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The Effects of HMG-CoA Inhibitors (Statins) on Rheumatoid Arthritis Disease Progression: A Systematic Review

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The Effects of HMG-CoA Inhibitors (Statins) on Rheumatoid Arthritis Disease Progression: A Systematic Review

Abstract

Background: Rheumatoid arthritis is a chronic, progressive autoimmune disease that erodes joint synovium and affects other body organs and vasculature. While current therapies, designed to address the impact of rheumatoid arthritis on joints, have been shown to be of benefit, the disabling and progression nature of the disease remains. In addressing the cardiovascular complications of this disease, providers may have stumbled upon another medication, a cholesterol lowering medication known as statins, which may prove beneficial for patients by decreasing inflammation and slowing disease progression. This review will examine the impact of statin medications of rheumatoid arthritis disease progression, as assessed by the DAS28.

Method: An exhaustive search of the literature was conducted in Medline (Ovid) and Web of Science using the following search terms: *rheumatoid arthritis, HMG Co-A inhibitor, statin, "severity of illness index", disease progression,* and *treatment outcome*. A search in CINAHL required the additional keywords *anticholesteremic agents* and *antilipemic agent*. Studies that assessed the effect of statin medications on DAS28, an index used to assess rheumatoid arthritis severity, were included. Studies were further limited to human subjects, adults, and English language.

Results: A total of 132 results were found, 17 of which were further screened using the eligibility criteria, and five studies qualified for this systematic review. Four studies are randomized clinical trials, including one crossover study, and one is a prospective cohort study. In all studies, statin medications were shown to improve specific inflammatory markers (such as swollen joint counts, tender joint counts, CRP, and ESR), however, only three studies demonstrated their improvement of the DAS28 itself.

Conclusion: The results of this systematic review demonstrate a trend of decreased inflammation in rheumatoid arthritis patients relatable to statin therapy; however, the picture remains unclear as to the improvement in rheumatoid arthritis disease progression with adjuvant statin use.

Keywords: *rheumatoid arthritis, DAS28, disease activity, disease progression, HMG-CoA inhibitor, severity of illness, statin, treatment outcome*

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Keywords
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NOTICE TO READERS

The Effect of HMG-CoA Inhibitors (Statins) on Rheumatoid Arthritis Disease Progression: A Systematic Review

Sarah K. Johnson

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2012

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Biography

[Information redacted for privacy]

Abstract

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Method: An exhaustive search of the literature was conducted in Medline (Ovid) and Web of Science using the following search terms: *rheumatoid arthritis*, *HMG Co-A inhibitor*, *statin*, "*severity of illness index*", *disease progression,* and *treatment outcome*. A search in CINAHL required the additional keywords *anticholesteremic agents* and *antilipemic agent*. Studies that assessed the effect of statin medications on DAS28, an index used to assess rheumatoid arthritis severity, were included. Studies were further limited to human subjects, adults, and English language.

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List of Abbreviations

ADR...Adverse Drug Reaction
CRP………………………………………………………………….C-Reactive Protein
DAS28………………………………………………………….. Disease Activity Score (28)
DMARD……………………………………….……Disease Modifying Anti-Rheumatic Drug
ESR……………………………………………………………….Erythrocyte Sedimentation Rate
EULAR……………………………………...European League Against Rheumatism
FMD……………………………………………………………Flow-Mediated Dilation
HDL…………………………………………………………..High-Density Lipoprotein
Hs-CRP…………………………………………Highly Sensitive C-Reactive Protein
LDL…………………………………………………...Low-Density Lipoprotein
LFT .……………………………………………………………Liver Function Test
MDA………………………………………………………..Malondialdehyde
NSAID…………………………………………Non-Steroidal Anti-Inflammatory Drug
Ox-LDL…………………………………………...Oxidized Low-Density Lipid Protein
RA…………………………………………………………Rheumatoid Arthritis
TNF-α……………………………………………….....Tumor Necrosis Factor-Alpha
TARA……………………………………………Trial of Atorvastatin in Rheumatoid Arthritis
VAS………………………………………………………...Visual Analog Scale

The Effect of HMG-CoA Inhibitors (Statins) on Rheumatoid Arthritis Disease Progression: A Systematic Review

BACKGROUND

Rheumatoid arthritis (RA) is a progressive autoimmune disease characterized by synovitis and leading to deformity and chronic disability. It may also affect organs, as well as vasculature. Currently, treatment for RA is based primarily in disease-modifying anti-rheumatic medications (DMARDs), which include TNF-alpha blockers, immune modulators, anti-folates, and purine synthesis inhibitors. These medications have been shown to slow RA disease progression, improve function, and decrease incidence of acute flares, and one particular DMARD, hydroxycholorquine, originally developed to treat malaria, has been shown to also improve lipid profiles in RA patients.[1] Adjunct therapy aims to address acute flares and disability by treating inflammation and pain using steroids and non-steroidal anti-inflammatory drugs (NSAIDs).

Unfortunately, current therapies, while systemically beneficial, do not target extraarticular manifestations of RA. Such manifestations include optic scleritis, pulmonary nodules, and most concerning, vasculitis. According to studies by del Rincon et al[2] and Avina-Zubieta et al,[3] in controlling for cardiovascular risk factors, patients with RA are at an increased risk of cardiovascular events compared to the general population. It is thought that the low-grade systemic inflammation of RA contributes to unexplained vascular disease in RA patients, however the pathophysiology behind such systemic inflammation remains in question. Some scholars believe it to be secondary to oxidative stress, while others attribute it to endothelial dysfunction, both theories supporting the notion that a biological stressor or injury leads to development of vasculitis and subsequent atherosclerotic changes.

Regardless of the underlying pathophysiology, to help decrease cardiovascular manifestations and complications, traditional cardioprotective therapies have been implemented in RA patients as adjuvant therapy to DMARDs, prednisone, and NSAIDs. One such cardioprotective therapy is the medication class 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (HMG-CoA inhibitors), also known as statins, which are touted for both their lipid lowering profile and also for what has been deemed an "anti-inflammatory" effect on endothelium. The role of statins as a means to control lipids and decrease cardiovascular risk has been well studied and shown to be significant. Results from the PROVE IT-TIMI22,[4] MIRACL,[5] JUPITER,[6] PRINCE,[7] and AFCAPS/TexCAPS[8] trials provide good evidentiary support for improvement in cardiovascular risk and decrease in CRP levels with statin use. However, the extent to which the pleiotropic effects of statins extend beyond the vessel wall is unclear.

