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Influence of Patients' Coronary Artery Calcium on Subsequent Medication Use Patterns

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Abstract

Objectives—To determine whether information on the presence and extent of coronary artery calcium (CAC) is associated with the likelihood of physicians' prescribing preventive therapies.

Method—In a longitudinal design, asymptomatic participants (N=510) were evaluated by computed tomography for CAC. Changes to medications were at the discretion of the patient's primary care provider, who received the CT report.

Results—In multivariable analysis, the likelihood of patients reporting that their primary care physician prescribed preventive therapies was significantly associated with the presence and extent of CAC.

Conclusions—This study suggests that physicians' prescribing practices are influenced by patients' CAC scores obtained via CT.

Keywords

coronary calcium; computed tomography; physician prescribing practices; preventive therapies

Coronary heart disease (CHD) is a leading cause of death in the United States.¹ Calcium in coronary arteries, which can be imaged via computed tomography (CT) and quantified by the coronary artery calcium (CAC) score, has been shown in several studies to be a significant and independent predictor of incident coronary events and all cause mortality in asymptomatic populations.^{2–6} A study from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrated that high CAC scores were predictive of coronary events over and above that of traditional risk factors.⁷ Moreover, studies show that individuals with a coronary calcium score of zero have very low risk of adverse cardiac events.⁸ Therefore, a CAC assessment in addition to traditional risk assessment can be used to guide CHD preventive treatments and interventions for asymptomatic individuals.^{2,7,9–11}

Although the use of aspirin, blood pressure medicines, and cholesterol lowering medications has been studied and widely accepted to prevent primary, acute coronary events, stroke, and mortality,¹² they are underused.^{13,14} There is evidence for underprescription and underuse of cardiac medications in a vast range of settings, such as in hospitals, primary prevention settings, and clinics; and in diverse patient groups, such as myocardial infarction survivors, the elderly, women, patients with angina, and patients with high copayments.^{15–19} Providing these medications to individuals at risk for CHD is a preventive measure associated with the greatest benefit to the US population.²⁰ Because 25 to 50% of coronary events are seen in asymptomatic persons considered to be at low risk by traditional screening techniques, expanding on existing risk assessment methods to identify undetected, high-risk patients has the potential to decrease morbidity and mortality.^{21,22} However, risk assessment alone without appropriate action does not change the natural course of disease. To understand how providing CAC scores might affect outcomes in a population, it would be important to know whether this additional risk information actually changes patient and provider behavior regarding primary prevention interventions.

Therefore, the aim of this study was to examine the effect of providing CAC scores to patients and their physicians on subsequent preventive care measures for CHD and, specifically, to determine treatment outcomes, including whether patients had started taking blood pressure medicine, cholesterol lowering medication, aspirin, or antioxidant vitamins (all of which were recommended practice during the time period of the study) due to the results of their CT scan.

METHODS

Subjects

Potential subjects were 8101 consecutive asymptomatic patients who underwent chest CT scans from October 1999 to May 2002 at a university-affiliated disease prevention center in San Diego, California, to examine the extent of atherosclerotic calcification in the coronary arteries. This clinical population of participants was either physician referred or self-referred as a supplement to their preventive health care. After the clinical evaluation, patients were contacted for potential enrollment in the current study, and those who agreed to participate received a mailed follow-up survey. Prior studies based on data from this cohort have been published.^{23–29} Patients who were taking lipid-altering medications, had known CHD, or had a history of CHD-related surgery were excluded from the current analysis. Exclusionary medications included hormonal therapies, fibrates, niacin, chelation therapies, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. The University of California at San Diego's Human Research Protection Program approved the study protocol, and the requirement for informed consent was waived by this group.

CT scans were performed at the first clinic visit (baseline), and all participants provided demographic information and completed a detailed health history questionnaire that collected information on diabetes, hypertension, smoking, alcohol consumption, diet, exercise, and family history of CHD at this time. Body mass index (BMI), body fat percentage, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (serum cholesterol indices), and glucose were also measured during this baseline clinic visit.

