





ORIGINAL RESEARCH

# Racial Disparities in Modifiable Risk Factors and Statin Usage in Black Patients With Familial Hypercholesterolemia

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**BACKGROUND:** Black men and women are at higher risk for, and suffer greater morbidity and mortality from, atherosclerotic cardiovascular disease (ASCVD) compared with adults of European Ancestry (EA). Black patients with familial hypercholesterolemia are at particularly high risk for ASCVD complications because of lifelong exposure to elevated levels of low-density-lipoprotein cholesterol.

**METHODS AND RESULTS:** This retrospective study analyzed ASCVD prevalence and risk factors in 808 adults with heterozygous familial hypercholesterolemia from 5 US-based lipid clinics, and compared findings in Black versus EA patients. Multivariate logistic regression models were used to determine the strongest predictors of ASCVD as a function of race. No significant difference was noted in the prevalence of ASCVD in Black versus EA patients with familial hypercholesterolemia (39% versus 32%, respectively;  $P=0.15$ ). However, Black versus EA patients had significantly greater prevalence of modifiable risk factors, including body mass index (mean,  $32\pm 7$  kg/m<sup>2</sup> versus  $29\pm 6$  kg/m<sup>2</sup>;  $P<0.001$ ), hypertension (82% versus 50%;  $P<0.001$ ), diabetes (39% versus 15%;  $P<0.001$ ), and current smoking (16% versus 8%;  $P=0.006$ ). Black versus EA patients also had significantly lower usage of statins (61% versus 73%;  $P=0.004$ ) and other lipid-lowering agents. In a fully adjusted multivariate model, race was not independently associated with ASCVD (odds ratio, 0.92; 95% CI, 0.60–1.49;  $P=0.72$ ).

**CONCLUSIONS:** The strongest predictors of ASCVD in Black patients with familial hypercholesterolemia were hypertension and cigarette smoking. These data support wider usage of statins and other lipid-lowering therapies and greater attention to modifiable risk, specifically blood pressure management and smoking cessation.

**Key Words:** familial hypercholesterolemia ■ hypertension ■ racial disparities ■ smoking

**B**lack men and women are at higher risk for atherosclerotic cardiovascular disease (ASCVD) and, when diagnosed with ASCVD, have greater morbidity and mortality compared with their counterparts of European ancestry (EA). In 2010, the self-reported prevalence of diagnosed coronary heart disease was 6.5% in Black individuals compared with 5.8% in individuals of EA.<sup>1,2</sup> Between 2006 and 2014, data from the ARIC (Atherosclerosis Risk in the Community) study showed that the incidence of myocardial infarction was higher for

Black versus EA men at all ages, and the incidence in Black women was roughly equivalent to that of EA men, and higher after age 65.<sup>3</sup> Black men and women are also less likely than other racial and ethnic groups to achieve ideal cardiovascular health metrics and have higher levels of several physiologic risk factors, including hypertension.<sup>4</sup> Many of the differences in risk factors for and outcomes from cardiovascular disease between Black patients and those of EA have been attributed to social determinants of health, including social and structural

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## CLINICAL PERSPECTIVE

### What Is New?

- The present study demonstrates disparities in lipid treatment and lipid medication usage in Black patients with familial hypercholesterolemia compared with those of European ancestry, and higher residual risk for future atherosclerotic cardiovascular disease in these patients attributable to racial differences in nearly all modifiable risk factors for atherosclerotic cardiovascular disease.

### What Are the Clinical Implications?

- There is a need for greater attention to lipid medication usage and to reduction in residual risk in Black patients with familial hypercholesterolemia through aggressive prevention strategies focused on medication acquisition and adherence, smoking cessation, and blood pressure management.

## Nonstandard Abbreviations and Acronyms

<b>ARIC</b>	Atherosclerosis Risk in the Community
<b>CASCADE-FH</b>	Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia
<b>EA</b>	European ancestry
<b>FH</b>	familial hypercholesterolemia

inequities in access to optimal health care, education, income, healthy food, and stable and healthy living environments, all of which negatively impact downstream behavioral and physiologic risk factors.