Furthermore, there is a school of thought that purports the "anti-inflammatory" effect of statins is, in fact, low-density lipoprotein (LDL)-dependent, meaning any LDL-lowering agent would provide similar anti-inflammatory benefits. If anti-inflammatory effects are both LDL-dependent and independent, implementation of statin therapy may prove to be dually beneficial in an adult RA patient with active disease by addressing both dyslipidemia and the low-grade systemic inflammation that further compromises cardiovascular health.

To better understand this association, a relationship between statin use and decreased systemic inflammation in RA patients must be determined. Ideally, either radiologic studies or a laboratory test would be used. However, comparison of hand/feet radiographs in relation to statin therapy has not been studied and C-reactive protein

(CRP) and erythrocyte sedimentation rate (ESR), both sensitive markers of inflammation, are easily influenced by many different biological and environmental factors. Thus, a different approach is required. The disease activity score, DAS28, is calculated at each visit using the patient's ESR, rating of health on a visual analog scale, and also the patient's number of tender and swollen joints (out of 28). According to the National Rheumatoid Arthritis Society,[9] a DAS28 > 5.1 demonstrates active disease, a DAS28 < 3.2 demonstrates well controlled disease, and a score < 2.6 qualifies for remission. If the DAS28 score is > 3.2 or trends higher over time, this may lead the provider to adjust current therapies to help slow disease progression.

As such, comparison of the DAS28 from RA patients with and without adjuvant statin treatment will demonstrate if statins provide a benefit to RA disease progression.

The use of statins will specifically address certain cardiovascular manifestations of RA, such as vasculitis and dyslipidemia, which significantly compromise RA patient longevity. Furthermore, as adjuvant therapy to traditional RA treatment, statins may both slow disease progression, and reduce use or dose of the traditional medications, thus lessening occurrence of related adverse drug reactions (ADRs) such as gastrointestinal bleed, osteomalacia, increased susceptibility to infection, and disruption of autologous cortisone production.

Additionally, the cost of DMARDs is very high and this year atorvastatin, Lipitor, will be available in generic form, making this adjuvant therapy cost effective in both the short term (monthly co-pay cost) and long term (cost of disease and disability over time).

Of note, statins can further be broken down into those that are lipophilic or hydrophilic. While all statin medications carry the risk of elevated liver function tests,

myalgias, and, rarely, rhabdomyolysis, lipophilic statin medications such as atorvastatin (Lipitor) and simvastatin (Zocor) are associated with a higher incidence of myalgias, a smaller reduction in LDL, and a smaller increase in HDL. Hydrophilic statin medications such as rosuvastatin (Crestor) and pravastatin (Pravachol) have better lipid profiles and fewer reports of myalgias. This paper will not differentiate the different classes and will consider the statin family as a whole.

METHODS

Literature Search

A systematic search was performed in the following databases: Medline, CINAHL, and Web of Science. Keywords included: *rheumatoid arthritis*, *HMG Co-A inhibitor*, *statin*, "*severity of illness index,*" *disease progression,* and *treatment outcome*. In CINAHL, the search required the additional keywords *anticholesteremic agents* and *antilipemic agent*. Studies were limited to human studies and English language. Editorials and meeting abstracts were not included. The last search was performed in April 2012. Articles were evaluated for validity using the GRADE criteria.[10] Based on the quality of evidence, articles were categorized as: high, medium, low, and very low. Table I summarizes the GRADE system as applied.

Inclusion and Exclusion Criteria

All randomized, placebo- or active-controlled double-blind clinical trials meeting criteria of adult patients with active RA (as defined by EULAR criteria)[11] on stable DMARD dosing and without a medical history significant for hypertension, dyslipidemia, artery disease, myocardial infarction, diabetes, allergy to statin, or elevated liver function

tests were included. All trials had a minimum of nine patients in each study group. Studies were included if either the primary or secondary outcome addressed the impact of statin use on DAS28. The intervention was considered to be statin and the control to be placebo. Trials and studies were included if they allowed DMARD, steroid, and NSAID treatment during the trial period, however, DMARD dosing had to be maintained at the same dose and rate in the three months prior to study inception.

Exclusion criteria included DMARD instability before study implementation, secondary analysis of original data, and use of the Markov model to expand existing study data gathered in six months out to ten years for cost analysis. Also, studies addressing only cardiovascular events and outcomes were excluded and studies that collected data sufficient to calculate DAS28 (ESR, VAS, and joint count) but that did not do so were also excluded. Of note, studies were not excluded if they measured highly sensitive-CRP (hs-CRP) rather than CRP, as hs-CRP is a measurement of CRP at lower concentrations.[12]

RESULTS

Once duplicates were removed, 132 results remained, 17 of which were further screened using the eligibility criteria. Five studies are reviewed. (See Figure I.) Four are randomized-controlled trials,[13-16] one of which is unblinded[16] and one of which is a crossover study,[14] with the fifth study being a prospective cohort observational study.[17] Two studies took place in the United States,[13, 15] one in Japan,[17] one in Britain,[14] and one in Egypt.[16] Study dates range from 2004[13] to 2011.[16] All studies are presented in Table I with summary of findings presented in Table II.

Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo controlled trial

McCarey et al (2004)

The 2004 *TARA trial* by McCarey et al[13] assessed 116 RA patients on stable RA treatment divided into 58 patients receiving 40mg atorvastatin (trade name Lipitor manufactured by Pfizer) and 58 patients receiving a placebo. The primary endpoint was change in DAS28 with secondary endpoints of change in ESR, CRP, lipid profile, and plasma viscosity. Patients were computer randomized by an independent administrator at an off-site location. Both patients and doctors were blinded to group allocation. Standard RA treatment included DMARDs, NSAIDs, and steroids was allowed. DMARD dose was maintained at a steady level both in the three months before study inception and through study duration. With the exception of the four weeks before clinical assessment, intramuscular and intraarticular steroid injections were allowed. Exclusion criteria included: diabetes, familial dyslipidemia, current lipid lowering therapy, oral prednisone > 10mg/day, significant renal disease, and elevated liver enzymes or creatinine kinase found to be twice the normal limit at baseline. Smoking was not an exclusion criteria, however, the number of patients that smoke was prognostically similar between groups. Also, with the exception of methotrexate use, the groups were prognostically similar.[13]

Follow-up was maintained for six months with five withdrawals in the statin group (one lost to follow-up, three with ADRs, and one with pregnancy) and 13 withdrawals in the control group (four lost to follow-up, two with ADRs, seven for inefficacy of treatment). Authors report atorvastatin to be well-tolerated in the intervention study population, with similar frequency in reported ADRs between study

groups. There was no significant elevation in LFTs or muscle abnormalities detected or reported by those taking atorvastatin. Dropouts were analyzed in the groups to which they were assigned under the assumption of no change in baseline laboratory or assessment values.

