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The effect of statin on major adverse cardiovascular events and mortality in patients with rheumatoid arthritis – a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The aim of this systematic review and meta-analysis is to assess the effect of statin on major adverse cardiovascular events (MACE) and mortality in patients with RA.

MATERIALS AND METHODS: A systematic literature search was performed using PubMed, Scopus, Embase, and Clinicaltrials.gov for studies investigating the effect of statin on MACE and mortality in RA patients up until 6 February 2022. The primary outcome was MACE, which can be defined as nonfatal myocardial infarction (MI), nonfatal presumed ischemic stroke, transient ischemic attack, any coronary or non-coronary revascularization, or cardiovascular death. The pooled effect estimated was reported as hazard ratio (HR).

RESULTS: There were 40,307 patients from a total of six studies, comprising of one double-blind placebo controlled randomized controlled trial, four propensity-score matched cohorts, and one observational study included in this meta-analysis. The rate of MACE was lower in RA patients receiving statin [OR 0.67 (95%CI 0.51, 0.89), p=0.005; I^2: 21.0%, p=0.29] (Figure 2). Sensitivity analysis using fixed-effect model showed that MACE was lower in the statin group [OR 0.73 (95%CI 0.62, 0.87), p<0.0051 I^2: 21.0%, p=0.29]. Mortality was lower in RA patients receiving statin [OR 0.73 (95%CI 0.62, 0.88), p<0.001; I^2: 29.0%, p=0.25] (Figure 3). Sensitivity analysis using fixed-effect model showed that mortality was lower in the statin group [OR 0.75 (95%CI 0.66, 0.85), p<0.001 I^2: 29.0%, p=0.25].

CONCLUSIONS: This systematic review and meta-analysis showed that statin was associated with reduction of MACE and mortality in patients with RA.

Key Words:
Statin, Rheumatoid arthritis, Major adverse cardiovascular events, Mortality, Rheumatology.

Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory arthritis that mainly affects small joints[1,2]. The etiology of RA is multifactorial, with a combination of genetic predisposition, various environmental, and lifestyle factors[1]. Until now, there is no definitive cure for RA.

Patients with RA also have an increased risk of mortality and morbidity compared to the general population. One of the main risks is the cardiovascular disease (CVD), which is significantly higher in RA patients compared to the general population[3,4].

Hydroxymethylglutaryl-coenzyme A reductase inhibitor is widely recognized to significantly reduce CVD through various mechanisms[5]. Improved vascular effects, lipid-lowering, and anti-inflammatory properties of statins are presumed

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to be the groundwork in decreasing the risk of cardiovascular (CV) events in the general population and are expected to bring a similar effect, if not greater, in RA patients[1]. Despite the aforementioned potential mechanisms, the true benefit of statin in RA patients remains obscure and needs to be clarified.

Therefore, this systematic review and meta-analysis are aimed to assess the effect of statin on major adverse cardiovascular events (MACE) and mortality in patients with RA.

Materials and Methods

This meta-analysis follows the reporting guideline Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Search Strategy and Study Selection

A systematic literature search was performed using PubMed, Scopus, Embase, and Clinicaltrials.gov for studies investigating the effect of statin on MACE and mortality in RA patients using the keywords "(statin OR atorvastatin OR rosuvastatin OR simvastatin OR Lovastatin OR Pitavastatin) AND (rheumatoid arthritis)" from the beginning of time up until 6 February 2022.

Title and abstracts were screened by two independent authors based on the inclusion and exclusion criteria. Discrepancies were resolved by discussion with a third author.

Inclusion and Exclusion Criteria

The sample was composed by patients with RA. The intervention group was formed by patients receiving statin. The secondary outcome was mortality, defined as death by any cause.

Studies that met the following criteria were included: 1) observational studies or randomized controlled trials evaluating use of statin in patients with RA, 2) comparing statin with non-statin users, and 3) reporting MACE and/or mortality.

Studies that met at least one of the following criteria were excluded: 1) abstract-only publication, 2) letters, 3) reviews, and 4) editorial. There was no language restriction imposed.

Data Extraction

Two independent authors performed data extraction from the included studies. Data of interest included in this study were the first author, study design, sample size, age, sex (male), hypertension, diabetes, non-steroidal anti-inflammatory drugs (NSAID), the most common statin used, MACE and mortality. Discrepancies were resolved by discussion with a third author.

Risk of Bias Assessment

The Newcastle Ottawa Scale (NOS) for cohort studies was used to assess the observational studies and Cochrane risk of bias assessment tool was used to assess the randomized controlled trials[6]. Two independent authors performed the risk of bias assessment and discrepancies were resolved by discussion.

