Antihypertensive Effects of Statins: A Meta-Analysis of Prospective Controlled Studies

Alexandros Briasoulis, MD;¹ Vikram Agarwal, MD, MPH;² Antonis Valachis, MD;³ Franz H. Messerli, MD²

From the Department of Medicine, ASH Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, IL;¹ the Department of Cardiology, St Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY,² and the Department of Oncology, Mälarsjukhuset, Eskilstuna, Sweden³

In experimental studies, statins have been shown to lower blood pressure through increased nitric oxide bioavailability and improved arterial compliance. The clinical significance of this effect remains poorly documented. The authors performed a meta-analysis of the effect of statins on systolic blood pressure (SBP) and diastolic blood pressure (DBP) including prospective randomized, controlled trials of statin therapy. EMBASE and MEDLINE searches for studies in which patients were randomized to treatment with a statin plus standard treatment (or placebo) vs standard treatment (or placebo) were conducted. Studies that provided data on SBP and DBP values before the initiation of the treatment and at the end of the follow-up period were included. A total of 40 studies with 51 comparison groups examining 22,511 controls and 22,602 patients taking statins were examined. Mean SBP in the statin group decreased by 2.62 mm Hg (95% confidence interval [CI], -3.41 to -1.84; P<.001) and DBP by 0.94 mm Hg (95% CI, -1.31 to -0.57; P<.001). In studies including hypertensive patients, the decrease in blood pressures with statins was slightly greater (SBP, -3.07 mm Hg; 95% CI, -4.00 to -2.15 and DBP, 1.04; 95% CI, -1.47 to -0.61). Similarly, statins effectively reduced SBP in diabetic patients. In this large meta-analysis of prospective controlled studies, the authors found a small but statistically significant reduction of SBP in patients taking statins. The decrease in blood pressure may contribute to the pleiotropic effect of statins in reducing cardiovascular risk. *J Clin Hypertens (Greenwich).* 2013;15:310–320. ©2013 Wiley Periodicals Inc.

Statins have pleiotropic effects such as improving endothelial-dependent vasodilation, increasing bioavailability of nitric oxide, and reducing levels of endothelin-1 (potent vasoconstrictor).¹ Statins also downregulate expression of angiotensin type 1 receptors, decrease expression of NAD(P)H oxidase subunit p22phox, and reduce free radical release in the vasculature² and have been shown to improve arterial compliance.³ These pleiotropic effects may directly lower blood pressure (BP) in addition to lowering cholesterol levels.³ Previous studies report a positive correlation between BP and cholesterol levels. Indirect evidence from several trials investigating cholesterollowering regimens suggests that lowering cholesterol simultaneously reduce BP by between may 2 mm Hg and 5 mm Hg.⁴ However, conflicting results have been reported with respect to BP-lowering effects of statins in humans.⁴ The present study was designed to systematically review prospective randomized trials and assess the antihypertensive effects of statins.

Address for correspondence: Franz H. Messerli, MD, Hypertension Program, Division of Cardiology, St Luke's-Roosevelt Hospital, Columbia University College of Physicians and Surgeons, 1000 10th Avenue, Suite 3B-30, New York, NY 10019 E-mail: messerli.f@gmail.com

Manuscript received: November 16, 2012; revised: January 13, 2013; accepted: January 18, 2013

DOI: 10.1111/jch.12081

MATERIALS AND METHODS

Search Strategy

We systematically searched the electronic databases MEDLINE, PubMed, EMBASE, and the Cochrane Library for Central Register of Clinical Trials using the MESH terms statins, HMG-CoA enzyme inhibitors, hypertension, blood pressure, and the names of individual statin agents. We limited our search to studies in humans and peer-reviewed journals in English language from 1996 to June 2012. Additionally, a manual search of all relevant references from the screened articles and reviews on statins was performed for additional clinical studies.

Study Selection

We included only prospective randomized, controlled trials published as original articles in peer-reviewed scientific journals in English. We excluded trials where we could not extract or calculate the difference between baseline and end-of-treatment systolic BP (SBP) and diastolic BP (DBP) in intervention and control groups and those that did not report any of the following variables: number of patients in both the statin and control groups, length of study, and description of the main relevant features of the study population, including sex, age, hypertensive status, and description of concomitant therapy, if any.

Data Extraction and Quality

The data were independently extracted by two authors (V.A. and A.B.) using standardized protocol and

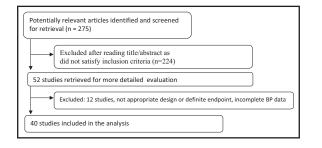


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. CI indicate 95% confidence interval.

reporting form (Figure 1). Disagreements were resolved by arbitration (F.M.), and consensus was reached after discussion. For our analysis we extracted characteristics of each study (type of design with duration of intervention and methods), baseline demographics, and SBP and DBP at baseline and at the end of the study. Authors of the papers were individually contacted if the data were unclear. The study quality was evaluated according to the Jadad composite score,⁵ which is a 5-point quality scale, with low-quality studies having a score of ≤ 2 and high-quality studies a score of $\geq 3.^{6}$

Outcomes Assessed

Our primary outcome was the difference in SBP and DBP among the treatment and control groups compared with baseline BPs.

Data Analysis and Synthesis

An intention-to-treat traditional meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. All analyses were performed by Review Manager (RevMan) 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Heterogeneity was assessed with the I^2 statistic, with I^2 <25% considered low and $I^2 > 75\%$ considered high. Since we expected individual studies to differ in baseline patient characteristics, choice of statin and its dose, and the length of follow-up, we decided a priori to use a DerSimonian-Laird random-effects model for relative risk (RR) estimation for all outcomes. Reported values are two-tailed, and hypothesis testing results were considered statistically significant at P=.05. Small study effect, including publication bias, was tested using funnel plot and Egger tests. If publication bias was found, the nonparametric trim and fill method of Duvall and Tweedie was performed to add studies that appeared to be missing. We separately analyzed the various groups of statins. We separately examined whether there were any differences in the outcomes between the studies that included an up-titration of the antihypertensive agents during the study vs the studies that kept the dosages of the antihypertensive medications stable. Meta-regression (OpenMeta analyst) was used to assess whether age, follow-up duration, and Jadad score were associated with the effect of statin therapy on BP.

RESULTS

Study Selection

We identified 40 clinical studies (Table I), with 40 control arms and 51 intervention arms, which examined the effects of statins on SBP and DBP based on our inclusion and exclusion criteria. The inter-rater reliability was measured by the use of the Cohen's kappa test, which in our study was 0.91 (standard error, 0.035), suggesting good agreement.

Baseline Characteristics

These studies enrolled 22,511 controls and 22,602 patients taking statins, with an average follow-up duration of 13.9 months. The mean age of patients taking statins was 57.9 ± 5.8 years, which was not significantly different from the mean age of the control group (57.7 ± 6.5 years). Atorvastatin was the statin used in 15 studies,^{7,9-12,14,16,20,24,31,34,36,37,41,43} pravastatin in 8 studies,^{8,13,19,26,28,39,40,42,46} simvastatin in 10 studies,^{13,23,29,30,35,39,44,45,47,49} fluvastatin in 4 studies,^{21,27,38,39} cerivastatin in 2 studies,^{15,25} and lovastatin in 1 study.⁴⁸ One study²⁷ compared fluvastatin plus orlistat (an inhibitor of intestinal lipid digestion) with orlistat alone. Some studies included only hypertensive patients,^{7,9,10,12,15–24,28,30,31,35–42,44,45} and other studies up-titrated the antihypertensive agents.^{7,9,10,12,15,17–19, 21,36,38–40,49} Four studies included only type 1 or only type 2 diabetic patients.

Quality Assessment

The included studies were of variable quality. Twentyfour studies were of good quality (Jadad score ≥ 3), with a low risk of bias, and 15 studies of low quality (Jadad score <3), with a high risk of bias. During the study selection process, we attempted to avoid duplication of data. However, the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) study¹⁰ recruited 891 patients already randomized into the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA).^{20,33} The CAFE-LLA study examined the effects of atorvastatin on aortic pressures and aortic stiffness, an endpoint not included in the ASCOT-LLA study. Additionally, according to the study protocol, the patients' brachial BPs and central hemodynamics were measured separately from the main ASCOT-LLA protocol. Therefore, we decided to include the study in our analysis. A sensitivity analysis excluding the CAFE-LLA results did not influence the effects on SBP, DBP, or heterogeneity.

Heterogeneity. For the outcomes measured, when all studies were combined, a highly significant level of statistical heterogeneity was evident, suggesting that it is