DAS28[1] in the statin group decreased by 0.50 compared to a 0.03 increase in the control group (p=0.004). ESR[†] decreased by 5.03mm/h in the statin group versus a 1.91mm/h increase in the placebo group (p=0.005). CRP[†] also decreased in the statin group by 0.46 log mg/L, but increased in the control group by 0.12 log mg/L (p<0.0001). Swollen joints decreased by 2.69 in the statin group [95% confidence interval (-3.81) – (-1.57)][2] versus a decrease of 0.53 in the control group [95% CI (-1.59) – 0.52], p=0.0058. Additionally, tender joints decreased by 1.21 [95% CI (-3.28) – 0.86] and increased by 0.38 [95% CI (-1.16) – 1.92] in the statin and control groups, respectively (p=0.22).[13]

Regarding changes in cholesterol, atorvastatin resulted in a decrease in total cholesterol by 1.48mmol/L [95% CI (-1.73) – (-1.23)], a decrease in triglycerides by 0.24mmol/L [95% CI (-0.34) – (-0.14)], a decrease in LDL by 1.40mmol/L [95% CI (-1.63) – (-1.17)], and an increase in HDL by 0.03mmol/L [95% CI (-0.03) – 0.09]. The control group demonstrated a decrease in total cholesterol by 0.01mmol/L [95% CI (-0.14) – 0.12], an increase in triglycerides by 0.07mmol/L [95% CI (-0.04) – 0.18], a decrease in LDL by 0.07mmol/L [95% CI (-0.23) – 0.10], and a decrease in HDL by 0.04mmol/L [95% CI (-0.10) – 0.02]. Statistically, differences in total cholesterol,

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[1] See Table II for 95% confidence interval
[2] For all results, where necessary, standard deviations were converted to 95% confidence intervals [95% CI]

triglycerides, and LDL between the intervention group and control group were p<0.0001. The difference in HDL was p=0.097.[13]

To account for the higher incidence of methotrexate use by patients in the atorvastatin group, patients within this group were further analyzed with a comparison showing a difference of 0.19 in DAS28 [95% CI (-0.31) – 0.69, p=0.46], 1.72mm/h in ESR [95% CI (-5.06) – 8.51, p=0.61], and 0.12 log mg/L in CRP [95% CI (-0.24) – 0.49, p=0.51] between those in the statin group taking methotrexate and those in the statin group using a different DMARD.[13]

The study concluded that statins have a beneficial impact on RA by decreasing ESR, CRP, tender joint counts, swollen joint counts, and DAS28. Also, the study demonstrated that those in the intervention group using methotrexate had similar results to those in the same group using a different DMARD.[13]

Under a "conflict of interest" statement, the study notes two principal authors received educational grants from Pfizer, the manufacturer of atorvastatin, to fund ex-vivo analyses included in the report and several authors received travel grants or honoraria from Pfizer in the three years before study inception. The study further states that there is no employment, consultant, stock ownership, paid expert testimony or patent application relationships between study authors and Pfizer.[13]

Ezetimibe and Simvastatin Reduce Inflammation, Disease Activity, and Aortic Stiffness and Improve Endothelial Function in Rheumatoid Arthritis

Maki-Petaja et al (2007)

In 2007, Maki-Petaja et al[14] performed a randomized, double-blind cross-over study to assess the difference between ezetimibe (available only under trade name Zetia)

and simvastatin (available both as generic and under trade name Zocor), both of which are manufactured by Merck, on inflammation, disease activity, and endothelial function in patients with RA. Twenty patients with active RA from Addenbrooke's Hospital rheumatology clinics and twenty age- and gender-matched control patients were recruited. Exclusion criteria included: cardiovascular disease, untreated hypertension, diabetes, dyslipidemia, renal disease, and current smokers. Study design consisted of four parts: a two-week placebo run-in, followed by a six-week exposure to simvastatin 20mg/day or ezetimibe 10mg/day, then a six-week wash-out period, and ending with a six-week exposure to simvastatin 20mg/day or ezetimibe 10mg/day, whichever medication was not administered during the first exposure. Exposure to medications was randomly assigned. There is no mention of how medications were dispensed or if packing was similar. The length of the washout period was calculated using a custom hypothesis test and found to be six-weeks in order to prevent carry-over effects of the previous medication.[14]

After the completion of each cross-over stage (the end of week 2, week 8, week 14, and week 20), fasting lipid profile, blood glucose, ESR, rheumatoid factor, hs-CRP, and oxidized low-density lipoprotein (ox-LDL) were drawn and DAS28 was calculated using number of swollen and tender joints (out of 28 assessed joints), ESR, and patient-assessed VAS of overall well-being. Results demonstrated a reduction in DAS28[†] from 4.41 at baseline to 3.86 after ezetimibe and from 4.65 at baseline to 3.98 after simvastatin (overall significance p<0.002 with significance between drugs of p=0.7). ESR[†] decreased from 18.2mm/h at baseline to 12.9mm/h after ezetimibe and from 18.6mm/h at

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[†] See Table II for 95% confidence interval

baseline to 13.8mm/h after simvastatin (overall p-value <0.006 and difference between drugs p=0.9). Ezetimibe decreased hs-CRP[†] from 14.2mg/L at baseline to 8.8mg/L, while simvastatin decreased hs-CRP from 15.3mg/L at baseline to 10.3mg/L (statistical significance p=0.002 overall and p=0.9 between drugs).

Mean total cholesterol decreased from 5.3mmol/L at baseline [95% CI 3.3 – 7.3] to 4.7mmol/L after ezetimibe [95% CI 2.7 – 6.7, p<0.001] and from 5.4mmol/L at baseline [95% CI 3.6 – 7.2] to 4.1mmol/L after simvastatin [95% CI 2.7 – 5.5, p<0.001], with a statistical significance between drugs at p<0.001. LDL was reduced from 3.08mmol/L at baseline [95% CI 1.24 – 4.92] to 2.53mmol/L after ezetimibe [95% CI 0.65 – 4.41, p<0.001] and from 3.18mmol/L at baseline [95% CI 1.62 – 4.74] to 1.95mmol/L after simvastatin [95% CI 0.83 – 3.07, p<0.001], statistical difference between drugs p=0.001. Triglycerides were reduced from 1.5mmol/L at baseline [95% CI 0.1 – 2.9] to 1.3mmol/L after ezetimibe [95% CI (-0.1) – 2.7, p<0.025] and from 1.4mmol/L at baseline [95% CI 0.4 – 2.4] to 1.3mmol/L after simvastatin [95% CI (-0.3) – 2.9], overall p=0.02 and difference between drugs of p=0.8. HDL increased from 1.59mmol/L at baseline [95% CI 0.49 – 2.59] to 1.65mmol/L with ezetimibe [95% CI 0.51 – 2.79] and from 1.62mmol/L at baseline [95% CI 0.60 – 2.64] to 1.65mmol/L with simvastatin [95% CI 0.79 – 2.51], statistical significance of p=0.4 overall and p=0.7 between drugs.