Outcome

The primary outcome was MACE, defined as nonfatal MI, nonfatal presumed ischemic stroke, transient ischemic attack, any coronary or non-coronary revascularization, or cardiovascular death. The pooled effect estimate was reported as hazard ratio (HR).

Statistical Analysis

Inverse variance method was used to pool the HR for the primary and secondary outcomes using random-effects model regardless of heterogeneity. Pooled analyses using fixed-effect model were performed as sensitivity analyses. *p*-values were considered as statistically significant if it were below 0.05. Cochran's Q test and I^2 statistics were used to assess heterogeneity; I^2 values above 50% or/and *p*-value below 0.10 indicated statistically significant heterogeneity. Review Manager 5.4 was used to perform the meta-analysis.

Results

Baseline Characteristics

There were 40,307 patients from a total of six studies[1,7-11], comprising of one double-blind placebo controlled randomized controlled trial, four propensity-score matched cohorts, and one observational study included in this meta-analysis (Figure 1). Baseline characteristics of the included studies are in Table I.

Major Adverse Cardiovascular Events

The rate of MACE was lower in RA patients receiving statin [OR 0.67 (95%CI 0.51, 0.89), p=0.005; I^2: 21.0%, p =0.29] (Figure 2). Sensitivity analysis using fixed-effect model showed that MACE was lower in the statin group [OR 0.73 (95%CI 0.62, 0.87), p<0.0051 I^2: 21.0%, p=0.29].

