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THE USE OF STATINS AND BLOOD PRESSURE

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Abstract

Background—Markers of inflammation like high sensitivity C-reactive protein (CRP) have been shown to be elevated in patients with hypertension. Small trials using statin therapy have shown blood pressure (BP) reductions, but it is unknown whether this association extends to larger populations. The objective of this study was to determine whether statin use was associated with better blood pressure control in adults with hypertension and whether inflammation levels mediated this relationship.

Methods—This was a cross-sectional study of 2584 hypertensive adults 40 years and older with no known CVD from the National Health and Nutrition Examination Survey 1999–2002. Logistic regression models were calculated to determine whether there was an association between statin use and blood pressure control. CRP was added to full model to determine its impact on the association.

Results—Compared to people not using statin medication, significantly more statin users had their blood pressure under control (52.2% vs. 38.0%). After adjustment for demographic factors, statin users were 2.00 times (95% confidence interval[CI] 1.46–2.72) more likely to have their blood pressure under control (<140/90 mmHg) than non-users. After further adjustment for BMI, diabetes, smoking, exercise, low-salt diet, and anti-hypertensive medications, the likelihood of having blood pressure under control remained more likely among statin users (OR 1.46, 95% CI 1.05–2.05). The association between statin use and lower BP was most evident among participants who used anti-hypertensive medication as well as statins, and was unchanged with the addition of CRP to the model.

Conclusions—Statin use was associated with a BP level below 140/90 mmHg in a representative sample of U.S. adults with hypertension. CRP levels did not attenuate the association. Further studies are needed to explore the effects of statin use on blood pressure and determine how best to apply this knowledge in clinical care.

Keywords

statins; blood pressure; hypertension; inflammation; C-reactive protein

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INTRODUCTION

Chronic low grade inflammation has been identified as an integral part in the pathogenesis of vascular disease, and also may be implicated in the development of hypertension, either as a primary or secondary event. (1) Indeed, clinical studies have demonstrated increased levels of well recognized inflammatory markers, such as high sensitivity C-reactive protein (hsCRP), in patients with hypertension, even after adjustment for potential confounding factors. (2) Furthermore, elevated hsCRP levels have also been documented in individuals with prehypertension. (3)

Further evidence demonstrates that drugs commonly used in the management of hyperlipidemia, such as HMG-CoA reductase inhibitors (statins), have anti-inflammatory properties and may also reduce blood pressure. (4) Kanbay and colleagues investigated the impact of atorvastatin 20mg/day in 49 hypertensive dyslipidemic patients (32 on statin and 17 controls on diet alone) and found reductions in systolic (−5.7mmHg) and diastolic (−4.2mmHg) blood pressures after 8 weeks. (5) Magen and colleagues (6) had similar findings using atorvastatin 20mg/day for 8 weeks in 48 resistant hypertensive patients; there were significant reductions of systolic (−13.7 +/− 5.6 mmHg, $P < 0.001$) and diastolic blood pressure (−7.8 +/− 5.7 mmHg, $P< 0.01$).

This study examined the relationship between blood pressure and statin use in individuals with hypertension. We conducted the investigation in a nationally representative sample of non-institutionalized Americans (National Health and Nutrition Examination Survey [NHANES]). The objective of the study was to determine whether statin use is associated with blood pressure levels below 140/90 mmHg in adults with hypertension without a history of cardiovascular disease, and whether CRP levels modify the association.

METHODS

This study was an analysis of existing data in the public use dataset of the most recent NHANES. We derived the study sample from the participants in the National Health and Nutrition Examination Survey 1999–2002 (NHANES 99–02), a recent release of this nationally representative, complex, multi-stage, probability based survey of the civilian, non-institutionalized population of the US. Detailed information about the survey design, questionnaires, laboratory analyses, and examination methodology can be found on the website for the Centers for Disease Control, National Center of Health Statistics (http://www.cdc.gov/nchs/nhanes.htm). From a total population of 21,004 individuals, 6671 were adults age 40 or older. Of these, 2584 had a history of hypertension or had measured blood pressure ≥140/90 mmHg, and did not have a previous history of cardiovascular disease (CVD). The IRB at our institution has reviewed this research and it is exempt.