Familial hypercholesterolemia (FH) is a genetic lipoprotein disorder with a frequency of about 1 in 250 in the population. FH leads to lifelong elevation of low-density lipoprotein cholesterol (LDL-C) levels.<sup>5</sup> Patients with heterozygous FH have about a 20-fold increased risk of ASCVD and its complications. However, racial differences in the risk of ASCVD and its predictors in Black patients with FH compared with those of EA have not been well studied and might be higher in Black patients with FH because of higher baseline risk. We compared the prevalence of, and risk factors for, ASCVD in Black patients with FH with those of EA with FH.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request to anandita.kulkarni@bswhealth.org.

## Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

## Study Design

We retrospectively collected data on 808 adult patients under treatment for heterozygous FH at 5 US-based lipid clinics: Washington University in St Louis, Baylor College of Medicine, University of Texas Southwestern Medical Center at Dallas, Geisinger Health, and the Brown University Lifespan Hospital system. Institutional review board approval was obtained from all participating institutions. All data extraction was done by trained research assistants who extracted deidentified data into a dedicated study spreadsheet. The institutional review boards at each site approved of the protocol, and waivers were obtained for retrospective data collection. Race was self-reported. Patients were diagnosed with either heterozygous or homozygous FH on the basis of validated clinical or genetic diagnostic criteria. Clinical diagnosis was based on, but was not limited to, Simon Broome, Dutch Lipid Clinic Network, MEDPED, or American Heart Association criteria. Patients included in this cohort either had genetically confirmed FH or had a possible, probable, or definite diagnosis per a clinical diagnostic score. The diagnosis of FH was made by the treating clinic based on validated clinical criteria or genetic testing. Given the heterogeneous means of diagnoses, patients with either a clinical or genetic diagnosis were characterized as having FH, and no distinction was made between patients who had a clinical or genetic diagnosis for the scope of this analysis. Data were independently collected at each of the participating clinical sites and retrospectively compiled for this analysis.

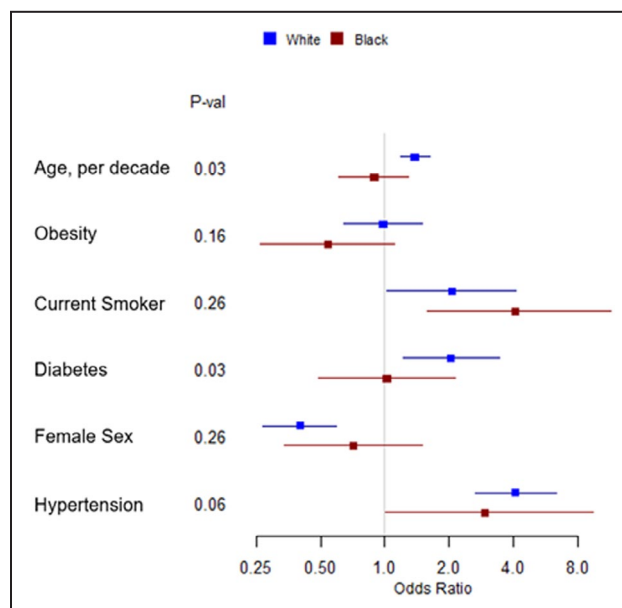
## Laboratory Values and Medical History Variables

Demographic data, medical history, and laboratory values were ascertained by retrospective chart review for current patients from the respective lipid clinics that provided their information. Age was reported from the most recent clinic visit to the time of data collection. Lipid measurements were obtained through standardized commercial or institutional laboratories. Laboratory measurements were reported as the most recent on-treatment values. Treated lipid values are reported for patients receiving pharmacologic lipid-lowering therapy. A history of ASCVD was defined through objective testing for coronary, peripheral, or cerebrovascular disease or a cardiovascular event, including angina, myocardial infarction, coronary angioplasty, peripheral arterial surgery, claudication,

peripheral angioplasty, transient ischemic attack, stroke, or carotid endarterectomy. Premature ASCVD was defined as age <55 years in men and <65 years in women. The presence of ASCVD was comprehensively assessed at the initial visit as well as read-dressed at subsequent visits.