Imaging

An Imatron C-150 was used to perform a single scan to obtain images of each patient's heart (General Electric, San Francisco, CA). The 100-ms scan time proceeded down from the level of the carina to the level of the diaphragm. Approximately 40–45 slices of each

participant's heart were obtained, each of which was 3 mm thick. Cardiac tomographic imaging was electrocardiographically triggered at 40% or 65% of the R-R interval, depending on the patient's heart rate. Imaging of the heart was conducted during one breath hold at one-half-maximal inspiration. The coronary vascular bed consisted of the left circumflex, left anterior descending, left main, and right coronary arteries.

Coronary calcification was defined as a plaque area = 1.00 mm^2 (3 pixels) with a density of 130 Hounsfield units (HU). Quantitative measures of calcium scores were determined according to the technique explained by Agatston et al.³² The calcium scoring was performed by either a CT technician or physician trained in the methodology outlined above. This method has been previously described in detail.²⁹

Laboratory

All patients underwent serum lipid analysis using the Cholestec LDX system (Cholestec, Hayward, CA). Blood specimens were obtained by finger-stick with the subject in the seated position using a 35 μl lithium heparin-coated capillary tube. Blood pressure was obtained by automated oscillometry after the patient rested for 5 minutes in a seated position. BMI was calculated with the patient clothed without shoes and expressed in kg/m^2 . Body fat was measured using bioimpedance on the OmronTM HBF-300 body fat analyzer (Omron, Schaumburg, IL).

Physician Consultation

The patients spent approximately 15 to 30 minutes with a physician who reviewed the results of the CT scan, showed the patients their CT images, discussed risk factors associated with CAC, and made recommendations for risk reduction based on the patient's CAC score. Patients were made aware that CAC identifies underlying coronary atherosclerosis and is associated with incident heart disease. The recommendations for risk reduction included nutritional advice, exercise suggestions, smoking cessation recommendations (if pertinent), and prescription medications if necessary. However, no medications were prescribed by the counseling physician. This and all subsequent clinical management was left to the discretion of the patient's primary care provider.

Treatment Assessment

An average of 6 ± 1 years (range 3 to 10 years) after the baseline clinic visit, 6086 patients were mailed a follow-up survey to their last known address that inquired about treatment outcomes, including whether they were put on blood pressure medicine, cholesterol lowering medication, aspirin, or antioxidant vitamins after the CT scan by their primary care provider. The specific question posed was as follows: "Due to the results of your body scan, did your doctor start you on any of the following? – Blood pressure medicine, cholesterol lowering medicine, aspirin, antioxidant vitamins." The CAC screening and physician consultation were performed prior to the majority of conflicting reports that focused on potential harms and benefits associated with antioxidant use, specifically vitamin E supplementation, in patients with cardiovascular disease.^{30,31}

Statistical Analysis

Hypertension was defined either by self-report of physician-diagnosed hypertension and current use of a prescription antihypertensive or as a diastolic blood pressure or systolic blood pressure ≥ 90 or ≥ 140 mm Hg, respectively.²⁹ Diabetes was defined either by self-report of physician-diagnosed diabetes and current use of antidiabetic medication or a blood glucose >200 mg/dl.³³ Dyslipidemia was defined either by total-to-HDL >5 or by

self-report of current use of prescription cholesterol-lowering medications.³⁴ Participants were grouped into never, former, or current smokers.

The outcome variables for this study were self-reported prescription of any of the following 4 medications/supplements by their primary physician as a result of their CT scan: blood pressure medicine, cholesterol lowering medication, aspirin, and antioxidant vitamins. The primary predictor variables were presence and extent of CAC, with covariates of age, gender, BMI, premature sibling and parent heart disease, hypertension, dyslipidemia, diabetes, and smoking status. The extent of CAC, age, and BMI were analyzed as continuous variables and presented as mean values $\pm$ S.D.; the remaining variables were dichotomized and presented as numbers (percent).

The CAC scores were both log transformed in order to normalize the distribution of this variable and dichotomized (ie, presence versus absence of calcification) for use in logistic regression. One-way between-groups analysis of covariance (ANCOVA) was conducted, adjusted for age and gender, to investigate multivariable associations between the primary predictor variables and outcome variables. Established risk factors for prevalent calcification/CHD were included in the final multivariable models – model 2 described below.

