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Reduction in Blood Pressure With Statins:

Results From the UCSD Statin Study, a Randomized Trial

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Abstract

Background—Some studies have suggested reductions in blood pressure (BP) with statin treatment, particularly in persons with hypertension. Randomized trial evidence is limited.

Methods—We performed a randomized, double-blind, placebo-controlled trial with equal allocation to simvastatin, 20 mg; pravastatin sodium, 40 mg; or placebo for 6 months. Nine hundred seventy-three men and women without known cardiovascular disease or diabetes mellitus, with low-density lipoprotein cholesterol screening levels of 115 to 190 mg/dL, had assessment of systolic and diastolic BP (SBP and DBP, respectively). Blood pressure values were compared for placebo vs statins by intention-to-treat (ITT) analysis. Additional analyses were performed that (1) were confined to subjects with neither high baseline BP (SBP >140 mm Hg or DBP >90 mm Hg) nor receiving BP medications, to exclude groups in whom BP medications or medication changes may have influenced results, and (2) separately evaluated simvastatin and pravastatin (vs placebo). The time course of BP changes after statin initiation and the effect of stopping statins on BP were examined.

Results—Statins modestly but significantly reduced BP relative to placebo, by 2.2 mm Hg for SBP ($P = .02$) and 2.4 mm Hg for DBP ($P < .001$) in ITT analysis. Blood pressure reductions ranged from 2.4 to 2.8 mm Hg for both SBP and DBP with both simvastatin and pravastatin, in

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Author Contributions: Dr Golomb had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Golomb, Dimsdale, White, and Criqui. *Acquisition of data:* Golomb, Ritchie, and Criqui. *Analysis and interpretation of data:* Golomb, Dimsdale, White, and Criqui. *Drafting of the manuscript:* Golomb, Ritchie, and Dimsdale. *Critical revision of the manuscript for important intellectual content:* Golomb, Dimsdale, White, and Criqui. *Statistical analysis:* Golomb and White. *Obtained funding:* Golomb. *Administrative, technical, and material support:* Ritchie, Dimsdale, and Criqui. *Study supervision:* Golomb.

those subjects with full follow-up, and without potential for influence by BP medications (ie, neither receiving nor meriting BP medications).

Conclusions—Reductions in SBP and DBP occurred with hydrophilic and lipophilic statins and extended to normotensive subjects. These modest effects may contribute to the reduced risk of stroke and cardiovascular events reported on statins.

Trial Registration—clinicaltrials.gov Identifier: NCT00330980

Some studies have suggested reductions in blood pressure (BP) with statin treatment, particularly in patients with hypertension. Many studies reporting BP reductions have been correlational, uncontrolled, tested against other active drugs with uncertain impact on BP, unblinded, nonrandomized, or without assessment of statistical significance.¹⁻⁹ Some double-blind, randomized studies failed to show an effect but had a small sample size.^{10,11} Two small, randomized, double-blind, crossover studies^{12,13} have shown significant ($P < .05$) benefit, but to our knowledge there are no published articles showing reductions in BP with statins in sizeable randomized trials.

The BP assessments performed in the double-blind, randomized, University of California, San Diego (UCSD) Statin Study were used to assess the impact of randomized assignment to statins vs placebo on systolic and diastolic BP (SBP and DBP, respectively).

METHODS

DESIGN OVERVIEW, SETTING, AND PARTICIPANTS

The UCSD Statin Study was a randomized, double-blind, placebo-controlled trial of 6 months' duration.

Subjects were 973 men and women from Southern California. A total of 1016 screenees were eligible to participate in the larger trial by virtue of having had a low-density lipoprotein cholesterol (LDL-C) level of 115 to 190 mg/dL (inclusive) at screening; no known cardiovascular disease or diabetes mellitus; and no factors that would preclude 8 months of participation in the study (to convert LDL-C to micromoles per liter, multiply by 0.0259). Blood pressure was not an entry criterion and did not influence eligibility to participate. The 973 subjects for the present BP study are the proper randomized subset of the larger sample in whom BP was assessed at screening. A more complete description of the purpose, eligibility criteria, and study design is presented elsewhere.^{14,15} The study protocol was approved by the UCSD human subjects committee, and all subjects gave written informed consent to participate. The recruitment period was from April 2000 through July 2003, and all subjects were seen at UCSD.