Tender joint count decreased from 8.45 at baseline [95% CI (-4.11) – 21.01] to 7.30 after ezetimibe [95% CI (-7.44) – 22.04] and from 10.20 at baseline [95% CI (-6.46) – 26.86] to 7.4 with simvastatin [95% CI (-7.14) – 21.94], p=0.03 overall, p=0.3 between

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[†] See Table II for 95% confidence interval

medications. Swollen joint count decreased from 5.50 at baseline [95% CI (-3.38) –

14.38] to 4.30 with ezetimibe [95% CI (-8.58) – 17.18] and from 5.45 at baseline [95%

CI (-5.29) – 16.19] to 4.65 with simvastatin [95% CI (-7.35) – 16.65], overall statistical

difference of p=0.4 and statistical difference between drugs of p=0.8. Visual analog scale

decreased from 33.85 at baseline [95% CI (7.37) – 75.07] to 33.80 with ezetimibe [95%

CI (-8.84) – 76.44] and from 38.15 at baseline [95% CI (-6.95) – 83.25] to 36.85 with

simvastatin [95% CI (-5.35) – 79.05], overall statistical difference and difference between

drugs of p=0.8.[14]

Adverse drug reactions, losses to follow-up, and other medical complications

were not provided.

Study authors believe their data reveals a similar decrease in inflammation, and

DAS28, with ezetimibe and simvastatin and question if this is a result of a small sample

size or whether the mere reduction of LDL is anti-inflammatory in and of itself.[14]

It is noted in the study that the principal author's doctoral studies were funded by

GlaxoSmithKline, a large pharmaceutical company, and a co-author received an

unrestricted grant from Pfizer to develop a website promoting cardiovascular risk

reduction.[14]

Effects of High-dose Atorvastatin on Antiinflammatory Properties of High Density

Lipoprotein in Patients with Rheumatoid Arthritis: A Pilot Study

Charles-Schoeman et al (2007)

Charles-Schoeman et al[15] investigated the effects of high-dose atorvastatin

(Lipitor) on certain lipid levels of RA patients. This 2007 study randomly assigned

twenty patients with active RA to receive 80mg of atorvastatin (n=11) or a placebo (n=9)

for 12 weeks. Both patients and physicians are blinded to group allocation. Patients were

recruited from the rheumatology clinic at University of California, Los Angeles (UCLA).

Primary outcomes of this study were changes in inflammatory properties of HDL, as

assessed by cell-free assay (CFA), and hs-CRP with atorvastatin therapy. Secondary

outcomes included: change to DAS28, tender or swollen joint counts, patient pain

assessment using VAS, ESR, and lipid levels. Patients' anti-rheumatic medications were

continued and study exclusion criteria included: changes to anti-rheumatic therapy

within three months, pregnancy, lactation, previous qualification for lipid-lowering

therapy, hepatic disease, elevated liver function tests, and treatment with

hydroxychloroquine in the three months before study enrollment. Groups were

prognostically similar at baseline with the exception of hs-CRP, which was higher in the

atorvastatin group (10.4mg/L) than the placebo group (3.2mg/L), p=0.04.[15]

Patients followed-up at weeks 0, 3, 6, 12, and 18, and fasting blood tests

performed for lipid analysis and liver function tests at weeks 0, 6, and 12 weeks. Hs-

CRP, ESR, interleukin 6, and tumor necrosis factor-alpha were assessed at weeks 0 and

12. Changes in outcomes were recorded, however, the study did not provide standard

deviations or 95% confidence intervals for the results. Instead, the range of values was

given.[15]

Mean differences in outcomes after 12 weeks demonstrated a decrease in DAS[*]

by 0.78 in the placebo group and by 0.80 in the atorvastatin group (p=0.98), a decrease in

ESR[*] of 0.0mm/h and 2.7m/h in the placebo and statin groups, respectively, (p=0.64),

and an increase in hs-CRP[*] with placebo by 4.8mg/L versus a decrease in hs-CRP of

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[*] See Table II for range of values.

5.6mg/L in the statin group (p=0.14).[15]

Total cholesterol increased by 1.0mg/dL with placebo group [range (-32) – 57], compared with a decrease of 63.1mg/dL in the statin group [range (-106) – (-40)], p<0.0001. LDL increased by 0.8mg/dL in placebo group [range (-23) – 45] versus a decrease by 57.9mg/dL with statins [range (-93) – (-37)], p<0.0001. In the placebo group, triglycerides increased by 4.5mg/dL [range (-53) – 101] and HDL decreased by 0.8mg/dL [range (-0.9) – 7.0], compared to a decrease in triglycerides of 16.8mg/dL [range (-86) – 22] and a decrease in HDL of 2.0mg/dL [range (-14) – 16] in the statin group, p=0.33 and p=0.76, respectively.[15]

Number of tender joints decreased by 10.1 in the placebo group [range (-34) – 32] and by 12 in the statin groups [range (-37) – 1.0], p=0.8. Swollen joint counts decreased by 3.8 in placebo group [range (-7.0) – 5.0] and by 0.4 in the statin group [range (-9.0) – 20], p=0.11.[15]

One patient from each group was lost to follow-up, one due to transportation (placebo), and the other due to concern of mild LFT elevation (atorvastatin).[15]

Pfizer provided Atorvastatin. Study authors include Dr Alan Fogelman, chair of the department of medicine at UCLA and founder of Bruin Pharma, a company with a specialized focus on medications that enhance the anti-inflammatory properties of HDL. Another study author is also a principal and stockholder at Bruin Pharma.[15]

Effect of Atorvastatin on Inflammation and Modification of Vascular Risk Factors in Rheumatoid Arthritis

El-Barbary (2011)

In a 2011 study, El-Barbary et al[16] investigated the effect of atorvastatin on

inflammation and vascular risk factors in RA patients. 30 DMARD-naive, prognostically similar patients with an RA diagnosis received within one year of study start were randomly divided into two groups: Group 1 (n=15) received methotrexate 0.2mg/kg/week plus prednisone 10mg/day, while Group 2 (n=15) received the same therapy plus atorvastatin 40mg/day. For further control, 10 healthy age- and gender-matched individuals were enlisted for comparison. Over six months, study investigators, unblinded to group allocation, assessed DAS28, CRP, lipid profile, endothelial dysfunction, and several other biochemical markers.[16]