### Statistical Analysis

The prevalence of ASCVD was evaluated in the entire cohort and stratified by race, that is, Black versus EA patients. Patients who did not identify as either Black or of EA were excluded from the analysis. The association of race with demographic and clinical variables was assessed univariately using a chi-squared test for categorical variables and a *t* test for continuous variables. Triglycerides were compared using the Mann-Whitney *U* test because of nonnormal distribution. Prediction of ASCVD was assessed in a generalized linear mixed-effects model with binomial distribution, where study center was modeled as a random effect to account for within-site correlation. Missing data were imputed using multiple imputation methodology (See Table S1 for missing data variables). Multiple imputation was performed using the Multivariate Imputation by Chained Equations algorithm in R (<https://www.jstatsoft.org/article/view/v045i03>), which allows for the imputation of both continuous and categorical variables. Missing values were imputed for body mass index (BMI), smoking, diabetes, and hypertension. The missing imputation values model included these variables, in addition to age, sex, and race. The imputation was done with 5 imputed data sets. (Cholesterol values could not be imputed because they were not missing at random. Imputation of these values may have resulted in a biased estimate, as subjects who were not on treatment were more likely to have missing both treated and untreated LDL-C values.) Two multivariable regression models were fitted. The first model included age, sex, and race. The second model included race, age, sex, BMI, diabetes, hypertension, and current smoking. In separate exploratory, hypothesis-generating models, the interaction of race with each clinical covariate was tested (data from this analysis are shown in the Figure). In addition, we assessed for the predictors of ASCVD stratified by race including all covariates. Standard regression diagnostics were performed. The results of the models using imputed data were confirmed in a sensitivity analysis including complete cases only (not shown). The standard criteria of a 2-sided *P* value <0.05 for statistical significance was used in this study. The analyses were performed using R statistical software version 4.0 (R Foundation for Statistical Computing, Vienna, Austria).



**Figure 1. Forest plot of the interaction of each clinical variable by race.**

\**P* value is for the interaction of clinical variable by race. There may be a potential difference by race in age and diabetes. We did not adjust for multiple testing, and these analyses were not prespecified. These analyses are exploratory and should be investigated further in future studies.

## RESULTS

Baseline characteristics of the 175 Black adult patients compared with 633 patients of EA are shown in Table 1. There was no significant difference in mean age between the 2 groups, and women outnumbered men in both. The absolute LDL-C was above recommended thresholds in both Black and EA patients with FH. Fewer Black versus EA patients were on statins (61% versus 73%, respectively; *P*=0.004), ezetimibe (29% versus 38%, respectively; *P*=0.03), and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (1% versus 12%, respectively; *P*<0.001). Approximately 23% of patients in our study were not reported to be on any lipid-lowering therapy; 33% of Black patients were not on lipid-lowering therapy, while 21% of patients of EA were not on lipid-lowering therapy.

No significant difference was noted in the prevalence of ASCVD and premature ASCVD in Black versus EA patients with FH (39% compared with 33%, *P*=0.15; and 26% versus 21%, *P*=0.17, respectively). Nonlipid risk factors for ASCVD were significantly higher in Black patients with FH, who had higher mean BMI (32±7 kg/m<sup>2</sup> versus 29±6 kg/m<sup>2</sup> in EAs; *P*<0.001), hypertension (82% versus 50% in EA; *P*<0.001), diabetes (39% versus 15% in EAs; *P*<0.001), and rate of current smoking (16% of Black patients versus 8% of

**Table 1. Baseline Characteristics of Patients with Heterozygous FH by Race\***

	Black patients	European ancestry	P Value
Number (%)	175 (21.4)	633 (78.6)	...
Age, y	56±11	56±15	0.84
Female sex	114 (65%)	399 (63%)	0.67
Treated total cholesterol, mg/dL	202±56	200±61	0.68
Treated LDL-C, mg/dL	127±47	120±53	0.21
Treated HDL-C, mg/dL	54±22	54±17	0.97
Treated triglycerides, mg/dL	44 (32–58)	50 (34–78)	0.002 <sup>‡</sup>
BMI	32±7	29±6	<0.001 <sup>‡</sup>
Hypertension	122 (82)	299 (50)	<0.001 <sup>‡</sup>
Current smoking	24 (16)	49 (8)	0.006 <sup>‡</sup>
Diabetes	68 (39)	97 (15)	<0.001 <sup>‡</sup>
ASCVD	70 (39)	207 (33)	0.15
Premature ASCVD <sup>†</sup>	45 (26)	130 (21)	0.17
Statin use	107 (61)	461 (73)	0.004 <sup>‡</sup>
High-intensity statin use	75 (61%)	279 (71)	0.084 <sup>‡</sup>
Ezetimibe use	50 (29)	239 (38)	0.03 <sup>‡</sup>
PCSK9 inhibitor use	2 (1)	78 (13)	<0.001 <sup>‡</sup>

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9 serine protease.