| | (| | | | | | | | |
|-------------------------------------|---------------------------|--------------------|---------|----------------------------------|-----------------|----------------------------|-------------------|----------------------------|-----------------------------|
| | | | | | | | Treatment Group | | |
| | Up-titration | | | HTN/ | Age | Treatment Group | Follow-Up | Control Group | Control Group |
| Stuchv | of Antihyper- tensives | Statin mo/d | Follow- | Follow- Hyperlipidemia/ In mo | Control SD | Baseline SBP/ DBP mm Hr | SBP/DBP, mm Hd | Baseline SBP/ DBP mm Hr | Follow Up SBP/ DBP mm Hd |
| orady | | 0.00011, 1119/0 | 200 | Labored | | B | P | , mu | S |
| Lavallee and | + | Atorvastatin (80) | e | -/+/+ | 61/60 | 132.7 (14.6)/ | -3.9 (2.1)/ | 133.7 (12.8)/ | -0.8 (2.24)/ |
| colleagues' | | | | | | 78 (8.3) | -2.8 (1.4) | 78.1 (7.7) | -1.4 (1.5) |
| Mancia and | I | Pravastatin (40) | 31 | -/+/+ | 58.5/58.3 | 159.6 (8.9)/ | -19.2 (1.94)/ | 160 (9.1)/ | -18.1 (1.94)/ |
| colleagues ⁸ | | | | | | 98.3 (4.1) | -12.4 (1.55) | 98.3 (4.4) | -12.8 (1.55 |
| Williams and | + | Atorvastatin (10) | 40 | -/+/+ | 62.6/62.9 | 159.6 (16.7)/ | 133.9 (0.6)/ | 160.3 (17.5)/ | 133.8 (0.6)/ |
| colleagues ¹⁰ | | | | | | 92.5 (9.7) | 79.1 (0.4) | 92.9 (9.2) | 79 (0.4) |
| Manisty and | + | Atorvastatin (10) | 12 | -/+/+ | 64/84 | 158 (20)/93 (10) | 141 (11)/81 (8) | 164 (20)/94 (10) | 142 (12)/81 (7) |
| colleagues ⁹ | | | | | | | | | |
| Orr and | I | Atorvastatin (80) | e | -/+/- | 53/55 | 129 (4)/74 (2) | 124 (4)/73 (3) | 127 (4)/75 (2) | 124 (4)/75 (2) |
| colleagues ¹¹ | | | | | | | | | |
| Ge and | I | Atorvastatin (20) | 4 | -/+/+ | 64/65 | 164.3 (14.8)/ | 123.2 (12.4)/ | 162.8 (13.4)/ | 136.7 (11.2) |
| colleagues ³⁷ | | | | | | 106.4 (9.2) | 82.5 (7.8) | 105.2 (8.6) | 91 (7.32) |
| Kuklinska and | I | Atorvastatin (80) | ი | -/+/+ | 53 | 129 (11)/76 (9) | 123.3 (8.9)/ | 129.5 (13)/ | 128.5 (9.7)/ |
| colleagues ¹⁶ | | | | | | | 72.1 (8.6) | 74 (7.6) | 74 (7.6) |
| Grimm and | I | Atorvastatin (20) | 1.5 | -/+/+ | 56.5/55.5 | 132.3 (11.3)/ | -4 (1)/ | 132.9 (12.3)/ | -1 (1.17)/ |
| colleagues ¹⁴ | | | | | | 81 (9.5) | -1.7 (0.8) | 81.9 (8.2) | -1.1 (0.7) |
| | | | c | | (0) 01 | | | | |
| Koh and colleagues ¹² | I | Atorvastatın (20) | N | -/+/+ | 53 (2) | (1) 96/(1) / GL | 138 (2)/85 (1) | 156 (2)/95 (1) | (1) 68/(1) 651 |
| Tonelli and | H | Dravactatin (10) | VC | 171 | 58 5/58 7 | 108 7 (18 A)/78 E | 0 7 /0 ///0 2 | 100 /17 8// | 10 0/ 0 0 |
| colleanies ¹⁹ | - | | r N | | | (10.9) | 7.0 1/1-00 1.0 | 78 6 (10 1) | (CO) 70- |
| 0011000000 | | | : | • | | | | | (0:0) + 0 |
| Ichihara and | + | Pravastatin (10) | 12 | -/+/+ | 60/60 | 142 (7)/84 (3) | 140 (5)/86 (2) | 142 (6)/89 (4) | 138 (10)/90 (3) |
| colleagues | | | | | | | | | |
| | | Simvastatin (5) | 12 | | 60 | 145 (4)/88 (2) | 142 (4)/86 (2) | | |
| | | Fluvastatin (20) | 12 | | 60 | 142 (6)/84 (3) | 141 (4)/85 (2) | | |
| Kushiro and | + | Pravastatin | 60 | -/+/+ | 60/60 | 140.9 (16)/ | 138.6 (16)/ | 141 (15)/83 (10) | 139.1 (15)/ |
| colleagues ⁴⁰ | | | | | | 82.9 (10) | 80.3 (10) | | 81.3 (10) |
| Terzoli and | + | Simvastatin, | 2 | -/+/+ | 62.7 (10.3)/ | 149.8 (15.9)/ | 143.6 (11.3)/ | 152.2 (12.4)/ | 150.6 (11.6)/ |
| colleagues ¹⁸ | | Pravastatin, | | | 62.7 (10.3) | 87 (9.3) | 83.7 (10.1) | 85.3 (5.8) | 87.4 (6.4) |
| | | Atorvastatin | | | | | | | |
| | | | | | | 135.2 (14.6)/ | 132.8 (13.7)/ | 140.3 (11)/ | 138.7 (10.6)/ |
| | | | | | | 78.7 (10.7) | 77.6 (9.5) | 82.6 (4.6) | 83.7 (6.4) |
| Collins and | + | Simvastatin (40) | 56 | -/+/+ | 65.5 (7.8)/ | -7.6 (27.5)/-4.5 | | -7.1 (28.9)/ | |
| colleagues ⁴⁹ | | | | | 65.1 (8.2) | (15.1) | | -4.6 (14.1) | |
| Sposito and | + | Pravastatin, | 4 | -/+/+ | 52 (3)/53 (3) | 153 (9)/100 (3) | 130 (5)/81 (4) | 149 (8)/102 (2) | 137 (6)/87 (8) |
| colleagues ¹⁷ | | Lovastatin | | | | | | | |
| Athyros and | I | Various Statins | 36 | -/+/+ | 58 (11)/58 (14) | 123 (14)/74 (8) | 122 (12)/74 (8) | 125 (16)/75 (9) | 122 (13)/73 (8) |
| colleagues ²² | | (various doses) | | | | | | | |
| Cohn and | + | Atorvastatin (10) | 2 | -/-/+ | 54.7 (8.9)/ | 146.7 (11.1)/91.8 | -7 (2)/-4.2 (1) | 147 (11)/93 (5.3) | -5 (2)/-3.4 (0.8) |
| colleagues ³⁴ | | | I | • | 55.3 (9.3) | (7.2) | | | |
| | I | Cerivastatin (0.8) | e | +/-/+ | 59 (8)/59 (8) | 148 (22)/86 9) | 141 (22)/82 (12) | 151 (14)/85 (11) | 157 (16)/88 (11) |
| | | |) | | | | | | |

| Study | Up-titration of Antihyper- tensives | Statin, mg/d | Follow- F Up, mo | HTN/ Follow- Hyperlipidemia/ Jb, mo Diabetes | Age Treatment/ Control, SD | Treatment Group Baseline SBP/ DBP, mm Hg | Treatment Group Follow-Up SBP/DBP, mm Hg | Control Group Baseline SBP/ DBP, mm Hg | Control Group Follow Up SBP/ DBP, mm Hg |
|--|---|--------------------------------------|---------------------|--|----------------------------------|--|---|--|---|
| Balletshoffer and | | | | | | | | | |
| colleagues | I | Cerivastin (0.2) Simvastatin (40) | р | -/+/+ | 59 (8)/59 (8) 38.7 (10)/ | 141 (22)/82 (12) 142 (11.8)/91 (10.8) | 149 (26)/86 (11) 136 (9.5)/84 (9.8) | 136 (9.5)/ | 131 (12.4)/82 (7.5) |
| and colleaques ⁴⁵ | | | | | 38.7 (10) | - | ~ | 86 (11) | ~ |
| Danaoglu and colleagues ³⁵ | I | Simvastatin (20) | ი | -/+/+ | 52 (3)/54 (4) | 160 (11)/99 (9) | 122 (9)/76 (6) | 158 (14)/ 104 (10) | 126 (19)/82 (8) |
| Derosa and | I | Fluvastatin (80) | 12 | -/+/ | 50.6 (9.4)/ 52 4 (10 2) | 133 (4)/86 (5) | 127 (5)/82 (3) | 132 (5)/84 (3) | 128 (3)/82 (2) |
| | | Fluvastatin (80) | 12 | | 53.1 (10)/ 51.6 (8.3) | 132 (4)/85 (3) | 123 (4)/79 (2) | 131 (3)/85 (4) | 125 (3)/81 (2) |
| Fassett and colleagues ³⁶ | + | Atorvastatin (10) | 12 | -/+/+ | 62.3 (16.3)/ 64.8 (15) | 147.6 (20.2)/75.8 (9.1) | -4.18 (8.35)/ -1.24 (5.22) | 148.3 (22.1)/ 79.3 (6.7) | -4.63 (8.98)/ -1.98 (3.51) |
| Glorioso and | I | Atorvastatin (20) | 4 | -/+/+ | 53 (2)/53 (2) | 149 (6)/97 (2) | 140 (5)/90 (4) | 149 (6)/97 (2) | 147 (8)/94 (4) |
| colleagues | + | Fluvastatin (40) | 12 | -/+/+ | 55.8 (7.9)/ | 141.8 (12.3)/90.5 | -1.7 (14.25)/ | 140.4 (15.3)/ | -1.5 (7.68)/ |
| colleagues Su and | 0 | Pravastatin (10) | 9 | -/+/+ | 61/64 (5.2) | (/.4) 175 (11)/105 (6) | 0.1 (9.1) 130 (9)/73 (6) | 88.0 (9) 174 (9)/104 (5) | -1.1 (7.08) 130 (8)/76 (7) |
| colleagues ⁴⁶ Teixeira and | + | Fluvastatin (20) | 12 | -/+/+ | 51/51 | 139 (14)/87 (11) | 126 (12)/80 (7) | 138 (12)/86 (9) | 131 (11)/82 (8) |
| Sever and colleagues | I | Atorvastatin (10) | 36 | -/+/+ | 63/63.3 | 164.3 (17.8)/95.1 (10.2) | 137.5 (17)/ 80.5 (9.5) | 164.7 (18.3)/ 95.1 (10.4) | 137.5 (16.8)/ 80.8 (9) |
| 0 | | Atorvastatin (10) | 36 | -/+/+ | 63.2/63 | 164.1 (17.7)/94.9 | 140 (16.5)/ | 163.7 (17.7)/ 05 (10.1) | 140.5 (16.5)/ |
| Colomb and colleagues ¹³ | I | Pravastatin (40) | 9 | -/-/- | 57.4/57.7 | (10.4) 126.8/75.2 | 02:3 (3.0) -2.5 (21.12)/ -2.8 (17.61) | 126.5/74 | 02.0 (3.0) -1 (21.1)/ -0.4 (17.8) |
| | | Simvastatin (20) | 9 | | | 126.8/75.2 | -2.7 (21.05)/ -2.4 (17.2) | | 0.2 (20.9)/ 0.6 (17.1) |
| Lee and | I | Pravastatin (40) | 9 | -/-/+ | 71/72 | 133 (16)/76 (10) | 130 (18)/79 (8) | 134 (15)/75 (9) | 132 (14)/79 (8) |
| colleagues colleagues ⁴³ | I | Atorvastatin (10) | N | -/+/+ | 54.1/51.4 | 153 (4.8)/87.1 (6.7) | 136.9 (6.1)/7 8.3 (4.2) | 151.1 (7.4)/ 84.7 (5.9) | 150.9 (6.8)/ 83.2 (5.7) |
| Nakamura and | 1 | Cerivastatin (0.15) | 9 | +// | 58/55 | 122 (14)/78 (10) | 118 (16)/76 (8) | 124 (12)/76 (12) | 126 (12)/76 (10) |
| Olkinuora and | I | Simvastatin (10) | ი | -/+/+ | 61/62 | 156 (12)/93 (9) | 142 (10)/86 (8) | 161 (12)/95 (9) | 147 (15)/88 (9) |
| Colleagues McDowell and | I | Simvastatin (40) | ю | -/+/ | 18–70 | 133 (18.7)/80 (11.2) | 136 (18.7)/78 (11.2) | 130 (20.8)/76 (10.4) | 137 (17.3)/80 (7) |

