The common apolipoprotein A-1 polymorphism -75A>G is associated with ethnic differences in recurrent coronary events after recovery from an acute myocardial infarction

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Abstract

Since data regarding the relationship between a common polymorphism (SNP) of the *apoA1* gene with apoA1 levels and risk of coronary artery disease are inconsistent, we hypothesized that its association with recurrent coronary events differs for White and Black individuals with diagnosed coronary heart disease. The apoA1 *-75G>A* SNP was genotyped in a cohort of 834 Black (n=129) and White (n=705) post-myocardial infarction patients. Recurrent coronary events (coronary-related death, non-fatal myocardial infarction, or unstable angina) were documented during an average follow-up of 28 months. Thirty percent of White and 21% of Black patients carried the SNP. Cox proportional-hazards regression analysis, adjusting for clinical and laboratory covariates, demonstrated that the SNP was not associated with recurrent events in the total cohort (HR=1.37, 95% CI 0.95-1.97; p=0.09) but was the only variable associated with an increased risk of recurrent cardiac events in Blacks (HR=2.40, 95% CI 1.07-5.40; p= 0.034). Conversely in Whites, the SNP was not associated with recurrent events (HR=1.12, 95% CI 0.75-1.67; p= 0.59) whereas apoB (HR=1.78, 95% CI 1.20 -2.65; p=0.0042) and calcium channel blocker use (HR=2.53, 95% CI 1.72-3.72; p<0.001) were associated; p=0.0024 for interaction between ethnicity and the SNP. A common apoA1 SNP is associated with a significantly increased risk of recurrent cardiac events among Black, but not White, post-myocardial infarction patients. Relationships with lipoproteins may help explain this finding.

Introduction

Apolipoprotein A-1 (apoA1) is the major surface protein constituent of high-density lipoprotein cholesterol (HDL-C) and plays a vital role in lipid transport and metabolism.[1]

A low level of high density lipoprotein cholesterol (HDL-C) is an established risk factor for cardiovascular disease [2] and low levels of apoA1 have been linked to a wide variety of cardiovascular events.[3] Low ApoA1 levels have also been associated with carotid intima media thickness (CIMT) in a cohort of Swedish men[4] and in the Atherosclerosis Risk in Communities Study low levels of apoA1 were associated with CIMT in men and women.[5]

ApoA1 polymorphisms have been reported on the long arm of chromosome 11, including the -75G>A variant in which guanine (G) is substituted by adenine (A).[6] This particular variant occurs frequently in Caucasians.[6] In healthy individuals, this variant has been associated with increased transcription of the *apoA1* gene and higher circulating levels of HDL-C and apo A1 in some studies[7-10] but not in others.[11,12] These conflicting data may be due to the fact that this polymorphism was evaluated in mixed ethnic groups and, therefore, we sought to determine whether the apoA1 -75G>A polymorphism is associated with cardiovascular events in post-myocardial infarction (MI) patients and whether ethnicity influences the association. If the polymorphism increases risk in only one ethnic group, this may have implications for risk stratification and in the design of therapeutics.

Materials and Methods

Study population

The THROMBO Study was a prospective, multicenter investigation that enrolled patients with acute myocardial infarction (MI) from 13 participating hospitals in the

United States between October 1, 1994, and June 30, 1997.[13] A total of 1,161 patients were enrolled at the time of hospital discharge. Blood samples for genetic analysis were collected at study enrollment from 1,012 of the recruited patients. The average follow-up was 28 months. The details of this study have been reported in the primary publication, and the clinical parameters that defined this study population included a full spectrum of traditional post-infarction risk factors. The study was composed mainly of 3 self-reported ethnic populations: Blacks (n=145), Latinos (n=81), and Whites (n=771) living in the United States; other populations including Asian or Pacific Islanders, American Indians, native Alaskans, and Indians composed a relatively small proportion of study patients (n=15). In the current study, we compared the clinical course of Black (n=129) and White (n=705) patients for whom follow-up data were available beginning two months after their index event. Demographic information and medical history were obtained on enrollment in the trial, and medication usage was recorded during the baseline visit two months after the index MI. Ejection fraction was determined by an echocardiogram, a nuclear study, or angiography during the initial hospitalization after the MI. This study was approved by institutional review boards for human subjects at all participating institutions.

End point

The pre-specified coronary event end point was first occurrence of death from coronary heart disease, enzyme-documented non-fatal MI, or hospitalization for unstable angina. A 2-member committee categorized the coronary events from appropriate medical records according to pre-specified written criteria, as previously described.[13] The risk of the end point was assessed by ethnicity and stratified by the presence of the 75G>A mutation (GG genotype carriers *vs*. AG or AA genotype carriers).

