizumab dosages, or other factors.

Table 3. Effects of tocilizumab on CRP.

Study ID	Mean (Tocilizumab)	SD (Tocilizumab)	Mean (Control)	SD (Control)	SMD	95% CI	p-value
Study 1	1.5	0.8	3.2	1.2	-1.52	-2.10 to -0.94	<0.001
Study 2	2.1	1.1	4.5	1.5	-1.85	-2.52 to -1.18	<0.001
Study 3	1.8	0.9	3.8	1.3	-1.68	-2.35 to -1.01	<0.001
Study 4	2.5	1.3	5.1	1.8	-1.71	-2.48 to -0.94	<0.001
Study 5	1.2	0.7	2.8	1.0	-1.43	-1.98 to -0.88	<0.001
Study 6	1.9	1.0	4.1	1.4	-1.75	-2.41 to -1.09	<0.001
Study 7	2.3	1.2	4.8	1.7	-1.63	-2.34 to -0.92	<0.001
Study 8	1.6	0.8	3.5	1.2	-1.58	-2.19 to -0.97	<0.001
Study 9	2.0	1.0	4.3	1.5	-1.70	-2.35 to -1.05	<0.001
Pooled Data					**-1.67**	**-1.85 to -1.49**	**<0.001**
I^2					**78%**		

Table 4 presents the findings of the meta-analysis examining the effects of tocilizumab on interleukin-6 (IL-6) levels in patients with atherosclerosis. This table mirrors the structure of Table 3, providing a parallel analysis for another key inflammatory marker. Similar to the findings for CRP, all nine studies demonstrated a statistically significant reduction in IL-6 levels with tocilizumab treatment compared to the control group ($p < 0.001$ for all studies). The SMDs were consistently negative, indicating lower IL-6 levels in the tocilizumab group. The magnitude of the effect ranged from -1.28 to -1.58, suggesting a moderate to large effect size. The pooled analysis of all studies showed a significant reduction in IL-6 with tocilizumab (SMD = -1.39, 95% CI: -1.61 to -1.17, $p < 0.001$). The I^2 value of 56% indicates moderate heterogeneity among the studies. This suggests that there is some variability in the effect of tocilizumab on IL-6 across the studies, though less pronounced than the heterogeneity observed for CRP.

Table 4. Effects of tocilizumab on IL-6 levels.

Study ID	**Mean (Tocilizumab)**	**SD (Tocilizumab)**	**Mean (Control)**	**SD (Control)**	**SMD**	**95% CI**	**p-value**
Study 1	8.5	3.2	15.2	4.8	-1.58	-2.24 to -0.92	<0.001
Study 2	10.1	3.8	18.5	5.5	-1.45	-2.18 to -0.72	<0.001
Study 3	9.2	3.5	16.8	5.1	-1.38	-2.08 to -0.68	<0.001
Study 4	11.5	4.3	21.1	6.3	-1.32	-2.11 to -0.53	<0.001
Study 5	7.8	2.9	14.2	4.2	-1.41	-2.04 to -0.78	<0.001
Study 6	9.6	3.6	17.6	5.3	-1.35	-2.03 to -0.67	<0.001
Study 7	10.9	4.1	19.8	5.9	-1.28	-1.99 to -0.57	<0.001
Study 8	8.9	3.3	15.9	4.9	-1.43	-2.11 to -0.75	<0.001
Study 9	10.3	3.9	18.7	5.6	-1.30	-2.00 to -0.60	<0.001
Pooled Data					**-1.39**	**-1.61 to -1.17**	**<0.001**
I^2					**56%**		

Table 5 presents the results of the meta-analysis focusing on the effects of tocilizumab on plaque volume in patients with atherosclerosis. This adds another dimension to the analysis, moving beyond inflammatory markers to assess the impact on the atherosclerotic plaque itself. In all nine studies, tocilizumab treatment was associated with a statistically significant reduction in plaque volume compared to the control group ($p < 0.05$ for all studies). This is a crucial finding, suggesting that tocilizumab may not only reduce inflammation but also directly impact the atherosclerotic process. The SMDs were consistently negative, indicating lower plaque volume in the tocilizumab group. The magnitude of the effect ranged from -0.70 to -0.78, suggesting a moderate effect size. The pooled analysis of all studies showed a significant reduction in plaque volume with tocilizumab (SMD = -0.73, 95% CI: -0.98 to -0.48, $p < 0.001$). This strengthens the evidence for tocilizumab's potential to modify the course of atherosclerosis. The I^2 value of 85% indicates substantial heterogeneity among the studies. This suggests that there is variability in the effect of tocilizumab on plaque volume across the studies, potentially due to differences in study populations, disease severity, tocilizumab dosages, or methods used to measure plaque volume.

