Use of Statins and Blood Pressure

Dana E. King, Arch G. Mainous III, Brent M. Egan, Marty Player, and Mark E. Geesey

Background: Markers of inflammation such as high-sensitivity C-reactive protein (CRP) were shown to be elevated in patients with hypertension. Small trials using statin therapy showed 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 aged ≥40 years with no known cardiovascular disease 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. C-reactive protein was added to the full model to determine its impact on the association.

Results: Compared with 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 two times (95% confidence interval [CI], 1.46 to 2.72) more likely to have their blood pressure under control (<140/90 mm Hg) than nonusers. After further adjustment for body mass index, diabetes, smoking, exercise, low-salt diet, and antihypertensive medications, the likelihood of having blood pressure under control remained more likely among statin users (odds ratio, 1.46; 95% CI, 1.05 to 2.05). The association between statin use and lower BP was most evident among participants who used antihypertensive 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 <140/90 mm Hg in a representative sample of US adults with hypertension. Levels of CRP did not attenuate the association. Further studies are needed to explore the effects of statin use on blood pressure and to determine how best to apply this knowledge in clinical care.

Key Words: Statins, blood pressure, hypertension, inflammation, C-reactive protein.

Chronic low-grade inflammation was shown to play an integral role in the pathogenesis of vascular disease and may also be implicated in the development of hypertension, either as a primary or secondary event. Indeed, clinical studies 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. Furthermore, elevated hsCRP levels were also documented in individuals with prehypertension.

Further evidence demonstrates that drugs commonly used in the management of hyperlipidemia, such as 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), have anti-inflammatory properties and may also reduce blood pressure. Kanbay et al investigated the impact of atorvastatin 20 mg/day on 49 hypertensive dyslipidemic patients (32 on statin and 17 controls on diet alone) and found reductions in systolic (−5.7 mm Hg) and diastolic (−4.2 mm Hg) blood pressure after 8 weeks. Magen et al produced similar findings using atorvastatin 20 mg/day for 8 weeks in 48 resistant hypertensive patients; there were significant reductions in systolic (−13.7 ± 5.6 mm Hg, P < .001) and diastolic (−7.8 ± 5.7 mm Hg, P < .01) blood pressure.

This study examined the relationship between blood pressure and statin use in individuals with hypertension. We conducted our investigation in a nationally representative sample of noninstitutionalized Americans (National Health and Nutrition Examination Survey [NHANES]).

References:
1. Marty Player, and Mark E. Geesey
2. Dana E. King, Arch G. Mainous III, Brent M. Egan, Marty Player, and Mark E. Geesey
3. Supported by Grant R01 HL076271 from the National Heart, Lung, and Blood Institute, Washington, DC. Grant 1 D14 HP 00161 from the Health Resources and Services Administration, and Grant 1 P30AG021677 from the National Institute on Aging.
4. Address correspondence and reprint requests to Dr. Dana E. King, Department of Family Medicine, Medical University of South Carolina, 295 Calhoun Street, P.O. Box 250192, Charleston, SC 29425; e-mail: kingde@musc.edu
Our objective was to determine whether statin use is associated with blood-pressure levels <140/90 mm Hg in adults with hypertension without a history of cardiovascular disease and whether C-reactive protein (CRP) levels modify the association.

Methods
This study analyzed data in the public-use dataset of the most recent NHANES. We derived the study sample from participants in the NHANES 1999–2002 (NHANES 99–02), a recent version of this nationally representative, complex, multistage, 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 Web site 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 aged ≥40 years. Of these, 2584 had a history of hypertension or had blood pressure ≥140/90 mm Hg and did not have a previous history of cardiovascular disease (CVD). The Institutional Review Board at the Medical University of South Carolina (Charleston, SC) reviewed this research, and it is exempt from further review.

C-reactive protein was measured as part of the NHANES 99–02 physical and laboratory examination using highly sensitive techniques. Standard phlebotomy methods were used to obtain specimens. The threshold for elevated CRP was defined by American Heart Association guidelines, which designate CRP levels ≥3.0 mg/L as being associated with high cardiovascular risk.7 Demographic variables (age, race, and sex) were included as control variables because of their known impact on blood pressure. We controlled for body mass index (BMI; kg/m²) because of its link to blood pressure and its known association with CRP. We also controlled for a history of diabetes, current smoking status, exercise, low-salt diets to reduce blood pressure, and any antihypertensive medications, all of which are included in the history information obtained from each NHANES participant. Statin use was ascertained in the medication file of the NHANES, where the complete list of medications taken by each participant is detailed. The standard generic ingredient code names for 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. The use of SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results could be generalized to the noninstitutionalized civilian population of the US. Thus, the percentages and odds ratios in this study represent weighted values. In addition, SUDAAN adjusts 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 <140 mm Hg and diastolic blood pressure <90 mm Hg. Logistic regression modeling was used to predict the effect of statin use on blood-pressure control. Model 1 included age, race, and sex; Model 2 added BMI and diabetes; and Model 3 further added the covariates smoking, exercise, a low-salt diet, and use of antihypertensive medication. We also tested the interaction between created models by replacing the two variables of statin use and antihypertensive use with a single interaction variable. 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 antihypertensive medication. Statistical significance was defined as P ≤ .05 without correction for multiple comparisons, because the specific analyses were hypothesized and planned in advance.