| TABLE I. | Intervention | TABLE I. Intervention, Characteristics, and I | d Effects | on BP in Ind | iividual Studi∈ | Effects on BP in Individual Studies (Continued) | | | |
|--|-------------------|---|-----------|-------------------------------------|------------------|---|-------------------------------|-------------------------|-----------------------------|
| | | | | | | | Treatment Group | | |
| | Up-titration | | | HTN/ | Age | Treatment Group | Follow-Up | Control Group | Control Group |
| | of Antihyper- | | Follow- | ⁻ ollow- Hyperlipidemia/ | Treatment/ | Baseline SBP/ | SBP/DBP, | Baseline SBP/ | Follow Up SBP/ |
| Study | tensives | Statin, mg/d | Up, mo | Diabetes | Control, SD | DBP, mm Hg | mm Hg | DBP, mm Hg | DBP, mm Hg |
| Hommel and colleagues ³⁰ | | Simvastatin (20) | ю | +/+/+ | 41/35 | 140 (18)/84 (11) | 135 (21)/82 (10) | 135 (19)/83 (11) | 138 (18)/86 (11) |
| Bak and colleagues ²⁶ | | Pravastatin+diet 1 (20) | 9 | -/+/- | 55.3/54.6 | 133 (14.1)/83.1 (7.4) | 2.5 (16.1)/2 (7.14) | 134.4 (14.9)/82.9 (8) | 0.6 (18.6)/0.9 (9.1) |
| | | Pravastatin+diet 2 (20) | | | 55.6/54.6 | 137.5 (16.3)/85.4 (6.1) | -5.1 (18.21)/ -0.9 (8.9) | 137.4 (14.2)/84.1 (7.3) | -2.8 (15.7)/0.1 (7.65) |
| Lee and colleanues ²⁸ | | Pravastatin (20) | 9 | -/+/+ | 52/50 | 121 (10)/70 (4) | 120 (11)/70 (6) | 117 (10)/69 (5) | 117 (8)/70 (4) |
| Hodis and colleagues ⁴⁸ | | Lovastatin (80) | 48 | -/+/ | 37–67 | 124.6 (13.3)/80.5 (7.2) | 122.5 (11.9)/ 78.7 (6.7) | 122.2 (14)/79.6 (8.1) | 121.1 (12.6)/78.7 (7.6) |
| Borghi and colleagues ²³ | | Simvastatin | 60 | -/+/+ | 55.2 (10) | 118 (5)/78.5 (6) | 3.54 (6.14)/ -1.57 (4.7) | 119.3 (6)/79.3 (7) | 3.58 (6)/-1.98 (3.49) |
|) | | Simvastatin | 60 | | 59.9 (7) | 130.3 (1)/82 (8) | -6.5 (10.42)/ -3.28 (6.56) | 132.6 (3)/84.7 (6) | 66 (9.78)/-1.7 (5.5) |
| | | Simvastatin | 60 | | 61.2 (8) | 145.6 (6)/88.3 (8) | -11.64 (7.2)/ -5.3 (7.5) | 145.3 (4)/89.5 (7) | 2.9 (5.25/ -2.68 (6.5) |
| | | Simvastatin | 60 | | 65.5 (8) | 164.7 (5)/97.2 (6) | -24.7 (7.2)/ -12.5 (7.5) | 166.8 (12)/95.6 (11) | -6.67 (11.2)/ -5/7 (9.7) |
| Fogari and colleagues ²⁴ | 4 | Atorvastatin (20) | ю | +/+/+ | 58.7/58.7 | 160 (11)/98 (5) | 137 (8)/80 (4) | 160 (11)/98 (5) | 143 (8)/84 (4) |
| Kanaki and colleagues ³¹ | - | Atorvastatin (10) | 6.5 | -/+/+ | 59.7/58.8 | 146.7 (7.2)/92.2 (10.3) | 141.6 (7.3)/ 89.6 (9.2) | 147.5 (6.7)/91.2 (8.5) | 147.8 (6.8)/90.6 (8.9) |
| Abbrevations | :: BP, blood pres | Abbrevations: BP, blood pressure; DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure; SD, standard deviation. | pressure; | HTN, hypertensio | n; SBP, systolic | blood pressure; SD, sta | ndard deviation. | | |

more suitable to group studies by statin type. However, total heterogeneity as well as heterogeneity for the subgroups with the higher number of studies (atorvastatin and simvastatin groups) were still evident (P<.001). Additionally, we conducted a sensitivity analysis excluding small studies (with <50 patients assigned to each study group) as well as studies with extreme BP reductions or elevations during the follow-up.^{23,37,43}

Effect of Statins on SBP. The overall effect for statin therapy on SBP was a mean difference of -2.62 mm Hg (95% confidence interval [CI], -3.41 to -1.84; P<.001), with significant heterogeneity between studies (P<.001, Figure 2). The funnel plot did not show asymmetry consistent with publication bias, and Egger's test result was not significant (P=.67).

Effect of Statins on DBP. The effect of statin therapy on DBP in all of the studies was in the same direction as for SBP, with a mean difference of -0.94 mm Hg (95% CI, -1.31 to -0.57; *P*<.001), with significant heterogeneity between studies (*P*<.001) (Figure 3). There was no evidence of publication bias (Egger's test, *P*=.58).

Subgroup Analysis. The effect of statin therapy on SBP was significant in studies that recruited patients who were hypertensive at baseline (-3.07 mm Hg; 95% CI,-4.00 to -2.15; P<.001; and DBP -1.04; 95% CI, -1.47 to -0.61; P<.001). In 4 trials that enrolled diabetic hypercholesterolemic patients, the combined effect of statins on BP was: SBP -6.50 (95% CI, -10.93 to -2.08; P=.004) and DBP -4 (95% CI, -6.26 to -1.74; P=.0005). In the studies that uptitrated the dosages of antihypertensive medications, the effect of statins on BP was less pronounced (SBP -0.86; 95% CI, -2.41 to 0.69; P=.28; DBP -0.56; 95% CI, -1.35 to 0.24; P=.17). The effects of different types of statins on SBP and DBP are presented in Figures 2 and 3. Simvastatin and atorvastatin had a greater effect on BP (simvastatin: SBP -4.16; 95% CI, -7.61 to -0.71; DBP -2.02; 95% CI, -3.37 to -0.68), atorvastatin: -2.43; 95% CI, -3.39 to -1.47; DBP -0.96; 95% CI, -1.40 to -0.52) compared with pravastatin (SBP -0.38; -1.26 to 0.50; DBP -0.09; -0.77 to 0.58). However, the meta-regression analysis did not show any statistically significant difference among different statin types.

In the sensitivity analysis of larger studies (study arms with >50 patients), 13 studies were included in the analysis. The effect of statins on SBP and DBP was attenuated as SBP decreased by -0.73 (95% CI, -1.53to 0.07; P=.07) and DBP by -0.18 (95% CI, -0.58 to 0.22; P=.37). The total heterogeneity and the heterogeneity in the atorvastatin group remained significant (P<.001), suggesting that exclusion of these trials was insufficient to fully explain this residual heterogeneity. Among the conducted analyses, grouping trials by statin type provides explanation for the some of the heterogeneity seen between trials. The total heterogeneity we identified may be attributed to design, participants, interventions, and outcomes studied.

In the group of studies using simvastatin, a significant effect was seen in the study by Borghi and colleagues,²³ but the remaining studies showed small effects on BP. A sensitivity analysis excluding the study by Borghi and colleagues²³ showed a nonsignificant decrease in SBP by -0.60 (95% CI, -1.32 to 0.12; P=.10) and DBP by -1.47 (95% CI, -2.97 to 0.03; P=.06).

Meta-Regression Analysis. We performed a metaregression analysis that demonstrated no evidence that any of the following factors were significantly related to the response to statin therapy: age (P=.75 for SBP and .687 for DBP), follow-up duration (P=.543 and .194, respectively), and Jadad score (P=.257 and .262, respectively).

DISCUSSION

The antihypertensive effect of statins documented by our analysis was small and reached statistical significance for SBP and DBP. The predominant reduction in SBP could not be explained on the basis of age, race, or severity of hypertension. However, we observed significant heterogeneity between trials in the efficacy of statins as antihypertensives. Much of this heterogeneity could be explained by differences in the methodological quality of the trials.

Our meta-regression analysis did not show any statistically significant difference among different statin types. This is probably attributed to the limited number of patients included in the studies with different statin types. Besides, evidence from published randomized placebo-controlled trials suggests that pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no statistically significant difference in their effect on long-term cardiovascular prevention.³²

Many clinical trials have demonstrated a statinrelated reduction in morbidity and mortality in patients at risk for cardiovascular disease; however, the data on the BP-reducing effects of statins in humans have been mixed. The main limitation of the published studies is that some of the reported results were from normotensive and some from hypertensive patients with different antihypertensive regimens. In addition, some of the studies had small numbers of patients, were unblinded, and/or allowed adjustment of antihypertensive medications throughout the trial.

Since it is probable that statins exert some hypotensive effects, the evaluation of their impact on BP in association with standard hypotensive drugs is relevant. Sposito and colleagues¹⁷ suggested a beneficial effect of combined 16-week therapy with statins (pravastatin or lovastatin) both on SBP and DBP in comparison to monotherapy with enalapril or lisinopril. Authors also observed a correlation between the magnitude of diastolic (but not systolic) BP reduction and the reduction in serum cholesterol. Moreover, a decrease in heart left ventricular mass was demonstrated in patients

