Journal of Cardiovascular Pharmacology and Therapeutics

http://cpt.sagepub.com/

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

J CARDIOVASC PHARMACOL THER 2010 15: 268 originally published online 14 May 2010
DOI: 10.1177/1074248410369110

The online version of this article can be found at:
http://cpt.sagepub.com/content/15/3/268

Published by:
SAGE
http://www.sagepublications.com

Additional services and information for *Journal of Cardiovascular Pharmacology and Therapeutics* can be found at:

Email Alerts: http://cpt.sagepub.com/cgi/alerts

Subscriptions: http://cpt.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Citations: http://cpt.sagepub.com/content/15/3/268.refs.html

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

Journal of Cardiovascular Pharmacology and Therapeutics
15(3) 268-273
© The Author(s) 2010
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1074248410369110
http://cpt.sagepub.com

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, MD[1], Mukesh Singh, MD[1], Param Puneet Singh, MD[1], Rohit Bhuriya, MD[1], Amol Bahekar, MD[1], Janos Molnar, MD[1], Sandeep Khosla, MD[1], and Rohit Arora, MD[1]

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 $\pm$ 33.3, after treatment 102.33 $\pm$ 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 factors[2,3] and the prevalence of cardiovascular disease.[4,5] Prospective studies[6,7] 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.

[1]Division of Cardiology, Department of Medicine, The Chicago Medical School, North Chicago, IL, USA

Corresponding Author:
Updesh Singh Bedi, Division of Cardiology, Mount Sinai Hospital, 1500 S California Ave, Chicago, IL 60608, USA
Email: bediupdesh@gmail.com

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

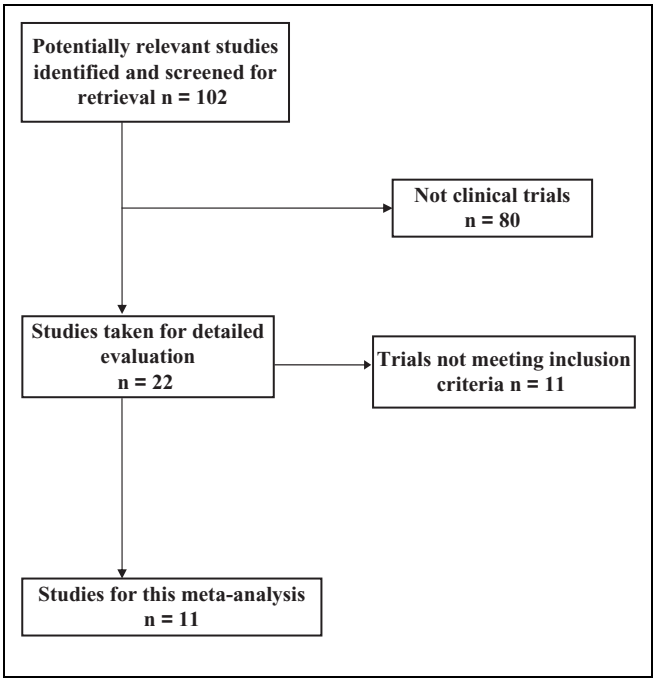

Figure 1. Study selection process for meta-analysis.

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

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

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

Study, Year	Study Design	Sample Size			Statin Regimen		Study Duration (Months)	Mean Age (years)	
		Total	Treatment Group	Placebo Group	Treatment Group	Placebo Group		Treatment Group	Placebo Group
Takahashi et al, (2005)[21]	RCT	30	15	15	Simvastatin	P	12	59.1 ± 5.5	57.1 ± 4.3
Takahashi et al, (2005)[21]	RCT	30	15	15	Pravastatin	P	12	57.9 ± 4.5	57.1 ± 4.3
Yu et al, (2007)[24]	RCT	112	57	55	Atorvastatin	P	6	66 ± 9	66 ± 10
REGRESS-US, (1998)[25]	RCT	255	131	124	Pravastatin	P	24	56.8 ± 8.1	55.2 ± 7.7
METEOR, (2007)[18]	RCT	984	702	282	Rosuvastatin	P	24	57 ± 6.2	57 ± 6
ACAPS, (1994)[10]	RCT	461	231	230	Lovastatin	P	36	61.9	61.3
ARBITER, (2002)[20]	RCT	161	79	82	Atorvastatin	Pravastatin	12	58 ± 11	61 ± 12
BCAPS, (2001)[23]	RCT	397	198	199	Fluvastatin	P	36	61.9 ± 5.2	61.9 ± 5.4
LIPID, (1998)[22]	RCT	522	273	249	Pravastatin	P	48	61	61
ASAP, (2001)[19]	RCT	280	141	139	Atorvastatin	Simvastatin	24	NA	NA
Hodis et al[8]	RCT	188	99	89	Lovastatin	P	48	58	58

NOTE: RCT = randomized controlled trial; P = placebo drug; NA = not available.