RANDOMIZATION AND INTERVENTIONS

A computer-generated, blocked, randomization sequence stratified on sex was designed by the statistician (H.L.W.) and provided to the study pharmacist who used the sequence to match assigned treatment to sequentially numbered bottles. Sequential subjects who met eligibility criteria and gave informed consent were assigned sequential study identification numbers and received the bottle with the corresponding number. Subjects received

simvastatin, 20 mg; pravastatin sodium, 40 mg; or placebo with equal (33%) probability. A more complete description of procedures is presented elsewhere.^{14,15} Simvastatin, 20 mg, and pravastatin sodium, 40 mg, were selected as the most lipophilic and hydrophilic statins, given at dosages approximately equivalent in terms of expected LDL-C reduction (the study drug was to be taken at bedtime).¹⁶ Neither subjects nor study staff were aware of subject assignment during subjects' participation.

OUTCOMES AND FOLLOW-UP

Visits occurred at screening, baseline, and at 1 and 6 months during treatment. Subjects received an 8-month (2 months after discontinuation) follow-up visit. Primary outcomes from this study will be reported elsewhere. Brachial BP was assessed but was not a designated primary or secondary end point. Blood pressure was obtained using the auscultatory method by trained psychometrists, in the morning, with subjects seated at rest and arm at chest height using cuff sizes appropriate to the subject. Using calibrated aneroid sphygmomanometers, staff identified SBP and DBP as phase I and phase V of the Karotkoff sounds (unless heard to a BP of 0, wherein phase IV was recorded as the DBP value).¹⁷ Although BP was not a primary outcome in the UCSD Statin Study,^{14,15} it was measured at the screening visit (prior to randomization) and at each on-treatment and posttreatment visit. All subjects whose screening value exceeded 140 mm Hg SBP or 90 mm Hg DBP were given a letter to bring to their physicians stipulating their elevated BP (n=210 subjects). Because of presumptive evidence suggesting a possible benefit of statins to BP and the relative ease of analysis of this end point, we received permission from the Data Safety Monitoring Board to unblind and analyze BP first, and the process of data cleaning for BP commenced prior to the last, 8-month (off-treatment) visit of the last subject. Lack of duplicate BP measurement at each time point must be considered in the context of lack of duplicate measurement of many other variables, including lipids, that show variability: this lack of duplicate measurement was *nondifferential across treatment groups*, and variance resulting from measurement variability, although potentially eroding power (and producing bias toward the null), can be offset by increased sample size.

Forty-three of 1016 subjects (4.2%) did not have BP measured at baseline, primarily owing to subjects' time constraints (Figure 1). The screening visit at which baseline BP was assessed comprised subjects' first trip to the study site, and some subjects were delayed in reaching the site or abridged their visit owing to other commitments. However, randomization was blinded to and independent of presence or value of screening BP. Thus, the subgroup with BP measurements (n=973 subjects) is equivalent to a proper randomized substudy and forms the sample analyzed herein. (Baseline comparability is shown across treatment arms in this group.)

Change scores in BP represented the primary BP end point, subtracting baseline BP from final on-treatment BP. This may enhance power by enabling subjects to serve as their own controls.

STATISTICAL ANALYSES

Analyses were conducted using Stata statistical software (version 8.0; StataCorp, College Station, Texas). The primary BP measure for the present analysis was the change from baseline (screening) BP to 6-month (final on-statin) BP. All analyses were performed for both SBP and DBP.

Baseline comparability across treatment arms was assessed in subjects to address comparability by treatment assignment. We performed *t* tests to compare the mean change in SBP and DBP across treatment arms, provided that comparability across treatment arms was present at baseline. If baseline disparities across treatment arms were identified, then we performed regression analysis to allow adjustment for baseline disparities. Secondary analyses evaluated the effect on BP separately for pravastatin and for simvastatin vs placebo.