Study exclusion criteria included: conditions affecting lipid profile, endothelial dysfunction, and arterial stiffness, conditions such as diabetes, hypothyroidism, obesity, current smokers, familial dyslipidemia, history of heart attack within six months of study start date, cancer, and current use of anticholesteremic medications, beta blockers, hormone therapy, and vitamin E. Methotrexate dose remained stable throughout study duration, however, providers were allowed to use their discretion and taper prednisone in accordance with patient improvement. In both groups, steroids were held in the four weeks leading up to clinical and laboratory assessment.[16]

Analysis of data revealed a decrease in DAS28[†] in Group 1 (methotrexate and prednisone only) from 6.19 at baseline to 5.27 with treatment compared to a decrease of 6.09 at baseline to 3.9 with treatment in Group 2 (methotrexate and prednisone plus atorvastatin), $p<0.001$. ESR[†] decreased from 56.93mm/h at baseline to 43.60mm/h in Group 1 and from 58.33mm/h at baseline to 26.73mm/h in Group 2, $p<0.001$. CRP[†] decreased from 33.06mg/L at baseline to 19.73mg/L in Group 1 and from 31.46mg/L at

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[†] See Table II for 95% Confidence interval

baseline to 7.20mg/L in Group 2, p<0.001.[16]

In Group 1, total cholesterol increased from 224.66mg/dL at baseline [95% CI 162.42 – 286.90] to 235.66mg/dL after treatment [95% CI 173.8 – 297.52, p<0.05], LDL decreased from 142.33mg/dL [95% CI 93.51 – 191.15] to 140.40mg/dL [95% CI 89.0 – 191.8], triglycerides decreased from 137.33mg/dL [95% CI 42.71 – 231.95] to 137.13mg/dL [95% CI 43.57 -230.69], and HDL increased from 44.06mg/dL [95% CI 25.82 – 62.30] to 51.73mg/dL [95% CI 31.63 – 71.83, p<0.001]. In Group 2, total cholesterol decreased from 228.13mg/dL at baseline [95% CI 204.63 – 251.63] to 191.80mg/dL after treatment [95% CI 166.26 – 217.34, p<0.001], LDL decreased from 142.66mg/dL [95% CI 94.0 – 191.32] to 120.26mg/dL [95% CI 91.98 – 148.54, p<0.001], triglycerides decreased from 126.93mg/dL [95% CI 62.99 – 190.87] to 96.60mg/dL [95% CI 59.22 – 133.98, p<0.001], and HDL increased from 41.60mg/dL [95% CI 19.9 – 63.3] to 60.07mg/dL [95% CI 41.31 – 78.83, p<0.001].[16]

In Group 1, swollen joint counts decreased from 6.73 at baseline [95% CI 2.05 – 11.41] to 4.20 after treatment [95% CI 0.64 – 7.76, p<0.001] and tender joint counts from 11.0 [95% CI 5.82 – 16.18] to 7.20 [95% CI 3.98 – 10.42, p<0.001]. In contrast, in Group 2, swollen joints decreased from 6.06 at baseline [95% CI 0.86 – 11.26] to 1.53 after treatment [95% CI (-0.13) – 3.19, p<0.001] and tender joint counts decreased from 11.13 [95% CI 4.87 – 17.39] to 3.8 [95% CI 1.16 - 6.44, p<0.001]. In Group 1, VAS improved from 54.66 at baseline [95% CI 27.56 – 81.76] to 42.00 [95% CI 20.36 – 63.64, p<0.001] and morning stiffness lasted at 77.0 minutes at baseline [95% CI 5.42 – 148.58] and dropped to 59.33 minutes after treatment [95% CI (-8.25) – 126.91, p<0.001] versus Group 2, in which VAS improved from 56.0 at baseline [95% CI 26.44 – 85.56] to 21.0

after treatment [95% CI 7.28 – 34.72, p<0.001] and morning stiffness improved from 86.0 minutes at baseline [95% CI (-3.6) – 175.6] to 19.33 minutes after treatment [95% CI (-1.99) – 40.65, p<0.001]. Statistical significance between drugs for above measurements is p<0.001.[16]

Authors report atorvastatin to be well-tolerated with mild gastrointestinal adverse events arising in both groups equally. There was no significant elevation in liver function or muscle abnormalities for those taking atorvastatin.

While the study does report that 12 of 15 patients in Group 1 and 11 of 15 patients in Group 2 received oral steroids between 5-10mg per day, the study reports neither the number of patients who decreased steroid dose or frequency nor the amount of such decreases. Also, study authors do not mention any conflicts of interest in terms of funding or associations with pharmaceutical companies.[16]

Beneficial Action of Statins in Patients with Rheumatoid Arthritis in a Large Observational Cohort

Okamoto et al (2007)

A prospective cohort observational study performed by Okamoto et al[17] in 2007 analyzed possible benefits of statins in RA disease activity. Using data from the seventh phase of the cohort, containing 4152 patients with active RA, authors examined the difference in DAS28, CRP, ESR, Pain VAS, physician VAS, swollen joint counts, and tender joint counts between those taking statins (n=279) and those who were not (n=3873). Data was collected at bi-annual visits, one in both the fall and spring, and consisted of patient questionnaires, physician assessment, and laboratory data. DAS28 was calculated using a method developed by Prevoo et al.[18] The groups were noted to be

prognostically dissimilar, the statin group being older (mean age 64 in statin group versus 58 in control group) and having a longer disease duration (mean duration of 13 years in statin group compared to almost 12 years in control group). No p-values or confidence intervals were given to support this statement.[17]

Results did not demonstrate an improvement in DAS28[†] (mean value of 3.45 in statin group versus 3.57 in control, $p>0.05$), however they did demonstrate improvement in CRP[†] (mean value of 0.85mg/dL in statin group versus 1.24mg/dL in control, $p<0.0001$). Additionally, pain VAS improved {mean of 27.32 in statin group [95% CI (-23.36) – 78.0) versus a mean of 31.13 in control group [95% CI (-22.65) – 84.91], $p<0.05$)}, physician assessment improved {(mean of 12.59 in statin group [95% CI (-11.61) – 36.79] compared to 15.89 in control group [95% CI (-14.23) – 46.01], $p<0.001$)}, and joint counts also improved {(mean swollen joint count of 1.80 [95% CI (-3.92) – 7.52] and mean tender joint count of 2.32 [95% CI (-5.88) – 10.52] in statin group versus mean swollen joint count of 2.55 [95% CI (-4.45) – 9.55] and tender joint count of 2.87 [95% CI (-6.99) – 12.73] in control group, $p<0.0001$ and $p<0.05$, respectively)}. Changes in ESR, total cholesterol, LDL, triglycerides, or HDL were not recorded.[17]

