Association Between ADAMTS1 Matrix Metalloproteinase Gene Variation, Coronary Heart Disease, and Benefit of Statin Therapy


Objective—The purpose of this study was to investigate the association between the Ala227Pro polymorphism in the ADAMTS1 matrix metalloproteinase gene and coronary heart disease and benefit from statin therapy in 2 independent cohorts.

Methods and Results—The frequency of the ADAMTS1 227Pro minor allele was 0.24 in 2421 male subjects from CARE, a randomized trial of pravastatin versus placebo. In the placebo arm, homozygotes (6.3% of study population) had a significantly increased risk of fatal coronary disease or nonfatal myocardial infarction (D/MI) compared with noncarriers (OR 2.12, 95% CI 1.07 to 4.19, P=0.03), and in the entire study the benefit of pravastatin in reducing the risk of D/MI was greater in these subjects (OR 0.21, 95% CI 0.06 to 0.69) than in heterozygotes (OR 0.74, 95% CI 0.48 to 1.14) or noncarriers (OR 0.99, 95% CI 0.68 to 1.42; Pinteraction=0.044). Results were tested in 1565 male subjects from WOSCOPS, also a randomized trial of pravastatin versus placebo. Similar to the results in CARE, in the placebo arm subjects homozygous for the minor allele were at increased risk of D/MI (OR 1.72, P=0.03), and in the entire study the benefit of pravastatin in reducing D/MI was greater in these subjects (OR 0.24, 95% CI 0.09 to 0.68) than in heterozygotes (OR 0.73, 95% CI 0.48 to 1.11) or noncarriers (OR 0.65, 95% CI 0.20 to 2.09) (Pinteraction=0.029).

Conclusions—In men not on pravastatin, those homozygous for the 227Pro allele of ADAMTS1 have a nearly 2-fold increased risk of coronary heart disease events compared with noncarriers. In this high-risk group, treatment with pravastatin is highly efficacious, reducing the odds of fatal coronary disease or nonfatal MI by approximately 75%, as compared with 25% in noncarriers or heterozygotes. (Arterioscler Thromb Vasc Biol. 2008;28:562-567)

Key Words: genetics ■ coronary heart disease ■ matrix metalloproteinases ■ statins

Statins effectively lower cholesterol levels and consistently and significantly reduce mortality and coronary events in patients with and without a history of coronary artery disease.1 Yet despite producing profound clinical benefits, statins induce only modest changes in the angio graphic severity of atherosclerotic lesions.2 These observations have led to the concept that statins confer clinical benefit in part by reducing inflammation and stabilizing atherosclerotic plaques.3

A critical destabilizing influence on plaques are the matrix metalloproteinases (MMPs) secreted by inflammatory cells.4 MMPs degrade the extracellular matrix and cause a loss of structural integrity that permits further inflammatory cell infiltration and predisposes the fibrous cap to rupture precipitating an acute coronary syndrome. ADAMTS-1 is a protein whose name is an acronym for “a disintegrin-like and metalloproteinase with thrombospondin motifs.”5 ADAMTS-1 has been shown to cleave versican,6 a key proteoglycan that regulates vascular smooth muscle cell (VSMC) migration and contributes to the structural integrity of the fibrous cap in atherosclerotic lesions.7

Recently, the Ala227Pro polymorphism of the ADAMTS1 gene has been reported to be associated with incident heart disease in a single cohort of healthy individuals.8 We investigated the association between the Ala227Pro polymorphism and incident and recurrent coronary events in 2 independent cohorts from the Cholesterol and Recurrent Events (CARE) and West of Scotland Coronary Prevention Study (WOSCOPS) trials,9,10 as well as whether the Ala227Pro polymorphism was associated with the magnitude of clinical benefit of statin therapy.
therapy in these 2 randomized placebo-controlled trials of pravastatin.

