Do Statins Reduce Blood Pressure?: A Meta-Analysis of Randomized, Controlled Trials

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Do Statins Reduce Blood Pressure?
A Meta-Analysis of Randomized, Controlled Trials

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Abstract—A meta-analysis was performed of the effect of 3hydroxy3methylglutaryl-coenzyme A reductase inhibitors (statins) on blood pressure in humans including the randomized, controlled trials of statin therapy (20 trials and 828 patients) in which concomitant antihypertensive treatment (if any) remained unchanged throughout the study. A total of 291 and 272 patients were given a statin or placebo, respectively, in parallel group trials, whereas 265 took part in crossover trials receiving a statin and placebo (or probucol, in 1 trial). Systolic blood pressure was significantly lower in patients on statin than in those on placebo or control hypolipidemic drug (mean difference: −1.9 mm Hg; 95% CI: −3.8 to −0.1). The effect was greater when the analysis was restricted to studies with a baseline systolic blood pressure >130 mm Hg (Δ systolic blood pressure: −4.0; 95% CI: −5.8 to −2.2 mm Hg). There was a trend for lower diastolic blood pressure in patients receiving statin therapy compared with control: −0.9 mm Hg (95% CI: −2.0 to 0.2) overall and −1.2 mm Hg (95% CI: −2.6 to 0.1) in studies with a baseline diastolic blood pressure >80 mm Hg. In general, the higher the baseline blood pressure, the greater the effect of statins on blood pressure ($P=0.066$ for systolic blood pressure and $P=0.023$ for diastolic blood pressure). The blood pressure response to statins was unrelated to age, changes in serum cholesterol, or length of the trial. In conclusion, statin therapy has a relatively small but statistically significant and clinically meaningful effect on blood pressure. (***Hypertension*. 2007;49:792-798.**)

Key Words: blood pressure ■ hypertension, arterial ■ hypercholesterolemia ■ drug therapy ■ statins ■ meta-analysis

High blood pressure (BP) is common in hypercholesterolemic and in diabetic patients and powerfully contributes to the increase in cardiovascular risk.[1] The prescription of both antihypertensive and cholesterol-lowering drugs is generally required for these patients. Inhibitors of 3hydroxy3methylglutaryl-coenzyme A reductase (statins) are the most effective and widely used cholesterol-lowering drugs in industrialized countries.[2] They significantly reduce the risk of cardiovascular events and death in both primary and secondary prevention of cardiovascular disease.[3,4] Although the long-term benefit by statin treatment is largely attributed to their cholesterol-lowering action, increasing attention focuses on additional actions of these substances, which are independent from 3hydroxy3methylglutaryl-coenzyme A reductase inhibition[5] and might help explain why part of the benefit in terms of cardiovascular protection is already seen shortly after the initiation of therapy.[6,7]

Very few relatively small studies have investigated the antihypertensive effect of statins in patients with hypertension associated with hypercholesterolemia.[8–10] The results of 2 recently published large statin studies, albeit not designed to answer this question, have attracted the interest on this subject.[11,12] Many other studies, also not specifically aimed at the evaluation of the statins' antihypertensive effect, have provided information concerning changes in BP during treatment with statins. Present knowledge is hampered by severe limitations, such as inadequate study design, small or very small sample size, too short treatment period, and modification of concomitant antihypertertensive therapy during the trial. Nevertheless, an effect of statins on BP is potentially important and not implausible bearing in mind the reported effects of statins on endothelial function,[13] their interaction with the renin–angiotensin system,[14] and their ability to affect large artery compliance.[15,16]

We systematically reviewed the existing literature of randomized trials of statin therapy. We carried out a meta-analysis of the effect of statins on systolic and diastolic BP including only those trials in which concomitant antihypertensive therapy, if any, was kept constant during the trial.