| Study or Subgroup | Stat Mean | ins SD Total | Co Mean | ontrol SD | Total | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% Cl |
|--|---|---|---|---------------------|---|--------------------------------------|---|---|
| 2.1.1 Atorvastatin Cohn J 2009 | -4.2 | 1 155 | -3.4 | 0.8 | 183 | 1.2% | -0.80 [-1.00, -0.60] | |
| Fassett RG 2010 | | .2 16 | -2 | 3.5 | 18 | 0.0% | 0.80 [-2.22, 3.82] | |
| Fogari R 2006 | | .4 50 | -14 | 6.4 | 50 | 0.0% | -4.00 [-6.51, -1.49] | |
| Ge GC 2008 | | 12 61 | | 11.3 | 65 | | -9.70 [-13.78, -5.62] | |
| Glorioso N 1999 | | .4 30 | -14.2 | 4.4 | 30 | 0.0% | -4.00 [-6.23, -1.77] | |
| Grimm R 2010 | | .8 118 | -1.1 | 0.7 | 115 | 1.2% | -0.60 [-0.79, -0.41] | |
| Kanaki Al 2011 | -2.6 13 | | -0.6 | | 25 | 0.0% | | |
| | | | | | | | -2.00 [-9.25, 5.25] | |
| Koh KK 2009 | | .4 14 | -10 | 1.4 | 14 | 0.0% | -1.00 [-2.04, 0.04] | ~ |
| Kuklinska AM 2010 | -3.9 12 | | | 10.7 | 17 | 0.0% | -3.90 [-10.32, 2.52] | Constant of the second s |
| Lavallee PC 2009 | | .4 45 | -1.4 | 1.5 | 46 | 0.1% | -1.40 [-2.00, -0.80] | ×. |
| Magen E 2004 | | .9 15 | -1.5 | 8.2 | 16 | | -7.30 [-12.97, -1.63] | Sec. Brian (Sec.) |
| Manisty C 2009 | -12 12 | | | | 62 | 0.0% | 1.00 [-3.17, 5.17] | and the second se |
| Orr JS 2009 | -1 3 | .6 16 | 0 | 2.8 | 10 | 0.0% | -1.00 [-3.47, 1.47] | 100 |
| Sever P 2006a | -14.6 13 | .8 2584 | -14.3 | 13.7 | 2554 | 0.1% | -0.30 [-1.05, 0.45] | |
| Sever P 2006b | -12.4 14 | .1 2584 | -12.4 | 13.8 | 2583 | 0.1% | 0.00 [-0.76, 0.76] | + |
| Williams B 2009 | -13.4 9 | | -13.9 | 21.6 | 457 | 0.0% | 0.50 [-1.68, 2.68] | - |
| Subtotal (95% CI) | | 6263 | | | 6245 | 2.7% | -0.73 [-0.86, -0.60] | |
| Heterogeneity: Chi ² = 54 Fest for overall effect: Z | | | 001); l ² = | = 73% | | | | |
| 1.1.2 Pravastatin | | | | | | | | |
| 3ak 1998b | 2 7 | .1 53 | 0.9 | 9.1 | 54 | 0.0% | 1.10 [-1.99, 4.19] | + |
| ak AA 1998a | | .9 53 | 0.1 | 7.7 | 55 | 0.0% | -1.00 [-4.14, 2.14] | - |
| Golomb BA 2008a | -2.8 17 | | | 17.8 | 309 | 0.0% | -2.40 [-5.19, 0.39] | |
| chihara A 2005a | | .6 21 | 1 | 5 | 22 | 0.0% | 1.00 [-1.60, 3.60] | +- |
| ushiro T 2009 | -2.6 13 | | 20.000 | 14.1 | 1664 | 0.0% | -0.90 [-1.86, 0.06] | - |
| ee TM 2002 | | .2 25 | 1 | 6.4 | 25 | 0.0% | -1.00 [-4.78, 2.78] | |
| ee TM 2009 | 3 12 | | 4 | 12 | 26 | 0.0% | -1.00 [-7.68, 5.68] | |
| fancia G 2010 | -12.4 1. | | | 1.55 | 224 | 0.6% | 0.40 [0.11, 0.69] | |
| u SF 2000 | | .5 20 | -28 | 8.6 | 20 | 0.0% | -5.00 [-10.30, 0.30] | |
| onelli M 2006 | | .4 2069 | -0.4 | 0.3 | 2057 | 96.2% | 0.60 [0.58, 0.62] | |
| ubtotal (95% CI) | 0.2 (| 4419 | 0.4 | 0.5 | 4456 | 96.8% | 0.60 [0.58, 0.62] | |
| leterogeneity: $Chi^2 = 22$ | 2.07, df = 9 | | $; I^2 = 59$ | 9% | | | 0.00 [0.00] 0.0E] | |
| est for overall effect: Z | = 54.50 (P | < 0.00001) | | | | | | |
| .1.3 Simvastatin | | | | | | | | 1 |
| orghi C 2004a | -1.6 4 | .7 111 | -2 | 3.5 | 111 | 0.0% | 0.40 [-0.69, 1.49] | ÷ |
| orghi C 2004b | | .6 105 | -1.7 | 5.5 | 104 | 0.0% | -1.60 [-3.25, 0.05] | |
| orghi C 2004c | | .5 123 | -2.7 | 6.5 | 123 | 0.0% | -2.60 [-4.35, -0.85] | |
| orghi C 2004d | | .5 113 | -5.7 | 9.7 | 113 | 0.0% | -6.80 [-9.06, -4.54] | |
| Danaoglou Z 2003 | -23 10 | | -22 | | 18 | 0.0% | -1.00 [-9.76, 7.76] | |
| Golomb BA 2008b | -2.4 17 | | | 17.1 | 309 | 0.0% | -3.00 [-5.70, -0.30] | |
| fommel E 1992 | -2 14 | | | 15.6 | 12 | 0.0% | -5.00 [-16.78, 6.78] | |
| IPS 2004 | | .1 10269 | | 14.1 | | 0.3% | | |
| | | | | 5 | | | 0.10 [-0.30, 0.50] | |
| chihara A 2005b | | | 1 | | 22 | 0.0% | -3.00 [-5.39, -0.61] | 10 |
| Lewandowski J 2010 | -7 14 | | | 13.3 | 16 | 0.0% | -3.00 [-12.85, 6.85] | 19 - 19 - 19 - 19 - 19 - 19 - 19 - 19 - |
| McDowell IF 1991 | -2 15 | | | 12.5 | 12 | 0.0% | -6.00 [-16.89, 4.89] | |
| Olkinuora J 2006 | | 12 27 | | 12.7 | 29 | 0.0% | 0.00 [-6.47, 6.47] | |
| Tonolo G 1997 | -2 2 | .4 10 | -1 | 4.2 | 9 | 0.0% | -1.00 [-4.12, 2.12] | |
| Subtotal (95% CI) | | 11154 | | | 11145 | 0.4% | -0.35 [-0.69, -0.01] | 1 |
| Heterogeneity: Chi ² = 5 Test for overall effect: Z | | | 001); l ² = | = 79% | | | | |
| 2.1.4 Fluvastatin | | | | | | | | |
| Derosa 2003b | -6 3 | .6 24 | -4 | 4.5 | 25 | 0.0% | -2.00 [-4.28, 0.28] | _ |
| Derosa G 2003a | | .1 24 | -2 | 3.6 | 23 | 0.0% | -2.00 [-4.52, 0.52] | |
| Hjelstuen A 2007 | | .1 24 | -1.1 | 7.7 | 41 | 0.0% | 1.20 [-2.42, 4.82] | 10 m m |
| chihara A 2005c | | .6 22 | -1.1 | 5 | 22 | 0.0% | | |
| reixeira AA 2005C | | | | 12 | 20 | | 0.00 [-2.57, 2.57] | 100 |
| ubtotal (95% CI) | -7 | 13 19 131 | -4 | 12 | 131 | 0.0% | -3.00 [-10.86, 4.86] -1.11 [-2.41, 0.19] | |
| | 56 df - 4 0 | | - 0% | | 131 | 0.0% | -1.11 [-2.41, 0.19] | 1 |
| eterogeneity: Chi ² = 3. est for overall effect: Z | | | = 0% | | | | | |
| .1.5 Cerivastatin | | | | | | | | |
| A DECEMBER OF THE OWNER OF THE OWNER OF THE OWNER | -4 | 15 20 | | 15.6 | 18 | 0.0% | -7.00 [-16.75, 2.75] | 2 BAT 1 |
| alletshoffer BM 2005a | | .8 30 | 0 | 15.6 | 30 | 0.0% | -2.00 [-9.22, 5.22] | |
| alletshoffer BM 2005a Iakamura T 2001 | -2 12 | | | | 48 | 0.0% | -3.77 [-9.57, 2.03] | |
| alletshoffer BM 2005a Iakamura T 2001 ubtotal (95% CI) | -2 12 | 50 | | | | | | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. | -2 12 65, df = 1 (| 50 P = 0.42); I ² | ^e = 0% | | 10 | | | - |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. 'est for overall effect: Z | -2 12 65, df = 1 (| 50 P = 0.42); I ² | ^e = 0% | | 10 | | | |
| alletshoffer BM 2005a Jakamura T 2001 J ubtotal (95% CI) Jeterogeneity: Chi ² = 0. Test for overall effect: Z 2.1.6 Lovastatin | -2 12 65, df = 1 (1 = 1.27 (P = | 50 P = 0.42); I ² 0.20) | | 11. | | | | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z 1.6 Lovastatin lodis H 1993 | -2 12 65, df = 1 (| 50 P = 0.42); l ² 0.20) 0.8 99 | ² = 0% | 11.1 | 89 | 0.0% | -0.60 [-3.61, 2.41] | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin lodis H 1993 ubtotal (95% CI) | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 | 50 P = 0.42); I ² 0.20) | | 11.1 | | | | • |
| alletshoffer BM 2005a akamura T 2001 ubtotal (95% CI) eterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin odis H 1993 ubtotal (95% CI) eterogeneity: Not appli | -2 12 65, df = 1 (l = 1.27 (P = -1.8 9 cable | 50 P = 0.42); l ² 0.20) 0.8 99 99 | | 11.1 | 89 | 0.0% | -0.60 [-3.61, 2.41] | • |
| alletshoffer BM 2005a Jakamura T 2001 Jubtotal (95% CI) Jeterogeneity: Chi ² = 0. Fest for overall effect: Z 2.1.6 Lovastatin Jodis H 1993 Jubtotal (95% CI) Jeterogeneity: Not appli Fest for overall effect: Z | -2 12 65, df = 1 (l = 1.27 (P = -1.8 9 cable | 50 P = 0.42); l ² 0.20) 0.8 99 99 | | 11.1 | 89 | 0.0% | -0.60 [-3.61, 2.41] | • |
| alletshoffer BM 2005a Jakamura T 2001 Jubtotal (95% CI) Jeterogeneity: Chi ² = 0. est for overall effect: Z 2.1.6 Lovastatin Jodis H 1993 Jubtotal (95% CI) Jeterogeneity: Not appli est for overall effect: Z 2.1.7 Various statins | -2 12 65, df = 1 () = 1.27 (P = -1.8 S cable = 0.39 (P = | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) | -1.2 | | 89 89 | 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] | • |
| Salletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Chi ² = 0. Fest for overall effect: Z 2.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Fest for overall effect: Z 2.1.7 Various statins thyros VC 2004 | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) 2 420 | -1.2 | 11.9 | 89 89 349 | 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] | |
| Salletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Chi ² = 0. Fest for overall effect: Z 2.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Fest for overall effect: Z 2.1.7 Various statins Athyros VG 2004 posito A 1999 | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 -19 | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) 2 420 5 35 | -1.2 -2 -15 | 11.9 8.2 | 89 89 349 35 | 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] | |
| alletshoffer BM 2005a Jakamura T 2001 Jubtotal (95% CI) Jeterogeneity: Chi ² = 0. Test for overall effect: Z 2.1.6 Lovastatin Jodis H 1993 Jubtotal (95% CI) Jeterogeneity: Not appli Test for overall effect: Z 2.1.7 Various statins thyros VG 2004 posito A 1999 Ferzoli L 2005 | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) 2 420 5 35 5.8 31 | -1.2 -2 -15 | 11.9 | 89 89 349 35 13 | 0.0% 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] -5.40 [-17.66, 6.86] | |
| alletshoffer BM 2005a Jakamura T 2001 Jubtotal (95% CI) Jeterogeneity: Chi ² = 0. Test for overall effect: Z 2.1.6 Lovastatin Jodis H 1993 Jubtotal (95% CI) Jeterogeneity: Not appli Test for overall effect: Z 2.1.7 Various statins thyros VC 2004 Joposito A 1999 Terzoli L 2005 Jubtotal (95% CI) | -2 12 65, df = 1 (0 = 1.27 (P = -1.8 5 cable = 0.39 (P = 0 11 -19 -3.3 13 | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) 2 420 5 35 5.8 31 486 | -1.2 -2 -15 2.1 | 11.9 8.2 20.7 | 89 89 349 35 | 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin lodis H 1993 ubtotal (95% CI) leterogeneity: Not appli est for overall effect: Z .1.7 Various statins uthyros VG 2004 posito A 1999 erzoll L 2005 ubtotal (95% CI) leterogeneity: Chi ² = 1: leterogeneity: Chi ² = 1: | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 -19 -3.3 13 L.73, df = 2 | 50 P = 0.42); l ² 0.20) 0.8 99 99 0.70) 2 420 5 35 3.8 31 486 (P = 0.003) | -1.2 -2 -15 2.1 | 11.9 8.2 20.7 | 89 89 349 35 13 | 0.0% 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] -5.40 [-17.66, 6.86] | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin lodis H 1993 ubtotal (95% CI) leterogeneity: Not appli est for overall effect: Z .1.7 Various statins thyros VG 2004 posito A 1999 erzoil L 2005 ubtotal (95% CI) leterogeneity: Chi ² = 1: est for overall effect: Z | -2 12 65, df = 1 () = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 -19 -3.3 13 L.73, df = 2 | 50 P = 0.42); I ² 0.20) 0.8 99 99 0.70) 0.2 420 5 35 8 31 486 (P = 0.003) 0.38) | -1.2 -2 -15 2.1 | 11.9 8.2 20.7 | 89 89 349 35 13 397 | 0.0% 0.0% 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] -5.40 [-17.66, 6.86] 0.65 [-0.80, 2.10] | |
| alletshoffer BM 2005a lakamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin lodis H 1993 ubtotal (95% CI) leterogeneity: Not appli est for overall effect: Z .1.7 Various statins thyros VG 2004 posito A 1999 erzoll L 2005 ubtotal (95% CI) leterogeneity: Chi ² = 1: est for overall effect: Z Total (95% CI) | -2 12 65, df = 1 () = 1.27 (P = -1.8 S cable = 0.39 (P = 0 111 -19 -3.3 13 1.73, df = 2 = 0.88 (P = | 50 P = 0.42); I' 0.20) 3.8 99 99 0.70) 2 420 5 35 8 31 486 (P = 0.003) 0.38) 22602 | -1.2 -15 2.1 ; l ² = 83 | 11.9 8.2 20.7 | 89 89 349 35 13 397 22511 | 0.0% 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] -5.40 [-17.66, 6.86] | |
| alletshoffer BM 2005a akamura T 2001 ubtotal (95% CI) leterogeneity: Chi ² = 0. est for overall effect: Z .1.6 Lovastatin odis H 1993 ubtotal (95% CI) leterogeneity: Not appli est for overall effect: Z .1.7 Various statins thyros VG 2004 posito A 1999 erzoil L 2005 ubtotal (95% CI) leterogeneity: Chi ² = 1: est for overall effect: Z | -2 12 65, df = 1 (l = 1.27 (P = -1.8 9 cable = 0.39 (P = 0 11 -19 -3.3 13 1.73, df = 2 = 0.88 (P = 89.51, df = 4 | 50 P = 0.42); I' 0.20) 3.8 99 0.70) 2 2 2 35 35 35 2 3 2 2 2 2 2 2 2 2 2 2 2 2 | -1.2 -2 -15 2.1 ; l ² = 83 00001); l ² | 11.9 8.2 20.7 | 89 89 349 35 13 397 22511 | 0.0% 0.0% 0.0% 0.0% 0.0% | -0.60 [-3.61, 2.41] -0.60 [-3.61, 2.41] 2.00 [0.36, 3.64] -4.00 [-7.18, -0.82] -5.40 [-17.66, 6.86] 0.65 [-0.80, 2.10] | -20 -10 0 10 20 Favours statins Favours control |