All subjects who received an on-treatment visit (except 3 [2 who received pravastatin and 1 who received simvastatin]) had an on-treatment BP measured and were included in the intention-to-treat analysis. In those with high measured BP at baseline, an “intervention” in the form of a letter to the subjects’ physicians was given—an intervention expected to contribute variance unrelated to treatment assignment, eroding power in samples in which this group is included. In addition, statin effects on BP could differentially affect implementation or modification of BP medications in the statin vs placebo groups in persons with baseline high BP or those receiving BP medications. Therefore, analyses were performed in subjects without high BP at baseline, those with neither high BP nor BP medications at baseline, and those who had never received BP medications to evaluate subjects in whom BP treatment could not have influenced results and for whom results cannot be attributed to statin interactions with BP medications. We examined subjects with higher-normal or lower-normal BP, within the subhypertensive range, by splitting SBP and DBP at the sample median among those with BP lower than 140/90 mm Hg at baseline, selecting the median to maximize power for each analysis. This suite of analyses permitted assessment of the possibility that statin effects occurred primarily at a higher BP as some have proposed¹² or solely through drug interactions with hypertensive agents (eg, the “synergistic” effects others have hypothesized⁴). Finally, because of reports that the endothelial benefits of statins (thought to underlie BP benefits) may fail to extend to subjects with low high-density lipoprotein cholesterol (HDL-C),¹⁸ coupled with an absence of observed BP benefits in the CARE study¹⁹ (comprising a low HDL-C sample), we analyzed BP effects in those with HDL-C values above and below the median HDL-C levels. The time course of the effect of statins on BP was assessed by examining the change in BP from baseline to 1 month of treatment, to 6 months of treatment, and to 2 months after treatment was discontinued.

RESULTS

Subject participation occurred from April 2000 to March 2004. Analysis supported baseline comparability of analyzed treatment arms on characteristics including age, sex, ethnicity, lipid profiles, glucose, smoking status, SBP, and fraction with elevated BP at baseline (Table 1). However, the baseline difference in DBP comparing pravastatin to placebo was not

significant; therefore, *t* tests were complemented by regression analysis, adjusting for baseline DBP values.

As Table 2 shows, in the intention-to-treat analysis, significant though modest BP reductions were present in the combined statin group relative to placebo, for SBP and for DBP. (The value $P = .05$ is for the test viewed in isolation. Viewing the tests as an ensemble, we obtain a Bonferroni P value of $P = .55$; ie, 0.05×11 tests, for the multiple hypothesis test of no differences between placebo and statin.) This finding was stronger when subjects with high BP at baseline were excluded (this group received a letter to their physicians which may have led to treatment changes that, although nondifferential by arm, may have amplified variance and attenuated significance). Reductions in BP were seen for subjects without hypertension—those with neither high BP at baseline nor receiving BP medications. This held true, separately, for those with SBP (or DBP) above or below the sample median.

Table 2 also suggests possible effect modification for SBP based on HDL-C, splitting the sample at the median baseline HDL-C (50 mg/dL). (To convert HDL-C to micromoles per liter, multiply by 0.0259.) The reductions in SBP were indeed focused in the high HDL-C group (mean HDL-C, 65 mg/dL) relative to the low HDL-C group (mean HDL-C, 40 mg/dL). In contrast to SBP, however, DBP reductions were not focused in the high HDL-C subgroup.

Figure 2A (SBP) and Figure 2B (DBP) show the change in BP from baseline to each time point for the 2 statins relative to placebo, selecting for illustration those subjects without high BP (>140/90 mm Hg) at baseline, who did not receive BP medications, and who had BP measured through the 8-month visit. At 1 month, nonsignificant ($P > .05$) reductions in SBP and DBP in the statin groups relative to placebo group were seen. By 6 months of treatment, both SBP and DBP differences from baseline showed significant reductions ($P < .05$) in each of the statin groups relative to placebo. By 2 months after discontinuation of treatment, these changes had dissipated.

COMMENT

Both simvastatin and pravastatin reduced SBP and DBP substantially, although the mean absolute magnitude of the change was modest in this largely nonhypertensive sample receiving relatively low statin dosages. To our knowledge, this is the first large, randomized, double-blind, placebo-controlled trial to report that statins lower both SBP and DBP relative to placebo; that the effect extends to persons with “prehypertension,”²⁰ those with lower-normal BP, and persons not receiving BP-lowering medications; and that it occurs and seems to be comparable for similar lipid-lowering potencies of the most hydrophilic and lipophilic statins. Our data enrich information on the time course of the effect: BP reductions with statins were suggestive and not significant in this sample at 1 month of treatment but were manifest and significant at 6 months (Figure 2). At 2 months after statins were discontinued, the difference in BP between the statin and placebo groups had dissipated. These findings extend our understanding of the BP effects of statins, as underscored by a previous statement suggesting that “statins may decrease elevated but not normal blood pressure”¹²(p1284); the present study modifies that conclusion. Moreover, because those not

receiving BP medications showed reductions in SBP and DBP with statin vs placebo that were significant (see Table 2 for *P* values), the effect of statins on BP could not be attributed purely to a drug interaction with existing antihypertensive medications.⁴