The potential impact of the presence and extent of CAC on the likelihood that patients reported that their physician prescribed one or more of the 4 medications was explored with a total of 8 separate binary logistic regression models. These models were first conducted adjusted only for age and gender (model 1). Next, the models were adjusted for accepted CHD risk factors and covariates, as well as age and gender (model 2). In these analyses, potential covariates included age, gender, BMI, hypertension, dyslipidemia, smoking status, diabetes, and parent and sibling history of premature heart disease. The Hosmer-Lemeshow goodness-of-fit test was used to assess the logistic regression models. This study specified a significance level of 0.05 or below (2-tailed) in the multivariable models. All statistical analyses were conducted using SPSS version 16.0 statistical package.

RESULTS

A total of 510 participants (response rate =8.4%, as 6086 participants met inclusion criteria) returned the mailed questionnaire and were included in the analyses. We tested differences between the respondents and nonrespondents in terms of age, race, gender, BMI, diabetes, hypertension, dyslipidemia, family history of heart disease, smoking, alcohol consumption, and CAC score. Characteristics of the participants who returned the mailed questionnaire were similar to those who did not return it, except with respect to BMI (26.6 vs 27.1, respectively; $P=.02$). Patients were an average of 64.5 years old (SD 9.69). Non-Hispanic whites were 95.7% of the sample. Women constituted 38.2% of the cohort. The average BMI in this population was 26.61(SD 4.08), and 41.8% were considered overweight based on BMI. Among these 510 patients, 21.4% had a parent with a history of premature heart disease; 7.1% had diabetes; 43.9% had hypertension; 35.1% had dyslipidemia; 45.3% had smoked at some point; 4.1% were smoking at the time of the scan; and 80.8% drank alcohol before the scan. Two hundred ninety-five participants (57.8%) were found to have CAC. The mean and median coronary calcium scores were 202.8 and 8.5, respectively (range 0 to 5117).

Subsequent to receiving results of the CT scan and physician consultation, 19.8% of patients reported that they were prescribed blood pressure medicine; 31.2% said they were prescribed cholesterol lowering medication; 30.6% said they were prescribed aspirin; and 14.5% reported being prescribed antioxidant vitamins on the follow-up survey.

As shown in Table 1, those with any CAC were significantly older (66.7 vs 61.5, $P<0.01$), with a significantly higher proportion of men (71.2 vs 28.8%, $P<0.01$). After adjusting for age and gender, participants with a CAC score >0 had a significantly higher prevalence of hypertension (52.5 vs 32.1%, $P<0.01$) and were more likely to have been prescribed blood pressure medicine (23.1 vs 9.8%, $P<0.01$), cholesterol lowering medicine (38.0 vs 14.9%, $P<0.01$), aspirin (39.7 vs 18.1%, $P<0.01$), and antioxidant vitamins (18.0 vs 9.8%, $P=0.01$). Figure 1 shows the percentage of patients who were prescribed specific medications according to presence or absence of CAC.

The characteristics of the study cohort by medication prescription status are shown in Table 2. There were significant differences in patients' age ($P=.02$), CAC score ($P<0.01$), presence vs absence of CAC ($P<0.01$), diabetes ($P<0.01$), hypertension ($P<0.01$), and dyslipidemia ($P<0.01$) among those who reported being prescribed blood pressure medicine compared to those who reported not being prescribed the medicine. Patients who reported being prescribed cholesterol lowering medication differed significantly in age ($P<0.01$), gender ($P<0.01$), parental heart disease ($P=.01$), CAC score ($P<0.01$), presence vs absence of CAC ($P<0.01$), hypertension ($P<0.01$), and dyslipidemia ($P<0.01$) compared to those who reported not being prescribed the medication. There were significant differences in patients' BMI ($P<0.01$), CAC score ($P<0.01$), presence vs absence of CAC ($P<0.01$), and hypertension ($P=.01$) among those who reported being prescribed anti-oxidant vitamins compared to those who reported not being prescribed vitamins. Patients who reported being prescribed aspirin differed significantly with regard to age ($P=.06$), gender ($P=.02$), parental heart disease ($P=.04$), CAC score ($P<0.01$), presence vs absence of CAC ($P<0.01$), hypertension ($P=.04$), and dyslipidemia ($P<0.01$) compared to those who reported not being prescribed aspirin.