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Methods

Identification and Selection of Trials

We searched online databases (PUBMED, HTA, and EMBASE) up to October 2005 for randomized, controlled trials of statins, using a search strategy based on the words *blood pressure* and/or *hypertension* (as either text words or Medical Subjects Heading terms) and *statin* (or individuals statin names) and *randomized, controlled trial* (Table S1, available in an online supplement at http://www.hypertensionaha.org). We also searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Clinical Effectiveness, the Health Technology Assessment Database, the National Health Service Economic Evaluation Database and the Web sites of the Centre for Reviews and Dissemination and of the Agency for Healthcare Research and Quality, for reviews regarding BP/hypertension and statins. Finally we examined the reference lists of relevant reviews and of all of the identified studies and reviewed cited literature. We identified 175 original reports (Table S2) and 63 reviews.

Inclusion and Exclusion Criteria

We included only randomized, controlled trials published as original articles in peer-reviewed scientific journals in English provided that they used either an identical placebo or a different hypolipidemic drug. We excluded trials where we could not extract or calculate the difference between baseline and end-of-treatment systolic and diastolic BP 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 group, length of study, description of the main relevant features of the study population, including gender, age, hypertensive status, and description of concomitant therapy, if any. If an antihypertensive treatment was given during the trial period, the study was included only if a statement that antihypertensive drug therapy (in terms of number, type, and dosage of drugs) was kept unchanged during the trial was clearly made.

Eighteen randomized, controlled trials met the inclusion criteria and were included in the meta-analysis[9,10,15–30] (Figure 1). Because 2 of them,[25,26] however, were characterized by having 2 different pairs of control and treatment groups, we considered them as being split in 2 independent studies; thus, the final number of studies analyzed was actually 20.

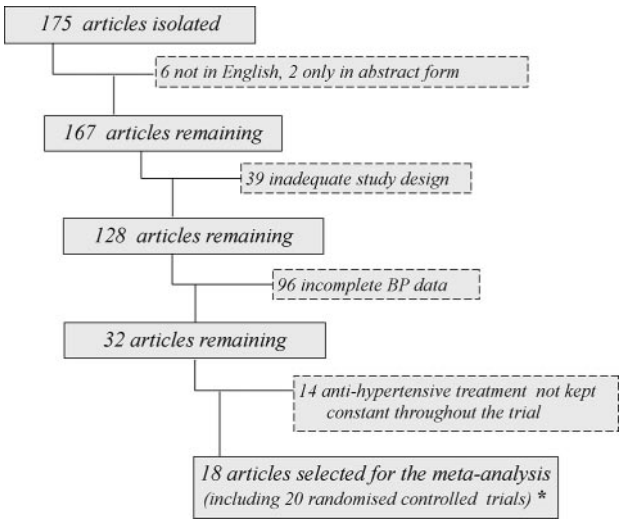

Figure 1. Schematic representation of the procedure followed to determine the trials to be included in the meta-analysis based on predetermined inclusion/exclusion criteria. Two of the studies described in the 18 articles, ie, the one by Bak et al[25] and the one by DeRosa et al,[26] were characterized by having 2 different pairs of control and treatment groups, so that they were analyzed as 2 independent trials; therefore, the final number of studies included in the meta-analysis was 20.

Data Extraction

Two reviewers (A.B. and M.V.) independently extracted data from text and tables. Discrepancies about inclusion of studies and interpretation of data were resolved on arbitration (P.S.), and consensus was reached after discussion.

Statistical Methods

We used a random effect model (Stata Corp). For parallel groups trials, the intervention effect was the between-group difference in the extent of BP change from baseline. In 4 studies, the confidence intervals of the change in BP were estimated from the *P* value,[9,16,26] and for 11 studies[15,17,19–22,24,27–30] SDs of the BP change were estimated by assuming a correlation coefficient between baseline and follow-up BP of 0.5.[31] For crossover trials, the outcome measure was given by the difference between the poststatin and the postplacebo BP. Also in this case, if the SD of the difference was not reported, we applied the same principle as for parallel group trials to the postplacebo and poststatin SD to estimate the SD of the difference. All of the trials, whether parallel groups or crossover, were analyzed together using the intervention effect and its SE for each study.

Potential publication bias was assessed by using a funnel plot and Egger's test.[32,33] The degree of heterogeneity between trials was tested by χ^2. Meta-regression was used to assess whether baseline BP, length of treatment, hypertensive or diabetic status, and serum cholesterol response to statin treatment were associated with the effect of statin therapy on BP. In testing the relation of the BP effect of statin to baseline BP, we included the studies in which patients were on antihypertensive treatment at the time of recruitment, and their antihypertensive therapy was kept unchanged throughout the trial; we did not include in this analysis 2 trials[28,29] in which patients were prescribed antihypertensive therapy at the same time that treatment with statins was started.