Methods

Study Population

The CARE trial randomized 4159 patients (86% men) residing in the United States or Canada with a prior myocardial infarction (MI) and a total cholesterol level <240 mg/dL to pravastatin 40 mg or placebo for a median of 5 years.5 WOSCOPS randomized 6595 men residing in Scotland without a history of MI and low-density lipoprotein levels >155 mg/dL to pravastatin 40 mg or placebo for a median of 5 years.6 Fasting lipid profiles were compared across genotypes at baseline and between genotypes stratified by treatment arm using the last measured lipid profile (at 5 years in 93% of subjects). The primary end point for both trials was fatal coronary disease or nonfatal MI, although defined slightly differently in each trial. To ensure consistency in disease phenotype in the present analysis, we used an end point of fatal coronary disease (defined as fatal MI or sudden death) or nonfatal MI for both trials. In the CARE trial, a total of 2998 subjects provided DNA. The baseline characteristics, treatment allocation, and rate of the primary end point were similar to the overall cohort. In WOSCOPS, genetic analyses were performed in a nested case-control study of 1565 subjects (350 cases with the end point and 1215 controls, matched for age and smoking status; of these subjects, 820 were treated with placebo and 745 with pravastatin).11 The parent trials and this genetic substudy were approved by the relevant institutional review boards, and informed consent was obtained from all subjects.

Genotyping

As part of a comprehensive genotyping project of candidate genes potentially related to cardiovascular disease and metabolism,12 we analyzed a missense SNP in ADAMTS1, rs428785. This SNP is characterized by a G→C substitution at basepair +1134 of NM_006988 that results in the nonconservative replacement of alanine by proline at amino acid 227. We also genotyped a second SNP in ADAMTS1 that is characterized by a G→C substitution at basepair 409 of NM_006988 (rs402007) in the 5′ untranslated region. However, because the strong linkage disequilibrium between rs428785 and rs402007 (Lewontin’s D′ = 0.998; P < 0.00001) produced virtually identical results for the 2 SNPs, we opted to focus our analysis on the coding SNP.

Genomic DNA was extracted from samples of peripheral whole blood using PURIGENE DNA purification kits (Gentra Systems). The genotype of each sample was determined using kinetic allele-specific polymerase chain reaction (PCR) as previously described.13 Samples were genotyped in random order by individuals blinded with respect to clinical outcomes. The genotyping error rate calculated from genotyping of 180 duplicated DNA samples was below 0.06%.

Statistical Analyses

To achieve comparability to the demographics of the WOSCOPS population (White males) that would be used in the validation phase, analyses in CARE were restricted to the 2432 White males among the cohort of 2998 genotyped subjects, 2421 (99.5%) of whom were successfully genotyped at the ADAMTS1 locus. The χ² test was used to compare the frequencies of the ADAMTS1 genotypes in this cohort were consistent with those expected under Hardy-Weinberg equilibrium. Baseline characteristics of subjects stratified by genotype were compared using analysis of variance (ANOVA) and χ² tests as appropriate. Given that genotype could modify the effect of statin therapy on the primary end point, it was decided a priori to analyze the risk associated with genotype separately in the placebo and pravastatin treatment arms. The unadjusted incidence of the primary end point in subjects within each treatment arm was compared across genotypes using a Cochran-Armitage test for trend. As follow-up was >99.9% complete and as the validation analyses in WOSCOPS would require conditional logistic regression, for the sake of consistency we used logistic regression in CARE to calculate odds ratios and 95% confidence intervals for the effect of genotype on the incidence of the primary end point and the effect of pravastatin therapy on the incidence of the primary end point, adjusting for age, history of diabetes, history of hypertension, body mass index, systolic blood pressure, diastolic blood pressure, and baseline lipids. Regression models contained all subjects and included terms for the interaction between genotype and pravastatin treatment to determine the effect of genotype in placebo subjects and to assess for modification of the effect of pravastatin treatment on the primary end point by genotype.