C-reactive protein (CRP) was measured as part of the NHANES 99–02 physical and laboratory examination using high sensitive techniques. Standard phlebotomy techniques were used to obtain specimens. The threshold for elevated CRP was defined by American Heart Association (AHA) guidelines that designate CRP levels ≥ 3.0 mg/l as associated with high cardiovascular risk. (7)

Demographic variables (age, race, and sex) were included as control variables because of their known impacts on blood pressure. We controlled for body mass index (BMI - kg/m^2) because of its link to blood pressure and its known association with CRP. We also controlled for having a history of diabetes, current smoking status, exercise, being on a low-salt diet to reduce blood pressure, and taking anti-hypertensive medication, all of which are included in the history information obtained from each NHANES participant.

Statin use was obtained from the medication file of the NHANES where the complete list of medications taken by the participant is detailed. The standard generic ingredient code names counted as statins included: atorvastatin calcium, cerivastatin sodium, fluvastatin sodium, lovastatin, pravastatin sodium, and simvastatin. No attempt was made to differentiate between statin type.

Because of the complex sampling design, appropriate weighting factors (based on statistical stratification and population estimates) were taken into account when calculating population-based frequency estimates. We used SUDAAN (Research Triangle Institute, Research Triangle, NC), a specialized statistical program that accounts for the complex weighting of the NHANES 99–02 sample. Using SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results can be generalized to the non-institutionalized civilian population of the U.S. Thus the percentages and odds ratios in this study represent weighted values. SUDAAN also adjusts the standard errors to account for the weighting, stratification, and clustering of the complex sampling design to ensure that expressed p values are valid.

Descriptive statistics for the two comparison groups (statin and no statin) were performed to illustrate the demographic characteristics of the study population. We calculated the percentage of each group who had their blood pressure under control, defined as systolic blood pressure under 140 mmHg and diastolic blood pressure under 90 mmHg. Logistic regression modeling was used to predict the effect of statin use on blood pressure control. Model #1 included age, race and gender, Model #2 added BMI and diabetes, Model #3 further added the covariates smoking, exercise, a low-salt diet, and taking anti-hypertensive medication. We also tested the interaction between created models by replacing the two variables of statin use and anti-hypertensive use with a single interaction variable. An additional model (#4) was created using Model #3 with the addition of CRP as a control variable to determine whether it affected the relationship between statin use and blood pressure control. Because CRP has a skewed distribution, we used the natural log transformation of CRP. Standardized betas and p-values were obtained from the multivariate analysis output. Model #5 was created to further control for cholesterol level. In addition, models were stratified according to whether participants used anti-hypertensive medication. Statistical significance was defined as $p \leq 0.05$ without correction for multiple comparisons since the specific analyses were hypothesized and planned in advance.

RESULTS

Among US adults age 40 or greater with a history of hypertension and no history of CVD, 14.2% were using statin medications. There were no significant distributions in the percent of the population using statins based on age, gender, BMI, or exercise status (Table 1). Whites were significantly more likely to be using statin medications than Blacks, and diabetics were more likely to be using statin medications than non-diabetics. Compared to people not using statin medication, significantly more statin users had their blood pressure below 140/90 mmHg (52.2% vs. 38.0%), were non-smokers (85.0% vs. 79.8%), were using anti-hypertensive medication (74.9% vs. 50.1%), were on a low-salt diet (53.2% vs. 38.2%), or had total cholesterol levels ≤200 mg/dl (50.4% vs. 35.6%). The median CRP among statin users (2.37 mg/l, 95% CI 1.97–2.74) was significantly less than among non-users (3.02 mg/l, 95% CI 2.80–3.31).