Results

Characteristics of Trials and Patients Included in the Meta-Analysis

A total of 828 patients from 20 studies was included in the analysis, 291 being allocated to statin treatment groups and 272 to control groups; 265 patients took part in crossover trials. In 18 studies, placebo was the treatment adopted for the control group. One study[9] used probucol, a lipid-lowering drug as control, whereas in another one[26] fluvastatin plus orlistat (an inhibitor of intestinal lipid digestion) were compared with orlistat alone. Pravastatin was the statin used in 8 studies,[9,10,17,21–23,25] simvastatin was used in 5,[15,19,20,24,28] fluvastatin in 2,[26] cerivastatin in 2 studies,[27,30] atorvastatin in 2 studies,[16,29] and lovastatin in 1 study.[18] The duration of treatment varied from 4 weeks[15] to 1 year.[24,26]

Some studies included only hypertensive patients,[10,16,17,23,28,29] others recruited either normotensive or treated hypertensive patients in reasonably good control,[22,30] and a few studies included only normotensive individuals.[22,23,28,30] Four studies included only type 1 or only type 2 diabetic patients,[19,24,27,30] whereas 9 studies excluded patients affected by diabetes[9,10,15,17,18,20,21,23,29] (Table S3).

In 7 studies, none of the participants received drugs different from statins or control medications.[15,21,23,25,26] In all of the others, the patients had a variety of concomitant medication regimes (Table) and, in particular, antihypertensive treatment: in 2 such studies,[28,29] antihypertensive therapy was started at the same time as statin treatment. In all of the cases, however, antihypertensive therapy was kept unchanged throughout the trial. Ten studies gave instructions for patients' diet.[10,17,19,20,23–26] In 1 study, the patients' previous

Type of Intervention Provided in Individual Studies

First Author, Year	Active Therapy	Average Dose, mg/day	Additional Drug Therapy	Duration of Treatment, mo	Dietary Treatment	Crossover Design	No. of Patients, Statin/Control	Mean Age, Statin/Control	% Male, Statin/Control
McDowell, 1991	S	20	NR	3	Dietary supervision	No	15/12	NR/NR[1]	NR/NR
Hommel, 1992	S	13	Yes	3	Dietary advice	No	12/9	41/35	50/67
O'Callaghan, 1994	P	23	Yes	3	None	No	12/12	56/62	50/50
Bak (1), 1998	P	20	None	6	STEP 1	No	49/51	55/55	100/100
Bak (2), 1998	P	20	None	6	STEP 2	No	46/51	56/55	100/100
Nakamura, 2001	C	0.15	Yes	6	None	No	30/30	58/55	60/66
Lee, 2002	P	12	None	6	None	No	25/25	52/50	60/64
De Rosa (1), 2003	F	80	None	12	Controlled energy intake/exercise	No	24/23	51/52	46/48
De Rosa (2), 2003	F	80	None	12	Controlled energy intake/exercise	No	24/25	51/52	46/48
Jenkins, 2003	L	20	Yes	1	Low fat	No	14/16	57/56	50/69
Balletshofer, 2005	C	0.2/0.8	Yes	3	None	No	40/18	60	67/50
Kool, 1995	P	40	Yes	2	Lipid lowering	Yes	19	52	58
Straznicky, 1995	P	40	None	2	Usual patient's diet	Yes	14	56	50
Tonolo, 1997	S	20	Yes	12	250 mg chol/day	Yes	20	60	80
Glorioso, 1999	P	20	NR	8	Constant sodium and calorie diet	Yes	30	53	43
Shige, 2001	S	30	None	1	Dietary review	Yes	20	54	55
Ferrier, 2002	A	80	NR	3	None	Yes	22	60	82
Fogari, 2004	A	20	Yes	3	None	Yes	41	41 to 70	48
Ikeda, 2004	P	10	Yes	6	None	Yes	52	63	42
Koh, 2004	S	20	Yes	2	None	Yes	47	57	42

