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Effects of Statins on Progression of Carotid Atherosclerosis as Measured By Carotid Intimal–Medial Thickness: A Meta-Analysis of Randomized Controlled Trials

Updesh Singh Bedi, MD¹, Mukesh Singh, MD¹, Param Puneet Singh, MD¹, Rohit Bhuriya, MD¹, Amol Bahekar, MD¹, Janos Molnar, MD¹, Sandeep Khosla, MD¹, and Rohit Arora, MD¹

Abstract
Background: Carotid intimal–medial thickness (CIMT) as measured by B-mode ultrasonography is a surrogate marker for carotid atherosclerosis. Studies have found conflicting results for the effect of statins on carotid atherosclerosis progression by measuring CIMT. Hence, this meta-analysis was conducted to evaluate the impact of statin therapy on CIMT progression. Methods: A systematic search using PubMed, EMBASE, and Cochrane library databases was performed. Heterogeneity of the studies was analyzed by the Cochran Q statistics. The significance of common treatment effect was assessed by computing common mean difference between the control and treatment groups. A 2-sided alpha error of less than 0.05 was considered to be statistically significant. Results: In all, 11 trials (N = 3806) fulfilled the criteria for inclusion in the analysis. The study population included 67.2% males and 22.8% females. The mean age was 58.7 years. Treatment with statins (mean treatment duration of 25.6 months) resulted in a significant reduction in the mean low-density lipoprotein ([LDL]; mg/dL, before treatment 168.6 ± 33.3, after treatment 102.33 ± 27.9, P < .05). No significant changes in the levels of LDL cholesterol were noted in the control group. A total of 7 trials showed regression and 4 trials showed slowing of progression of CIMT. Pooled analysis of all 11 trials showed that there was a statistically significant benefit with statin therapy in slowing down the progression of CIMT and the common mean difference between statin therapy arm and placebo arm was −0.040 (CI: −0.052−0.028; P value < .001). Conclusions: Statins therapy slows down the progression of carotid atherosclerosis as measured by CIMT, indicating benefits at subclinical stage of the disease process.

Keywords
statins, atherosclerosis, carotid intimal media thickness

Background
Carotid artery disease is an established risk marker for atherosclerotic complications. B-mode ultrasound allows early atherosclerotic changes in the walls of the carotid arteries to be seen, and it has been shown to correlate, and standardized for measurement of carotid intima–media thickness (CIMT).¹ Cross-sectional studies indicate an association between CIMT and cardiovascular risk factors²,³ and the prevalence of cardiovascular disease.⁴,⁵ Prospective studies⁶,⁷ have shown that CIMT can predict underlying coronary artery disease (CAD). Consequently, assessment of CIMT changes over time has become important in clinical intervention trials.⁸⁻¹⁰ Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have been shown in primary and secondary cardiovascular prevention trials to reduce the incidence of cardiovascular events.¹¹,¹² A total of 3 meta-analyses pooled the data of the 2 trials conducted in patients with CAD and other smaller previously published trials involving a total of 20 000 patients.¹¹,¹³⁻¹⁶ The consistent result among these meta-analyses was a stroke risk reduction of 2% to 30%. It is not clear whether this is attributable to a reduction in low-density lipoprotein cholesterol (LDL-C) or to other pleiotropic effects of statins. Various studies assessing the effect of statins on CIMT progression have shown conflicting results. Hence, this meta-analysis was conducted to evaluate the impact of statin therapy on CIMT progression.

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Methods

Literature Search

We performed this review in accordance with the quality of reporting of meta-analysis (QUOROM) statement and the Consolidated Standards of Reporting Trials (CONSORT) Group recommendations.17 A computerized search was performed to identify all relevant studies published in English language through January 2009 in EMBASE, CINAHL, Pub Med, and Cochrane database. We also searched for relevant review articles and their bibliographies for articles. The following search terms were used: carotid atherosclerosis, carotid intima–media thickness, carotid ultrasound, and statins.

Study Selection

There was a written protocol with explicit inclusion and exclusion criteria, which was followed for all articles that were screened. All titles and abstracts from the results of our computerized search were reviewed by the authors for potential inclusion in our study. We also went into the related links of all relevant articles. In addition to our computerized search, we manually reviewed the reference list of all retrieved articles to complete our search. Study selection process is outlined in Figure 1. Those studies that were not done in human participants, not randomized, published in nonpeer reviewed journals, or with inadequate follow-up were excluded from our analysis.

Inclusion Criteria

All studies had to meet all the following criteria to be included in the analysis:

1. Randomized controlled trials.
2. Minimum 6 months follow-up period.
3. Statins were 1 of the pharmacological agents in cases arm to study the benefit on CIMT.
4. Compare statin therapy with placebo or control group.
5. Follow-up ultrasound was done at least twice to assess changes in CIMT.

Exclusion Criteria

Studies that did not meet the above criteria were excluded.