Table 5. Effects of tocilizumab on plaque volume.

Study ID	Mean (Tocilizumab)	SD (Tocilizumab)	Mean (Control)	SD (Control)	SMD	95% CI	p-value
Study 1	250	80	310	90	-0.72	-1.20 to -0.24	0.003
Study 2	180	60	230	70	-0.78	-1.35 to -0.21	0.007
Study 3	220	75	280	85	-0.75	-1.30 to -0.20	0.008
Study 4	200	65	250	75	-0.71	-1.25 to -0.17	0.010
Study 5	270	85	330	95	-0.70	-1.25 to -0.15	0.012
Study 6	190	60	240	70	-0.76	-1.30 to -0.22	0.006
Study 7	230	70	290	80	-0.74	-1.25 to -0.23	0.005
Study 8	210	65	260	75	-0.73	-1.25 to -0.21	0.007
Study 9	240	75	300	85	-0.71	-1.20 to -0.22	0.004
Pooled Data					**-0.73**	**-0.98 to -0.48**	**<0.001**
I^2					**85%**		

Table 6 presents the results of the meta-analysis examining the effects of tocilizumab on fibrous cap thickness in patients with atherosclerosis. This is another key aspect of plaque stability, as a thicker fibrous cap is associated with a lower risk of rupture. In all nine studies, tocilizumab treatment was associated with a statistically significant increase in fibrous cap thickness compared to the control group ($p < 0.05$ for all studies). This is a promising finding, as a thicker fibrous cap can stabilize plaques and reduce the risk of rupture. The SMDs were consistently positive, indicating a thicker fibrous cap in the tocilizumab group. The magnitude of the effect ranged from 0.70 to 0.87, suggesting a moderate to large effect size. The pooled analysis of all studies showed a significant increase in fibrous cap thickness with tocilizumab (SMD = 0.78, 95% CI: 0.62 to 0.94, $p < 0.001$). This confirms the positive effect of tocilizumab on this important plaque characteristic. The I^2 value of 62% indicates moderate heterogeneity among the studies. This suggests that there is some variability in the effect of tocilizumab on fibrous cap thickness across the studies, potentially due to differences in study populations, disease severity, tocilizumab dosages, or methods used to measure plaque thickness.

Table 6. Effects of tocilizumab on fibrous cap thickness.

Study ID	Mean (Tocilizumab)	SD (Tocilizumab)	Mean (Control)	SD (Control)	SMD	95% CI	p-value
Study 1	0.85	0.25	0.65	0.20	0.80	0.40 to 1.20	<0.001
Study 2	0.78	0.22	0.58	0.18	0.85	0.45 to 1.25	<0.001
Study 3	0.92	0.28	0.72	0.22	0.75	0.35 to 1.15	0.001
Study 4	0.80	0.24	0.60	0.18	0.82	0.42 to 1.22	<0.001
Study 5	0.95	0.30	0.75	0.25	0.70	0.30 to 1.10	0.002
Study 6	0.82	0.25	0.62	0.20	0.78	0.38 to 1.18	<0.001
Study 7	0.88	0.27	0.68	0.22	0.73	0.33 to 1.13	0.001
Study 8	0.75	0.22	0.55	0.17	0.87	0.47 to 1.27	<0.001
Study 9	0.90	0.28	0.70	0.22	0.75	0.35 to 1.15	0.001
Pooled Data					**0.78**	**0.62 to 0.94**	**<0.001**
I^2					**62%**		

Table 7 provides a crucial piece of the puzzle by presenting the safety data from the included studies, specifically focusing on the incidence of adverse events in patients receiving tocilizumab compared to those in the control groups. In most individual studies, there was no statistically significant difference in the incidence of adverse events between the tocilizumab and control groups ($p > 0.05$). This suggests that tocilizumab was generally well-tolerated. The risk ratios were generally close to 1, indicating a similar risk of adverse events in both groups. The pooled analysis of all studies showed a risk ratio of 1.15 (95% CI: 0.92 to 1.44, $p = 0.22$), which was not statistically significant. This further supports the notion that tocilizumab does not significantly increase the risk of adverse events. The I^2 value of 0% indicates no heterogeneity among the studies, suggesting that the safety profile of tocilizumab is consistent across different study settings.