Mechanisms by which statins may reduce BP include up-regulation and/or activation of endothelial nitric oxide synthase (a potent vasodilator)^{21,22} and improvements in endothelial function and flow-mediated vasodilation.^{23–29} Statins may reportedly induce down-regulation of angiotensin II type-I receptor expression.³⁰ Of note, statins' benefits to endothelial function and vasodilation are thought to be founded on statins' antioxidant effects^{27,31} and have been absent or attenuated in some groups—such as persons with low HDL-C or diabetes mellitus.^{18,32–34} In Cholesterol and Recurrent Events (CARE) study subjects—who showed no BP reduction with statins³⁵—15% had diabetes mellitus and the mean HDL-C level was low (39 mg/dL). In contrast, our sample, evidencing a modest but significant BP reduction (see Table 2 for *P* values), excluded those with diabetes mellitus and had a higher mean HDL-C level (52 mg/dL). Subgroup analysis supported preferential SBP reduction in those with higher HDL-C. However, the same was not seen for DBP.

Large statin trials have seldom commented on statin effects on BP. For trials of longer duration, more BP reduction in the statin group may result over time in more BP medication use in the placebo group, undermining the ability to detect a statin effect on BP. Successful randomization produces comparability at baseline but cannot protect against differential clinical decisions arising as a result of changes induced by the treatment.

Alternatively, BP effects may genuinely fail to be sustained because physiological responses to statin effects evolve over time (eg, tachyphylaxis). Finally, through effect modification, a true absence of effect may characterize studies that differ from this study in subject selection and/or statin drug or dosage. Future studies can further evaluate the impact of statins on BP with attention to these issues.

One large, randomized, double-blind trial showed no significant effect on BP in nonhyperlipidemic subjects with cardiovascular disease.³⁵ A recent meta-analysis of randomized controlled trials of statins reporting effects on BP, with an aggregate sample size of 828 subjects, reported significant reduction in systolic BP (only).³⁶ The largest of the 20 included studies had a sample size of 100, raising potential concerns about publication bias among small studies. Other recent reviews and meta-analyses have also supported effects but have further emphasized the methodological shortcomings of most of the published literature in this area.^{37,38} A larger, parallel-design study has reported benefit to BP but has been published only as an abstract.³⁹

We included BP assessment in our randomized controlled trial to address an important finding reported previously in observational and small crossover studies. Blood pressure was not a primary end point. Although duplicate BP measurements were not performed at each study time point, in contrast to the clinical setting (in which duplicate measurements are requisite to improve precision of the estimate for the individual), in the research setting, precision can be enhanced for group level inferences through increased sample size, averaging single values over multiple subjects. Indeed, randomized controlled trials

commonly assess the impact of interventions on outcomes that have considerable test-retest variability, and this variability is typically overcome by boosting sample size rather than by duplicate assessment. Any nondifferential measurement error incurred as a result of measurement variability arising from single BP measurements produces expected bias toward the null, making the findings reported herein conservative.

The study addresses persons without diabetes mellitus, known cardiovascular disease, or extreme high or low LDL-C level; findings may not extend to excluded groups. Subjects with hypertension, those most in need of BP reduction, were not strongly represented; however, effects in persons with high-normal BP suggest clinical relevance given reported implications of prehypertension.^{20,40–42}

Some issues were not addressed in this study and will require different study designs. These include the impact of different statin dosages, other statin drugs, and longer duration of treatment.

This study adds to our understanding of the effects of statins, currently the best-selling prescription drugs in the world. It provides the first published confirmation in a large, parallel-design, randomized controlled trial of a finding that has been reported with other study designs: that effects of statins extend to reduction in a second primary cardiovascular risk factor, namely, BP. It suggests that this effect extends to lipophilic and hydrophilic statins. The reduction in BP seen with statins may contribute—among other identified factors⁴³—to some of the “rapid” cardiovascular benefits of statins, arising too swiftly to be explained by effects of statins on plaque accumulation.⁴⁴ Statin-induced reductions in BP, although modest, could contribute to reductions in transient ischemic attacks and stroke reported with statins,^{45–50} because stroke incidence, although inconsistently related to LDL-C, is strongly related to BP.