FIGURE 2. Mean differences and 95% confidence intervals (CIs) in diastolic blood pressure (DBP) achieved in patients taking a statin compared with those taking placebo or other control treatment.

| Study or Subgroup | Mean | Statins SD | | Mean | ontrol SD | | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|--|--|---|---|--|---|---|---|--|--|
| 1.1.1 Atorvastatin | 21 | 15294 | 2000000 | NOA1 | 2010 | - 232-242-24 | Dent Marrie | Management and south and souther | |
| Cohn J 2009 | -7 | 2 | 155 | -5 | 2 | 183 | 3.7% | -2.00 [-2.43, -1.57] | |
| Fassett RG 2010 | -4.2 | 8.4 | 16 | -4.6 | 9 | 18 | 1.5% | 0.40 [-5.45, 6.25] | |
| Fogari R 2006 | | 13.6 | 50 | -17 | 13.6 | 50 | 1.7% | -6.00 [-11.33, -0.67] | 1.00 |
| Ge GC 2008 | -41.1 | | 61 | -26.2 | | 65 | 1.4% | -14.90 [-20.94, -8.86] | |
| Glorioso N 1999 | -9 | 7.7 | 30 | -2 | 9.9 | 30 | 2.0% | -7.00 [-11.49, -2.51] | 1 m m |
| Grimm R 2010 | -4 | 1 | 118 | -1 | 1.2 | 115 | 3.7% | -3.00 [-3.28, -2.72] | |
| Kanaki Al 2011 | | | 25 | 0.3 | 9.6 | 25 | 1.6% | -5.40 [-10.89, 0.09] | - 2003 |
| Koh KK 2009 | -19 | 2.5 | 14 | -17 | 2.2 | 14 | 3.3% | -2.00 [-3.74, -0.26] | - |
| Kuklinska AM 2010 | | 14.1 | 39 | | 16.2 | 17 | 0.8% | -4.70 [-13.58, 4.18] | |
| Lavallee PC 2009 | -3.9 | 2.1 | 45 | -0.8 | 2.2 | 46 | 3.6% | -3.10 [-3.98, -2.22] | (*) |
| Magen E 2004 | -16.1 | 7.8 | 15 | -0.2 | 10 | 16 | 1.4% | -15.90 [-22.19, -9.61] | 32 |
| Manisty C 2009 | | 22.8 | 77 | | 17.2 | 62 | 1.3% | 5.00 [-1.65, 11.65] | |
| Orr JS 2009 | -5 | 4.5 | 16 | -3 | 5.7 | 10 | 2.1% | -2.00 [-6.16, 2.16] | 14 |
| Sever P 2006a | -26.8 | 24.4 | | -27.2 | | 2554 | 3.4% | 0.40 [-0.95, 1.75] | Ť |
| Sever P 2006b | -24.1 | | | -23.2 | | 2583 | 3.4% | -0.90 [-2.21, 0.41] | - |
| Williams B 2009 | -25.7 | 16.7 | | -26.5 | 17.5 | 457 | 3.0% | 0.80 [-1.45, 3.05] | 1 |
| Subtotal (95% CI) Heterogeneity: Tau ² = 1 | | | | 15 (P < | 0.000 | 6245 01); I ² = | 37.9% 85% | -2.43 [-3.39, -1.47] | |
| Test for overall effect: Z | = 4.97 (| P < 0.(| 00001) | | | | | | |
| 1.1.2 Pravastatin | ()_cm.co | | 212 | 2 | 1000 | 110000 | 1000 | | |
| Bak 1998b | | 18.2 | 53 | -2.8 | | 55 | 1.3% | -2.30 [-8.72, 4.12] | |
| Bak AA 1998a | | 16.1 | 53 | | 18.6 | 54 | 1.3% | 1.90 [-4.69, 8.49] | |
| Golomb BA 2008a | | 21.1 | 308 | | 21.1 | 309 | 2.5% | -1.50 [-4.83, 1.83] | |
| Ichihara A 2005a | -2 | 8.6 | 21 | | 11.7 | 22 | 1.4% | 2.00 [-4.12, 8.12] | |
| Kushiro T 2009 | -2.3 | | 1613 | -1.9 | 21.2 | 1664 | 3.4% | -0.40 [-1.90, 1.10] | + |
| Lee TM 2002 | | 14.9 | 25 | | 12.8 | 25 | 1.0% | -1.00 [-8.70, 6.70] | 1000 C |
| Lee TM 2009 | | 24.1 | 27 | | 20.5 | 26 | 0.5% | -1.00 [-13.03, 11.03] | |
| Mancia G 2010 | -19.2 | 1.9 | 230 | -18.1 | 1.9 | 224 | 3.7% | -1.10 [-1.45, -0.75] | * |
| Su SF 2000 | | 14.2 | 20 | -44 | 12 | 20 | 1.0% | -1.00 [-9.15, 7.15] | |
| Tonelli M 2006 | 0.7 | 0.4 | 2069 | -0.2 | 0.3 | 2057 | 3.7% | 0.90 [0.88, 0.92] | L. |
| Subtotal (95% CI) Heterogeneity: Tau ² = 1 | .82: Chi ² | = 131 | 4419 .78. df = | = 9 (P < | 0.000 | 4456 (01): I ² = | 19.8% 93% | -0.28 [-1.63, 1.07] | 1 |
| Test for overall effect: Z | | | | | | | | | |
| 1.1.3 Simvastatin | | | | | | | | | |
| Borghi C 2004a | 3.5 | 6.1 | 111 | 3.6 | 6 | 111 | 3.3% | -0.10 [-1.69, 1.49] | + |
| Borghi C 2004b | -6.5 | 10 | 105 | -0.7 | 9.8 | 104 | 2.8% | -5.80 [-8.48, -3.12] | 0.000 |
| Borghi C 2004c | -11.6 | 7 | 123 | -2.9 | 5.3 | 123 | 3.3% | -8.70 [-10.25, -7.15] | - |
| Borghi C 2004d | -24.7 | 10.2 | 113 | -6.7 | 11.2 | 113 | 2.8% | -18.00 [-20.79, -15.21] | |
| Danaoglou Z 2003 | -38 | 14.2 | 21 | -32 | 23.6 | 18 | 0.5% | -6.00 [-18.48, 6.48] | 100 100 100 100 100 100 100 100 100 100 |
| Golomb BA 2008b | | 21.2 | 310 | | 20.9 | 309 | 2.5% | -2.90 [-6.22, 0.42] | 1000 C |
| Hommel E 1992 | -5 | 27.6 | 14 | 3 | 26.2 | 12 | 0.2% | -8.00 [-28.71, 12.71] | 1000 C C C C C C C C C C C C C C C C C C |
| HPS 2004 | -7.6 | 27.5 | 10269 | -7.1 | 28.9 | 10267 | 3.6% | -0.50 [-1.27, 0.27] | |
| chihara A 2005b | -3 | 5.7 | 22 | -4 | 11.7 | 22 | 1.6% | 1.00 [-4.44, 6.44] | |
| Lewandowski J 2010 | | 15.1 | 15 | | 15.1 | 16 | 0.6% | -1.00 [-11.64, 9.64] | 10 TO 10 TO 10 |
| McDowell IF 1991 | | 26.4 | 14 | | 27.1 | 12 | 0.2% | -4.00 [-24.65, 16.65] | |
| Olkinuora J 2006 | -14 | 15.6 | 27 | -14 | 19.2 | 29 | 0.8% | 0.00 [-9.14, 9.14] | 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
| Tonolo G 1997 | 2 | 3.6 | 10 | -3 | 4.6 | 9 | 2.3% | 0.00 [-3.74, 3.74] | |
| | -3 | | 11154 | | | 11145 | 24.6% | -4.16 [-7.61, -0.71] | - |
| | | $i^2 = 22$ | 4.04. df | = 12 (F | $^{\prime} < 0.0$ | 0001): | $^{2} = 95\%$ | | • |
| Heterogeneity: $Tau^2 = 2$ | 8.86; Chi | | | = 12 (F | ² < 0.0 | 0001); I | ² = 95% | | • |
| Subtotal (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin | 8.86; Chi = 2.36 (I | P = 0.0 |)2) | | | | | | • |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b | 8.86; Chi = 2.36 (I -9 | P = 0.0 | 24 | -6 | 4.2 | 25 | 2.8% | -3.00 [-5.78, -0.22] | - |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a | 8.86; Chi = 2.36 (I -9 -6 | P = 0.0 5.6 5.3 | 24 24 | -6 -4 | 4.2 5.8 | 25 23 | 2.8% 2.6% | -2.00 [-5.18, 1.18] | - |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 | 8.86; Chi = 2.36 (l -9 -6 -1.7 | P = 0.0 5.6 5.3 14.3 | 24 24 42 | -6 -4 -1.5 | 4.2 5.8 7.7 | 25 23 41 | 2.8% 2.6% 1.8% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] | - |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 chihara A 2005c | 8.86; Chi = 2.36 (1 -9 -6 -1.7 -1 | P = 0.0 5.6 5.3 14.3 7.2 | 24 24 42 22 | -6 -4 -1.5 -4 | 4.2 5.8 7.7 11.7 | 25 23 41 22 | 2.8% 2.6% 1.8% 1.5% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] | - |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 chihara A 2005c Teixeira AA 2010 | 8.86; Chi = 2.36 (1 -9 -6 -1.7 -1 | P = 0.0 5.6 5.3 14.3 | 22) 24 24 42 22 19 | -6 -4 -1.5 -4 | 4.2 5.8 7.7 | 25 23 41 22 20 | 2.8% 2.6% 1.8% 1.5% 0.6% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] | |
| Heterogeneity: Tau ² = 2 Fest for overall effect: Z L.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 chihara A 2005c Feixeira AA 2010 Subtotal (95% CI) | 8.86; Chi = 2.36 (1 -9 -6 -1.7 -1 -13 | P = 0.0 5.6 5.3 14.3 7.2 18.2 | 24 24 42 22 19 131 | -6 -4 -1.5 -4 -7 | 4.2 5.8 7.7 11.7 16.3 | 25 23 41 22 20 131 | 2.8% 2.6% 1.8% 1.5% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] | |
| Heterogeneity: Tat# ² = 2 Fest for overall effect: Z L.1.4 Fluvastatin Derosa 2003b Derosa C 2003a djelstuen A 2007 chihara A 2005 Feixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 | 8.86; Chi = 2.36 (l -9 -6 -1.7 -1 -13 | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.4 | 22) 24 24 42 22 19 131 0, df = 4 | -6 -4 -1.5 -4 -7 | 4.2 5.8 7.7 11.7 16.3 | 25 23 41 22 20 131 | 2.8% 2.6% 1.8% 1.5% 0.6% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 Ichihara A 2005C Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z | 8.86; Chi = 2.36 (l -9 -6 -1.7 -1 -13 | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.4 | 22) 24 24 42 22 19 131 0, df = 4 | -6 -4 -1.5 -4 -7 | 4.2 5.8 7.7 11.7 16.3 | 25 23 41 22 20 131 | 2.8% 2.6% 1.8% 1.5% 0.6% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Ichihara A 2005 Cibitotal (95% Ci) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin | 8.86; Chi = 2.36 (i -9 -6 -1.7 -1 -13 -48; Chi2 = 1.73 (i | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.4 | 22) 24 24 42 22 19 131 0, df = 4 | -6 -4 -1.5 -4 -7 (P = 0. | 4.2 5.8 7.7 11.7 16.3 | 25 23 41 22 20 131 | 2.8% 2.6% 1.8% 1.5% 0.6% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] | |
| Heterogeneity: Tau ² = 2 Fest for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Ichihara A 2007 Eixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Fest for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a | 8.86; Chi= 2.36 (l-9-6-1.7-1-13-13-48; Chi2= 1.73 (l-7 | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.40 P = 0.0 | 24 24 42 22 19 131 0, df = 4 08) | -6 -4 -1.5 -4 -7 (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² | 25 23 41 22 20 131 = 9% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] | |
| Heterogeneity: Tau ² = 2 Fest for overall effect: Z L.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Chihara A 2005 Creixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Fest for overall effect: Z L.1.5 Cerivastatin Salletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) | 8.86; Chi = 2.36 (l -9 -6 -1.7 -1 -13 0.48; Chi ² = 1.73 (l -7 -4 | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 | 24 24 42 22 19 131 0, df = 4 08) 20 30 50 | -6 -4 -1.5 -4 -7 (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 | 25 23 41 22 20 131 = 9% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluxastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Chihara A 2005C Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Ballesthoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 | 8.86; Chi = 2.36 (l -9 -6 -1.7 -1 -13 0.48; Chi ² = 1.73 (l -7 -4 0.00; Chi ² | $P = 0.0$ 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 $= 0.4^{-1}$ | 24 24 42 22 19 131 0, df = 4 08) 20 30 50 4, df = 1 | -6 -4 -1.5 -4 -7 (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 | 25 23 41 22 20 131 = 9% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z J.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Ichihara A 2007 Erixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z J.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z | 8.86; Chi = 2.36 (l -9 -6 -1.7 -1 -13 0.48; Chi ² = 1.73 (l -7 -4 0.00; Chi ² | $P = 0.0$ 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 $= 0.4^{-1}$ | 24 24 42 22 19 131 0, df = 4 08) 20 30 50 4, df = 1 | -6 -4 -1.5 -4 -7 (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 | 25 23 41 22 20 131 = 9% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa G 2003a Hjelstuen A 2007 Chihara A 2005C Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin | 8.86; Chi = 2.36 () -9 -6 -1.7 -1 -13 0.48; Chi2= 1.73 () $-7-40.00; Chi2= 1.72 ()$ | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 $= 0.44$ $P = 0.0$ | 22) 24 24 42 22 19 131 0, df = 4 08) 20 30 50 4, df = 1 08) | -6 -4 -1.5 -4 -7 (P = 0. (P = 0.) (P = 0.) | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² | 25 23 41 22 0 131 = 9% 18 30 48 = 0% | 2.8% 2.6% 1.8% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa C2003a Hjelstuen A 2007 Chihara A 2005 Cibitotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura 7 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 | 8.86; Chi = 2.36 () -9 -6 -1.7 -1 -13 0.48; Chi2= 1.73 () $-7-40.00; Chi2= 1.72 ()$ | $P = 0.0$ 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 $= 0.4^{-1}$ | 22) 24 24 42 22 19 131 0, df = 4 08) 20 30 50 50 6 5 1 1 1 1 1 1 1 1 1 1 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0.) (P = 0.) | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 | 25 23 41 22 20 131 = 9% 18 30 48 8 = 0% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] | |