Laboratory methods

Biochemical measurements

Blood was drawn in the fasting state at the baseline clinic visit two months after the index MI. Plasma and serum samples were each separated, frozen, and sent to Rochester, NY, for central storage in a freezer at -70°C. Biomarker measurements were conducted using standard methods described in the parent study publication.[13]

Genotyping

Buffy coats were isolated and stored at -70°C until extracted for DNA analysis. Genotyping was performed through a contractual agreement with Millennium Pharmaceuticals. The apoA1 (*75G>A*) polymorphism (refSNP ID rs670) was typed using the TaqMan method.[14] TaqMan assays were validated by retesting 10% of samples using melting curve analysis (Light Cycler, Roche Diagnostics) based on G-nucleobase quenching using a 5'-FAM labeled probe (cagccccggccctgttg) spanning the polymorphic locus, in which the A variant results in a base pair mismatch. The frequency of the A allele in our population (0.28) was consistent with previously published reports, and the population was in Hardy-Weinberg equilibrium with respect to this polymorphism.

Statistical analysis

The clinical characteristics and genotype frequencies of Black and White patients were compared using the χ^2 test and Fisher's exact test, as appropriate. The Hardy–Weinberg equilibrium was tested in both ethnic groups.[15] Due to prior evidence,[16] we also tested for linkage disequilibrium between the apoA1 and apoCIII *C3238G SstI* single nucleotide polymorphisms. The Kaplan-Meier life table method was used to assess the time to first coronary end point and the cumulative event rates for each ethnic group and within each ethnic group by genotype. The results were compared using the log-rank test.

The outcome analysis used Cox multivariable proportional-hazards regression with adjustment for significant clinical covariates to follow outcomes over time. The outcome measure was time from enrollment to a first recurrent coronary event with follow-up beginning at the baseline visit two months after the MI. For regressions, blood marker variables were dichotomized (highest *vs.* combined lower three quartiles except for apoA1 and HDL which was lowest *vs.* combined highest three quartiles) as was the apoA-I SNP (AG plus AA *vs.* GG). The algorithm for choosing model covariates was that utilized in the parent study.[13] Multivariable analyses were performed by initial evaluation of univariate significance of clinical covariates (age, ethnicity, sex, diabetes mellitus, prior MI being any MI occurring before the MI of study enrollment, smoking, BMI, pulmonary congestion, hypertension, and cluadication; $p<0.10$), blood biomarkers (apoB, apoA-I, total cholesterol, triglycerides, glucose, HDL cholesterol, and insulin; $p<0.05$),

Table 1. Baseline clinical characteristics.

Characteristics	White (n=705)	Black (n=129)
Age, y (mean±SD)	60±12	57±11*
Female gender (%)	22	33*
MI prior to Index MI (%)	19	22
Hypertension (%)	39	66*
Diabetes (%)	15	26*
Smoking (%)	32.5	34.1
BMI	27.7±5	29.4±6*
Q-wave MI as Index MI (%)	50.9	42.6
LV ejection fraction (%)	47±13	50±11
Systolic BP (mm/Hg)	118±16	123±16*
Diastolic BP (mm/Hg)	69±24	72±11*
Aspirin (%)	83	85
Statins (%)	34	36
ACE inhibitors (%)	34	45*
ß-blockers (%)	79	69*
Calcium channel blockers (%)	19	32*
Nitrates (%)	37	47*
Total Cholesterol (mg/dL)	196±43	196±45
LDL (mg/dL)	118±36	123±41
HDL (mg/dL)	39±12	42±12*
Triglycerides (mg/dL)	208±119	157±87*
Apo A1 (mg/dL)	119±25	118±26
Apo B (mg/dL)	122±27	124±32
Glucose (mg/dL)	101±44	109±46*
Insulin (IU/mL) 18±24 23±41*		

*$p<0.05$. MI: myocardial infarction; BP: blood pressure.

and the apoA-I SNP ($p<0.05$). Multivariable models were then formulated for main effects with simultaneous entry of all univariate significant covariates. Medication effects (beta blockers, aspirin, calcium channel blockers, diuretics, ACE-inhibitors, statins, other lipid-lowering drugs; $p<0.05$) were assessed subsequently by individual entry of medications to multivariable models. Interaction effects were assessed by inclusion of interaction terms into multivariable models. Analyses were performed with Statistica 7.0 (StatSoft, Inc., Tulsa, OK, USA). A 2-sided $p<0.05$ was used for declaring statistical significance.