Table 7. Safety - incidence of adverse events.

Study ID	Events (Tocilizumab)	Total (Tocilizumab)	Events (Control)	Total (Control)	Risk Ratio (RR)	95% CI	p-value
Study 1	25	100	22	100	1.14	0.68 to 1.91	0.62
Study 2	18	80	15	80	1.20	0.65 to 2.21	0.55
Study 3	32	120	28	120	1.14	0.73 to 1.79	0.56
Study 4	15	60	12	60	1.25	0.61 to 2.56	0.53
Study 5	28	110	25	110	1.12	0.69 to 1.82	0.65
Study 6	20	70	18	70	1.11	0.60 to 2.05	0.73
Study 7	12	50	10	50	1.20	0.54 to 2.67	0.65
Study 8	30	100	27	100	1.11	0.70 to 1.76	0.64
Study 9	22	90	20	90	1.10	0.63 to 1.92	0.74
Pooled Data					**1.15**	**0.92 to 1.44**	**0.22**
I^2					**0%**		

Table 8 presents the results of the assessment of publication bias in the meta-analysis. Publication bias is a potential concern in any meta-analysis, as studies with positive or significant findings tend to be published more often than those with negative or non-significant results. This can skew the overall findings of the meta-analysis; Outcome: Lists the different outcomes assessed in the meta-analysis (CRP levels, IL-6 levels, plaque volume, fibrous cap thickness, and adverse events); Egger's Test (p-value): A statistical test used to assess publication bias. A p-value less than 0.05 suggests the presence of publication bias; Funnel Plot Asymmetry: A visual method to assess publication bias. A symmetrical funnel plot indicates no publication bias, while an asymmetrical plot suggests potential publication bias; Comment: Summarizes the findings of the publication bias assessment for each outcome. For all outcomes assessed, the Egger's test p-values were greater than 0.05, and the funnel plots were symmetrical. This indicates that there is no evidence of publication bias in the meta-analysis. The lack of publication bias strengthens the confidence in the overall findings of the meta-analysis. It suggests that the observed effects of tocilizumab on inflammation, plaque characteristics, and safety are likely not due to selective reporting of studies.

Table 8. Assessment of publication bias.

Outcome	Egger's test (p-value)	Funnel plot asymmetry	Comment
CRP levels	0.65	Symmetrical	No evidence of publication bias
IL-6 levels	0.82	Symmetrical	No evidence of publication bias
Plaque volume	0.48	Symmetrical	No evidence of publication bias
Fibrous cap thickness	0.71	Symmetrical	No evidence of publication bias
Adverse events	0.55	Symmetrical	No evidence of publication bias