NR indicates not reported; S, simvastatin; P, pravastatin; C, cerivastatin; F, fluvastatin; L, lovastatin; A, atorvastatin.

diets were reviewed.[13] Eight studies did not define a particular diet profile.[9,16,21,22,27–30]

Most studies included only hypercholesterolemic patients (serum total cholesterol ≥5.2 mmol/L),[9–12,18–27,29] and 2 studies included subjects with low-density lipoprotein cholesterol >2.6 mmol/L.[28–30] One study enrolled normocholesterolemic subjects,[16] whereas 2 studies did not use specified inclusion criteria for serum cholesterol.[15,17] Details on blood lipid levels, inclusion criteria, and nonpharmacological treatments adopted (diet and lifestyle suggestions) in the single trials are reported in the Table.

Estimate of the BP Effect of Statins in the Trials Included in the Meta-Analysis

Systolic BP

The overall intervention effect for statin therapy on systolic BP (SBP) was a 1.9-mm Hg reduction (95% CI: −3.8 to −0.1), with significant heterogeneity between studies ($P<0.01$; Figure 2). The funnel plot did not show asymmetry consistent with publication bias, and Egger's test was not significant ($P=0.58$).

Diastolic BP

For diastolic BP (DBP), the effect of statin therapy in all of the studies was in the same direction as for SBP but less marked: −0.9 mm Hg (95% CI: −2.0 to 0.2 mm Hg; Figure 2), with significant heterogeneity between studies ($P<0.01$). There was no evidence of publication bias (Egger's test $P=0.48$).

Meta-Regression and Subgroup Analysis

The effect of statin therapy on BP was greater in studies that recruited patients with higher baseline BPs ($P=0.023$ for diastolic and $P=0.066$ for systolic BP; Figure 3). When the analysis was restricted to studies where baseline SBP was >130 mm Hg, the effect of statin therapy was −4.0 mm Hg (95% CI: −5.8 to −2.2 mm Hg), and heterogeneity was not statistically significant ($P=0.26$). In studies with average baseline DBP >80 mm Hg, the effect of statin therapy on DBP was −1.2 mm Hg (95% CI: −2.6 to 0.1 mm Hg; heterogeneity $P=0.069$; Figure 2). In those trials where SBP at baseline was ≤130 mm Hg and/or DBP ≤80 mm Hg, the average net effect of statin on systolic and diastolic BP, respectively, was negligible. In 4 trials that enrolled diabetic hypercholesterolemic patients, the weighted combined effect of statins on BP was −3.7 mm Hg (95% CI: −8 to 1.5 mm Hg)/−0.8 mm Hg (95% CI: −1.9 to 0.4 mm Hg).

Using meta-regression analysis, no evidence was obtained that any of the following factors were significantly related to the response to statin therapy: age ($P=0.86$ for SBP and 0.79 for DBP), length of the trial ($P=0.79$ and 0.66, respectively), baseline serum cholesterol ($P=0.58$ and 0.91), change in serum total cholesterol ($P=0.51$ and 0.86), or low-density lipoprotein cholesterol ($P=0.40$ and 0.69), whether patients were diabetic or not ($P=0.50$ and 0.51) and whether antihypertensive drugs were being used by at least some patients ($P=0.53$ and 0.98).