As shown in Table 3, when controlling only for age and gender in model 1, the odds of participants' reporting that they were prescribed blood pressure medicine, cholesterol lowering medicine, aspirin, and antioxidant vitamins by their physician after the CT scan and consultation were 2.41 ($P<0.01$), 3.55 ($P<0.01$), 2.56 ($P<0.01$), and 2.01 ($P=0.02$) times greater, respectively, for those with any CAC compared to those without CAC. Using a 1-unit increment in the log transformed CAC score, and with adjustment for age and gender (model 1), the odds of participants' reporting that they were prescribed blood pressure medicine, cholesterol lowering medicine, aspirin, and antioxidant vitamins by their physician were 1.37 ($P<0.01$), 1.85 ($P<0.01$), 1.63 ($P<0.01$), and 1.43 ($P<0.01$) times higher, respectively.

With additional adjustment for the appropriate CVD risk factors (model 2), the odds of participants' reporting that they were prescribed blood pressure medicine, cholesterol lowering medicine, aspirin, and antioxidant vitamins by their physician after the scan and physician consultation were 3.78 ($P=0.01$), 2.50 ($P=0.03$), 2.00 ($P=0.03$), and 1.25 ($P=0.61$) times higher, respectively, for those with any CAC compared to those without CAC. With this model, using a 1-unit increment in the log transformed CAC score, the odds of a participant's reporting that he or she was prescribed blood pressure medicine, cholesterol lowering medicine, aspirin, and antioxidant vitamins by a physician were 1.46 ($P=0.08$), 1.79 ($P<0.01$), 1.46 ($P=0.01$), and 1.24 ($P=0.25$) times higher, respectively.

Discussion

In this longitudinal follow-up study of 510 asymptomatic men and women, patients with any or a higher CAC score were more likely to report that their physician prescribed blood pressure medicine, cholesterol lowering medication, aspirin, and antioxidant vitamins after receiving their CAC scan results. Perhaps CT results provided incremental clinical data and influenced physician decision making such that patients with any or a higher CAC score were more likely to receive appropriate treatment. The current results corroborate those of a

previous study by Taylor et al, in which statin and aspirin use was significantly greater among patients with coronary calcification.³⁵ These differences persisted after adjustment for CHD risk factors, which suggests that the CAC score independently affected physician's prescribing behavior.

CAC assessed with CT can be used as a measure of subclinical coronary atherosclerosis in patients at intermediate risk for CHD. In the Multi-Ethnic Study of Atherosclerosis (MESA), addition of CAC score data to standard risk assessment resulted in improved risk prediction, with 77% of patients classified as high or low risk versus 69% with risk factor analysis alone. Twenty-three percent of patients who experienced adverse cardiac events were incorrectly categorized as intermediate or low risk but became high risk with inclusion of CAC score in the model.³⁶ Accurate risk stratification is crucial in order to properly target primary prevention efforts to those truly at high risk.³⁷ The American Heart Association, American College of Cardiology, and the National Cholesterol Education Program recommend that CAC be used to further refine risk assessment in selected low-risk patients and those at intermediate risk.^{38–40}

In another large prospective trial, CAC scores successfully categorized CHD risk in participants, independent of the Framingham Risk Score (FRS).⁴¹ Despite the fact the FRS has been evaluated in numerous diverse settings and validated in whites and African Americans, its accuracy for estimating risk of CHD events in some European, Asian, Hispanic, Japanese-American, and Native American populations is limited.^{11,42} Conversely, screening for CAC has been shown in several reports to have prognostic efficacy among men and women in ethnically diverse populations.^{7,43} Facing the uncertainty of existing risk-prediction models, it is important to find new strategies that identify patients who would benefit most from primary prevention efforts.

CAC scores in this cohort appear to have motivated physicians to more aggressively treat risk factors such as dyslipidemia and high blood pressure that are associated with coronary artery disease. The presence of coronary calcium, a marker for atherosclerosis, may have improved the likelihood of early interventions targeting CHD risk factors among asymptomatic patients. Only a few studies to date have investigated the effects of CAC scores on physician prescribing behaviors for primary prevention of CHD. Among participants in the MESA cohort, researchers found a positive correlation between patients' CAC scores and the likelihood of initiating and continuing use of lipid-lowering medication, blood pressure-lowering medication, and regular aspirin.⁴⁴ Similarly, a study by Bybee et al revealed that physicians were significantly more likely to prescribe established medical therapy for CHD to patients with CAC compared to those without CAC directly following PET/CT myocardial perfusion imaging.⁴⁵ It remains to be seen whether the addition of CAC to traditional risk factor screening can lead to improved outcomes.