Data Abstraction

After identifying all relevant articles, we extracted characteristics of the study (author, year, design, duration, sample size, statin use, and follow-up percentage) and participants (age, gender). A total of 2 reviewers independently extracted data and assessed outcomes. The interrater agreement was 90%, and disagreements were resolved by consensus. Data were entered in the Revman software for analysis using the double data entry system to prevent any data entry errors.

Statistical Analysis

A systematic review of the literature revealed 11 eligible studies. Heterogeneity of the studies was analyzed by the Cochran Q and $I^2$ statistics for each outcome. If the studies were found heterogenic for an outcome, the meta-analysis was performed by using the random effects model. Otherwise, the fixed effects model was used. The significance of common treatment effect was assessed by computing common mean difference between the control and treatment groups using the Comprehensive Meta-Analysis software (Biostat, Englewood, New Jersey). A 2-sided alpha error of less than .05 was considered statistically significant ($P < .05$).

Role of Funding Source

The funding source had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

Results

Literature Search

A total of 102 potentially relevant studies were identified and screened for retrieval. After title and abstract screening, 80 studies were excluded and the remaining 22 studies were retrieved for further evaluation. Of these 22 clinical studies, 11 were excluded as they did not meet inclusion criteria.
(because the data were repeated from previously published studies or no data on the outcome were available). Thus, 11 studies were included in our meta-analysis.8,10,18-25 Takahashi et al21 had 2 groups with different statin therapy regimens compared to placebo group. For the purpose of this meta-analysis, these 2 groups were treated as separate studies. The trial by Takahashi et al21 was a 3-way trial between placebo, pravastatin, and simvastatin. We split the 2 groups of statins and compared them with placebo group separately.

Overview of Carotid Intimal–Medial Thickness Studies and Patient Characteristics

The 11 trials included in the meta-analysis consisted of a total of 3806 patients (cases, n = 2132 with controls, n = 1674). About two third (67.2%) of study participants were males and about one third (32.8%) were females. The mean age of all patients was 58.7 years. Hypertension or diabetes was present in 20% and 8.7% patients, respectively. The main characteristics of the 11 studies included in the meta-analysis are listed in Table 1.

Ultrasound Examination

In addition to the baseline measurement, CIMT was measured during follow-up once in 3 trials (Takahashi et al21 and Yu et al24), twice in 4 trials (ASAP, ARBITER, LIPID, and BCAPS19,20,22,23), and 3 times or more frequently in 3 trials (ACAPS, METEOR, and REGRESS10,18,22,25). Carotid intimal–medial thickness was measured at both sides in 8 studies (ACAPS, METEOR, ASAP, ARBITER, Takahashi et al [2 groups considered as 2 different studies], Yu et al, and REGRESS10,18,21,24,25), only at the right in 3 studies (Hodis et al, LIPID and BCAPS22,23), at both the near and far arterial walls in 5 studies (ACAPS, METEOR, ASAP, LIPID, and REGRESS10,18,19,22,25), or only at far wall in 5 trials (ARBITER, Takahashi et al [2 groups considered as 2 different studies], BCAPS, Yu et al21,23,24).

LDL-Cholesterol Lowering

After treatment with statins (mean treatment duration of 25.6 months), there was a significant reduction in the mean LDL (pretreatment 168.6 ± 33.3 mg/dL, posttreatment 102.33 ± 27.9 mg/dL, P < .05, n = 2132) and total cholesterol levels (pretreatment 243.9 ± 31.6 mg/dL, posttreatment 174.2 ± 31.6, P < .05 mg/dL, n = 2132). No significant changes in the levels of LDL and total cholesterol were noted in the control group (n = 1674).

Effect of Statin Therapy on Carotid Intimal–Medial Thickness

In the pooled analysis, the common mean difference between statin therapy arm and placebo arm was −0.040 (CI: −0.052 to −0.028; P value < .001; Figure 2). This indicates that statin therapy has a statistically significant negative impact on CIMT.

Discussion

Our meta-analysis of >3000 randomized patients confirms that treatment with statins in high-risk patients with diabetes mellitus or coronary heart disease, irrespective of their background treatment, not only slows down the progression but also leads

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Table 1. Characteristics of Clinical Studies and Participants Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Statin Regimen</th>
<th>Mean Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment Group</td>
<td>Placebo Group</td>
<td>Treatment Group</td>
</tr>
<tr>
<td>Takahashi et al, (2005)21</td>
<td>RCT</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Takahashi et al, (2005)21</td>
<td>RCT</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
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<td>RCT</td>
<td>461</td>
<td>231</td>
<td>230</td>
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<tr>
<td>BCAPS, (2001)23</td>
<td>RCT</td>
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<td>RCT</td>
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<td>RCT</td>
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<td>Hodis et al19</td>
<td>RCT</td>
<td>188</td>
<td>99</td>
<td>89</td>
</tr>
</tbody>
</table>

NOTE: RCT = randomized controlled trial; P = placebo drug; NA = not available.
to regression of carotid atherosclerosis as measured by CIMT. Statin therapy was shown to slow the progression in 4 studies, and even caused regression of CIMT as seen in 7 of 11 studies included in this meta-analysis.