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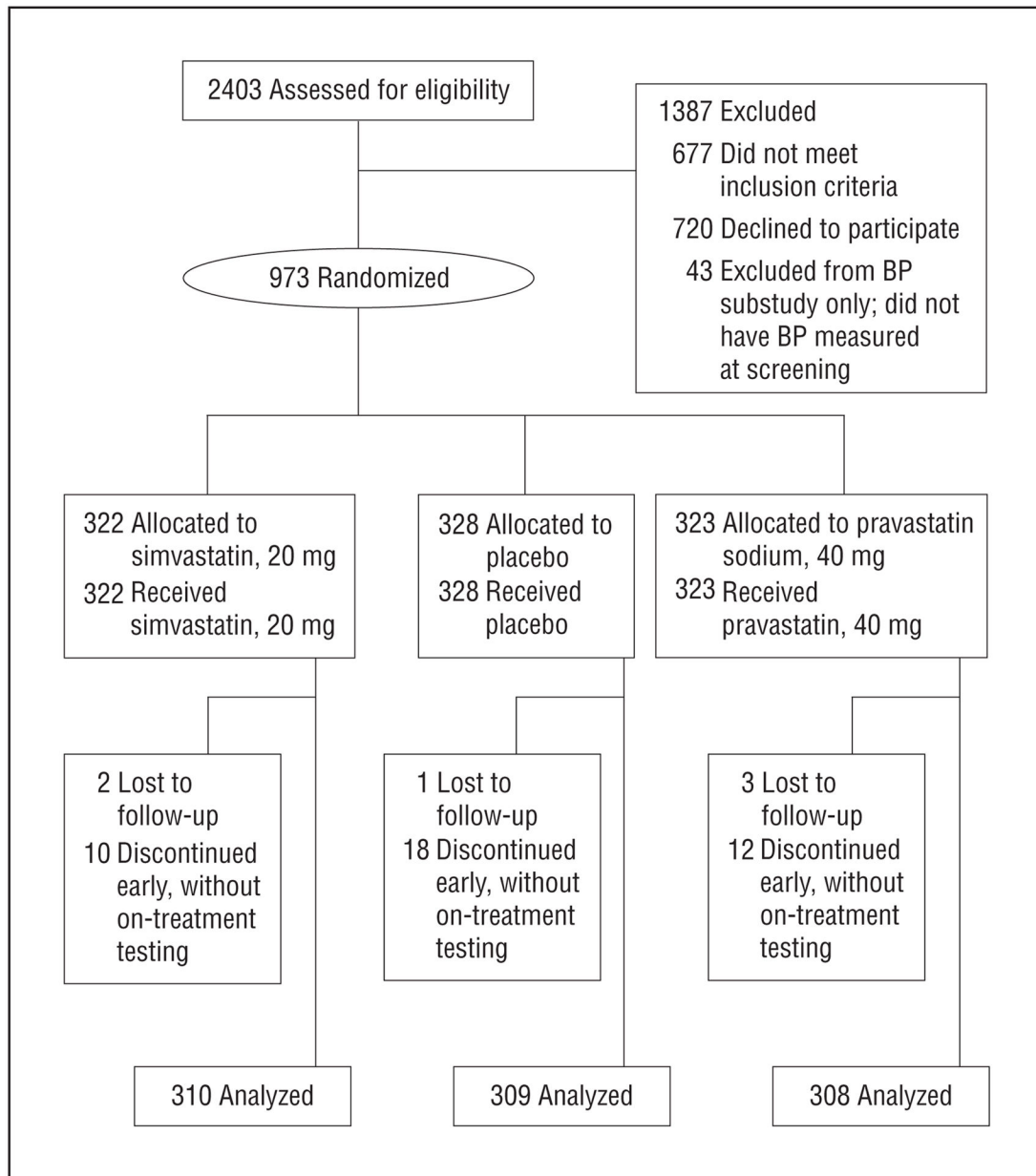


Figure 1.
Flowchart of participants.