After controlling for age, race, and gender (Model #1), statin users were 2.00 times (95% confidence interval [CI] 1.46–2.72) more likely to have their blood pressure below 140/90 mmHg than non-users of statin medications (Table 2). This likelihood remained unchanged when adding BMI and diabetes to the model (Model #2). The likelihood of having blood

pressure below 140/90 mmHg was still 46% more likely among statin users compared to non-users (95% CI 1.05–2.05) after adding smoking, exercise, low-salt diet, and anti-hypertensive medications to the model (Model #3). Adding CRP to the model, either as the log-transformed (see Table 2) or categorical (OR 1.43, 95% CI 1.02–2.02), had virtually no effect on the calculated likelihood of having blood pressure under control (Model #4). Adding cholesterol as a control variable resulted in statins no longer being significantly associated with blood pressure <140/90mmHg (Model #5). Further models were constructed, stratified according to use of anti-hypertensive medication. In these analyses, shown in the last two columns of Table 2, the association between statin use and blood pressure is present in participants who use anti-hypertensive medication, but is not present among those who do not use such medications.

DISCUSSION

The findings of this study from a nationally representative sample of non-institutionalized adults indicate that use of a statin is associated with a BP level below 140/90 mmHg in people with hypertension and no history of previous CVD. The relationship was maintained after controlling for factors that could confound the association, including age, race, gender, BMI, diabetes, smoking, exercise, a low-salt diet, and taking anti-hypertensive medication. After the addition of CRP to the model, the relationship between statin use and blood pressure was still present to essentially the same degree, which indicates that the relationship may be independent of statins' anti-inflammatory effects.

The finding of better blood pressure control in individuals from a nationally representative sample of people using statins adds to the emerging evidence from small clinical trials regarding the impact of statins on blood pressure (8). Borghi (9) followed 1356 people for 5 years in his team's investigation of different cholesterol-lowering strategies in the Brisighella Heart Study, and found that use of statins was significantly related to lower blood pressure at follow up. Glorioso (10) examined the effect of pravastatin and placebo in 30 patients with hypertension and dyslipidemia over 32 weeks and found that pravastatin decreased systolic and diastolic blood pressure (−8 and −5 mm Hg, both P=0.001). However, not all clinical studies to date have demonstrated a blood pressure lowering effect from statins. Two studies using simvastatin for 8–16 weeks showed no impact on blood pressure (11,12). Another study found no effect from 10–80mg of lovastatin daily for 6 months in 213 patients with hypertension (13). In a more recent study of 85 individuals with hypertension and hyperlipidemia, no reduction in BP was demonstrated after 12 months among participants who were randomized to receive either pravastatin, fluvastatin, simvastatin, or a non-statin drug (14). The finding in the current study of better blood pressure control in individuals receiving statins is consistent with the hypothesis that statins may have an anti-hypertensive effect (8).

Mechanistically, use of statins may be linked to hypertension through inflammation, endothelial dysfunction or arterial stiffness. (15) The finding in the current study that the use of statins was related to blood pressure <140/90mmHg only when also using anti-hypertensive medication may be due to some physiologic effects, may be a marker of improved adherence with medications, or may be due to other causes. As for possible physiologic effects, Endres' recent review (16) emphasizes the 'pleiotropic' effects of statins, including improved endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, stabilisation of atherosclerotic plaques, and anti-inflammatory effects. In the current study, the association between statin use and lower blood pressure remained unchanged after controlling for CRP level. Thus, the relationship of statin use and blood pressure may not be due to inflammation, but to other mechanisms such as effects on the renin-angiotensin system or endothelial vasoreactivity (8). Another possibility is that

CRP may not be an accurate measure of the anti-inflammatory activity of statins, although CRP is considered the best available measure of vascular inflammation to date (17).