Results

Clinical characteristics

Table 1 shows the baseline clinical characteristics in the study population by ethnicity. Blacks were frequently women, younger, hypertensive, diabetic, and had a higher average body mass index compared to Whites. The use of angiotensin converting enzyme inhibitors, nitrates, and calcium channel blockers was higher among Blacks, whereas beta-blockers were administered more frequently in Whites.

Laboratory parameters

Blacks had higher levels of HDL-C, triglycerides, glucose, and insulin than Whites (Table 1) but similar levels of apoA1 and apoB. Thirty percent of Whites and 21% of Blacks, respectively, were carriers of the high-risk allele of the *apoA1* gene (A/A or A/G) (Table 2). In Blacks, the presence of the A allele was associated with non-significantly lower apoA1 ($p= 0.59$) (Table 3) and in Whites with higher apoA1 of borderline significance ($p=0.07$). ApoA1 levels were identical in Blacks and Whites who did not carry the A allele, whereas among patients with the A allele there was a trend for lower levels in Blacks compared with Whites ($p=0.3$). In Blacks, the presence of the A allele was associated with higher apoB ($p=0.035$) whereas in Whites the allele was not associated with significantly higher apoB ($p=0.22$). ApoB levels were very similar in Blacks and Whites ($p=0.88$) who did not carry the A allele whereas among patients with the A allele, there was a trend for higher levels in Blacks than Whites ($p=0.095$). In addition, compared with Whites, Blacks without the A allele had higher HDL-C ($p=0.014$) whereas Blacks and Whites with the A allele had similar HDL-C levels ($p=0.35$). Blacks and Whites without the A allele had similar LDL-C levels ($p= 0.34$) as did Blacks and Whites with the A allele ($p= 0.14$).

Table 2. Frequency of ApoA1 -75G>A genotypes by race.

ApoA1 Genotype	N	Overall (n=834)	White (n=705)	Black (n=129)
G/G (%)	600	72	70.5	79.8
A/G (%)	215	25.8	27	19.4
A/A (%)	19	2	2.5	0.8

χ^2 $p=0.048$

Table 3. Comparison of lipid values by genotype within each racial group.

	White		Black	
	G/G	A/G or A/A	G/G	A/G or A/A
ApoA1(mg/dL)	118±24	122±26	118±26	116±28
ApoB (mg/dL)	121±26	124±28	122±32	133±31
HDL(mg/dL)	39±12	39±11	42±12	41±10
LDL(mg/dL)	117±36	120±38	121±41	131±37

Table 4. Baseline clinical characteristics.

Characteristics	Blacks with AA or AG (n = 26)	Blacks with GG (n = 103)	Blacks with Event (n=27)	Blacks without Event (n=102)
AA or AG (%)			37	16*
GG (%)			63	84*
Age, y (mean±SD)	57	56.7	60±11	56±11
Female gender %	30	30	30	33
MI prior to Index MI %	20	20	26	21
Hypertension %	60	70	70	65
Diabetes %	20	30	30	25
Smoking %	30	30	26	36
BMI	27.02	29.97*	27±5	30±7*
Q-wave MI as Index Event %	40	40	22	48*
Ejection fraction (%	50.5	49.5	51±13	49±10
Systolic BP (mm/Hg)	122.1	122.4	120±17	124±16
Diastolic BP (mm/Hg)	72.8	72.1	70±12	73±11
Aspirin %	81	85	85	84
Statins %	39	36	26	39
ACE inhibitors %	39	47	33	48
β-blockers %	77	67	74	68
Calcium channel blockers %	46	28*	48	28*
Nitrates %	54	46	63	43*

*$p<0.10$ for Blacks with or without A allele and for Blacks with or without events. MI: myocardial infarction; BP: blood pressure.

End point

The Kaplan-Meier cumulative probability of recurrent cardiac events during follow-up for White and Black patients by presence or absence of the -75 G>A allele is presented in Figure 1. In Blacks, those with the A allele were more likely to experience a recurrent event ($p=0.006$). In Whites, those with the A allele did not have an increased risk ($p=0.348$).

In the entire study population, significant univariate Cox regression covariates were age, diabetes, prior MI, pulmonary congestion, and claudication ($p<0.10$); and apoB, total cholesterol, glucose, and insulin ($p< 0.05$). Multivariable Cox regression results adjusted for these covariates found that only apoB was significant. To further assess potential effects of ethnicity and the A allele in the entire study population, these parameters were individually and dually forced into the multivariable model. Neither was found to be significant; however, inclusion in the model of an

interaction term between ethnicity and the A allele revealed significant interaction (p=0.0024).