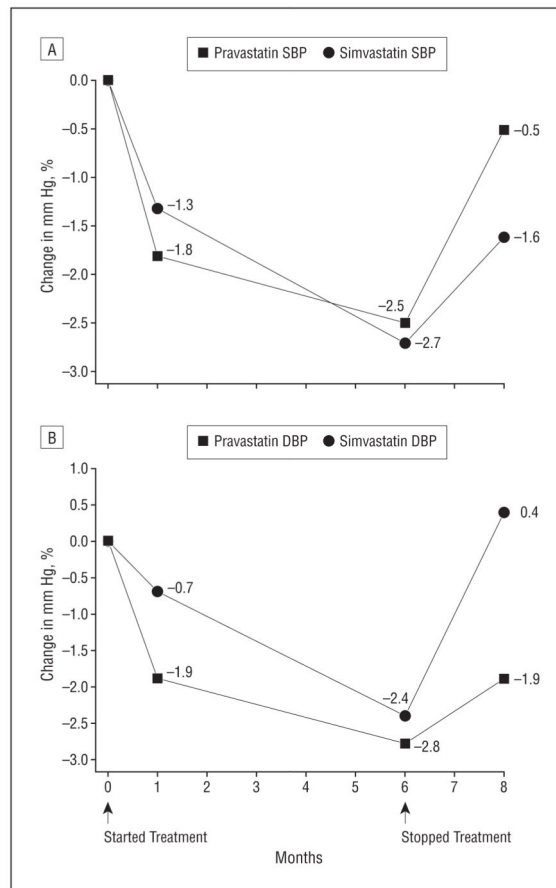


Figure 2.

Difference between the statin and placebo groups. A, Systolic blood pressure (SBP), change from baseline. This figure shows values for subjects who were not hypertensive at baseline, were never prescribed BP medications, and had BP measured through the 8-month visit. This mitigates the influence of changes distinct from treatment assignment across time. The change values differed significantly from placebo ($P < .05$) at month 6 (only) for both pravastatin sodium and simvastatin. Standard errors for pravastatin: month 1, 1.3; month 6, 1.2; month 8, 1.2. Standard errors for simvastatin: month 1, 1.2; month 6, 1.2; month 8, 1.2. P values for pravastatin: month 1, $P = .18$; month 6, $P = .04$; month 8, $P = .69$. P values for simvastatin: month 1, $P = .30$; month 6, $P = .02$; month 8, $P = .18$. B, DBP, change from baseline. This figure shows values for subjects who were not hypertensive at baseline, were never prescribed BP medications, and had BP measured through the 8-month visit. This mitigates the influence of changes distinct from treatment assignment across time. The change values differed significantly from placebo ($P = .01$) at month 6 (only) for both pravastatin and simvastatin. Standard errors for pravastatin: month 1, 0.98; month 6, 0.96; month 8, 1.0. Standard errors for simvastatin: month 1, 0.97; month 6, 0.98; month 8, 1.0. P values for pravastatin: month 1, $P = .06$; month 6, $P = .004$; month 8, $P = .06$. P values for simvastatin: month 1, $P = .46$; month 6, $P = .01$; month 8, $P = .66$.

Table 1

Randomized Substudy Groups Compared at Baseline

Variable	Placebo	Statin (Pravastatin Sodium or Simvastatin)	P Value, Statin vs Placebo	Pravastatin	P Value, Pravastatin vs Placebo	Simvastatin	P Value, Simvastatin vs Placebo
SBP, screening, mm Hg	126.5	126.8	.73	126.3	.91	127.3	.49
DBP, screening, mm Hg	74.0	75.2	.05 ^a	75.4	.05	75.0	.15
Total cholesterol, mg/dL	229.3	230.0	.71	233.2	.10	226.9	.31
LDL-C, mg/dL	150.5	151.2	.68	152.8	.28	149.7	.68
HDL-C, mg/dL	52.6	52.2	.70	53.5	.48	50.9	.16
Triglycerides, mg/dL	134.1	134.7	.91	134.7	.91	134.6	.93
Glucose, mg/dL	89.9	90.1	.75	90.0	.99	90.3	.59
Male, %	68.0	68.1	.96	67.9	.98	68.4	.91
Age, y	57.7	56.8	.31	57.4	.72	56.3	.29
White, %	82.2	80.9	.63	80.8	.66	81.0	.69
Smoker, %	8.1	7.9	.93	8.1	.99	7.7	.87

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

SI conversion factors: To convert cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; to convert glucose and triglycerides to millimoles per liter, multiply by 0.0555 and 0.0113, respectively.

^aThe value $P = .05$ is for the test viewed in isolation; viewing the tests as an ensemble, we obtain a Bonferroni P value of $P = .55$ (ie, 0.05×11 tests) for the multiple hypothesis test of no differences between placebo and statin.