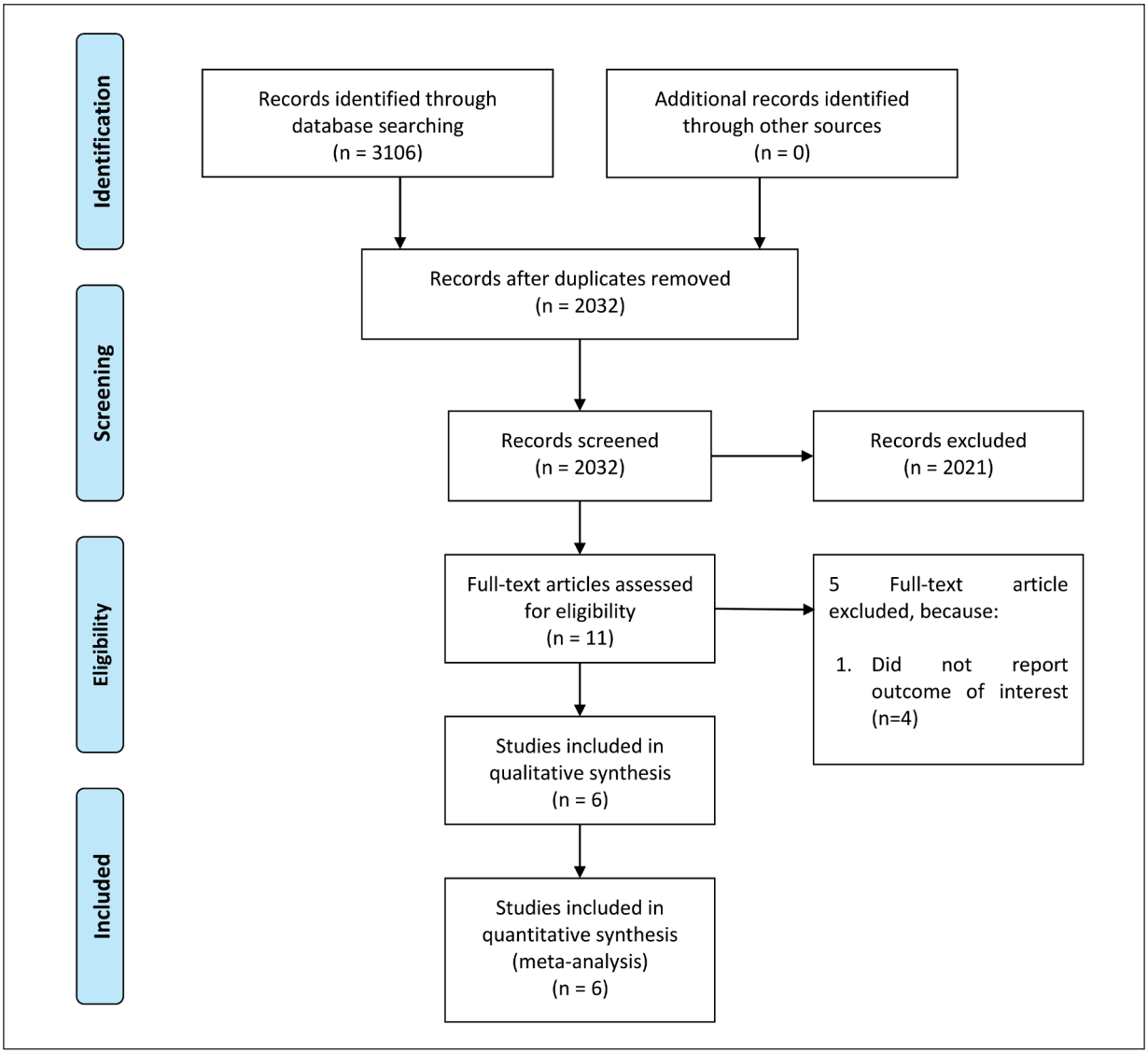

Figure 1. PRISMA Flowchart.

All-Cause Mortality

Mortality was lower in RA patients receiving statin [OR 0.73 (95%CI 0.62, 0.88), $p<0.001$; I^2: 29.0%, $p=0.25$] (Figure 3). Sensitivity analysis using fixed-effect model showed that mortality was lower in the statin group [OR 0.75 (95%CI 0.66, 0.85), $p<0.001$ I^2: 29.0%, $p=0.25$].

Discussion

This systematic review and meta-analysis showed that statin was associated with a reduction of MACE and mortality in patients with RA. Statin has a well-known safety profile as demonstrated by multiple clinical trials. Its pleiotropic effects may have contributed to reduce CV events in susceptible population[12,13]. Statin is also renowned for its dual "lipid-lowering" and "anti-inflammatory" effects, which are beneficial for preventing future CV events. Despite the promising results, the true benefit of statin in primary CV prevention in RA patients is still unclear, since the development of CVD in RA patients is presumed to involve various pathways.

Rheumatoid arthritis is associated with an increased risk of morbidity and mortality attributed to increased CVD, responsible for over 50% of premature death[9]. The presence of traditional CV risk factors such as smoking, hypertension,

Table I. Baseline characteristics of the included patients [1,7,8,9,10,11].

Authors	Design	Sample	Male (%)	Age (years)	HT (%)	Diabetes (%)
Chhibber et al[1] 2021	PSM RO	3,766	34	61	NA	20
Huang et al[9] 2017	PSM RO	27,415	21	NA	62	25
Karpouzas et al[8] 2021	PO	146	12	52	47	16
Kitas et al[7] 2019	RCT	3,002	26	61	22	0
Schoenfeld et al[10] 2015	PSM RO	5,886	35	66	54	19
Sheng et al[11] 2012	PSM RO	78	51	68	NA	18

HT: Hypertension, NSAID: Non-steroidal Anti-inflammatory Drugs, NOS: Newcastle-Ottawa Scale

DM, and dyslipidemia cannot fully explain this elevated CV events phenomenon in the RA population[14]. However, RA and CVD may share a common foundation, which involves inflammation in both of their pathogenesis[14].

The inflammation, which plays a role in RA disease progression, might have altered the lipid profile. Low total and low-density lipoprotein (LDL) levels have been showing a period of high-grade inflammation in RA. In addition, a greater but proportional suppression of high-density lipoprotein (HDL) level is found and resulting in an unfavorable ratio of total to HDL cholesterol[14]. Interestingly, the lipid level has a paradoxical relationship with CAD risk in RA patients[14]. Lower lipid level is associated with more severe systemic inflammation which leans toward increased coronary artery disease (CAD) risk[15]. Moreover, the inflammation also possibly alters the structure and function of lipoprotein. The HDL carries more serum amyloid A and less apolipoprotein A-I, therefore modifying its anti-atherogenic effect into pro-atherogenic effect[16]. However, a previous study showed a modest improvement of HDL function in RA patients receiving statin therapy[17,18].