(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 al[21] 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 al[21] 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 al[21] and Yu et al[24]), twice in 4 trials (ASAP, ARBITER, LIPID, and BCAPS[19,20,22,23]), and 3 times or more frequently in 3 trials (ACAPS, METEOR, and REGRESS[10,18,25]). 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 REGRESS[10,18-21,24,25]), only at the right in 3 studies (Hodis et al, LIPID and BCAPS[22,23]), at both the near and far arterial walls in 5 studies (ACAPS, METEOR, ASAP, LIPID, and REGRESS[10,18,19,22,25]), or only at far wall in 5 trials (ARBITER, Takahashi et al [2 groups considered as 2 different studies], BCAPS, Yu et al[21,23,24]).

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

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

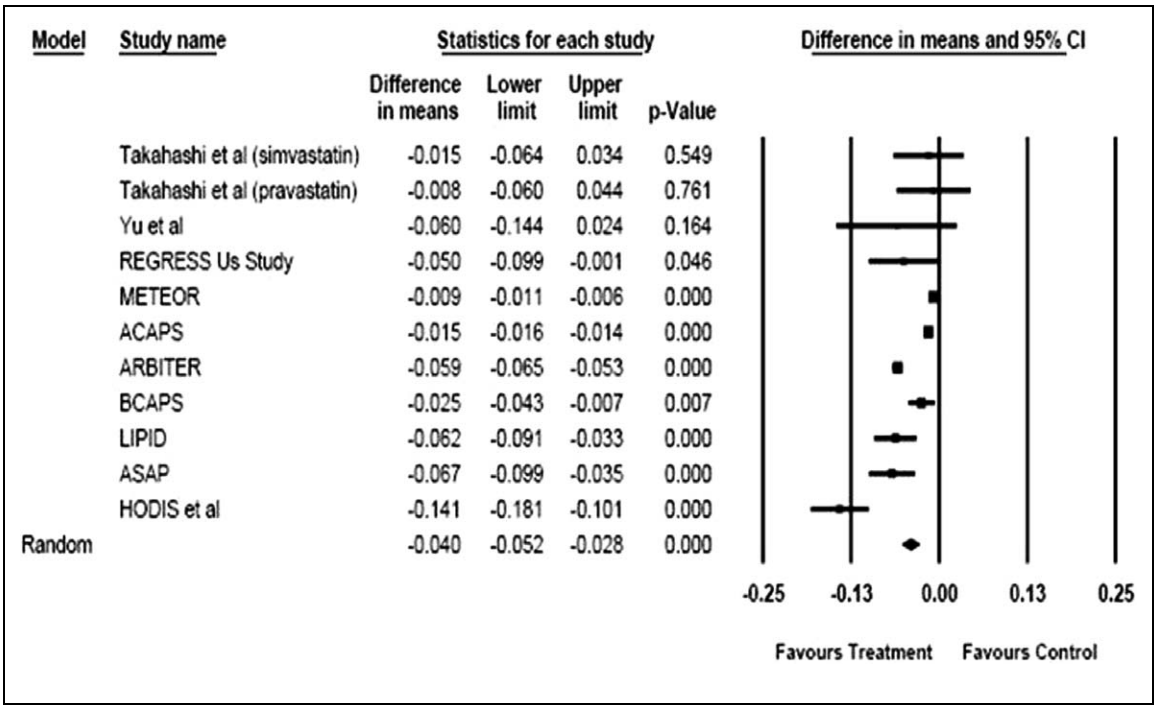

Figure 2. Change in carotid intimal–medial thickness (CIMT) statin therapy: mean difference between treatment and control.

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 al[29] showed that lovastatin inhibited oxidized LDL both in vivo and in vitro, suggesting a role in preventing generation of atherogenic lipoproteins. Sindermann et al[30] demonstrated inhibition of smooth muscle cell proliferation by lovastatin and simvastatin. Takahashi et al[21] 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 indicate 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 al[21] along with the METEOR[18] and REGRESS trial[25] showed slowing of progression of carotid atherosclerosis, while 7 studies[8,10,19,20,22-24] 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 trial[23] 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 ASAP[19] and ARBITER trial.[20] ASAP compared 80 mg atorvastatin to 40 mg simvastatin and ARBITER compared 80 mg atorvastatin to 40 mg

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

lovastatin. The results of both the trials indicated incremental benefit with intensive LDL cholesterol lowering than less intense lowering. A previous meta-analysis by Amarenco et al[34] 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 Amarenco et al,[34] 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

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure/Funding

The authors received no financial support for the research and/or authorship of this article.