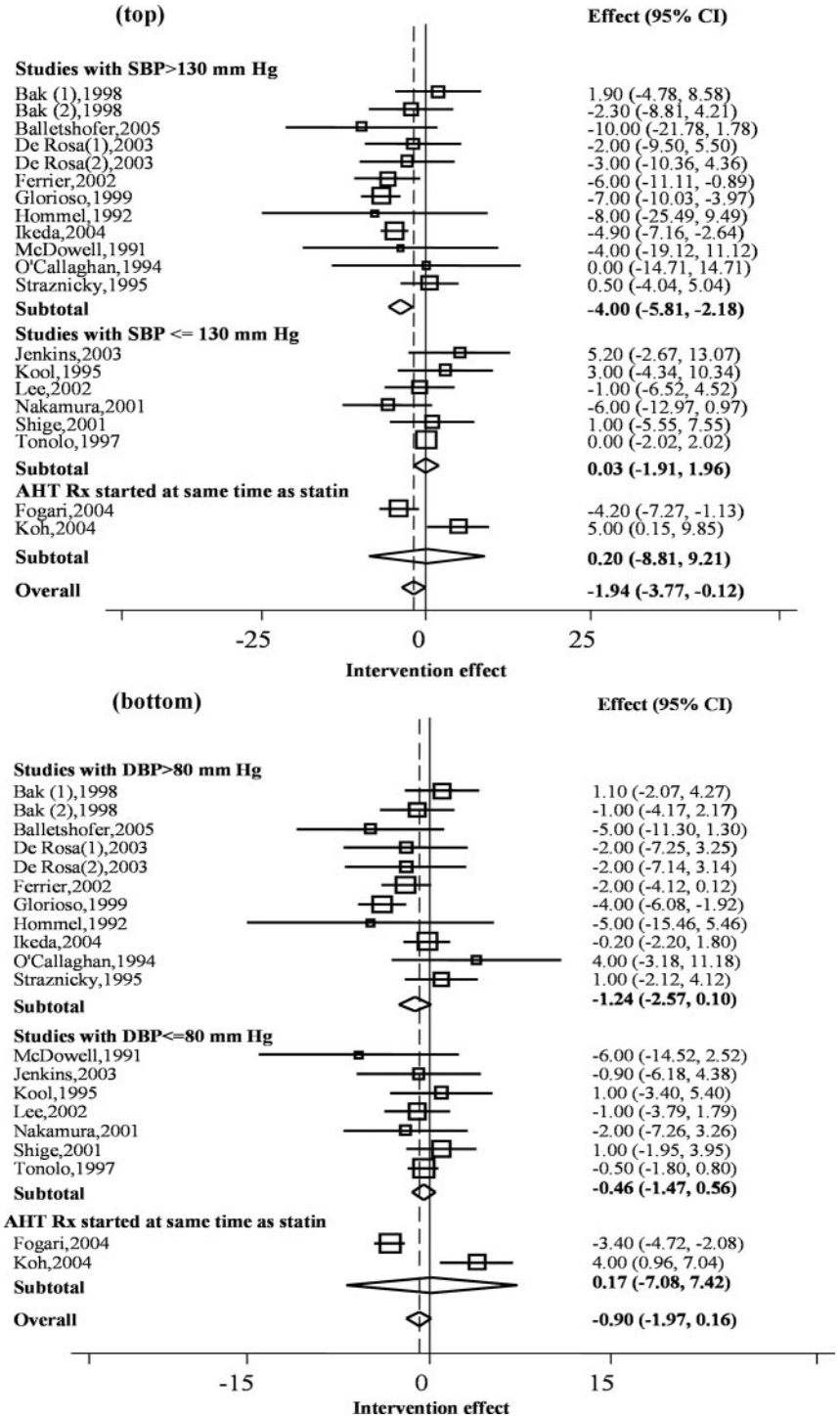

Figure 2. Mean differences and 95% CIs in SBP (top) and DBP (bottom) achieved in patients taking a statin compared with those taking placebo or other control treatment. Separate evaluations were made for studies in which baseline SBP was >130 or ≤130 mm Hg (top) and for those in which DBP was >80 or ≤80 mm Hg (bottom). Separate evaluation of the effects on SBP (top) and DBP (bottom) was also made for the 2 studies (see text) in which concomitant antihypertensive therapy was initiated after recruitment, that is, at the same time as treatment with statin.

Results From Other Trials Not Included in the Meta-Analysis

Two studies, composed of a total number of 64 patients, could not be included in the meta-analysis, because they provided only mean BP values at the start and end of treatment.[34,35] The net effect of statin therapy on BP in these 2 studies was a mean BP reduction of 4.0 mm Hg (95% CI: −19.6 to 11.6) and of 2.0 mm Hg (95% CI: −19.9 to 15.9), respectively. The estimated combined effect in the 2 studies was a 3.1-mm Hg fall in mean BP (95% CI: −14.9 to 8.6).