Initially, CIMT was shown to correlate with risk factors for atherosclerosis; however, CIMT was later established as an independent risk factor for future cardiovascular events. Now it is well established that even in its early stages, increased CIMT is associated with an increased risk of cardiovascular events.26-28 HMG-CoA reductase inhibitors have been shown to have antiatherogenic effects both in vitro and in vivo in animal models and in humans. In addition to cholesterol-lowering effect of statins, other mechanisms have been reported for their antiatherogenic effects. Aviram et al29 showed that lovastatin inhibited oxidized LDL both in vivo and in vitro, suggesting a role in preventing generation of atherogenic lipoproteins. Sindermann et al30 demonstrated inhibition of smooth muscle cell proliferation by lovastatin and simvastatin. Takahashi et al21 demonstrated that oxidized LDL, atherogenic lipoprotein, could induce macrophage growth in vitro,31,32 and statins suppress macrophage growth induced by oxidized LDL. This suggests that a noncholesterol metabolite/metabolites of the mevalonate pathway plays an important role in oxidized LDL-induced macrophage growth.33

Cholesterol lowering was among the first factors to be tested by the CIMT method. In the Asymptomatic Carotid Artery Progression Study (ACAPS), asymptomatic men and women 40 to 79 years of age were randomized to 20 to 40 mg/d of lovastatin or placebo.12 After 2 years of treatment, CIMT was lowered in the lovastatin group and increased in the placebo group. In the recent MEASURING Effects on Intima–Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial, participants with subclinical carotid atherosclerosis and low Framingham risk score were randomized to 40 mg/d of rosuvastatin or placebo. Participants on placebo had progression of CIMT, whereas those on rosuvastatin had unchanged CIMT.18

Our meta-analysis clearly indicates that cholesterol lowering with statins does affect the gradual thickening of the arterial wall, either by halting the process or reducing the CIMT. Both statin therapy groups in the trial of Takahashi et al21 along with the METEOR18 and REGRESS trial25 showed slowing of progression of carotid atherosclerosis, while 7 studies8,10,19,20,22-24 revealed regression of carotid atherosclerosis as measured by CIMT. In the LIPID trial,22 progressive benefit with prolonged statin therapy was seen. The carotid wall thickness was unchanged at 2 years on therapy, decreased at 4 years after starting the treatment, while it continued to increase in the placebo group. The difference between the treatment and placebo groups was statistically significant at both 2 years (P = .03) and 4 years (P < .001). However, the BCAPS trial23 found a significant reduction of CIMT at 18 months on fluvastatin therapy. This was not sustained and CIMT increased at 36 months, though the difference between the placebo and statin groups still remained statistically significant.

Moreover, there appears to be an incremental benefit with intensive lipid lowering as seen in ASAP19 and ARBITER trial.20 ASAP compared 80 mg atorvastatin to 40 mg simvastatin and ARBITER compared 80 mg atorvastatin to 40 mg...
lovastatin. The results of both the trials indicated incremental benefit with intensive LDL cholesterol lowering than less intense lowering. A previous meta-analysis by Amareno et al \textsuperscript{14} included 9 randomized controlled trials in which statins were given in the treatment group, and a strong relationship between reduction in LDL cholesterol and reduction in CIMT was shown. However, the trials were different in that meta-analysis, as the end point was stroke. All trials in which stroke events (brain infarction and hemorrhage) were recorded and the data were reported in intention-to-treat were included in this meta-analysis. However, we specifically included only those trials where effect of statin therapy on CIMT was recorded. We also included 2 new trials published in 2007, after the publication of meta-analysis by Amareno et al,\textsuperscript{14} which makes our results more relevant for current practices using latest antilipid therapy guidelines.

As with any meta-analysis, our study has some limitations. First, we included only published data and therefore there is a potential of publication bias. Second, both symptomatic and asymptomatic patients were included in these trials. Third, the methodology used for measurement of CIMT was different in different studies which may lead to detection bias and this could not be corrected in our meta-analysis. However, because serial measurements of CIMT were done and the mean difference was taken for analyzing the effect of statin therapy in individual studies, the effect of this bias seems to be small.

**Conclusion**

Compared to placebo group, statin therapy not only attenuates the rate of progression of carotid atherosclerosis but also causes its regression as measured by CIMT. Whether these findings are attributable to cholesterol lowering or pleotropic effects of statins is not clear. Thus, statin therapy is beneficial in patients with carotid disease at early subclinical stages as evaluated by surrogate imaging methods.

**Declaration of Conflicting Interests**

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