Plasma Homocysteine Concentration, Statin Therapy, and the Risk of First Acute Coronary Events

Paul M. Ridker, MD, MPH; Jessie Shih, PhD; Thomas J. Cook, BS; Michael Clearfield, DO; John R. Downs, MD; Aruna D. Pradhan, MD; Stephan E. Weis, DO; Antonio M. Gotto, Jr, MD, DPhil; for the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) Investigators

Background—Elevated homocysteine levels are associated with increased coronary risk, and it has been suggested that homocysteine screening may provide a method to identify high-risk patients for aggressive primary prevention.

Methods and Results—Homocysteine was measured at baseline and after 1 year among 5569 participants in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a randomized trial of lovastatin in the primary prevention of acute coronary events. The effects of homocysteine, LDL cholesterol, and lovastatin on risk were assessed over 5.2 years of trial follow-up. Median baseline homocysteine levels were significantly higher among study participants who subsequently had acute coronary events compared with those who did not (12.1 versus 10.9 μmol/L, P<0.001). The relative risks of future events from lowest (referent) to highest quartile of homocysteine were 1.0, 1.6, 1.6, and 2.2 (P<0.001). These effects were similar among those allocated to lovastatin and those allocated to placebo and were modestly attenuated after adjustment for other traditional risk factors. As predicted, the subgroup of participants with elevated LDL cholesterol and elevated homocysteine levels were at high risk and benefited greatly from statin therapy (relative risk, 0.46; 95% CI, 0.29 to 0.75; number needed to treat=26). However, in contrast to findings in this trial for C-reactive protein, homocysteine evaluation did not help to define low LDL subgroups with different responses to lovastatin therapy.

Conclusions—Although homocysteine predicted future coronary events in AFCAPS/TexCAPS, we found little evidence that homocysteine evaluation provided an improved method to target statin therapy among those with low-to-normal LDL cholesterol levels. (Circulation. 2002;105:1776-1779.)

Key Words: prevention ■ myocardial infarction ■ lipids ■ lipoproteins

Inexpensive methods to distinguish high-risk from low-risk patients may allow better targeting of statin therapy in the primary prevention of cardiovascular disease, particularly for individuals with normal-to-low levels of LDL cholesterol who may be at high risk yet are outside guidelines for therapeutic intervention.1 For example, in a recent analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), we observed that individuals with LDL cholesterol below the study median of 149 mg/dL who had elevated levels of C-reactive protein (CRP) were not only at high risk for future vascular events but also benefited greatly from statin therapy.2 This observation is intriguing because statins have also been shown to significantly reduce plasma CRP levels.3,4 However, it is unknown whether this effect is unique to CRP or whether other novel risk factors might also provide an improved method to target statin therapy in the setting of primary prevention.

In several epidemiological studies, elevated homocysteine levels have been associated with increased risk of first5–8 as well as recurrent myocardial infarction.9–11 Partly on the basis of these observations, homocysteine screening also has been advocated as a method to improve detection of high-risk patients. However, no data are available assessing whether homocysteine evaluation might, like CRP, provide a method to better target statin therapy among those with low-to-normal LDL cholesterol levels.

Methods

We measured homocysteine levels at baseline and after 1 year of follow-up among 5569 participants enrolled in AFCAPS/TexCAPS, a randomized, double-blind, placebo-controlled trial of lovastatin in the primary prevention of cardiovascular events conducted among...
men and women with average cholesterol levels and below-average HDL levels. Conducted at the Lackland Air Force Base and the University of North Texas Health Science Center, AFCAPS/TexCAPS enrolled men 45 to 73 years of age and postmenopausal women 55 to 73 years of age. Individuals with uncontrolled hypertension, secondary hyperlipidemia, diabetes requiring insulin, or a body mass 50% greater than desirable were excluded.

Participants who provided written informed consent, met all entrance criteria, and completed a 12-week American Heart Association Step I diet run-in were randomly assigned to 20 mg of lovastatin per day or matching placebo. Participants in the lovastatin group were titrated in a double-blind manner to 40 mg of lovastatin per day if their LDL cholesterol levels were >110 mg/dL at the 3-month visit. Participants were followed over an average period of 5.2 years for the occurrence of first acute coronary events, prospectively defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. It was previously reported that allocation to lovastatin, as compared with placebo, was associated with a 37% reduction in this primary clinical end point (relative risk [RR], 0.63; 95% CI, 0.50 to 0.79; P<0.001).

The ImX Homocysteine assay (Abbott Laboratories) was used to determine total plasma homocysteine levels in blood obtained at randomization and at 1 year. Lipid levels were measured in a laboratory accredited through the Centers for Disease Control and Prevention Lipid Standardization Program. In total, 5569 (84%) of 6605 participants enrolled in AFCAPS/TexCAPS had blood available for analysis and underwent successful evaluation for both homocysteine and lipid levels. Lipid levels observed in this group are virtually identical to that observed in the AFCAPS/TexCAPS cohort as a whole.