To account for the increased use of steroids in the statin group, the results were further analyzed to compare results between those using low-dose (0-1mg prednisone per day), medium-dose (1-5mg prednisone per day), and high-dose steroids (>5mg prednisone per day). While the authors noticed a positive relationship between high-dose steroid use and serum cholesterol, they also noted that comparison within steroid dose groups showed those taking statins to have lower measures of disease activity (CRP, joint

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[†] See Table II for 95% Confidence interval

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counts, pain VAS, and physician VAS) while demonstrating no difference in DAS28.[17]

Authors note the research is supported by a grant from 33 different pharmaceutical groups, including Wyeth, Novartis, Pfizer, AstraZeneca, Aventis, and GlaxoSmithKline. The authors do not note an association or relationship between the companies and the authors themselves.[17]

DISCUSSION

While all studies[13-17] show statins to improve individual markers of inflammation, the picture remains mixed as to the effect of statins on RA disease progression. Three of the five studies[13, 14, 16] analyzed demonstrated a statistically significant improvement (p=0.004, p=0.002, and p<0.001, respectively) in DAS28 with adjuvant statin use, while the other two studies demonstrated either a statistically insignificant improvement (p>0.05)[15] or almost no statistical difference between the placebo and statin (p=0.98).[17]

While not all studies demonstrated a statistically significant decrease in DAS28 with statin use, they all showed improvement in one or more individual markers of systemic inflammation. Four studies[13, 14, 16, 17] found statins to improve CRP (p<0.0001, p=0.002, p<0.001, and p<0.001, respectively) and three studies showed an improvement in ESR (p=0.005, p=0.006, and p<0.001, respectively),[13, 14, 16] a decreased incidence of swollen joint counts (p=0.0058, p<0.001, and p<0.0001),[13, 16, 17] and an improvement in tender joint counts (p=0.03, p<0.001, and p<0.05, respectively).[14, 16, 17] Only one study[17] showed a decrease in VAS (p<0.001). Interestingly, while Charles-Schoeman et al[13] did not demonstrate improvement in the outcomes of interest to systematic review, it did demonstrate an improvement in the anti-inflammatory activity of HDL (p=0.026), an

outcome not investigated by the other four studies.[13, 14, 16, 17]

The results of the studies do not appear dependent upon specific statin medications or dosages. Of the studies demonstrating statistically significant improvement in DAS28, McCarey et al[13] and El-Barbary et al[16] used atorvastatin 40mg daily, while Maki-Petaja et al[14] compared simvastatin 20mg daily and ezetimibe 10mg daily. On the other hand, of the two studies showing statistically insignificant improvement, Charles-Schoeman et al[15] used atorvastatin 80mg daily and Okamoto et al[17] did not differentiate between statin drugs or dosages.

Interestingly, differences in DAS outcomes may be related to study quality (see Table I). Those studies that demonstrated a benefit to adjuvant statin use on RA disease progression were of higher study quality than those that did not. The three studies[13, 14, 16] that demonstrate statistically significant improvements in DAS28 are all considered either "high" or "moderate" quality. Given their study design, each study received an initial "high quality" rating and after analysis, one remained "high quality" while two were subsequently downgraded by one-point to a "moderate quality" rating for potential publication bias (financial ties to pharmaceutical industry)[13] or an unblinded study design.[16] The two studies that did not demonstrate such improvement are of lower quality. Charles-Schoeman et al was originally considered "high quality" but was downgraded by two-points to a "low quality" rating for indirectness and potential for bias.[15] Also, due to its study design, Okamoto et al received an initial "low quality" rating and was subsequently downgraded to "very low quality" for inconsistency and potential publication bias.[17]

It does not appear that changes in DAS28 are related to changes in cholesterol

levels. Of the four studies[13-16] that assessed changes in lipid levels between control and intervention groups, all demonstrated statistically significant decreases in total cholesterol and LDL with statin use, while only three of the four studies[13, 14, 16] demonstrated improvements in the DAS28.

Furthermore, in Maki-Petaja et al,[14] ezetimibe (Zetia), a non-statin anticholesteremic medication, and simvastatin (Zocor) both demonstrated statistically significant decreases in total cholesterol and LDL ($p<0.001$), however simvastatin demonstrated a statistically significant advantage over ezetimibe in decreasing these levels ($p=0.001$). Interestingly, despite the better total cholesterol and LDL-lowering profile of simvastatin, both ezetimibe and simvastatin resulted in similar improvements in the DAS28 (a statistical difference between drugs of $p=0.7$). This finding provides support to the theory that the decrease in the DAS28 by statin medications is related to the anti-inflammatory effects associated with the lowering of LDL, rather than a pleiotropic anti-inflammatory effect of statins. If the former proves true, and the anti-inflammatory effects are LDL-dependent, it would indicate that any anticholesteremic drug could be used to slow disease progression in rheumatoid arthritis. This finding would offer medical providers a greater ability to tailor treatment plans to individual patients and would allow those RA patients with contraindications to statins to receive a statin-alternative without forgoing anti-inflammatory benefits. Likewise, it may prompt providers to expand the use of hydroxycholorquine, secondary to its possible lipid-lowering profile,[1] and could potentially provide a reduction in current RA therapies and their associated ADRs.

Explanation of Downgrades to Study Quality

The GRADE assessment tool[10] was used to assess the quality of each study. Per GRADE protocol, the four randomized control trials[13-16] reviewed by this systematic analysis were given an initial "high" quality rating. The fifth study[17] is an observational study, which qualifies it for an initial quality rating of "low". Using GRADE criteria, review of the studies resulted in a downgrading of study quality for four of the five studies[13, 15-17] secondary to indirectness, imprecision, and/or bias (see Table I).

Charles-Schoeman et al[15] is considered to have an aspect of indirectness as the primary objective of this review, the DAS28, is a secondary outcome in their study, resulting in a one-point downgrade in study quality. The study quality of El-Barbary el al[16] was also downgraded by one-point, however, this was due to the unblinded nature of the study, which results in inherent imprecision. Inconsistency was noted in Okamoto et al,[17] resulting in a one-point downgrade for prognostically dissimilar groups.