Analogous statistical analyses were then performed in a validation population consisting of the WOSCOPS nested case-control study using conditional logistic regression where subjects were stratified on age and smoking status. The covariates used were the same as in CARE, with the exception of age, which was a stratification variable. As we were validating the results from CARE (and would reject results that were nominally significant but opposite in direction from what was observed in CARE), we constructed directional statistical tests with 1-sided probability values for risk and statin benefit.

To estimate the effect sizes using all available data, we created a nested case-control study from the CARE cohort (using 241 cases and 2140 controls matched for age and smoking status) and combined this dataset with the WOSCOPS nested case-control dataset to create a pooled CARE-WOSCOPS dataset. This dataset was analyzed using conditional logistic regression in the same manner as the WOSCOPS data. We corrected for multiplicity using a Benjamini-Hochberg False Discovery Rate (FDR) adjustment,14 based on all the SNPs that were associated with an interaction with statin therapy in CARE that were then tested in WOSCOPS.

Results

CARE

The frequency of the minor allele of the ADAMTS1 +1134 G→C polymorphism, which causes a nonconservative change from alanine to proline at amino acid 227 (409/227G→C), was 0.24 in the CARE White male cohort, and the genotypes showed no departure from Hardy-Weinberg equilibrium (P = 0.31). The baseline characteristics of subjects stratified by genotype are shown in Table 1. There were no significant differences except for a modestly different prevalence of hypertension across the three genotypes. Although the proportion of subjects with more than 1 prior MI did not differ statistically across the 3 groups, there was a trend toward a higher proportion in subjects homozygous for the 227C allele than in those who were not (21.6% versus 16.0%; P = 0.07). There was no association between ADAMTS1 genotype and lipid levels at follow-up in either the placebo or pravastatin arms (P = NS for all lipid parameters; supplemental Figure I, available online at http://atvb.ahajournals.org).

Genotype and Risk of Coronary Events

The incidence of the primary end point of fatal coronary disease or nonfatal MI was significantly associated with ADAMTS1 genotype in the placebo arm, with rates of 9.5%, 12.3%, and 17.4% in subjects who were noncarriers, heterozygotes, and homozygotes for the 227C allele, respectively (P = 0.026 for trend, Figure 1). After adjusting for age, history of diabetes, history of hypertension, body mass index, systolic blood pressure, diastolic blood pressure, and baseline lipids, the ORs for the risk of the end point in heterozygotes and homozygotes compared with noncarriers were 1.32 (95% CI 0.89 to 1.95, P = 0.17) and 2.12 (95% CI 1.07 to 4.19, P = 0.03), respectively. There was directional consistency for
the individual components of the composite end point (supplemental Table I). In contrast, there was no increased risk of coronary events by genotype across pravastatin treated subjects (Figure 1; Table 2), suggesting an interaction with statin therapy.

**Table 1. Baseline Characteristics and ADAMTS1 Genotype in CARE White Male Cohort**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADAMTS1 Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ala/Ala</td>
</tr>
<tr>
<td>n (%)</td>
<td>1394 (57.6)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.1 (9.3)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.5 (4.0)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic, mean (SD), mm Hg</td>
<td>128 (18)</td>
</tr>
<tr>
<td>Diastolic, mean (SD), mm Hg</td>
<td>79 (10)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>525 (37.7)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>162 (11.6)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>223 (16.0)</td>
</tr>
<tr>
<td>Past</td>
<td>907 (65.1)</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>558 (40.0)</td>
</tr>
<tr>
<td>&gt;1 prior MI, n (%)</td>
<td>218 (15.6)</td>
</tr>
<tr>
<td>Baseline lipids, mean (SD), mg/dl</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>208 (18)</td>
</tr>
<tr>
<td>LDL</td>
<td>139 (15)</td>
</tr>
<tr>
<td>HDL</td>
<td>38 (8)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>157 (60)</td>
</tr>
<tr>
<td>Cardiac Medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1190 (85.4)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>573 (41.1)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>194 (13.9)</td>
</tr>
</tbody>
</table>

*P value for Hardy-Weinberg equilibrium.