In view of the significant interaction of ethnicity and the A allele, separate multivariable Cox models were created for Whites and Blacks. Cox regression adjusted for univariate significant clinical covariates in Whites (age, diabetes, prior MI, pulmonary congestion, and claudication) and with simultaneous entry of univariate significant laboratory markers in Whites (apoB, glucose, and insulin) revealed apoB and insulin as significant. When the A allele was added to this model and medication use assessed by individual entry into the model, significant resulting markers included apoB (HR=1.78, 95% CI 1.20-2.65; p=0.0042) and calcium channel blockers (HR=2.53, 95% CI 1.72-3.72; p<0.001); the A allele was not significant (HR=1.12, 95% CI 0.75-1.67; p=0.59). In Blacks, the only univariate significant clinical covariate was BMI; while none of the laboratory markers including apoB were univariate significant. Thus, in Blacks with entry of the A allele into a model adjusted for BMI and with medication use assessed by individual entry into the model, only the allele was found to be significant (HR=2.40, 95% CI 1.07-5.40; p=0.034). Thus, in Whites apoB predicts risk; the allele does not. In Blacks, the allele predicts risk; apoB does not. The allele was not associated with recurrent events in the total cohort (HR=1.37, 95% CI 0.95-1.97, p=0.09). Table 4 outlines the distribution of clinical risk variables in Blacks with and without recurrent coronary events and the A allele.

The A allele and apoCIII SNPs were found to be in strong linkage disequilibrium in the whole population (chi-square=47; p<0.0001) but did not show significant evidence of Hardy-Weinberg disequilibrium ("LDA" Java application as described by Ding, *et al.*[17])

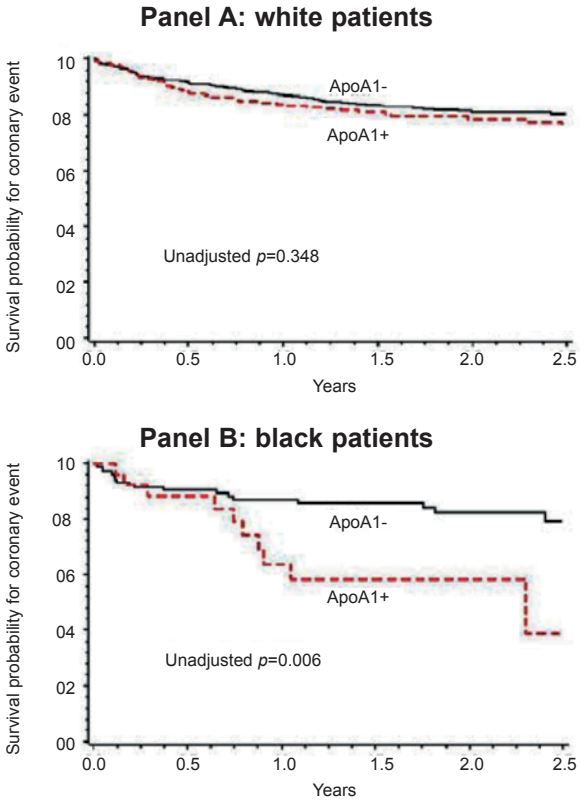

Figure 1. Survival free of a recurrent cardiac event in patients by presence of apoA1 polymorphisms (A/A or A/G).

Discussion

These data suggest that the A allele for the *ApoA1* gene is associated with an increased risk of recurrent ischemic cardiac events compared to those without this variant; but only in Black individuals. Survival free of a recurrent event for Blacks with the variant (40%) was half that for those without the variant (80%) after 2.5 years of follow-up. In contrast, survival free of an event was virtually identical for Whites with and without the polymorphism. To our knowledge, this is the first study to document an association of this polymorphism with recurrent ischemic events and to find an association with events in Blacks but not Whites. The frequency of the variant differed slightly for Blacks and Whites but the prevalence overall was 28%; similar to that noted in prior studies. [6,9,12,16]