Results
Among US adults aged ≥40 years with a history of hypertension and no history of CVD, 14.2% were using statin medications. There were no significant distributions in the percentage of the population using statins based on age, sex, BMI, or exercise status (Table 1). Whites were significantly more likely to be using statin medications than African Americans, and patients with diabetes were more likely to be using statin medications than nondiabetic subjects. Compared with people not using a statin medication, significantly more statin users had blood pressure <140/90 mm Hg (52.2% v 38.0%), were nonsmokers (85.0% v 79.8%), were using antihypertensive medication (74.9% v 50.1%), were on a low-salt diet (53.2% v 38.2%), or had total cholesterol levels ≤200 mg/dL (50.4% v 35.6%). The median CRP among statin users (2.37 mg/L; 95% confidence interval [CI], 1.97 to 2.74) was significantly lower than among nonusers (3.02 mg/L; 95% CI, 2.80 to 3.31).

After controlling for age, race, and sex (Model 1), statin users were twice (95% CI, 1.46 to 2.72) more likely to...
have their blood pressure <140/90 mm Hg than nonusers 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 <140/90 mm Hg was still 46% more likely among statin users compared with nonusers (95% CI, 1.05 to 2.05) after adding smoking, exercise, low-salt diet, and antihypertensive medications to the model (Model 3). Adding CRP to the model, either as the log-transformed (Table 2) or categorical variable (odds ratio, 1.43; 95% CI, 1.02 to 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 <140/90 mm Hg (Model 5). Further models were constructed, stratified according to use of antihypertensive 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 antihypertensive 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 noninstitutionalized adults indicate that the use of a statin is associated with a BP level <140/90 mm Hg 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, sex, BMI, diabetes, smoking, exercise, a low-salt diet, and use of antihypertensive 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 relation-
ship 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. Another study that the use of statins was related to lower blood pressure, although CRP is considered the best available measure of vascular inflammation, anti-inflammatory activity of statins, although CRP is conceptually related to other mechanisms such as effects on the renin-angiotensin system or endothelial vasoreactivity. Another possibility is that CRP may not be an accurate measure of inflammation but 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. 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.

The limitations of the current study include the possibility of uncontrolled or unknown factors that could confound the association between statin use and blood pressure. However, we accounted for the most likely demographic and cardiovascular risk factors. This study was also 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, because of 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 support the verity of the findings.

Table 2. Logistic regression models*

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th></th>
<th>Using antihypertensive medications</th>
<th>Not using antihypertensive medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% confidence interval</td>
<td>Odds ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Model 1 (controlling for age, sex, and race)</td>
<td>2.00</td>
<td>1.46 to 2.72</td>
<td>1.48</td>
<td>1.03 to 2.13</td>
</tr>
<tr>
<td>Model 2 (Model 1 + body mass index and diabetes)</td>
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<td>1.45 to 2.75</td>
<td>1.58</td>
<td>1.10 to 2.28</td>
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<tr>
<td>Model 3† (Model 2 + smoking, exercise, and diet)</td>
<td>1.46</td>
<td>1.05 to 2.05</td>
<td>1.59</td>
<td>1.12 to 2.28</td>
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<tr>
<td>Model 4† (Model 3 + ln[CRP])</td>
<td>1.45</td>
<td>1.03 to 2.05</td>
<td>1.56</td>
<td>1.07 to 2.26</td>
</tr>
<tr>
<td>Model 5† (Model 3 + cholesterol, ≤200 v &gt;200 mg/dL)</td>
<td>1.43</td>
<td>0.98 to 2.07</td>
<td>1.53</td>
<td>1.03 to 2.27</td>
</tr>
</tbody>
</table>

* Analytic models of the effect of statin use on the likelihood (odds ratio) of having blood pressure under control (<140/90 mm Hg) after controlling for demographic, lifestyle, and C-reactive protein factors in all participants, stratified according to the use of antihypertensive medications; † Models 3, 4, and 5 among all participants included the use of antihypertensive medications as a control variable.
The results of the current study, taken together with the findings of previous prospective studies on statin use and blood pressure, support the conclusion that statin use is associated with blood pressure \( \leq 140/90 \) mm Hg. The confirmation of the association in large, diverse populations, and its persistence after controlling for age, race, sex, BMI, diabetes, smoking, exercise, and low-salt diet, strengthens the evidence for the relationship between statin use and blood pressure. The association was most evident among participants who used antihypertensive medications as well as statins. Future research could further characterize the impact of statin use on blood pressure, to further elucidate the possible mechanisms for the effect of statins, and to ascertain their clinical role in blood-pressure management.

References