Discussion

Main Findings

This meta-analysis of 20 randomized, controlled trials showed a small but statistically significant reduction of systolic BP and a trend to reduction of diastolic BP with statin therapy. These effects would have been slightly larger if 2 studies that provided only mean BP values and showed a combined net effect of statin of 3.1 mm Hg could have been included in the meta-analysis.[34,35] Meta-regression analysis showed that statins were more effective on BP in subjects

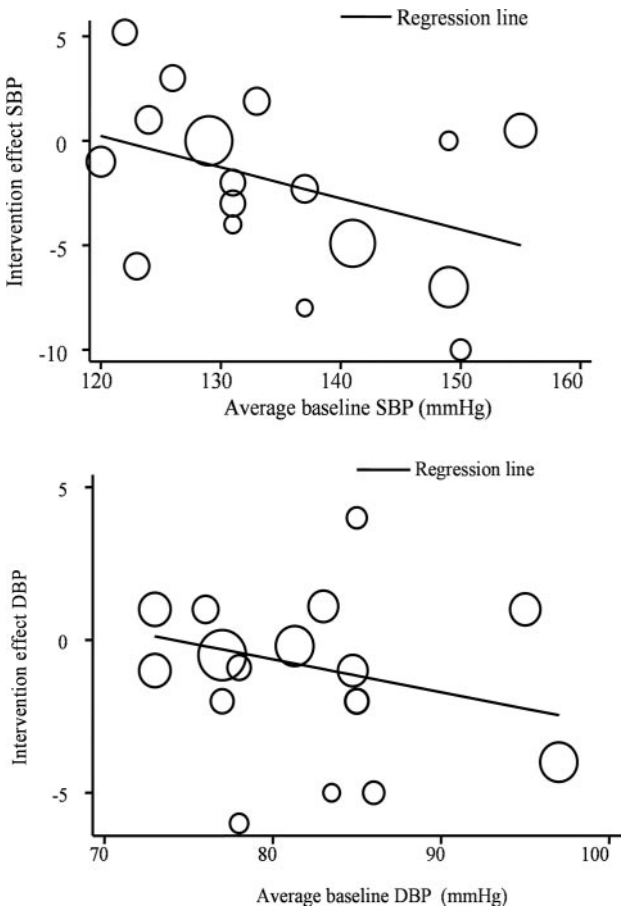

Figure 3. Meta-regression of intervention effect as a function of baseline SBP (top; $P=0.066$) and DBP (bottom; $P=0.023$).

who had higher baseline BP levels. A subanalysis of the studies that enrolled patients with SBP >130 or DBP >80 mm Hg indicated that, in fact, the BP-lowering effect of statins was restricted to these patients.

None of the large trials that highlighted the value of statin treatment in primary and secondary prevention of cardiovascular disease could be included in our meta-analysis, because BP values were not reported and/or concomitant antihypertensive treatment in participants with high BP was not kept constant during the study (Table S4). A recent communication (published as abstract) from the Anglo-Scandinavian Cardiac Outcomes Trial showed that between the week-6 visit and 2.5-year visit, BP was significantly lower in patients on atorvastatin than in those on placebo, with a maximum difference of 1.1/0.7 mm Hg.[12] Similarly, in the University of California at San Diego Statin Study,[11] both during and at the end of the trial, the patients' groups treated with simvastatin or pravastatin had a significantly lower SBP and DBP compared with the placebo groups, with a maximum difference of 2.8/2.7 mm Hg. In both of these studies, the participants were prescribed antihypertensive medications that could be titrated at any time during the trial. Although both trials were, thus, not eligible for our meta-analysis, their results appear to be consistent with those of our study.

The BP effect of statins detected by our analysis was definitely lower than the average effect of regular antihypertensive drugs and reached statistical significance only for systolic BP; yet, it was clinically relevant, also considering that in most of the studies included in our meta-analysis the average BP at entry was lower than that observed in most trials of antihypertensive therapy and that, in addition, in several studies, the patients were already placed on regular treatment for high BP. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, a 2 mm Hg lower on-trial systolic BP in the chlorthalidone compared with the lisinopril arm was associated with a 15% lower rate of stroke and a 19% lower rate of congestive heart failure.[36] Likewise, in the Hypertension Optimal Treatment Study, a 4/4 mm Hg difference in BP was associated with a 50% reduction in the rate of cardiovascular events in diabetic participants.[37]