Another limitation is the risk of publication bias, which is quite high in three of the studies[13, 15, 17] due to reported conflicts of interest secondary to funding, partnership, or association with pharmaceutical companies, resulting in a one-point downgrade in study quality. In what is considered one of the most influential studies demonstrating the benefits of statins on RA disease progression, the *TARA* trial,[13] the study is associated with Pfizer, the manufacturer of the investigated medication, atorvastatin (Lipitor). Furthermore, in Charles-Schoeman el al,[15] which assessed impact of statins on high-sensitivity CRP and inflammatory components of HDL, the principle author is the founder of a pharmaceutical company that is developing medications to enhance the anti-inflammatory properties of HDL, resulting in a significant conflict of interest. Finally, the observational study, Okamoto et al,[17] reports substantial conflict of interest, with its

authors noting association with 33 pharmaceutical companies.

The potential for bias in these studies[13, 15, 17] calls into question the motives of the authors and pharmaceutical companies for writing or sponsoring the studies. Perhaps the motives are based in altruism, however, with Pfizer's patent in Lipitor ending this year, allowing for generic production of atorvastatin, each company may be looking for new indications for their anticholesteremic medications in an attempt to extend the sunset provisions on their patents. The motives remain unclear and the bias decreases study quality.

Other Factors Affecting Study Quality

In addition to the aforementioned downgrades to study criteria, there are other limitations to consider which may impact study directness, precision, and consistency without being so significant as to qualify the study for further downgrade. In several studies,[14-16] sample sizes are small, allowing for imprecision. Also, Maki-Petaja et al[14] makes no mention as to the packing of the intervention and control medication, calling into question the thoroughness of study blinding. Furthermore, in all studies[13-17] patients were allowed to change their dose of prednisone or NSAID during course of study, however, not all changes were documented, and only one study[16] controlled for DMARD medications. Such changes are important to consider as DMARDs, prednisone, and NSAIDs directly impact the inflammatory markers used to calculate DAS28, causing an overestimation of treatment effect, and leading to imprecision and inconsistency.

Additionally, several studies[13, 15, 17] did not exclude certain patient populations, which introduces imprecision and inconsistency into the results. McCarey et al,[13] Charles-Schoeman et al,[15] and Okamoto et al[17] included smokers in their study

populations, contributing to inherent imprecision, as smoking has been proven to promote both an inflammatory and a hypercoaguable state. Interestingly, only one study, Charles-Schoeman et al,[15] listed concurrent hydroxychloroquine therapy as qualification for study exclusion. As questions remain as to the exact pathophysiology underlying why statins decrease inflammation in RA (pleiotropic versus lipid-lowering effects), and in light of the potential lipid-lowering effects of hydroxycholorquine,[1] the inclusion of patients receiving this treatment in the reviewed studies directly impacts results and decreases precision and consistency.

Additionally, while Charles-Schoeman et al[15] did not receive a downgrade in study quality for aspects listed above, the validity of its results could be called into question given that it did not demonstrate a statistically significant improvement in CRP with atorvastatin 80mg daily, a finding that is contradictory to the results of the PROVE IT-TIMI22 trial.[4] The PROVE IT-TIMI22 trial is one of the most prominent trials demonstrating the reduction in cardiovascular events with statin therapy; their intervention was atorvastatin 80mg daily.[4]

While CRP is not the main outcome assessed by this review, the discrepancy between the CRP outcomes of these two studies is important to examine as the contradictory findings may be due to study design. Charles-Schoeman et al[15] is a double-blind randomized controlled study comprised of 20 subjects with rheumatoid arthritis, 11 of whom received atorvastatin, from one center, UCLA, and all of whom, at baseline, did not qualify for lipid-lowering therapy (a specific cholesterol level cut-off was not provided). Follow-up for the study was 12 weeks.[15] In comparison, the PROVE IT-TIMI22 trial,[4] also a randomized double-blind controlled study, included 4162 subjects,

2099 of whom received atorvastatin, from 349 sites in eight countries, and all of whom had a total cholesterol of 240mg/dL or less, which, patient-dependent, could qualify them for lipid-lowering therapy. Rheumatoid arthritis diagnosis was not considered a demographic category. Study follow-up was 18 to 36 months.[4]

These two studies[4, 15] demonstrate obvious differences in study design; differences which could arguably influence CRP results. However, as no other studies reviewed in this paper used atorvastatin 80mg as their intervention, it is impossible to elucidate if the specific patient population, small study size, single study center, or short follow-up period of Charles-Schoeman et al[15] contributed to the statistically insignificant improvement in DAS28.

It is also important to consider the subjective nature of the DAS28 itself. While this review chose the DAS28 as the primary endpoint to assess RA disease progression, it is truly a compilation of several markers of RA disease progression, several of which are subjective. Tender joint counts and VAS are based on patient perception and ESR is easily influenced by factors other than inflammation. Therefore, only swollen joint count could be considered an objective marker of inflammation. While objective, this review found swollen joint counts to be an appropriate way to assess RA disease progression as swollen joint counts fluctuate variably, making them poor predictor for disease progression. As science progresses and the cellular-level biological processes of RA are better understood, a new marker, specific to RA and indicative of RA disease progression, may be uncovered, at which time the effectiveness of statins on RA disease progression can be screened using this specific, objective marker.

Recommendations for Further Studies

Further studies, including larger, long-term studies, are the next appropriate step both to assess the impact of statin medications on RA disease progression, and also to differentiate if the effect of statins on DAS28 is LDL-dependent or independent. Future studies should consider the direct impact of DMARDs, prednisone, and NSAIDs on systemic inflammatory markers and attempt to control for this imprecision. It is unethical to withhold these treatments from RA patients, so studies should both document dosing of these medications and also attempt to improve data precision by providing regimented dosing. Also, should future studies prove statin effects to be LDL-independent, and therefore, containing benefits attributable to statin medications alone, further investigation must be undertaken to assess if there is a benefit differential between the statin classes (hydrophilic or lipophilic) given their different drug profiles. Similarly, should the anti-inflammatory effects of statins prove to be LDL-dependent, non-statin anticholesteremic medications and medications with lipid-lowering profiles, such as hydroxychloroquine, must be investigated to assess the extent to which these medications provide benefit to RA patients.

In addition to assessing which medications slow RA disease progression, further studies should also focus on the cost of RA medications versus the cost of chronic disease. It may be tempting for providers, patients, and insurance companies alike to forgo a particular medication due to its monthly cost, however, research may demonstrate that the long-term costs related to excluding certain medication from RA therapy, such as decreased function and increased number of hospital visits, far outweigh the monthly co-pay cost of certain medications.