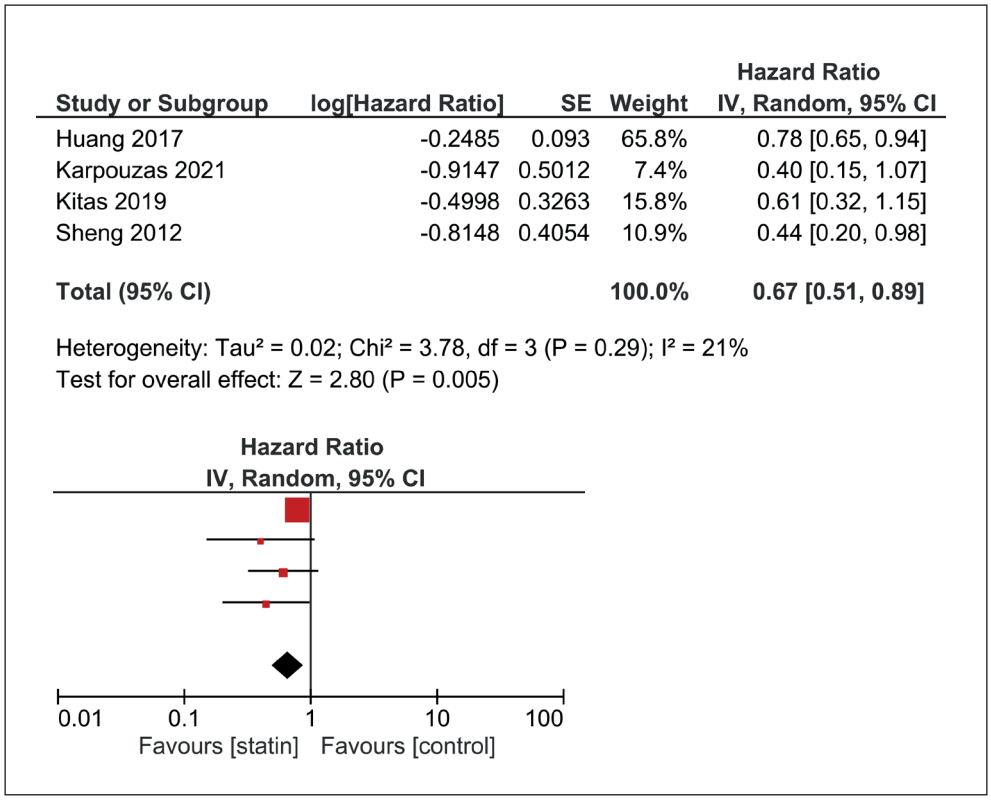

Figure 2. Statin and Major Adverse Cardiovascular Events in patients with Rheumatoid Arthritis.

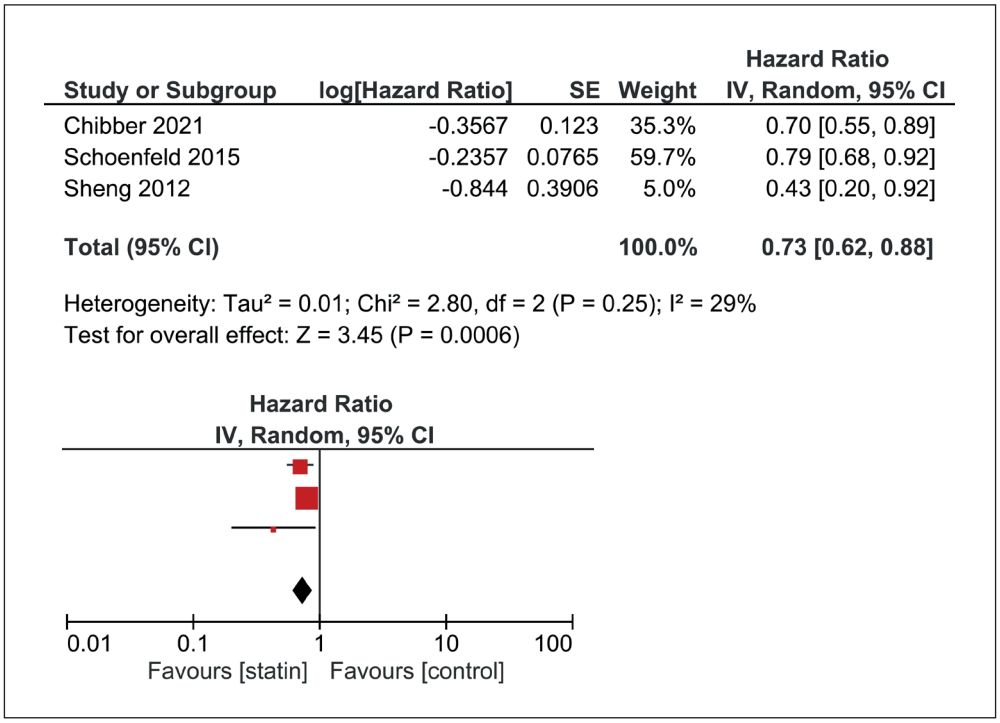

Figure 3. Statin and Mortality in patients with Rheumatoid Arthritis.