Limitations

The patients' population in whom the analysis was carried out was not very large, because large-scale studies of statin therapy did not provide BP values at the start and end of the trial or did not conform to our necessarily strict inclusion criteria with respect to concomitant use of antihypertensive medications or both. Also, the studies included in this quantitative review were rather heterogeneous, because they were carried out in a variety of settings, with different methods, using various criteria and different comparative groups. Although we selected only randomized, controlled trials, few of the studies had been specifically designed to test the hypothesis evaluated by our meta-analysis. The major parts of the studies were conducted on hypercholesterolemic patients. We were unable to examine a possible dose–effect relationship or possible differences in the BP effects of different statins given the relatively small number of trials and the limited sample size available. Many studies required an estimation of the SD of the effect size; in 4 studies, the *P* value was used, and this may have resulted in a slight overestimate of the SD, possibly reducing the significance of the effect size. For 1 study that provided both intention-to-treat and on-treatment analysis, the intention-to-treat analysis was used; also, this choice may have led to a conservative estimate of the effect.

Possible Mechanisms of the BP Effect of Statins

There are several mechanisms whereby statins may affect BP. In experimental studies, statins increase the endothelial production of NO, an effect correlated with upregulation of endothelial NO synthase expression.[38–41] This effect may be reinforced by simultaneous inhibition of G proteins with reduced endothelial NO synthase mRNA degradation and, thus, increased NO bioavailability.[42] Moreover, it may also be reinforced by a decrease in the release and circulating levels of the vasoconstrictor endothelin-1.[43] These effects are translated in substantial improvements of endothelial function, assessed by vasodilator response to acetylcholine or as flow-mediated vasodilation, in various pathological conditions characterized by marked endothelial dysfunction.[44–50] These various effects manifest themselves early after statin administration and, thus, appear substantially unrelated to their cholesterol-lowering action.[12,51] This notion is in keeping

with the result of our meta-regression analysis indicating no significant association with the cholesterol response and no relationship with length of treatment.

Statins inhibit the production of reactive oxygen species, such as superoxide anion, and hydroxyl radicals in animal vessel models, and also this action can contribute to vasodilation.[52] Statins have been shown to reduce large artery stiffness and improve systemic arterial compliance,[15,16] an effect ascribed to alterations in the relative content of vascular smooth muscle cells in large arteries and to restoration of endothelial function.[15] This mechanism could be expected to affect, in particular, SBP, which is in line with our results.

A further possible mechanism of the BP-lowering effect of statins is downregulation of the angiotensin II–type 1 receptor. The angiotensin II–type 1 receptor is overexpressed in hypercholesterolemic patients, and this alteration was corrected by administration of statins,[14] which also markedly reduced the vasoconstrictor response to angiotensin II infusion.[14]

Conclusions

Whatever the mechanism(s), our meta-analysis provided evidence of a favorable effect of statins on BP, particularly SBP, and indicated that the effect was larger in individuals with elevated BP. No statistically significant relationship could be demonstrated between the BP effect of statin therapy and baseline serum cholesterol or change in serum total or low-density lipoprotein cholesterol during the treatment period.

Perspectives

This study provided the first demonstration of a statistically significant effect of statin therapy on BP. Its main feature was the inclusion in the meta-analysis of only randomized, controlled trials in which concomitant antihypertensive treatment (if any) was kept constant throughout the study. Its most important limitation, on the other hand, was the relatively small patients' population enrolled. Also, the study results derived mainly, although not exclusively, from the analysis of trials carried out in hypercholesterolemic patients. It remains to be clarified whether the BP effect of statins is a class effect or is a property of 1 or few substances in the class.

Although the effect on BP was moderate and statistically significant only for systolic pressure, it may be, nevertheless, relevant from the point of view of cardiovascular prevention. It can be speculated that, in hypertensive patients in whom the prescription of a statin is indicated (eg, because of concomitant hypercholesterolemia, diabetes, and/or previous myocardial infarction), this might reduce, to some extent, the dose and number of drugs required to achieve satisfactory BP control. Further studies to test the extent and the mechanism(s) of the BP effect of statins in these and other selected categories of very high-risk patients are warranted.

Disclosures

None.

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