The risk associated with the A allele in Blacks was not associated with a reduction in levels of apoA1. The allele's association with recurrent events independent of a clear association with apoA1 is puzzling given its transcription for apoA1.[18] However, its relationship to levels of apoA1 and HDL-C is controversial as exemplified by inconsistencies in well-designed studies.[8,9,11,12,16,19-22] The reason for inconsistent relationships of the A allele to apoA1 levels between studies is unclear. We speculate that variation among different ethnic groups could be a confounder. Danek *et al*. suggest that the allele does not directly affect the transcriptional efficiency of the apoA1 gene, although it may be in linkage disequilibrium with other regulatory sequences and the combination of these elements may explain the contradictory results of the allele's expression.[23] However, a meta-analysis aggregating data from over 3,000 healthy individuals demonstrated that, despite inconsistencies among the study findings regarding the magnitude of the effect, the allele was overall associated with an increase in apoA1 levels by approximately 5 mg/dL.[24]

Compared to Blacks without the allele, those with the allele had significantly higher levels of apoB. In addition, Blacks without the allele had higher levels of HDL-C compared with Whites, consistent with prior evidence,[25,26] whereas Blacks and Whites with the A allele had similar HDL-C levels. A similar association of the allele with higher levels of apoB but with no effect on apoA1 has been described in women enrolled in the Pritikin Longevity Center Program.[6] This suggests that the allele may not increase risk in Black individuals by affecting apoA1 levels, but rather, by increasing levels of apoB.[27-29]

Commonly encountered SNPs are often not found in both Black and non-Black populations.[30] At the same time, individuals from different ethnic groups tend to have fairly consistent biological associations when the same genetic variants are present among the different populations in which they exist, as suggested by an analysis of genetic association investigations in 43 diseases.[31] Conversely, other evidence suggests that genetic variants can influence risk differently for common diseases among populations with different geographical ancestry.[32] Thus, the possibility exists that inconsistent relationships of the allele with serum lipids and risk among Blacks and Whites in this study could be due to differences in genetic susceptibility between ethnic groups.[33]

Linkage disequilibrium is present between the allele and the apolipoprotein CIII C3238G SstI SNP in this study. Impaired functions in two or more of the multiple genes that control lipid metabolism and transport have been thought to lead to inherited lipoprotein disorders or atherosclerosis.[34] The apo *AI-CIII-AIV*

cluster gene is one example of these groups. The *apoAI* gene is closely linked to, and tandemly arranged with, *apoCIII* and *apoAIV* genes within a 15-kb DNA segment on chromosome 11.[16] Evidence also suggests that all three genes are derived from a common ancestral precursor[35] and, together, have an effect on apoA1 levels.[16] Polymorphisms of *apoAIV* and *apoCIII* have also been associated with dyslipidemia[35] and atherosclerosis, independent of plasma lipids[36] and thus could be implicated as risk factors. Thus, given the genetic diversity among ethnic groups, it is possible that the relationship of apoA1 alleles to plasma lipoprotein levels and coronary heart disease may be modulated by AIV and/or CIII alleles as they may be in linkage disequilibrium with the *-75 G>A* apo A1 allele in certain populations but not in others[34] or interact with other genes, and/or with environmental factors.[9,12,37]

In summary, this is the first study to identify an increased risk for an acute coronary syndrome among Black individuals with a prior myocardial infarction if they have a common polymorphism for the *apoA1* gene. Until much more is known about the complexities of the interaction between the *-75G>A* single nucleotide polymorphism and other genes, these data should be viewed as hypothesis generating.

Study limitations

Our results do not provide evidence for a direct mechanism leading to the adverse outcome. Further investigation would be required to determine if the *-75 G>A* polymorphism influences coronary risk or, instead, is a marker of other gene polymorphisms. Although we were able to test for the presence of linkage disequilibrium of the *-75 G>A* polymorphism with *apoCIII*, we were not able to do so for *apoAIV*. Inconsistencies across populations may be explained by the approach of studying single, perhaps non-functional, polymorphisms.[38] The findings in this study may have resulted from chance association. The possibility also exists that the effect of specific alleles may depend upon the presence of environmental factors including smoking, medications, diet, and physical activity, and we were able to control for a limited number of such factors.

We cannot be certain that a "survival of the fittest" bias in our post-MI cohort was not present. Black and White patients with the *-75 G>A* allele could have died with their index myocardial infarction, resulting in a reduced effect of the allele on the risk of recurrent events amongst survivors. The proportion of patients who die at the time of their first MI is estimated at 15%.[39]

The relatively small sample size of Black individuals relative to Whites limited our ability to detect a significant difference in apoA1 and HDL-C levels in Blacks with and without the *-75 G>A* polymorphism. Also, this is a single population study, and these findings need to be validated in prospective studies involving larger populations.

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