Cox regression analysis was used to test for association between increasing levels of homocysteine at baseline and the risk of future cardiovascular events after dividing the study sample into quartiles of homocysteine. Analyses were performed for the study group as a whole and after stratification by random assignment to either lovastatin or placebo. Adjusted risk estimates were obtained from analyses that additionally controlled for age, sex, smoking status, hypertension, parental history of coronary disease, lipid levels, and CRP, all of which have previously been shown to be independent predictors in this cohort. The dose-response relation between homocysteine and coronary events was estimated by generalized additive logistic regression performed in SPLUS, a method that allows for graphical representation of the association between homocysteine concentration and the log odds of coronary risk; because this method is sensitive to outlying values, we excluded from this analysis those individuals with baseline homocysteine levels in the upper or lower 2.5% of the distribution. The absolute and percent change in homocysteine associated with the use of lovastatin at the end of 1 year of therapy was additionally computed and compared with the absolute and percent change in homocysteine observed among those allocated to placebo.

Table 1. Crude and Risk Factor–Adjusted RRs of First Acute Cardiovascular Events According to Baseline Quartile of Homocysteine

<table>
<thead>
<tr>
<th>Quartile of Baseline Homocysteine (range, μmol/L)</th>
<th>Study Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants (n=5569)</td>
<td>RRCrude</td>
<td>1.0</td>
<td>1.60</td>
<td>1.64</td>
<td>2.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.00–2.54</td>
<td>1.03–2.59</td>
<td>1.43–3.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.05</td>
<td>0.04</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRAdjusted†</td>
<td>1.0</td>
<td>1.51</td>
<td>1.34</td>
<td>1.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.95–2.40</td>
<td>0.85–2.13</td>
<td>1.09–2.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.08</td>
<td>0.2</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Baseline homocysteine values in AFCAPS/TexCAPS were similar to those observed in prior studies. Specifically, the median homocysteine level at study entry was 11.27 μmol/L, the 90th percentile cutpoint was 16.03 μmol/L, and the interquartile ranges for homocysteine were <9.34, 9.34 to 11.27, 11.28 to 13.52, and >13.52 μmol/L. As would be expected, a small number of individuals had baseline homocysteine values >40 μmol/L, and 3 participants had values >80 μmol/L.

Median homocysteine levels at baseline were higher among the 207 participants who subsequently had a first acute coronary event during follow-up as compared with the 5362 study participants who did not (12.1 versus 10.9 μmol/L, P<0.001). Coronary event rates increased with baseline homocysteine levels such that the RRs from lowest (referent) to highest quartiles of baseline homocysteine were 1.0, 1.6, 1.6, and 2.2 (P=0.001) (Table 1). The computed odds ratios for coronary risk increased across the spectrum of homocysteine levels (Figure 1). These effects were similar in stratified analyses according to lovastatin or placebo allocation. The effect of baseline homocysteine level on vascular risk in AFCAPS/TexCAPS was attenuated but remained significant after additional adjustment for age, sex, marital status, hypertension, parental history of coronary artery disease, smoking status, lipid levels, and CRP. Analyses for all study participants are additionally controlled for treatment assignment.

At the end of 1 year of treatment, median homocysteine levels declined in 52% of the placebo group and in 58% of the lovastatin
The absolute magnitude of this effect was small but somewhat greater among those allocated to lovastatin (−3.7%) compared with those allocated to placebo (−1.8%) (Table 2).

Table 3 presents results of the efficacy analyses for lovastatin in the AFCAPS/TexCAPS trial stratified by LDL cholesterol and homocysteine values above or below the study medians. As shown, the highest-risk subgroup included those with elevated LDL and elevated homocysteine levels, a subgroup in which lovastatin was clearly effective (RR, 0.46; 95% CI, 0.29 to 0.75; NNT = 26). However, as also shown, homocysteine evaluation had no impact on discriminating lovastatin efficacy among those with below-median LDL cholesterol levels, the critical group of study participants currently outside guidelines for statin therapy. Specifically, the placebo event rate in the below-median LDL/ below-median homocysteine subgroup (0.033 events per 5 years) was similar to the placebo event rate in the below-median LDL/above-median homocysteine subgroup (0.038 events per 5 years). Furthermore, estimates of lovastatin efficacy in the two low LDL subgroups were similar, such that the NNT among those with increased homocysteine levels (NNT = 130) was not significantly different from that observed among those with lower homocysteine levels (NNT = 104) or from the low LDL participants taken as a whole (NNT = 113). As shown in Figure 2, this result for homocysteine was in marked contrast to our prior observation in this trial, in which evaluation for the inflammatory biomarker CRP led to the definition of low LDL subgroups with very different event rates as well as very different efficacies associated with lovastatin therapy.

**Discussion**

Among participants in AFCAPS/TexCAPS, baseline homocysteine levels were an independent predictor of first acute cardiovascular events. Furthermore, participants in the highest-risk subgroup defined on an a priori basis were those with elevated LDL cholesterol and elevated homocysteine levels. However, despite these observations, we found little evidence in this randomized trial setting that homocysteine evaluation provided an improved method to target statin therapy among those with below-median LDL cholesterol levels, a critical group currently outside treatment guidelines for statin therapy.