\*The diagnosis of FH was made based on validated clinical or genetic diagnostic criteria. Clinical diagnosis was based on, but was not limited to, Simon Broome, Dutch Lipid Clinic Network, MEDPED or American Heart Association criteria.

<sup>†</sup>Premature ASCVD is defined as ASCVD at age <55 in men and <65 in women.

<sup>‡</sup>P value of statistical significance.

EA patients;  $P=0.006$ ). Assessment of risk factors in Black patients with and without ASCVD revealed that those with ASCVD had no significantly higher prevalence of hypertension (89% versus 77%;  $P=0.075$ ) but were significantly more likely to be current smokers (26% versus 9%;  $P=0.009$ ) (Table 2). In a mixed-effects model, after multivariate adjustments for age and sex, race was independently associated with ASCVD (odds ratio, 1.60; 95% CI, 1.05–2.44;  $P=0.028$ ). However, after further adjustment for hypertension, smoking status, BMI, and diabetes, the association between race and ASCVD was attenuated and no longer statistically significant (odds ratio, 0.92; 95% CI, 0.60–1.49;  $P=0.72$ ).

Age, female sex, hypertension, and current smoking remained significant predictors of ASCVD in patients with FH (Table 3). In a stratified multivariable regression model (Table 4), the strongest predictors of ASCVD in Black patients with FH were smoking and hypertension (odds ratio, 3.63; 95% CI, 1.40–10.38;  $P=0.01$  for current versus no smoking, and odds ratio, 3.25; 95% CI, 1.11–10.64;  $P=0.04$  for hypertension versus no

hypertension). In a sensitivity analysis, including only complete cases, the results were similar and the same variables were significant (data not shown).

The Figure shows a forest plot with odds ratios of all predictors by race, with BMI converted into a dichotomous obesity variable for ease of presentation. Interaction terms of each factor by race indicate potential effect modification for age and diabetes by race. There may be a potential difference by race in age and diabetes. We did not adjust for multiple testing, and these analyses were not prespecified. These analyses are exploratory and should be investigated further in future studies.

## DISCUSSION

In this cohort of 808 patients (175 Black adult patients compared with 633 adult patients of EA) with FH treated in specialized lipid clinics across several regions of the United States, Black patients with FH did not have a statistically significant higher prevalence of documented ASCVD compared with patients of EA. However, Black patients had a significantly higher prevalence of nonlipid risk factors for future ASCVD events, including hypertension, diabetes, and current smoking. Also, fewer Black versus EA patients with FH were on lipid-lowering medications, including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors. After multivariate adjustment for hypertension, smoking status, BMI, and diabetes, race was not a significant predictor of ASCVD. On the other hand, traditional risk factors in Black patients with FH, including hypertension and current cigarette smoking, were significant predictors of ASCVD in multivariate models. These findings have important implications, as they show that traditional and modifiable nonlipid risk factors, including hypertension and current smoking, are highly prevalent and significant drivers of ASCVD risk in Black patients with FH.

This study also demonstrated significant gaps in the use of statins and other lipid-lowering therapies in Black patients versus EA patients with FH, suggesting lower treatment and/or adherence. This finding is particularly concerning since observational data have shown that statin treatment is associated with significant reductions in ASCVD risk in FH, and randomized trials of proprotein convertase subtilisin/kexin type 9 inhibitors in patients with FH have demonstrated further reductions in ASCVD risk.