**Genotype and Efficacy of Pravastatin**

In the overall cohort, treatment with pravastatin reduced the risk of fatal coronary disease or nonfatal MI (OR 0.81, 95% CI 0.62 to 1.06). However, there was significant heterogeneity in the benefit of pravastatin therapy in relation to ADAMTS1 genotype. When stratified by genotype, pravastatin significantly reduced the incidence of fatal coronary disease or nonfatal MI in subjects who were homozygotes for the 227Pro allele (OR 0.21, 95% CI 0.06 to 0.69), whereas more modest effects were seen in heterozygotes (OR 0.74, 95% CI 0.48 to 1.14) and noncarriers (0.99, 95% CI 0.68 to 1.42), with a significant test for interaction (P=0.044). Again, there was directional consistency for the individual components of the composite end point (supplemental Table II).

![Figure 1. Rate of primary end point of fatal coronary disease or nonfatal MI in CARE over a median of 5 years, stratified by ADAMTS1 genotype. Numbers inside each bar represent the number of patients in that genotype. Probability value is for test for trend across the genotypes, stratified by treatment arm.](image-url)
Table 3. Number of Subjects in WOSCOPS With and Without End Point of Fatal Coronary Disease or Nonfatal MI by Treatment Arm and Genotype

<table>
<thead>
<tr>
<th>ADAMTS1 Genotype</th>
<th>Both Arms</th>
<th>Placebo Arm</th>
<th>Pravastatin Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>No Event</td>
<td>Event</td>
</tr>
<tr>
<td>Ala/Ala</td>
<td>211</td>
<td>715</td>
<td>129</td>
</tr>
<tr>
<td>Ala/Pro</td>
<td>116</td>
<td>429</td>
<td>67</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>23</td>
<td>71</td>
<td>16</td>
</tr>
</tbody>
</table>

WOSCOPS

To see whether we could replicate the findings in CARE, we then examined the association of the ADAMTS1 Ala227Pro polymorphism with both clinical outcomes and pravastatin efficacy in a separate population based on a nested case-control study from WOSCOPS. In the control subjects, the minor allele frequency was 0.23 and the genotypes showed no departure from Hardy-Weinberg equilibrium (P = 0.53).

Genotype and Risk of Coronary Events

In the placebo arm, compared with noncarriers, heterozygous carriers were not at an increased risk for fatal coronary disease or nonfatal MI (adjusted OR 0.85, 95% CI 0.60 to 1.21), but there was a trend for homozygous carriers of the 227Pro allele to be at greater risk (OR 1.64, 95% CI 0.85 to 3.18). The probability value for the directional test for increased risk in homozygous carriers versus heterozygotes or noncarriers was 0.052 with an OR of 1.72 and a 1-sided 95% CI of >0.99. As seen in CARE, there was no increased risk of coronary events by genotype across subjects treated with pravastatin (Table 3).

Genotype and Efficacy of Pravastatin

Mirroring the pattern observed in CARE, in WOSCOPS pravastatin significantly reduced the incidence of fatal coronary disease or nonfatal MI in subjects who were homozygotes for the 227Pro allele (OR 0.23, 95% CI 0.10 to 0.49), whereas more modest effects were seen in heterozygotes (OR 0.72, 95% CI 0.53-0.98) and noncarriers (0.77, 95% CI 0.60-0.97). The interaction probability value for the directional test for greater risk in homozygotes versus heterozygotes or noncarriers was 0.029.

CARE and WOSCOPS Pooled

Given the consistency of the CARE results in WOSCOPS, we pooled CARE and WOSCOPS data to obtain more reliable odds ratio estimates for each genotype.