The present data for those with low-to-normal cholesterol levels contrast with recent observations made in this trial with regard to another novel biomarker of risk, CRP. As shown in Figure 2, stratification of participants with low LDL in AFCAPS/TexCAPS according to CRP levels led to a distinction between groups at high and low risk and between groups with and without efficacy of statin therapy in primary prevention. That this effect was not observed among these same study participants for homocysteine adds important information to our understanding of mechanisms of statin effect because they suggest that potential interactions between HMG CoA reductase inhibitors and CRP are not due solely to the ability of CRP to determine a high-risk subset. Rather, these null data for homocysteine provide indirect evidence that the interaction between

**Figure 1.** Calculated odds ratios (and 95% CIs) of future acute coronary events according to baseline plasma homocysteine concentration. Referent value (OR = 1.0) has been set at median homocysteine value for the study population (11.27 μmol/L). Because of the sensitivity of this analysis to outlying values, individuals with homocysteine levels in the upper or lower 2.5% of the study distribution were conservatively excluded.

**Figure 2.** RRs (and 95% CIs) associated with lovastatin therapy among participants in AFCAPS/TexCAPS with LDL cholesterol levels below the study median (149 mg/dL), according to baseline homocysteine and CRP levels. Median values for CRP and homocysteine are 1.6 mg/L and 11.27 μmol/L, respectively.

**TABLE 2.** Median Homocysteine Levels at Baseline and After 1 Year of Therapy Among Participants in AFCAPS/TexCAPS Randomly Allocated to Lovastatin or Placebo Therapy

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Median Homocysteine Level, μmol/L</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Year</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>11.3</td>
<td>10.9</td>
</tr>
<tr>
<td>(n = 2705)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11.3</td>
<td>11.1</td>
</tr>
<tr>
<td>(n = 2610)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis limited to those participants with baseline and 1-year blood samples who did have a cardiovascular event during at least the first year of follow-up. P < 0.001 for treatment group difference.
statins and CRP has a biologically mediated mechanism, which is consistent with recent laboratory observations regarding inflammation and statins\textsuperscript{16} and with the fact that statin-induced changes in CRP are substantially greater than the statin-associated changes in homocysteine observed in the present study.\textsuperscript{3,4}

Our data describing a direct positive relation between homocysteine and subsequent vascular events within the AFCAPS/TexCAPS cohort are consistent with most but not all prior studies of homocysteine and vascular risk.\textsuperscript{5,11,17} Particular strengths of the present analysis that we believe increase its validity and generalizability include our large sample size, the use of a validated commercial assay for homocysteine assessment, and clear end point definitions and complete cohort ascertainment.

There are several possible explanations for our finding of a small reduction in homocysteine concentration in association with lovastatin use. First, because homocysteine levels declined significantly between baseline and 1 year in both the placebo and lovastatin groups, it is probable that at least part of this effect is due simply to regression to the mean. It is also possible that the reductions in homocysteine seen across the study groups reflect an overall cohort effect, perhaps caused by increased usage of folic acid--containing multivitamins during the study follow-up period. Although multivitamin use was not assessed at baseline or during follow-up in AFCAPS/TexCAPS, the likelihood of a major shift within 1 year seems unlikely, particularly because fortification of the US food supply did not occur until well after the samples were collected.\textsuperscript{18} In any event, the absolute difference in homocysteine levels associated with lovastatin use was very small and of uncertain biological significance.

In sum, the present data confirm in a large-scale population of apparently healthy American men and women that homocysteine levels are an independent predictor of future vascular risk. Indeed, participants in the AFCAPS/TexCAPS trial with elevated LDL cholesterol and elevated homocysteine levels were found to be at particularly high vascular risk and benefited greatly from lovastatin therapy. Data from this trial do not, however, support the use of homocysteine screening as a method to better target statin therapy among individuals with low-to-normal levels of LDL cholesterol, subgroups with potentially high risk who currently are outside treatment guidelines for statin therapy.\textsuperscript{1}

Acknowledgments

This study was supported by grants from the National Heart, Lung, and Blood Institute (HL-58755, HL-63293) and the Leducq Foundation, Paris, France. Dr Ridker is additionally supported by an Established Investigator Award from the American Heart Association and a Doris Duke Distinguished Clinical Scientist Award from the Doris Duke Charitable Foundation.

References

Plasma Homocysteine Concentration, Statin Therapy, and the Risk of First Acute Coronary Events
Paul M. Ridker, Jessie Shih, Thomas J. Cook, Michael Clearfield, John R. Downs, Aruna D. Pradhan, Stephan E. Weis and Antonio M. Gotto, Jr
for the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) Investigators

Circulation. 2002;105:1776-1779; originally published online April 1, 2002;
doi: 10.1161/01.CIR.0000014447.06099.FB
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/15/1776

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/