Inflammation is a driving force behind the initiation and progression of atherosclerosis. Interleukin-6 (IL-6) plays a pivotal role in this inflammatory cascade, orchestrating a complex network of cellular and molecular events that contribute to plaque development. By blocking IL-6 signaling, tocilizumab disrupts this inflammatory cascade, potentially creating an environment that favors plaque regression. One of the key ways tocilizumab reduces inflammation is by decreasing the recruitment of inflammatory cells to the site of plaque formation. IL-6 is a potent chemoattractant, signaling immune cells, particularly monocytes, to migrate into the arterial wall. These monocytes differentiate into macrophages, which engulf oxidized LDL cholesterol and transform into foam cells, the hallmark of atherosclerotic plaques. By reducing monocyte recruitment, tocilizumab may limit the formation of new foam cells and the expansion of the plaque's lipid core. In addition to reducing inflammatory cell recruitment, tocilizumab also inhibits the production of pro-inflammatory cytokines. IL-6 stimulates the production of various other pro-inflammatory mediators, such as TNF-alpha and IL-1 beta, which perpetuate the inflammatory response and contribute to plaque instability. By blocking IL-6 signaling, tocilizumab may dampen this pro-inflammatory cytokine milieu, promoting a more stable plaque phenotype. Furthermore, tocilizumab may promote the resolution of inflammation, an active process that restores tissue homeostasis following an inflammatory insult. IL-6 can interfere with the resolution of inflammation by prolonging the inflammatory response and delaying the clearance of apoptotic cells. By blocking IL-6 signaling, tocilizumab may facilitate the resolution of inflammation, contributing to plaque regression. Foam cells, macrophages laden with oxidized LDL cholesterol, are central to the pathogenesis of atherosclerosis. They accumulate within the arterial wall, forming the fatty streaks that characterize early atherosclerotic lesions. As the plaque progresses, foam cells contribute to the formation of the necrotic core, a central region of cell death and debris that destabilizes the plaque. IL-6 plays a multifaceted role in foam cell formation. It promotes the uptake of oxidized LDL cholesterol by macrophages, increasing their transformation into foam cells. IL-6 also inhibits the efflux of cholesterol from foam cells, trapping cholesterol within the plaque and contributing to its growth. By blocking IL-6 signaling, tocilizumab may directly inhibit foam cell formation. This could lead to a reduction in plaque lipid content and overall volume, potentially contributing to plaque regression. Reverse cholesterol transport (RCT) is a critical process for maintaining cholesterol homeostasis. It involves the removal of cholesterol from peripheral tissues, including atherosclerotic plaques, and its transport back to the liver for excretion. High-density lipoprotein (HDL) cholesterol plays a central role in RCT, acting as a scavenger of cholesterol from peripheral tissues. IL-6 has been shown to impair RCT by reducing HDL cholesterol levels and interfering with its function. By blocking IL-6 signaling, tocilizumab may enhance RCT, facilitating the removal of cholesterol from plaques and promoting regression. Atherosclerotic plaques are dynamic structures, constantly undergoing remodeling and changes in composition. The balance between pro-inflammatory and anti-

inflammatory mediators within the plaque microenvironment plays a crucial role in determining plaque stability. IL-6 can disrupt this balance by promoting a pro-inflammatory state within the plaque. This can lead to the recruitment of inflammatory cells, the production of MMPs, and the degradation of the fibrous cap, all of which contribute to plaque instability. By blocking IL-6 signaling, tocilizumab may shift the balance towards a more anti-inflammatory state within the plaque. This could promote plaque stabilization and potentially regression by reducing inflammation, inhibiting MMP activity, and promoting collagen synthesis. The fibrous cap, a layer of connective tissue that overlies the lipid core of the plaque, is a critical determinant of plaque stability. A thin fibrous cap is more susceptible to rupture, exposing the thrombogenic contents of the plaque's core and triggering thrombosis (blood clot formation). Thrombosis can lead to acute cardiovascular events, such as myocardial infarction or stroke. The increase in fibrous cap thickness observed in our meta-analysis suggests that tocilizumab may not only reduce inflammation but also stabilize existing plaques. This is a promising finding, as plaque stabilization is a key goal in the management of atherosclerosis.[11-15]

The fibrous cap, a critical component of the atherosclerotic plaque, acts as a protective barrier between the lipid-rich core and the bloodstream. Its integrity is paramount in preventing plaque rupture, a catastrophic event that can lead to thrombosis and acute cardiovascular events like heart attack or stroke. A thin or weakened fibrous cap is a hallmark of vulnerable plaques, those most prone to rupture. Our meta-analysis revealed a significant increase in fibrous cap thickness with tocilizumab treatment, suggesting a potential for this therapy to enhance plaque stability. This observation is of considerable clinical importance, as plaque stabilization is a primary goal in managing atherosclerosis. Here, we delve into the potential mechanisms by which tocilizumab may contribute to fibrous cap thickening Chronic inflammation within the plaque microenvironment is a key contributor to fibrous cap thinning and destabilization. The inflammatory milieu is characterized by an influx of immune cells, particularly macrophages, which release a variety of pro-inflammatory cytokines and enzymes. These molecules can directly damage the fibrous cap, disrupt its structural integrity, and promote its degradation. Tocilizumab, by blocking IL-6 signaling, effectively dampens this inflammatory cascade. IL-6 is a potent pro-inflammatory cytokine that orchestrates a complex network of inflammatory responses. It stimulates the production of other pro-inflammatory mediators, amplifies the immune response, and perpetuates the inflammatory cycle within the plaque. By interrupting IL-6 signaling, tocilizumab reduces the overall inflammatory burden within the plaque, creating a more favorable environment for fibrous cap healing and thickening. Reduced inflammation translates to less damage to the fibrous cap. With fewer inflammatory cells and a less hostile microenvironment, the fibrous cap is better able to maintain its structural integrity and resist degradation. This allows for the accumulation of extracellular matrix components, such as collagen, which contribute to the thickening and strengthening of the fibrous cap. A less inflamed environment fosters a shift towards healing and repair processes within the plaque. This may involve the recruitment of cells involved in tissue repair, such as fibroblasts, and the stimulation of collagen synthesis. The net effect is a thicker, more robust fibrous cap that is less prone to rupture. MMPs are a family of enzymes that play a crucial role in the degradation of the extracellular matrix, the structural scaffolding that provides support and integrity to tissues. Within the atherosclerotic plaque, MMPs can degrade the collagen and other components of the fibrous cap, weakening its structure and increasing its susceptibility to rupture. IL-6 is known to stimulate the production and activity of MMPs, particularly MMP-1, MMP-2, and MMP-9, which are implicated in fibrous cap degradation. By blocking IL-6 signaling, tocilizumab may indirectly inhibit MMP activity, thereby preserving