References

1. Chambless LE, Zhong MM, Arnett D, Folsom AR, Riley WA, Heiss G. Variability in B-mode ultrasound measurements in the atherosclerosis risk communities (ARIC) study. *Ultrasound Med Biol*. 1996;22(5):545-54.
2. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular high risk factors in the general population of a Japanese city: the Suita study. *Stroke*. 1997;28(3):518-525.
3. Smilde TJ, van den Berkmortel FW, Boers GH, et al. Carotid and femoral wall thickness and stiffness in patients at risk for cardiovascular disease, with special emphasis on hyperhomocysteinemia. *Arterioscler Thromb Vasc Biol*. 1998;18(12):1958-1963.
4. Bots ML, Breslau PJ, Briët E, et al. Cardiovascular determinants of carotid artery disease: the Rotterdam Elderly Study. *Hypertension*. 1992;19(6 pt 2):717-720.
5. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle aged adults: the Atheorsclerosis Risk in Communities (ARIC) study. *Stroke*. 1995;26(3):386-391.
6. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerotic Risk in Communities (ARIC) study, 1987–1993. *Am J Epidemiol*. 1997;146(6): 483-494.
7. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima media thickness in predicting clinical coronary events. *Ann Intern Med*. 1998;128(4):262-269.
8. Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomised, controlled clinical trial. *Ann Intern Med*. 1996; 24(6):548-556.
9. Kroon AA, Asten van WNJC, Stalenhoef AFH. Effects of apheresis of low-density lipoprotein on peripheral vascular disease in hypercholesterolaemic patients with coronary artery disease. *Ann Intern Med*. 1996;125(12):945-954.
10. Furberg CD, Adams HP Jr, Applegate WB, et al for the Asymptomatic Carotid Artery Progression Study (ACAPS) research group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90(4):1679-1687.
11. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.
12. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333(20):1301-1307.
13. Sacks FM, Pfeffer MA, Moyé LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;336(13): 1001-1009.
14. Blauw GJ, Lagaay AM, Smelt AHM, Westendorp RGJ. Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke*. 1997;28(5):946-950.
15. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med*. 1997;157(12):1305-1310.
16. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol-lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *J Am Med Assoc*. 1997;278(4): 313-321.
17. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010

controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896-1900.
18. Crouse JR, Raichlen JS, Riley WA, et al. for the METEOR study group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis. The METEOR Trial. *JAMA*. 2007;297(6):1344-1353.
19. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJP, Stalanhoef AFH. Effects of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP). *Lancet*. 2001;357(8):577-581.
20. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness (ARBITER). *Circulation*. 2002; 106(3):2055-2060.
21. Takahashi T, Ishii N, Itai K, Goto R, Higashi K, Kobori S. HMG-CoA reductase inhibitors suppress the development and progression of carotid artery intimal medial thickening in hypercholesterolemic type 2 diabetic patients. *J Atheroscler Thromb*. 2005; 12(6):149-153.
22. MacMahon S, Sharpe N, Gamble G, et al. Effects of Lowering Average or Below-Average Cholesterol Levels on the Progression of Carotid Atherosclerosis: Results of the LIPID Atherosclerosis Substudy. *Circulation*. 1998;97(8):1784-1790.
23. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-Dose Metoprolol CR/XL and Fluvastatin Slow Progression of Carotid Intima-Media Thickness: Main Results From the ß-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001;103(1):1721-1726.
24. Yu CM, Zhang Q, Lam L, et al. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intimal-medial thickness in patients with coronary heart disease. *Heart*. 2007;93(7):933-939.
25. Groot E, Jukema JW, van Swijndregt ADM, et al. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). *J Am Coll Cardiol*. 1998;31(4): 1561-1567.
26. Touboul PJ, Elbaz A, Koller C, et al. on behalf of the GENIC Investigators. Common carotid artery intimamedia thickness and brain infarction: The Étude du Profile Genetique de l I'nfarctus Cerebral (GENIC) case-control study. *Circulation*. 2000;102(5): 313-318.
27. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis*. 2007;23(8):75-80.
28. Stein JH, Korcarz CE, Hurst RT, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21(10):93-112.
29. Aviram M, Dankner G, Cogan U, Hochgraf E, Brook G. Lovastatin inhibits low-density lipoprotein oxidation and alters its fluidity and uptake by macrophages: in vitro and in vivo studies. *Metabolism*. 1992;41(18):229-235.
30. Sindermann JR, Fan L, Weigel KA, et al. Differences in the effects of HMG-CoA reductase inhibitors on proliferation and viability of smooth muscle cells in culture. *Atherosclerosis*. 2000;150(3):331-341.
31. Sakai M, Miyazaki A, Hakamata H, et al. Lysophosphatidylcholine plays an essential role in the mitogenic effect of oxidized low density lipoprotein on murine macrophages. *J boil Chem*. 1994;269(6):31430-31435.
32. Sakai M, Miyazaki A, Hakamata H, et al. Lysophosphatidylcholine potentiates the mitogenic activity of modified LDL for Human Monocyte derived Macrophages. *Arterioscler Thromb Vasc Biol*. 1996;16(2):600-605.
33. Sakai M, Kobori S, Matsumura T, et al. HMG-CoA reductase inhibitors suppress macrophage growth induced by oxidized low density lipoprotein. *Atherosclerosis*. 1997;133(6):51-59.
34. Amarenco P, Labreuche J, Lavallee Touboul PJ. Statins in stroke prevention and carotid atherosclerosis. *Stroke*. 2004;35(12): 2902-2909.

Downloaded from cpt.sagepub.com at JOHNS HOPKINS UNIV on October 31, 2010