Placebo Subjects

In the pooled dataset that combined the CARE and WOSCOPS nested case-control studies, compared with noncarriers, subjects heterozygous for the ADAMTS1 227Pro allele were not at increased risk for fatal coronary disease or nonfatal MI (adjusted OR 1.04, 95% CI 0.80 to 1.34), but subjects homozygous for the ADAMTS1 227Pro allele were at a significantly increased risk (OR 1.78, 95% CI 1.11 to 2.87) compared with noncarriers (Figure 2).

Pravastatin Versus Placebo

In the pooled dataset, treatment with pravastatin significantly reduced the odds of fatal coronary disease or nonfatal MI by 77% in subjects homozygous for the ADAMTS1 227Pro allele (OR 0.23, 95% CI 0.10 to 0.49). In contrast, in subjects who were noncarriers or heterozygous carriers of the ADAMTS1 227Pro allele, treatment with pravastatin only reduced the odds of fatal coronary disease or nonfatal MI by 25% (Figure 3). The probability value for the interaction between ADAMTS1 genotype and pravastatin treatment was P = 0.008, with a false discovery rate of 17%.

Discussion

We found that the Ala227Pro polymorphism in ADAMTS1 is significantly associated with both clinical outcomes and the magnitude of benefit with pravastatin therapy. Specifically, males homozygous for the 227Pro allele were at nearly a 2-fold increased risk of fatal coronary disease or nonfatal MI compared with noncarriers. The magnitude of risk for coronary events in those homozygous for the 227Pro allele (OR 2.30, 95% CI 1.12-4.69) did not differ from that of noncarriers (OR 1.04, 95% CI 0.80 to 1.34) or heterozygous carriers (OR 1.21, 95% CI 0.95-1.56). However, there was a significant interaction between ADAMTS1 genotype and pravastatin treatment in reducing the odds of fatal coronary disease or nonfatal MI by 25% (P = 0.008, false discovery rate 17%).
In that study, the geographically diverse US communities (the ARIC cohort).

independent study conducted in healthy individuals from 4 disease was only 0.052 in WOSCOPS. Furthermore, our value for the association of genotype with cardiovascular our study are the consistent effects we observed in the 2 independent cohorts. Nonetheless, additional replication of our observed interaction between the ADAMTS1 Ala227Pro polymorphism and the clinical benefit of statin therapy will be necessary.

An unresolved issue is whether heterozygous carriers of the 227Pro allele, who constitute 36% of these populations, are at increased risk of coronary events. An excess risk was seen in these subjects in CARE, but not in WOSCOPS. However, the 95% confidence interval for the risk estimate in heterozygous carriers in WOSCOPS was broad and could not exclude up to a 21% excess risk. Future studies in large cohorts should clarify the risk in heterozygous carriers. Additionally, studies in women and non-Whites will be important to define the effect of the 227Pro allele is those populations.

As with any genetic epidemiology study, associations can be demonstrated, but causality cannot be proven. The ADAMTS1 Ala227Pro polymorphism results in a nonsynonymous, nonconservative replacement of alanine with proline, whose cyclic side chain could distort normal protein structure. Nonetheless, it remains possible that the ADAMTS1 polymorphism we studied is in linkage disequilibrium with the true causative locus. More comprehensive genotyping of the ADAMTS1 gene using tagging SNPs will be important to potentially refine the locus of interest. Furthermore, molecular studies of the expression levels and function of the variant ADAMTS1 protein and immunohistochemical studies of atheroma in animals engineered to express the 227Pro allele will be important future experiments as the mechanism of action appears to be distinct from modulation of measured lipid levels. As is the nature of genetic epidemiological studies, significant associations are only a first, albeit important step, in gaining a better understanding of the fundamental biology.