The pleiotropic properties of statin lead to a growing interest in their potential effect on the inflammatory process in RA. The use of statin may extend beyond its original design as statin might help to regulate endothelial nitric oxide, endothelial expression of cytokines and chemokines, and therefore decreasing vascular inflammation and vascular atherogenic process[19]. Furthermore, statin shows possible beneficial effects on the disease progression, as it reduces inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6, and C-reactive protein (CRP)[20].

Patients with RA commonly suffer from asymptomatic myocardial disease. Symptomatic clinical myocarditis is a rare finding in RA patients. Diffuse myocardial fibrosis and inflammation were found to be evident among patients with RA in one study[21], with the fibrotic and inflammatory changes being associated with disease activity and impaired strain. The occurrence of this subclinical myocarditis is believed to be the major contributor to the development of heart failure in patients with RA[21,22].

A phenomenon that is interesting to note in rheumatoid arthritis is the occurrence of "Lipid Paradox" that involves dyslipidemia secondary to systemic inflammation. This dyslipidemia can be seen within one year of RA diagnosis. In this phenomenon, the antiatherogenic function of high-density lipoprotein is impaired. The HDL does not confer protection against cardiovascular diseases in patients with RA. Interestingly, in patients with RA, HDL has been found to possess proinflammatory activity *in vitro,* as opposed to patients without RA. This form of HDL has been found in a cross-sectional observational study[23] to be associated with active RA disease and joint injury in RA patients and was inversely associated with the use of Methotrexate. HDL's ability to extract cholesterol from atherosclerotic plaques is also impaired in patients with active RA[23,24]. With these findings, patients with inadequate control of RA are jeopardized by both the innate risk of LDL in relation to MACE and also the "paradox" of HDL function that occurs in RA patients. Intensification of statin in these patients can help curb these problems.

Another form of alteration in lipid metabolism in patients with RA manifests as rheumatoid cachexia, in which patients with RA often present with a reduced muscle mass and a high fat mass. This alteration between muscle and fat ratio is also caused by an inadequately controlled systemic inflammation in RA and contributes to the alterations of lipid profile and CV risk in RA patients[25].

Adequate control of systemic inflammation on RA is essential. Patients with inadequately controlled systemic inflammation have been found to experience rapid progression of carotid intima-media thickness, a marker of elevated cardiovascular risk[26]. Currently, Disease-Modifying Anti Rheumatoid agents (DMARDs) are used to adequately control systemic inflammation in RA. However, the utilization of these agents is not without consequences.

Several immunomodulatory agents have been found to cause alterations in lipoprotein profile in RA patients. These agents include tocilizumab and Janus Kinase Inhibitor class of agents. These agents can increase total cholesterol, triglycerides, HDL, and LDL in RA patients. However, with the general anti-inflammatory properties of these agents, the overall alteration in cardiovascular risk remains unclear. One randomized controlled trial compared tocilizumab with etanercept, finding higher lipid levels in the tocilizumab arm[27]. We believe that these findings serve as a further inclination for statin intensification in RA.

Study Limitation

Due to the novelty of this topic, study literatures regarding the use of statin in Rheumatoid Arthritis patients are limited. Only six studies[1,7-11] were included in this meta-analysis. Funnel Plot analysis and Egger's test to detect publication bias were also not done, due to the limited number of included studies.

Clinical Implications

This meta-analysis showed that statin can be potentially used in patients with RA to reduce mortality and MACE, especially in those meeting other indications for statin use. Due to the lipid paradox, LDL may not be a reliable indicator for statin initiation. Statin has been widely used for primary prevention of cardiovascular diseases in patients having risk factors or high atherosclerotic cardiovascular disease risk. With the currently available data, we are not able to perform stratified analysis and determine whether the benefit was due to initiation of statin in high-risk individuals or RA is a significant risk factor that is not yet incorporated into the consideration for initiating statin. Thus, more extensive randomized control trials (RCTs) are required before routinely initiating statin in RA patients with low risk of atherosclerotic cardiovascular disease.

Conclusions

Patients with Rheumatoid Arthritis suffer from lipoprotein alteration and increased risk for atherogenesis and ultimately MACE, and this is caused by systemic inflammation that occurs in RA patients. The use of statin can help to reduce MACE by controlling blood lipids and endothelial inflammation. Results of this systematic review and meta-analysis showed that statin was associated with a reduction of MACE and mortality in patients with RA.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Ethical Approval

Not Applicable.

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