Racial and ethnic disparities in the treatment and management of cardiovascular disease and its risk factors have long been recognized as major contributors to health inequities.<sup>6,7</sup> Our study is unique in that it uncovered gaps in care even among Black patients at high risk for ASCVD attributable to FH. A prior analysis from the CASCADE-FH (Cascade Screening for Awareness

**Table 2. Baseline Characteristics of Patients With Heterozygous FH With and Without ASCVD by Race**

	Black			European ancestry		
	ASCVD	No ASCVD	P Value	ASCVD	No ASCVD	P Value
N	68	107	...	207	426	
Age, y	56±11	56±11	0.83	62±12	53±16	<0.001*
BMI	31±6	33±8	0.046*	30±7	29±6	0.07
Treated total cholesterol, mg/dL	196±70	201±53	0.25	196±74	202±52	0.27
Treated LDL-C, mg/dL	122±60	121±45	0.88	120±62	121±47	0.84
Treated HDL-C, mg/dL	50±17	56±18	<0.001	50±17	56±16	<0.001*
Treated triglycerides, mg/dL	52 (36–84)	46 (34–68)	0.003*	55 (38–98)	46 (34–72)	<0.001*
Female sex	40 (59)	74 (69)	0.22	103 (50)	296 (70)	<0.001*
Hypertension, Y/N (%Y/%N)	59/7 (89/11)	63/19 (77/23)	0.075	161/45 (78/ 22)	138/252 (35/65)	<0.001*
Current smoking, Y/N (%Y/%N)	17/49 (26/74)	7/75 (9%/92%)	0.009*	21/179 (11/ 90)	27/352 (7/93)	0.21
Diabetes, Y/N (%Y/%N)	30/38 (44/56)	38/69 (36/65)	0.33	56/151 (27/73)	41/385 (10/ 90)	<0.001*

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

\*P value of statistical significance.

and Detection of Familial Hypercholesterolemia) registry demonstrated that Black patients with FH are nearly 50% less likely to achieve target LDL-C levels compared with patients with FH of EA.<sup>8</sup> Our study demonstrated no significant differences in on-treatment LDL-C levels, but significant disparities in the usage of lipid-lowering therapies in Black patients with FH. Reasons for these disparities may include patient factors (differences in access to care and/or medication adherence attributable to socioeconomic and/or psychological factors), provider factors (including treatment biases), and/or health system factors.

Our findings extend those of others to show that Black patients with FH have multiple traditional risk factors for ASCVD (hypertension, diabetes, and smoking), and this higher risk factor burden is associated with a higher prevalence of ASCVD in Black patients with FH. Hypertension and cigarette smoking were found to be key risk factors for ASCVD in FH patients, suggesting

that primary and secondary prevention efforts aimed at targeting these risk factors could mitigate future ASCVD risk in Black patients with FH. Future studies might explore the socioeconomic links between medication usage and nonusage in Black patients with FH, whether there may be a benefit from lower therapeutic blood pressure and/or LDL-C targets in this group of patients, and which self-management support and care delivery strategies lead to greater smoking cessation rates in Black patients.

### Strengths and Limitations

Our study has several limitations. Our analysis was retrospective, and residual confounding may have contributed to our findings. Additionally, patients in our study were selected from specialized preventive cardiology and lipid clinics around the United States and treated by experts within the field and subsequently compiled together, which may have introduced

**Table 3. Mixed Effects Model of the Strongest Predictors of ASCVD for All Patients With Random Site Adjustment**

Model 1			Model 2		
	Odds ratio (95% CI)	P Value		Odds ratio (95% CI)	P Value
Age, y	1.04 (1.03–1.06)	<0.001*	Age	1.03 (1.01–1.04)	<0.001*
Black race	1.60 (1.05–2.44)	0.028*	Black race	0.99 (0.96–1.02)	0.52
Female sex	0.39 (0.28–0.54)	<0.001*	Female sex	0.46 (0.32–0.65)	<0.0001*
			BMI	0.99 (0.96–1.02)	0.41
			Hypertension	4.09 (2.73–6.20)	<0.0001*
			Current smoker	2.69 (1.54–4.74)	0.001*
			Diabetes	1.59 (1.05–2.42)	0.03*

ASCVD indicates atherosclerotic cardiovascular disease; and BMI, body mass index.

Covariates in model 1 include age, race, and female sex. Covariates in Model 2 include age, race, female sex, BMI, hypertension, current smoking, and diabetes.

\*P value of statistical significance.