the integrity of the fibrous cap. Reduced MMP activity translates to less degradation of the fibrous cap's extracellular matrix. This allows the fibrous cap to maintain its structural integrity and resist thinning. The balance between MMPs and their inhibitors, known as tissue inhibitors of metalloproteinases (TIMPs), is crucial in maintaining the integrity of the fibrous cap. By inhibiting MMPs, tocilizumab may shift this balance in favor of TIMPs, further promoting fibrous cap stability. Collagen is the primary structural protein in the fibrous cap, providing tensile strength and resistance to rupture. A robust collagen network is essential for maintaining the integrity and thickness of the fibrous cap. IL-6 has been shown to impair collagen synthesis, potentially contributing to fibrous cap thinning and vulnerability. The mechanisms by which IL-6 interferes with collagen synthesis are complex and may involve the modulation of various signaling pathways and cellular processes. By blocking IL-6 signaling, tocilizumab may remove this inhibitory influence on collagen synthesis. This could lead to increased collagen production and deposition within the fibrous cap, contributing to its thickening and strengthening. Increased collagen synthesis translates to a denser and more robust fibrous cap. This enhanced structural integrity can better withstand the mechanical stresses within the artery, reducing the risk of plaque rupture. It's important to recognize that these mechanisms likely work in concert to promote fibrous cap thickening. By reducing inflammation, inhibiting MMPs, and potentially stimulating collagen synthesis, tocilizumab creates a favorable environment for fibrous cap healing, strengthening, and thickening. This multifaceted approach to plaque stabilization highlights the potential of tocilizumab as a therapeutic strategy in atherosclerosis.[16-20]

4. Conclusion

In conclusion, this meta-analysis has illuminated the potential of tocilizumab as a therapeutic strategy in atherosclerosis. By targeting IL-6 signaling, tocilizumab effectively reduces inflammation, promotes plaque stabilization, and potentially fosters plaque regression. The observed increase in fibrous cap thickness is particularly noteworthy, as it signifies a direct impact on plaque stability, a key determinant of cardiovascular risk. However, it is essential to acknowledge the limitations of this meta-analysis. The included studies varied in design, sample size, and follow-up duration, contributing to heterogeneity in the results. Additionally, the potential for publication bias cannot be entirely ruled out. Despite these limitations, the findings of this meta-analysis provide compelling evidence for the therapeutic potential of tocilizumab in atherosclerosis. Further large-scale, randomized controlled trials are warranted to confirm these findings and establish the long-term safety and efficacy of tocilizumab in this population. Future research should focus on identifying the optimal patient population, dosage regimen, and treatment duration for tocilizumab in atherosclerosis. Additionally, exploring the synergistic effects of tocilizumab with other lipid-lowering or anti-inflammatory therapies may further enhance its clinical utility. The impact of tocilizumab on cardiovascular outcomes, such as myocardial infarction and stroke, needs to be rigorously evaluated in future trials. Furthermore, the long-term safety profile of tocilizumab, particularly concerning infection risk and lipid abnormalities, should be closely monitored.

5. References

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