Table 2

BP Difference, Statin Groups vs Placebo

Analysis Type	t Test of Difference in Mean Change (vs Placebo)			Regression, Adjusted for Corresponding Baseline (SBP or DBP)		
	Statins	Pravastatin Sodium ^e	Simvastatin ^e	Statins	Pravastatin	Simvastatin
Intention to treat ^b						
SBP	2.2	1.5	2.9	2.0	1.6	2.4
P value	.02	.20	.009	.009	.095	.006
DBP	2.4	2.3	3.0	1.8	1.5	2.0
P value	<.001	.002	<.001	.001	.02	.003
Excluding high BP at baseline (to whom BP "referral" was given) ^{c,d}						
SBP	2.9	2.5	3.4	2.7	2.3	3.0
P value	.001	.02	.001	.002	.03	.002
DBP	2.5	2.2	2.8	2.1	1.8	2.4
P value	<.001	.006	<.001	.001	.01	.001
Excluding high BP or BP medications at baseline ^{e,f}						
SBP	2.6	2.2	3.0	2.2	1.8	2.7
P value	.006	.048	.005	.009	.07	.006
DBP	2.5	2.3	2.7	2.0	1.7	2.3
P value	<.001	.006	.002	.002	.02	.002
Full 6 mo, no BP medications ^f						
SBP	2.7	2.6	2.8	2.2	2.3	2.3
P value	.009	.03	.02	.02	.04	.03
DBP	2.5	2.5	2.6	2.1	1.9	2.3
P value	.002	.008	.007	.003	.02	.005
BP below median (no HTN, never prescribed BP medications)						
SBP if baseline	122	NA	NA	2.9	NA	NA
P value	.02	NA	NA	.009	NA	NA
DBP if baseline	72	NA	NA	2.5	NA	NA
P value	.001	NA	NA	.002	NA	NA
BP above median (no HTN, never prescribed BP medications)						

Analysis Type	t Test of Difference in Mean Change (vs Placebo)			Regression, Adjusted for Corresponding Baseline (SBP or DBP)		
	Statins	Pravastatin Sodium ^e	Simvastatin ^e	Statins	Pravastatin	Simvastatin
SBP if baseline	122 ^g	NA	NA	2.2	NA	NA
<i>P</i> value	.03	NA	NA	.08	NA	NA
DBP if baseline	72	NA	NA	1.4	NA	NA
<i>P</i> value	.06	NA	NA	.10	NA	NA
DBP if SBP baseline	122	NA	NA	2.2	NA	NA
<i>P</i> value	NA	NA	NA	.004	NA	NA
DBP if SBP baseline	122	NA	NA	1.4	NA	NA
<i>P</i> value	NA	NA	NA	.06	NA	NA
HDL-C above median, 50 mg/dL						
SBP	4.7	NA	NA	4.1	NA	NA
<i>P</i> value	<.001	NA	NA	.001	NA	NA
DBP	2.8	NA	NA	2.2	NA	NA
<i>P</i> value	.01	NA	NA	.02	NA	NA
HDL-C below median, 50 mg/dL						
SBP	1.5	NA	NA	1.2	NA	NA
<i>P</i> value	.30	NA	NA	.30	NA	NA
DBP	2.7	NA	NA	2.1	NA	NA
<i>P</i> value	.01	NA	NA	.02	NA	NA

Abbreviations: BP, blood pressure; DBP, diastolic BP; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; NA, not assessed; SBP, systolic BP.

SI conversion factor: To convert HDL-C to millimoles per liter, multiply by 0.0259.

^aNot significant ($P > .05$): simvastatin vs pravastatin.

^bPlacebo group, n=309; pravastatin group, n=308; simvastatin group, n=310.

^cIntention to treat within this proper randomized subgroup. "BP referral" refers to letter to physician; see "Methods" section.

^dFor this analysis, the number of subjects in each group are as follows: placebo group, n=244; statin group, n=486; pravastatin group, n=241; simvastatin group, n=245.

^eFor this analysis, the number of subjects in each group are as follows: placebo group, n=207; statin group, n=445; pravastatin group, n=227; simvastatin group, n=218.

^fFor this analysis, the number of subjects in each group are as follows: placebo group, n=171; statin group, n=371; pravastatin group, n=181; simvastatin group, n=190.

^gLoses significance for BP>median if analysis includes subjects for whom BP medications were prescribed at any time during study participation; remains significant for BP<median.