| Heterogeneity: Tau ² = 2 Fest for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 chihara A 2007 chihara A 2007 Feixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) | | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.40$ $P = 0.0$ 30.1 21.3 $= 0.44$ $P = 0.0$ | 22) 24 24 42 22 19 131 0, df = 4 08) 20 30 50 4, df = 1 08) | -6 -4 -1.5 -4 -7 (P = 0. (P = 0.) (P = 0.) | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² | 25 23 41 22 0 131 = 9% 18 30 48 = 0% | 2.8% 2.6% 1.8% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa G 2003a Hjelstuen A 2007 chihara A 2005 Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli | 8.86; Chi = 2.36 () -9 -6 -1.7 -1.7 -1.3 0.48; Chi ² = 1.73 () -7 -4 0.00; Chi ² = 1.72 () -2.1 icable | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.44$ $P = 0.0$ 30.1 21.3 $= 0.4$ $P = 0.0$ 17.9 | 22) 24 24 22 19 131 131 10, df = 4 08) 20 30 50 4, df = 1 08) 99 99 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0.) (P = 0.) | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² | 25 23 41 22 20 131 = 9% 18 30 48 8 = 0% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Chihara A 2005 Context A 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura 7 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins | 8.86; Chi = 2.36 () -9 -6 -1.7 -1.7 -1.3 0.48; Chi ² = 1.73 () -7 -4 0.00; Chi ² = 1.72 () -2.1 icable | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.44$ $P = 0.0$ 30.1 21.3 $= 0.4$ $P = 0.0$ 17.9 | 22) 24 24 22 19 131 131 10, df = 4 08) 20 30 50 4, df = 1 08) 99 99 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0.) (P = 0.) | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² | 25 23 41 22 20 131 = 9% 18 30 48 8 = 0% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 6 2003a Hjelstuen A 2007 Chihara A 2007 Citati A 2007 Citati A 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 | | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.44$ $P = 0.0$ 30.1 21.3 $= 0.4$ $P = 0.0$ 17.9 | 22) 24 24 22 19 131 131 10, df = 4 08) 20 30 50 4, df = 1 08) 99 99 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² | 25 23 41 22 20 131 = 9% 18 30 48 8 = 0% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Chihara A 2005 Context A 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura 7 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins | | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.44 P = 0.0 30.1 21.3 = 0.44 P = 0.0 17.9 P = 0.0 | 22) 24 24 24 22 19 131 0, df = 4 08) 20 30 50 4, df = 1 08) 99 99 99 99 99 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 | 25 23 41 22 20 131 = 9% 18 30 48 = 0% | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Ichihara A 2007 Etxieria AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 Sposito A 1999 | $\begin{array}{r} 8.86; Chi \\ = 2.36 (i) \\ -9 \\ -6 \\ -1.7 \\ -1 \\ -13 \\ 0.48; Chi^2 \\ = 1.73 (i) \\ -7 \\ -4 \\ 0.00; Chi^2 \\ = 1.72 (i) \\ -2.1 \\ icable \\ = 0.42 (i) \\ -1 \\ -23 \end{array}$ | P = 0.0 5.6 5.3 14.3 7.2 18.2 = 4.44 P = 0.0 30.1 21.3 = 0.4.4 P = 0.0 17.9 P = 0.6 18.4 | 22) 24 42 22 19 131 20 30 50 4, df = 1 08) 99 99 58) 420 | -66 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. -1.2 -2 | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 | 25 23 41 22 20 131 = 9% 18 30 48 = 0% 89 89 | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.8% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -11.00 [-1.5.78, -6.2] -4.60 [-16.11, 6.2] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003a Hjelstuen A 2007 chihara A 2005 Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura 7 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 Sposito A 1999 Terzoli L 2005 | $\begin{array}{r} 8.86; Chi \\ = 2.36 (i) \\ -9 \\ -6 \\ -1.7 \\ -1 \\ -13 \\ 0.48; Chi^2 \\ = 1.73 (i) \\ -7 \\ -4 \\ 0.00; Chi^2 \\ = 1.72 (i) \\ -2.1 \\ icable \\ = 0.42 (i) \\ -1 \\ -23 \end{array}$ | P = 0.0 5.6 5.3 14.3 7.2 18.2 21.8 2 30.1 21.3 = 0.44 P = 0.0 17.9 P = 0.6 18.4 10.4 | 24 24 24 22 19 31 30, df = 4 20 30 50 4, df = 1 28) 99 99 99 5 58) 420 35 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. -1.2 | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 | 25 23 41 22 20 131 = 9% 18 30 48 = 0% 89 89 35 | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.1% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -1.00 [-1.78, 3.78] -11.00 [-15.78, -6.22] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z L.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa C 2003a ijelstuen A 2007 chihara A 2005c Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z L.1.5 Cerivastatin Balletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z L.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z L.1.7 Various statins thhyros VC 2004 posito A 1999 Terzoll L 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 5 | | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.4(P = 0.0)$ 30.1 21.3 $= 0.4(P = 0.0)$ 17.9 $P = 0.6(P = 0.0)$ 18.4 10.4 19.5 | 22) 24 24 24 24 24 24 26 29 131 131 131 20 30 0 50 50 99 99 99 99 58) 420 35 31 486 486 487 487 487 487 487 487 487 487 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. -1.2 -1.2 | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 11.1 20.5 10 17 | 255 23 41 22 23 131 = 9% 18 30 48 = 0% 89 89 89 89 349 35 3397 | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.8% 1.9% 0.6% 5.2% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -11.00 [-1.5.78, -6.2] -4.60 [-16.11, 6.2] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa C2003a Hjelstuen A 2007 Ichihara A 2007 Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 Sposito A 1999 Terzol L 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 5 Test for overall effect: Z | | P = 0.0 5.6 5.3 14.3 7.2 18.2 $= 4.4(P = 0.0)$ 30.1 21.3 $= 0.4(P = 0.0)$ 17.9 $P = 0.6(P = 0.0)$ 18.4 10.4 19.5 | 224 24 24 24 22 22 29 131 30 0, df = 4 99 99 99 99 99 99 99 9 9 | -6 -4 -1.5 -4 -7 (P = 0. (P = 0. (P = 0. -1.2 -1.2 | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 11.1 20.5 10 17 | 25 23 41 22 29 131 = 9% 18 300 48 = 0% 89 89 89 35 13 397 79]; l ² = | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.1% 2.8% 1.9% 0.6% 5.2% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -11.00 [-1.78, 3.78] -11.00 [-1.78, -6.22] -4.60 [-16.11, 6.91] -4.75 [-13.97, 4.47] | |
| Heterogeneity: $Tau^2 = 2$ Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa 2003b Derosa C 2003a Hjelstuen A 2007 Chihara A 2005c Teixeira AA 2010 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Nakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 Sposito A 1999 Terzoli L 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 5 Test for overall effect: Z Total (95% CI) | | $P = 0.0$ 5.6 5.3 14.3 7.2 18.2 = 4.44 P = 0.0 30.1 21.3 = 0.4 P = 0.0 17.9 P = 0.6 18.4 10.4 19.5 $P^{2} = 18$ P = 0.3 | 22) 24 24 24 24 24 24 26 29 131 131 10, df = 4 138) 20 30 00 50 50 58) 420 35 31 486 62, 28, df = 31 22602 | $\begin{array}{c} -6 \\ -4 \\ -1.5 \\ -4 \\ -7 \\ \end{array}$ $(P = 0. \\ (P = 0. \\ (P = 0. \\ -1.2 \\ -1.2 \\ -1.6 \\ = 2 (P = 2 (P = -1) \\ \end{array}$ | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 20.5 10 17 0.0000 | 25 23 41 22 20 131 = 9% 48 89 89 89 89 89 89 349 35 13 397 1); I ² = 22511 | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.1% 2.8% 1.9% 0.6% 5.2% 89% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -11.00 [-1.5.78, -6.2] -4.60 [-16.11, 6.2] | |
| Heterogeneity: Tau ² = 2 Test for overall effect: Z 1.1.4 Fluvastatin Derosa 2003b Derosa 2003b Derosa 2003b Derosa 2003a Hjelstuen A 2007 chihara A 2007 Chihara A 2007 Generation Contention Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 Cerivastatin Balletshoffer BM 2005a Vakamura T 2001 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.6 Lovastatin Hodis H 1993 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z 1.1.7 Various statins Athyros VG 2004 Sposito A 1999 Terzoll L 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 5 Test for overall effect: Z | | $P = 0.0$ 5.6 5.3 14.3 7.2 18.2 = 4.44 P = 0.0 30.1 21.3 = 0.4.4 P = 0.0 17.9 P = 0.6 18.4 10.4 19.5 $P^2 = 18$ P = 0.3 | 22) 24 24 24 42 22 21 19 131 10, df = 4 20 30 50 4, df = 1 28) 99 99 99 95 58) 420 35 486 6.28, df = 1 22602 22602 22602 4.466, df | $\begin{array}{c} -6 \\ -4 \\ -1.5 \\ -4 \\ -7 \\ \end{array}$ $(P = 0. \\ (P = 0. \\ (P = 0. \\ -1.2 \\ -1.2 \\ -1.6 \\ = 2 (P = 2 (P = -1) \\ \end{array}$ | 4.2 5.8 7.7 11.7 16.3 36); I ² 27.2 17 51); I ² 11.1 20.5 10 17 0.0000 | 25 23 41 22 20 131 = 9% 48 89 89 89 89 89 89 349 35 13 397 1); I ² = 22511 | 2.8% 2.6% 1.8% 1.5% 0.6% 9.3% 0.2% 0.7% 1.0% 2.1% 2.1% 2.1% 2.8% 1.9% 0.6% 5.2% 89% | -2.00 [-5.18, 1.18] -0.20 [-5.13, 4.73] 3.00 [-2.74, 8.74] -6.00 [-16.86, 4.86] -1.72 [-3.66, 0.23] -13.00 [-31.22, 5.22] -6.00 [-15.75, 3.75] -7.56 [-16.16, 1.04] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -0.90 [-5.11, 3.31] -11.00 [-1.78, 3.78] -11.00 [-1.78, -6.22] -4.60 [-16.11, 6.91] -4.75 [-13.97, 4.47] | |