Limitations of the current study include the possibility of uncontrolled or unknown factors that could confound the association between statin use and BP. However, we have accounted for the most likely demographic and cardiovascular risk factors. The study also is limited by the lack of availability of other measures of endothelial function and oxidative stress in the NHANES database. In addition, misclassification bias also is possible, due to the use of self-reported data for medication use, exercise, and diet information. Individuals may have only just begun taking a statin, and were likely taking statins for varying amounts of time. Finally, due to the cross-sectional nature of the data, no definitive statement can be made regarding cause and effect.

The strengths of the study include the large and nationally representative sample size, and the ability to control for a variety of possible confounding factors. The consistent direction and strength of the association after controlling for demographic, lifestyle, and cardiovascular risk factors supports the verity of the findings.

The results of the current study, taken in consideration with the findings of previous prospective studies on statin use and BP, support the conclusion that statin use is associated with blood pressure <140/90mmHg. The confirmation of the association in a large diverse population, and its persistence after controlling for age, race, gender, BMI, diabetes, smoking, exercise, low-salt diet, strengthens the evidence for the relationship between statin use and blood pressure. The association was most evident among participants who used anti-hypertensive medication as well as statins. Further research should be done to further characterize the impact of statin use on blood pressure, to further elucidate the possible mechanisms for the effect, and to ascertain the clinical role of statins in blood pressure management.

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REFERENCES

1. Boos CJ, Lip GY. Is hypertension an inflammatory process? Curr Pharm Des. 2006; 12(13):1623–1635. [PubMed: 16729874]
2. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA. 2003; 290(22):2945–2951. [PubMed: 14665655]
3. King DE, Egan BM, Mainous AG 3rd, Geesey ME. Elevation of C-reactive protein in people with hypertension. J Clin Hypertens. 2004; 6(10):562–568.
4. Thomas MK, Narang D, Lakshmy R, Gupta R, Naik N, Maulik SK. Correlation between inflammation and oxidative stress in normocholesterolemic coronary artery disease patients “on” and “off” atorvastatin for short time intervals. Cardiovasc Drugs Ther. 2006; 20(1):37–44. [PubMed: 16534549]
5. Kanbay M, Yldirir A, Bozbas H, Ulus T, Bilgi M, Muderrisoglu H, Akcay A, Ozdemir FN. Statin therapy helps to control blood pressure levels in hypertensive dyslipidemic patients. Ren Fail. 2005; 27(3):297–303. [PubMed: 15957546]
6. Magen E, viskoper R, Michal J, Priluk R, Berezovsky A, Laszt A, London D, Yosefy C. Resistant arterial hypertension and hyperlipidemia: atorvastatin, not vitamin C, for blood pressure control. Isr Med Assoc J. 2004; 6(12):742–746. [PubMed: 15609886]

7. Pearson TA, Mensah GA, Alexander RW, Anderson AL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hony Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. AHA/CDC Scientific Statement. Markers of Inflammation and Cardiovascular Disease. Circulation. 2003; 107:499–511. [PubMed: 12551878]
8. Milionis HJ, Liberopoulos EN, Achimastos A, Elisaf MS, Mikhalidis DP. Statins: another class of antihypertensive agents? Journal of Human Hypertension. 2006; 20:320–335. [PubMed: 16511505]
9. Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A. 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(2):285–292. [PubMed: 15308998]
10. Glorioso N, Troffa C, Filigheddu F, Dettori F, Soro A, Parpaglia PP, Collatina S, Pahor M. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. Hypertension. 1999; 34(6):1281–1286. [PubMed: 10601131]
11. Sartor G, Katzman P, Eizyk E, Kalen J, Nilsson A, Ugander L, et al. Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabetes mellitus. Int J Clin Pharmacol Ther. 1995; 33:3–6. [PubMed: 7711988]
12. Antonicelli R, Onorato G, Pagelli P, Pierazzoli L, Paciaroni E. Simvastatin in the treatment of hypercholesterolemia in elderly patients. Clin Ther. 1990; 12:165–171. [PubMed: 2354486]
13. D'Agostino RB, Kannel WB, Stepanians MN, D'Agostino LC. Efficacy and tolerability of lovastatin in hypercholesterolemia in patients with systemic hypertension. Am J Cardiol. 1993; 71:82–87. [PubMed: 8093585]
14. Ichihara A, Hayashi M, Koura Y, Tada U, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. J Hum Hypertens. 2005; 19:103–109. [PubMed: 15361892]
15. Schillaci G, Pirro M. C-reactive protein in hypertension: clinical significance and predictive value. Nutr Metab Cardiovasc Dis. 2006; 16(7):500–508. [PubMed: 16979884]
16. Endres M. Statins: potential new indications in inflammatory conditions. Atheroscler. 2006; 7 Suppl(1):31–35.
17. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, et al. AHA/CDC scientific statement. Markers of Inflammation and Cardiovascular Disease—application to clinical and public health practice. Circulation. 2003; 107(3):499–511. [PubMed: 12551878]