CONCLUSION

It is too early to declare adjuvant statin use to slow RA disease progression, however the results of this systematic review are encouraging and demonstrate adjuvant statin use in rheumatoid arthritis to have great potential. Although only three studies[13, 14, 16] demonstrated statin medications to provide a statistically significant decrease the DAS28, all five studies[13-17] demonstrated their use to improve other markers of systemic inflammation. Application of these results to current clinical practice means, in addition to their cardiovascular benefits, statins may allow for decreased traditional RA medication use, less ADRs attributable to standard RA therapies, decreases in short-term and long-term medical costs, and improvements in daily function and quality of life. While further research is necessary, the results are promising and, given the implications, may cause a shift in the basics of rheumatoid arthritis treatment.

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Table I. Characteristics of Reviewed Studies

		Quality Assessment					Summary of Findings	
			Downgrade Criteria				Quality	Importance
Design	Outcomes	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely		
McCarey et al, 2004[13]								
RCT	**Primary**: DAS28	None	None	No serious imprecision	No serious inconsistency	Industry Funded	Moderate	High
	Secondary: ESR, CRP, lipid profile, plasma viscosity							
Maki-Petaja et al, 2007[14]								
RCT	**Primary**: endothelial function (FMD, aPWV), disease activity (DAS28), inflammatory markers (CRP, ESR),	None	None	No serious imprecision	No serious inconsistency	No	High	High
	Secondary: lipid profile, blood pressure, tender and swollen joints,							
Charles-Schoeman et al, 2007[15]								
RCT	**Primary**: hs-CRP, inflammatory HDL	None	DAS28 considered secondary outcome	No serious imprecision	No serious inconsistency	Conflict of interest likely	Low	High
	Secondary: DAS28, ESR, tender and swollen joints, pain VAS							
El-Barbary et al, 2011[16]								
RCT	Primary: disease activity (DAS28), lipid profile, cytokines (TNF-α, resistin, adiponectin and MDA) and endothelial function (FMD)	Unblinded	None	No serious imprecision	No serious inconsistency	No	Moderate	High
	Secondary: tender and swollen joint counts							
Okamoto et al, 2007[17]								
Observational	Primary: CRP, pain assessment, swollen and tender joint counts, DAS, HAQ	None	None	None	Groups prognostically dissimilar	Industry Funded	Very Low	High
	Secondary: ESR, steroid use							

Table II. Summary of Findings

Study	Design	Intervention	Control	DAS28*	P-value	ESR*	P-value	CRP*	P-value
McCarey et al[13]	Double-blind randomized control trial	Atorvastatin 40mg, (n=58)	Placebo, (n=58)	Mean change [95% CI]		Mean change [95% CI]		Mean change [95% CI]	
				Atorvastatin: -0.50 [(-0.75) – (-0.25)] Control: 0.03 [(-0.23) – 0.28]	0.004	Atorvastatin: -5.03 [(-8.4) – (-1.67)] Control: 1.91 [(-1.61) – 5.44]	0.005	Atorvastatin: -0.46 [(-0.64) – (-0.28)] Control: 0.23 [(-0.09) – 0.34]	<0.0001
Maki-Petaja et al[14]	Double-blind randomized crossover trial	Ezetimibe 10mg or simvastatin 20mg, (n=20)	Placebo, (n=20)	Baseline [95% CI]; Post-treatment [95% CI]		Baseline [95% CI]; Post-treatment [95% CI]		Baseline [95% CI]; Post-treatment [95% CI]	
				Simvastatin: 4.65 [2.95 – 8.35]; 3.98 [1.36 – 6.6] Ezetimibe: 4.41 [2.01 – 6.81]; 3.86 [0.72 – 7.0]	Overall: 0.002 / Between drugs: 0.7	Simvastatin: 18.6 [(-6.2) – 43.4]; 13.8 [(-4.0) – 31.6] Ezetimibe: 18.2 [(-13.0) – 49.4]; 12.9 [(-6.9) – 32.7]	Overall: 0.006 / Between drugs: 0.9	Simvastatin: 15.3 [(-15.1) – 45.7]; 10.3 [(-10.5) – 31.1] Ezetimibe: 14.2 [(-15.2) – 43.6]; 8.8 [(-10.0) – 27.6]	Overall: 0.002 / Between drugs: 0.9
Charles-Schoeman et al[15]	Double-blind randomized control trial	Atorvastatin 80mg, (n=9)	Placebo, (n=11)	Mean change [range of values]¥		Mean change [range of values]¥		Mean change [range of values]¥	
				Atorvastatin: -0.80 [(-3.9) – 1.1] Control: -0.78 [(-2.5) – 2.2]	0.98	Atorvastatin: -2.7 [(-28.0) – 14] Control: 0 [(-10.0) – 19.0]	0.64	Atorvastatin: -5.6 [(-24.9) – 1.3] Control: 4.8 [(-3.5) – 41.2]	0.14
El-Barbary et al[16]	Randomized control trial	Atorvastatin 40 mg, (n=15)	No statin, (n=15)	Baseline [95% CI]; Post-treatment [95% CI]		Baseline [95% CI]; Post-treatment [95% CI]		Baseline [95% CI]; Post-treatment [95% CI]	
				Atorvastatin: 6.09 [4.33 – 7.85]; 3.9 [3.0 – 4.8] Control: 6.19 [4.55 – 7.83]; 5.27 [3.95 – 6.59]	Overall: <0.001 / Between drugs: <0.001	Atorvastatin: 58.33 [14.29 – 58.33]; 26.73 [9.61 – 43.85] Control: 56.93 [15.31 – 98.55]; 43.60 [3.0 – 84.2]	Overall: <0.001 / Between drugs: <0.001	Atorvastatin: 31.46 [2.8 – 60.12]; 7.2 [1.02 – 13.38] Control: 33.06 [4.8-61.32]; 19.73 [(-1.95) – 41.41]	Overall: <0.001 / Between drugs: <0.001
Okamoto et al[17]	Prospective cohort study	Statin, (n=279)	No statin (n=3873)	Mean change [95% CI]		Mean change [95% CI]		Mean change [95% CI]	
				Statin: 3.45 [1.21 – 5.69] No statin: 3.57 [1.09 – 6.05]	>0.05	-	-	Statin: 0.85 [-1.87 – 3.57] No statin: 1.24 [2.24 – 4.72]	<0.0001

*Where possible, standard deviations were converted to 95% confidence intervals [95% CI]

¥ Study did not provide standard deviations or 95% confidence intervals for results.

Figure I. Flow Diagram of Reviewed Studies