FIGURE 3. Mean differences and 95% confidence intervals (CIs) in systolic blood pressure (SBP) achieved in patients taking a statin compared with those taking placebo or other control treatment.

treated with statins. Results by Borghi and colleagues²³ suggested that the addition of statin treatment (pravastatin or simvastatin) to conventional antihypertensive therapy might improve BP control in hypertensive patients with hypercholesterolemia.

In one of the first large randomized trials on the topic, the University of California San Diego (UCSD) Statin Study, evaluated the impact of statins on BP in 1016 patients with increased levels of serum cholesterol.¹³ A significant decrease in BP with statin therapy was observed, compared with the placebo group. However, the observed effect for SBP in the pravastatin group and for DBP in the simvastatin group disappeared during the 2-month follow-up period.

A previous meta-analysis⁴ included 20 controlled clinical trials, which had enrolled 828 normotensive and hypertensive patients. The antihypertensive effect was more pronounced in studies in which the initial SBP was >130 mm Hg (mean difference for SBP -4.0; 95% CI, -5.8 to -2.2). In addition, there was a tendency toward lower DBP values in statin-treated patients compared with the control groups (mean difference -0.9 mm Hg; 95% CI, -2.0 to -0.2) and greater reduction of DBP in patients with baseline DBP >80 mm Hg (mean difference, -1.2 mm Hg; 95% CI, -2.6 to -0.1). The authors concluded that the impact of statins on BP was dependent on the initial BP, with higher initial values associated with a more pronounced influence of statins. Although we showed comparable BP reductions with the previous metaanalysis, methodological differences between the two studies exist: (1) we used 12 studies that were included in the meta-analysis by Strazzullo and colleagues, (2) we did not exclude studies in which concomitant antihypertensive treatment remained unchanged throughout the study, (3) we included large random-ized studies published after 2007,^{13,40} and (4) we excluded studies with follow-up <8 weeks as well as prospective crossover studies with or without an insufficient wash-out period.

The beneficial effects of statins on the vasculature are present early after statin administration and appear to be independent of their cholesterol-lowering actions.⁵⁰ Statins up-regulate the expression and activity of endothelial nitric oxide synthase via activation of phosphatidylinositol 3-kinase,⁵¹ inhibition of geranylgeranylation of the small G-protein Rho,⁵² and of vascular Rac1-mediated activation of NADPH-oxidase.⁵⁰ Statins have also been shown to inhibit several angiotensin II–activated intracellular signaling systems, delay hypertension-induced vascular alterations,⁵³ reduce large artery stiffness, and improve systemic arterial compliance.³ These mechanisms may, in part, explain the BP effects of statins suggested by our analysis.

LIMITATIONS

Despite the substantial data on the effectiveness of statin therapy in the primary and secondary prevention

of cardiovascular events in patients with hypercholesterolemia, it is difficult to assess the antihypertensive effects of statins and the impact on cardiovascular risk. This lack of clarity is caused by several factors: (1) BP effect is not one of the primary endpoints of clinical trials, (2) statistical power to assess antihypertensive effects is insufficient, and (3) study groups were composed of both hypertensive and normotensive patients. Additionally, the effects of antihypertensive therapies may have varied between trials because of variations in how and when the BP was measured. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different inclusion criteria, different designs, variable follow-up duration with differing attrition rates, and different patient populations. As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for compliance to assigned therapy.

OUTLOOK

Further studies evaluating the magnitude of the antihypertensive effects of statins should: (1) use 24-hour ambulatory BP measurements to accurately determine the extent and duration of antihypertensive effects, (2) have BP changes as one of the primary endopoints (3) keep the dosages of other antihypertensives steady during the study, (4) assess the effects of different statin dosages, (5) examine the effects of statins on hypertensive subgroups (eg, dippers vs nondippers and diabetics vs nondiabetics), (6) determine the onset and duration of antihypertensive actions of statins, and (7) evaluate possible synergistic effects of statin and other antihypertensive agents.