**Table 4. The Strongest Predictors of ASCVD in Black Patients vs Patients of European Ancestry with FH**

	Black patients		European ancestry	
	Odds ratios (95% CI)	P Value	Odds ratios (95% CI)	P Value
Age, y	0.99 (0.95–1.03)	0.53	1.03 (1.02–1.05)	<0.001*
Female sex	0.77 (0.36–1.61)	0.48	0.40 (0.26–0.59)	<0.001*
BMI	0.95 (0.90–1.00)	0.06	1.00 (0.97–1.03)	0.95
Hypertension	3.25 (1.11–10.62)	0.04*	4.04 (2.62–6.32)	<0.001*
Current smoking	3.65 (1.40–10.38)	0.01*	2.27 (1.11–4.60)	0.02*
Diabetes	1.04 (0.50–2.16)	0.92	2.06 (1.23–3.48)	0.001*

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; and FH, familial hypercholesterolemia.

Covariates include age, sex, BMI, hypertension, current smoking, and diabetes.

\*P value of statistical significance.

selection bias as well as limited the availability of certain information, including consistent data on plasma lipoprotein(a) levels, which are higher among Black individuals.<sup>9</sup> Furthermore, our relatively small sample size may have limited our ability to demonstrate between-group differences in LDL-C control and/or ASCVD as well its risk factors. Of note, ~23% of patients in our cohort were not on treatment with lipid-lowering therapy. There may be several reasons for this: Many of the patients referred to lipid clinics have either declined or not been able to tolerate standard therapy leading to a much more complex patient population. There are multiple reasons for the lower rates of treatment, which include statin intolerance and patient preference against using lipid-lowering therapy. Furthermore, the data presented in the current study are cross-sectional in nature. Patients who may not have been on lipid-lowering therapy at the time of this data collection may have been new to the clinic and requested trials of lifestyle modifications initially, followed by lipid treatment at a later date. However, a strength of our study is that our cohort was enriched with Black patients, a demographic group that historically has been understudied in FH care. To our knowledge, our cohort contains the largest proportion of Black patients with FH studied in this manner.<sup>10,11</sup> The proportional increase in Black patients with FH in our cohort likely helped demonstrate differences in their usage of lipid-lowering medications and residual risks from hypertension and cigarette smoking, which were found even though our cohort was receiving care at specialized preventive cardiology and lipid clinics. Given these findings, one may presume that these racial disparities are greater among Black patients with FH who have inadequate access to either primary or lipid specialty care.

## Conclusions

FH is a common lipoprotein disorder with an estimated prevalence of 1 in 250 US adults, in whom the relative

risks of cardiovascular morbidity and mortality are high. Black patients also have a higher risk of ASCVD that has been linked to a higher burden of some physiologic risk factors and to socioeconomic determinants. The present study has demonstrated disparities in lipid treatment and lipid medication usage in Black patients with FH and higher residual risk for future ASCVD in this cohort. The latter has been found to be attributable to racial differences in nearly all modifiable risk factors for ASCVD, particularly hypertension and cigarette smoking, which are highly prevalent and associated with elevated risk of ASCVD in Black patients with FH. These findings support the need for greater attention to lipid medication usage and to reduction in residual risk in Black patients with FH through aggressive prevention strategies focused on medication acquisition and adherence, smoking cessation, and blood pressure management.

## ARTICLE INFORMATION

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## Supplementary Material

Table S1

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# **Supplemental Material**



**Table S1. Missing Variables.**

	<b>N Missing</b>	<b>% Missing</b>
<b>Age</b>	<b>0</b>	<b>0</b>
<b>Sex</b>	<b>0</b>	<b>0</b>
<b>Hypertension</b>	<b>64</b>	<b>8</b>
<b>Current Smoking</b>	<b>81</b>	<b>10</b>
<b>Diabetes Mellitus</b>	<b>0</b>	<b>0</b>
<b>BMI</b>	<b>73</b>	<b>9</b>
<b>Treated Total Cholesterol</b>	<b>174</b>	<b>22</b>
<b>Treated LDL-C</b>	<b>173</b>	<b>21</b>
<b>Treated HDL-C</b>	<b>174</b>	<b>22</b>
<b>Treated Triglycerides</b>	<b>180</b>	<b>22</b>
<b>Statin</b>	<b>0</b>	<b>0</b>