Study Limitations

This study is not without limitations. The cohort of physician- or self-referred, predominantly white patients may not be a representative sample of the population as a whole. The patients in the study who returned the mailed questionnaire may be more likely to be health conscious, more willing to change behaviors based on scan results, and more educated than the general population. The low response rate to the mailed questionnaires may have resulted in selection bias. However, characteristics of the participants who returned the mailed questionnaire are not materially different from those who did not return the questionnaire. Unfortunately, differences between unmeasured variables are possible. This study also lacked a true control group and was observational in nature. Additionally, self-reporting of prescribed medications was subjective, nonquantitative, and reported approximately 6 years after the baseline CT scan and physician consultation. Therefore,

responses to the survey questions may suffer from recall bias.^{46,47} Lastly, those with higher CAC scores may have overreported prescribed medications.

Conclusions

In summary, this study suggests that, according to patient report, physicians' prescribing practices were influenced by the presence and extent of a patient's CAC, revealed by CT data. CAC results may have altered patient management, exhibited by the increased provision of preventive cardiovascular therapies among those with higher CAC scores. Obtaining a CAC score, which may aid in superior CHD risk stratification among asymptomatic patients, could further initiate patient-provider discussion that focuses on medical therapy and behavior changes to reduce risk of CHD onset and progression.

Screening tools that improve the implementation of CHD preventive strategies are desirable, as proper CHD treatment, guided by risk assessment, has the potential to significantly reduce long-term risk at the population level. There is a need for properly designed, larger prospective trials to investigate whether knowledge of CAC data, followed by an increase in CHD preventive treatments among those with medium to high CAC scores, results in superior health outcomes compared to those of patients who do not get screened for CAC.

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Figure 1.
Percent of Patients Prescribed Medications, According to Presence or Absence of Coronary Artery Calcium

Table 1

Cohort Characteristics Stratified by the Presence/Absence of Coronary Artery Calcium (ANCOVA)

Variable	CAC > 0 (N=295)	CAC = 0 (N=215)	P Value
Age (years), mean (SD) ^a	66.69 (10.18)	61.48 (11.07)	<0.01
Female, n (%) ^b	85 (28.81%)	110 (51.16%)	<0.01
Ethnicity, n (%) ^c			0.27
White	285 (96.61)	203 (94.42)	
Other	6 (2.03)	10 (4.65)	
BMI (kg/m ²), mean (SD) ^c	26.70 (3.83)	26.49 (4.41)	0.51
Parent heart disease before 55, n (%) ^c	65 (22.03%)	44 (20.47%)	0.11
Sibling heart disease before 55, n (%) ^c	28 (9.49%)	15 (6.98%)	0.17
Diabetic, n (%) ^c	26 (8.81%)	10 (4.65%)	0.23
Hypertension, n (%) ^c	155 (52.54%)	69 (32.09%)	<0.01
Dyslipidemia, n (%) ^c	114 (38.64%)	65 (30.23%)	0.38
Smoked at time of scan ^c	12 (4.07%)	9 (4.19%)	0.67
Drank alcohol before scan ^c	236 (80.00%)	176 (81.86%)	0.31
Prescribed blood pressure medications ^c	68(23.05%)	21(9.77%)	<0.01
Prescribed cholesterol lowering medications ^c	112 (37.97%)	32 (14.88%)	<0.01
Prescribed aspirin ^c	117 (39.66%)	39 (18.14%)	<0.01
Prescribed antioxidant vitamins ^c	53 (17.97%)	21 (9.77%)	0.01

Note.