CONCLUSIONS

The available data support only a modest BP-lowering effect of statins that is most prominent in patients with poorly controlled hypertension. Overall, the small antihypertensive effect may add to the reduction in cardiovascular risk conferred by statin therapy and may be clinically significant in patients with intermediate to high cardiovascular risk.

Acknowledgments and Disclosures: No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

References

- 1. Haug C, Schmid-Kotsas A, Zorn U, et al. Endothelin-1 synthesis and endothelin B receptor expression in human coronary artery smooth muscle cells and monocytederived macrophages is up-regulated by low density lipoproteins. *J Mol Cell Cardiol*. 2001;33:1701–1712.
- Iow density lipoproteins. J Mol Cell Cardiol. 2001;33:1701–1712.
 Wassmann S, Laufs U, Baumer AT, et al. HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. *Hypertension*. 2001;37:1450–1457.
- Ferrier KE, Muhlmann MH, Baguet JP, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol. 2002;39:1020–1025.
 Strazzullo P, Kerry SM, Barbato A, et al. Do statins reduce blood
- Strazzullo P, Kerry SM, Barbato A, et al. Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hyper*tension. 2007;49:792–798.

- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
- Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in metaanalyses. *Ann Intern Med.* 2001;135:982–989.
- Lavallée PC, Labreuche J, Gongora-Rivera F, et al. Placebo-controlled trial of high-dose atorvastatin in patients with severe cerebral small vessel disease. *Stroke*. 2009;40:1721–1728.
- 8. Mancia G, Parati G, Revera M, et al. Statins, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial. *BMJ*. 2010;340:c1197.
- Manisty C, Mayet J, Tapp RJ, et al. Atorvastatin treatment is associated with less augmentation of the carotid pressure waveform in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT). *Hypertension*. 2009;54:1009–1013.
 Williams B, Lacy PS, Cruickshank JK, et al. Impact of statin therapy
- Williams B, Lacy PS, Cruickshank JK, et al. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study. *Circulation*. 2009;119:53–61.
 Orr JS, Dengo AL, Rivero JM, Davy KP, Arterial destiffening with
- Orr JS, Dengo AL, Rivero JM, Davy KP. Arterial destiffening with atorvastatin in overweight and obese middle-aged and older adults. *Hypertension*. 2009;54:763–768.
- Koh KK, Quon MJ, Han SH, et al. Additive beneficial effects of atorvastatin combined with amlodipine in patients with mild-tomoderate hypertension. *Int J Cardiol.* 2011;146:319–325.
- adorvatine connect with animotive in particles with initial or moderate hypertension. Int J Cardiol. 2011;146:319–325.
 Golomb BA, Dimsdale JE, White HL, et al. Reduction in blood pressure with statins: results from the UCSD Statin Study, a randomized trial. Arch Intern Med. 2008;168:721–727.
- 14. Grimm R, Malik M, Yunis C, et al.; TOGETHER Investigators. Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial. Vasc Health Risk Manag. 2010;6:261–271.
- Balletshofer BM, Goebbel S, Rittig K, et al. Intense cholesterol lowering therapy with a HMG-CoA reductase inhibitor does not improve nitric oxide dependent endothelial function in type-2-diabetes –a multicenter, randomised, double-blind, three-arm placebo-controlled clinical trial. *Exp Clin Endocrinol Diabetes*. 2005;113:324– 330.
- 16. Kuklinska AM, Mroczko B, Musial WJ, et al. Influence of atorvastatin on blood pressure control in treated hypertensive, normolipemic patients—An open, pilot study. *Blood Press*. 2010;19:260–266.
- Špósito AC, Mansur AP, Coelho OR, et al. Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). *Am J Cardiol.* 1999;83:1497–1499.
- Terzoli L, Mircoli L, Raco R, Ferrari AU. Lowering of elevated ambulatory blood pressure by HMG-CoA reductase inhibitors. *J Cardiovasc Pharmacol.* 2005;46:310–315.
- Tonelli M, Sacks F, Pfeffer M, et al. Effect of pravastatin on blood pressure in people with cardiovascular disease. J Hum Hypertens. 2006;20:560–565.
- Sever PS, Poulter NR, Dahlof B, Wedel H; ASCOT Investigators. Antihypertensive therapy and the benefits of atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm extension. J Hypertens. 2009;27:947–954.
- 21. Teixeira AA, Buffani A, Tavares A, et al. Effects of fluvastatin on insulin resistance and cardiac morphology in hypertensive patients. *J Hum Hypertens*. 2011;25:492–499.
- Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. Effect of statins and ACE inhibitors alone and in combination on clinical outcome in patients with coronary heart disease. *J Hum Hypertens*. 2004;18:781– 788.
- Borghi C, Dormi A, Veronesi M, et al; Brisighella Heart Study Working Party. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. Am Heart J. 2004;148:285–292.
- Fogari R, Derosa G, Lazzari P, et al. Effect of amlodipine-atorvastatin combination on fibrinolysis in hypertensive hypercholesterolemic patients with insulin resistance. *Am J Hypertens*. 2004;17:823–827.
- 25. Nakamura T, Ushiyama C, Hirokawa K, et al. Effect of cerivastatin on urinary albumin excretion and plasma endothelin-1 concentrations in type 2 diabetes patients with microalbuminuria and dyslipidemia. *Am J Nephrol.* 2001;21:449–454.
- Bak AA, Huizer J, Leijten PA, et al. Diet and pravastatin in moderate hypercholesterolaemia: a randomized trial in 215 middle-aged men free from cardiovascular disease. *J Intern Med.* 1998;244:371–378.

- 27. Derosa G, Mugellini A, Ciccarelli L, Fogari R. Randomized, doubleblind, placebo-controlled comparison of the action of orlistat, fluvastatin or both, on anthropometric measurements, blood pressure and lipid profile in obese patients with hypercholesterolemia prescribed a standardized diet. *Clin Ther.* 2003;25:1107–1122.
- Lee TM, Chou TF, Tsai CH. Association of pravastatin and left ventricular mass in hypercholesterolemic patients: role of 8-isoprostaglandin F2_ formation. J Cardiovasc Pharmacol. 2002;40:868 -874.
- McDowell IF, Smye M, Trinick T, et al. Simvastatin in severe hypercholesterolaemia: a placebo controlled trial. Br J Clin Pharmacol. 1991;31:340–343.
- Hommel E, Andersen P, Gall MA, et al. Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy. *Diabetologia*. 1992;35:447–451.
- Kanaki AI, Sarafidis PA, Georgianos PI, et al. Low-dose atorvastatin reduces ambulatory blood pressure in patients with mild hypertension and hypercholesterolaemia: a double-blind, randomized, placebocontrolled study. *J Hum Hypertens*. 2011;26:577–584 doi: 10.1038/ jhh.2011.80.
- 32. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. *Am Heart J.* 2006;151:273–281.
- 33. Sever PS, Dahlof B, Poulter NR, et al., on behalf of the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lowerthan-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149– 1158.
- 34. Cohn JN, Wilson DJ, Neutel J, et al. Coadministered amlodipine and atorvastatin produces early improvements in arterial wall compliance in hypertensive patients with dyslipidemia. *Am J Hypertens*. 2009;22:137–144.
- Danaoğlu Z, Kültürsay H, Kayikçioğlu M, et al. Effect of statin therapy added to ACE-inhibitors on blood pressure control and endothelial functions in normolipidemic hypertensive patients. *Anadolu Kardiyol Derg.* 2003;3:331–337.
- Fassett RG, Robertson IK, Ball MJ, et al. Effects of atorvastatin on arterial stiffness in chronic kidney disease: a randomised controlled trial. J Atheroscler Thromb. 2010;17:235–241.
- 37. Ge CJ, Lu SZ, Chen YD, et al. Synergistic effect of amlodipine and atorvastatin on blood pressure, left ventricular remodeling, and Creactive protein in hypertensive patients with primary hypercholesterolemia. *Heart Vessels*. 2008;23:91–95.
- Hjelstuen A, Anderssen SA, Holme I, et al. Effect of lifestyle and/or statin treatment on soluble markers of atherosclerosis in hypertensives. *Scand Cardiovasc J.* 2007;41:313–320.
 Ichihara A, Hayashi M, Koura Y, et al. Long-term effects of statins on
- Ichihara A, Hayashi M, Koura Y, et al. Long-term effects of statins on arterial pressure and stiffness of hypertensives. J Hum Hypertens. 2005;19:103–109.
- Kushiro T, Mizuno K, Nakaya N, et al. Pravastatin for cardiovascular event primary prevention in patients with mild-to-moderate hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. *Hypertension*. 2009;53:135–141.
- Glorioso N, Troffa C, Filigheddu F, et al. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. *Hypertension*. 1999;34:1281–1286.
- Lee TM, Chen CC, Shen HN, Chang NC. Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Clin Sci (Lond)*. 2009;116:497– 505.
- Magen E, Viskoper R, Mishal J, et al. Resistant arterial hypertension and hyperlipidemia: atorvastatin, not vitamin C, for blood pressure control. *Isr Med Assoc J.* 2004;6:742–746.
 Olkinuora JT, Viikari J, Vanhanen H, et al. Effects of celiprolol and
- Olkinuora JT, Viikari J, Vanhanen H, et al. Effects of celiprolol and simvastatin on the calculated risk of coronary heart disease (the Celisimva study). *Scand Cardiovasc J.* 2006;40:160–166.
 Lewandowski J, Siński M, Bidiuk J, et al. Simvastatin reduces
- Lewandowski J, Siński M, Bidiuk J, et al. Simvastatin reduces sympathetic activity in men with hypertension and hypercholesterolemia. *Hypertens Res.* 2010;33:1038–1043.
- Su SF, Hsiao CL, Chu CW, et al. Effects of pravastatin on left ventricular mass in patients with hyperlipidemia and essential hypertension. *Am J Cardiol.* 2000;86:514–518.
 Tonolo G, Ciccarese M, Brizzi P, et al. Reduction of albumin
- Tonolo G, Ciccarese M, Brizzi P, et al. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. *Diabetes Care*. 1997;20:1891–1895.

- Hodis HN, Blankenhorn DH, Azen SP, et al; MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med. 1993;119:969–976.
- 49. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet.* 2004;363:757–767.
- Antoniades C, Bakogiannis C, Leeson P, et al. Rapid, direct effects of statin treatment on arterial redox state and nitric oxide bioavailability in human atherosclerosis via tetrahydrobiopterin-mediated endo-

thelial nitric oxide synthase coupling. Circulation. 2011;124:335-345.

- 51. Sun W, Lee TS, Zhu M, et al. Statins activate AMP-activated protein kinase in vitro and in vivo. *Circulation*. 2006;114:2655–2662.
- Laufs U, Liao JK. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. J Biol Chem. 1998;273:24266-24271.
- 53. Rupérez M, Rodrigues-Díez R, Blanco-Colio LM, et al. HMG-CoA reductase inhibitors decrease angiotensin II-induced vascular fibrosis: role of RhoA/ROCK and MAPK pathways. *Hypertension*. 2007;50:377–383.