In summary, we have shown that a polymorphism in the gene encoding ADAMTS-1, a MMP involved in atherosclerosis, is significantly associated with both long-term cardiovascular events and the magnitude of benefit with pravastatin therapy in men. Our findings add to a growing body of literature documenting the importance of metalloproteinases in human atherosclerosis and cardiovascular disease and support the importance of genetic variability in determining clinical events and response to therapy. Although patients homozygous for the 227Pro allele demonstrated a greater clinical benefit with pravastatin therapy than did heterozygotes or noncarriers, both of the latter groups still enjoyed a significant risk reduction with pravastatin therapy. Thus, determination of ADAMTS1 genotype should not be used clinically to restrict statin therapy. Rather, we believe that additional molecular and clinical studies of ADAMTS-1 and the 227Pro variant could offer important further insights into the biology of acute coronary syndromes, generate novel targets for therapeutic intervention, and ultimately lead to better-tailored therapy for our patients.
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Disclosures
M.S.S. has received a research grant from Schering-Plough and has received honoraria and served on scientific advisory boards for Bristol-Myers Squibb.

L.P., K.L.S., T.G.K., K.R., Z.T., and K.E.Z. are employees of and/or have ownership interest in Bristol-Myers Squibb.

O.A.I., D.U.L., C.H.T., and J.J.D. are or were employees of and have or had ownership interests in Celera.

C.J.P. has received a research grant from Wyeth; honoraria from AstraZeneca and GlaxoSmithKline; and has served on advisory boards for AstraZeneca, Merck & Co, and GlaxoSmithKline, and Organon.

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J.S. has received honoraria from AstraZeneca, Pfizer, and Merck & Co, and served on advisory boards for Nicoc, Merck & Co, and Pfizer.

H.C. reports no potential conflicts of interest.

F.M.S. has received honoraria from AstraZeneca; served for advisory boards for Aegerion and Genzyme; and served as an expert witness for Pfizer.

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References
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**Online Table I.** Risk of Fatal Coronary Disease and Non-Fatal Myocardial Infarction and *ADAMTS-1* genotype in patients treated with placebo in CARE.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ala/Ala (n=705)</th>
<th>Ala/Pro (n=416)</th>
<th>Pro/Pro (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Coronary Disease or non-fatal MI (n=130)</td>
<td>1.0 (reference)</td>
<td>1.32 (0.89-1.95)</td>
<td>2.12 (1.07-4.19)</td>
</tr>
<tr>
<td>Fatal Coronary Disease (n=33)</td>
<td>1.0 (reference)</td>
<td>2.03 (0.95-4.32)</td>
<td>3.26 (1.00-10.64)</td>
</tr>
<tr>
<td>Non-fatal MI (n=104)</td>
<td>1.0 (reference)</td>
<td>1.24 (0.80-1.92)</td>
<td>1.92 (0.89-4.12)</td>
</tr>
</tbody>
</table>
**Online Table II.** Efficacy of Pravastatin in Reducing the Incidence of Fatal Coronary Disease and Non-Fatal Myocardial Infarction in Relation to *ADAMTS1* genotype

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ala/Ala (n=1394)</th>
<th>Ala/Pro (n=874)</th>
<th>Pro/Pro (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Coronary Disease or non-fatal MI (n=241)</td>
<td>0.99 (0.68-1.42)</td>
<td>0.74 (0.48-1.14)</td>
<td>0.21 (0.06-0.69)</td>
</tr>
<tr>
<td>Fatal Coronary Disease (n=64)</td>
<td>1.33 (0.63-2.80)</td>
<td>0.68 (0.31-1.47)</td>
<td>0.35 (0.06-2.03)</td>
</tr>
<tr>
<td>Non-fatal MI (n=190)</td>
<td>0.92 (0.61-1.38)</td>
<td>0.77 (0.47-1.25)</td>
<td>0.14 (0.03-0.68)</td>
</tr>
</tbody>
</table>

ORs are for the likelihood of the endpoint in patients treated with pravastatin relative to the likelihood in patients treated with placebo.
Mean change in LDL (mg/dl) from baseline to last measurement (at 5 years in 93% of patients), stratified by treatment arm and genotype. T bars represent standard error of the mean. There were no statistically significant differences across genotypes within each treatment arm.