Table 1.

Population characteristics of adults age 40 or greater, with a history of hypertension, and no previous CVD (n=2584) representing a US population of 45,456,104.

	US Population	Using Statins	Not Using Statins
Sample Number	2584	332	2252
Population Percentage	100.0%	14.2%	85.8%
Age (Mean ± SE)	60.2 ± 0.31	63.0 ± 0.67	59.8 ± 0.30
Gender			
Male	41.7%	44.4%	41.3%
Female	58.3%	55.6%	58.7%
Race *			
White	74.0%	81.2%	72.8%
Black	12.8%	6.8%	13.8%
Other	13.2%	12.0%	13.4%
Diabetes *			
Yes	11.9%	19.2%	10.6%
No	88.1%	80.8%	89.4%
BMI			
<25	21.3%	20.4%	21.4%
25–29.9	36.5%	42.4%	35.5%
30+	42.3%	37.2%	43.1%
Smoker *			
Yes	19.5%	15.0%	20.2%
No	80.5%	85.0%	79.8%
Exercise			
None	47.0%	42.1%	47.8%
Moderate	30.8%	37.7%	29.6%
Vigorous	22.2%	20.2%	22.6%
BP medication Use *			
Yes	53.6%	74.9%	50.1%
No	46.4%	25.1%	49.9%
Low Salt Diet *			
Yes	40.3%	53.2%	38.2%
No	59.7%	46.8%	61.8%
Blood Pressure *			
<140/90	40.0%	52.2%	38.0%
≥140/90	60.0%	47.8%	62.0%
Total Cholesterol *			
≤200	37.7%	50.4%	35.6%

	US Population	Using Statins	Not Using Statins
>200	62.3%	49.6%	64.4%
Median CRP † (interquartile range)	2.87 (1.30–6.20)	2.37 (0.95–4.55)	3.02 (1.38–6.56)

* Significant X^2 distribution ($p<0.05$).

† Significantly different ($p<0.05$)

Table 2.

Logistic Regression Models. Analytic models of the effect of statin use on likelihood (OR) of having blood pressure under control (<140/90) after controlling for demographic, lifestyle and CRP factors, in all participants and stratified according to use of anti-hypertensive medication.

	All Participants		Using Anti-hypertension Medication		Not Using Anti-hypertension Medication	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1: Controlling for Age, Gender and Race	2.00	1.46–2.72	1.48	1.03–2.13	1.37	0.64–2.94
Model 2: Model 1 + BMI and Diabetes	2.00	1.45–2.75	1.58	1.10–2.28	1.24	0.60–2.59
Model 3*: Model 2 + Smoking, Exercise, Diet	1.46	1.05–2.05	1.59	1.12–2.28	1.41	0.69–2.89
Model 4*: Model 3 + ln(CRP)	1.45	1.03–2.05	1.56	1.07–2.26	1.48	0.73–3.03
Model 5*: Model 3 + Cholesterol (≤200 vs. >200 mg/dl)	1.43	0.98–2.07	1.53	1.03–2.27	1.45	0.70–3.02

*Models 3, 4, and 5 among All Participants included use of anti-hypertension medications as a control variable.