^a Adjusted for gender^b Adjusted for age^c Adjusted for age and gender

CAC = coronary artery calcium

BMI = body mass index

Table 2

Separate Analyses of Covariance (ANCOVA) Examining Multiple Characteristics as Indicators of Physicians' Prescribing Practices (n=510)

Characteristics	Prescribed BPRx (N=83)		Prescribed CholRx (N=144)		Prescribed VitRx (N=74)		Prescribed ASA (N=156)	
	P Value		P value		P value		P value	
Age (yrs), mean (SD) ^a	0.02	68.34 (9.87)	0.02	65.79 (9.55)	<0.01	63.34 (9.25)	0.39	66.03 (10.94)
Female, n (%) ^b	0.12	25 (28.1)	0.12	35 (24.3)	<0.01	47 (30.1)	0.74	47 (30.1)
Ethnicity ^c	0.99		0.72		0.46		0.30	
BMI (kg/m ²), mean (SD) ^c	0.78	27.92 (4.01)	0.68	26.77 (3.35)	<0.01	26.65 (3.90)	0.01	26.63 (3.78)
Parent heart disease before age 55, n (%) ^c	0.18	21 (23.6)	0.01	36 (25.0)	0.38	19 (25.7)	0.38	40 (25.6)
Sibling heart disease before age 55, n (%) ^c	0.44	9 (10.1)	0.60	12 (8.3)	0.76	7 (9.5)	0.76	16 (10.3)
CAC score, mean (SD) ^c	<0.01	300.41 (517.35)	<0.01	327.98 (546.64)	<0.01	296.14 (570.74)	<0.01	388.46 (761.03)
CAC>0, n (%) ^c	<0.01	68 (76.4)	<0.01	112 (77.8)	<0.01	53 (71.6)	<0.01	117 (75.0)
Diabetes, n (%) ^c	<0.01	11 (12.4)	0.34	13 (9.0)	0.11	8 (10.8)	0.11	15 (9.6)
Hypertension, n (%) ^c	<0.01	89 (100)	<0.01	83 (57.6)	<0.01	41 (55.4)	0.01	81 (51.9)
Dyslipidemia, n (%) ^c	<0.01	42 (47.2)	<0.01	78 (54.2)	<0.01	27 (36.5)	0.83	73 (46.8)
Smoked at time of scan, n (%) ^c	0.58	5 (8.6)	0.44	4 (5.6)	0.39	5 (13.2)	0.39	5 (5.8)
Drank alcohol before scan, n (%) ^c	0.19	76 (87.4)	0.67	122 (84.7)	0.95	61 (82.4)	0.95	132 (85.2)

Note.

^a Adjusted for gender

^b Adjusted for age

^c Adjusted for age and gender

CAC = Coronary artery calcium

BMI = Body mass index

BPRx = blood pressure medicine

CholRx = cholesterol lowering medication

VitRx = antioxidant vitamins

ASA = aspirin

Table 3

Binary Logistic Regression Models [Odds Ratios (95% Confidence Intervals)]

Variables	Model	BPRx ^a	CholRx ^b	ASA	VitRx
CAC (Yes/No)	1	2.41 (1.34,4.33)	3.55 (2.17,5.79)	2.56 (1.64,4.01)	2.01 (1.10,3.65)
	2	3.78 (1.31,10.93)	2.50 (1.12,5.62)	2.00 (1.06,3.77)	1.25 (0.56,2.93)
CAC (Continuous - Log Transformed)	1	1.37(1.08,1.74)	1.85 (1.50,2.28)	1.63 (1.34,1.97)	1.43(1.12,1.84)
	2	1.46 (0.96,2.22)	1.79 (1.25,2.56)	1.46 (1.11,1.91)	1.24 (0.86,1.77)

Note.

BPRx = blood pressure medication

CholRx = cholesterol lowering medication

VitRx = antioxidant vitamins ASA = aspirin

Model 1 = Primary predictor (independent) variables + Age + Gender +BMI

Model 2 = Model 1 + Hypertension + Diabetes + Dyslipidemia + Family History of CHD + Smoking

^aBPRx (Model 2) = Age + Gender + BMI + [SBP + DBP (Replaced Hypertension)] + Diabetes + Dyslipidemia + Smoking + Family History of CHD

^bCholRx (Model 2) =Age + Gender + BMI + Hypertension + Diabetes + [Total Cholesterol/HDL (Replaced Dyslipidemia)] + Smoking + Family History of CHD.