

Use of Carotid Intima-Media Thickness and Vascular Age to Modify Cardiovascular Risk Prediction

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Background: This study identified predictors of patients for whom carotid artery intima-media thickness (CIMT) measurement and determination of vascular age could change cardiovascular disease (CVD) risk assessment.

Methods: We studied consecutive patients who were asymptomatic and nondiabetic, referred for ultrasound measurement of CIMT. Individuals with CIMT 75th percentile or greater for age, sex, and race were defined as having advanced subclinical atherosclerosis. CIMT values were converted to vascular age estimates and were used to modify Framingham 10-year CVD risk estimates. **Results:** Of 506 patients, 261 (51.6%) were not taking lipid-lowering therapy. Advanced subclinical

atherosclerosis was present in 77 (30%). There were 62 patients (23.8%) with a change in CVD risk of 5% or more. Predictors of 5% or more change in CVD risk were systolic blood pressure ($P < .001$), total/high-density lipoprotein cholesterol ratio ($P < .001$), and male sex ($P < .001$). Of the 97 patients at moderate or moderately high risk, 56.7% changed risk classification.

Conclusions: Measurement of CIMT and determination of vascular age can identify individuals with advanced subclinical atherosclerosis, resulting in clinically meaningful alterations in CVD risk estimates. (J Am Soc Echocardiogr 2006;19:1170-1174.)

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the United States and worldwide.^{1,2} Because atherosclerosis begins at a young age, identifying subclinical atherosclerosis provides a distinct opportunity to intervene and hopefully prevent future CVD events and their sequelae.³⁻⁶ High-resolution B-mode ultrasound can be used to measure carotid artery intima-media thickness (CIMT). Epidemiologic studies and clinical trials have shown that CIMT can identify prevalent and incident CVD events, and progression and regression of atherosclerosis.^{7,8} Autopsy studies have demonstrated a direct histologic relationship between carotid and coronary atherosclerosis.^{9,10} Using CIMT measurements to detect subclinical atherosclerosis and to modify CVD risk predictions has been recom-

mended but is uncommonly used outside of research settings.⁶

Our vascular health screening program is an example of successful use of CIMT in a clinical setting. A unique aspect of this program is the use of vascular age to modify risk prediction.¹¹ The purpose of this study was to identify predictors of patients in whom CIMT measurement and determination of vascular age could change CVD risk assessment.

METHODS

Vascular Health Screening Program

Our institutional review board determined that this study was exempt from review. From October 1, 2001, to December 31, 2004, more than 500 asymptomatic patients aged 40 to 70 years were referred for CIMT measurement by their physicians for additional data to help clarify CVD risk. These patients were free of CVD (coronary artery, cerebrovascular, or peripheral arterial disease). CIMT was measured in each patient, as was systolic blood pressure, fasting blood glucose, fasting lipids, waist circumference, body mass index, and age, and categorical risk factors (hypertension, diabetes mellitus, cigarette smoking status, family history of premature CVD, sex) were assessed. Metabolic syndrome was diagnosed using

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the National Cholesterol Education Program Adult Treatment Panel III definition.¹² Laboratory tests were performed using standard serum enzymatic assays in a clinical laboratory in which procedures have been validated by the American College of Pathology and Pacific Biometrics Proficiency Testing Programs.

Carotid Ultrasonography and Measurement

Each patient underwent scanning of the right and left carotid arteries using B-mode ultrasound (Acuson Sequoia, Siemens Medical Solutions, Mountain View, Wash) with an 8.0-MHz linear-array transducer. Far-wall images of the common carotid, bulb, and internal carotid artery segments were obtained following the standardized imaging protocol from the Atherosclerosis Risk in Communities (ARIC) study.^{11,13} All ultrasound examinations were performed by one of 4 registered sonographers and interpreted by a single reader (J. H. S.). Images were recorded digitally and analogue video output was digitized to enable measurement using a workstation (Vericis, Camtronics Medical Systems, Hartland, Wis). No videotape was involved, so image resolution was limited by the ultrasound system and transducer and was constant at 85.67 pixels/cm (0.11 mm/pixel). Far-wall, 1-cm segments of the carotid arteries were measured in triplicate and averaged. Composite CIMT was calculated by taking the mean of the right and left segmental mean thicknesses (total of 6 measurements).¹¹ On duplicate blinded scanning, the reproducibility of composite CIMT values was 0.004 ± 0.087 mm ($r = 0.983$, $P < .001$).¹¹ CIMT measurements previously have been shown to be bioequivalent to those of a core laboratory previously associated with the ARIC study.¹⁴

Determination of Vascular Age and CVD Risk Prediction

Vascular age was determined using linear regression models created from published nomograms of age-, sex-, and race-specific CIMT percentiles.^{11,15} Vascular age was defined as the age at which the composite CIMT value for an individual of a given race and sex would represent the median (50th percentile) value in the ARIC study. That is, the linear 50th percentile function by chronologic age, sex, and race was used to project the age of each patient based on their composite CIMT value.¹¹ On duplicate scanning, the reproducibility of vascular age determination was 0.2 ± 2.6 years ($r = 0.981$, $P < .001$).¹¹ Framingham 10-year CVD risk calculations were used to determine the 10-year risk of cardiac death or myocardial infarction.¹² Risk calculations were made: (1) using chronologic age; and (2) after substituting vascular age for chronologic age. The maximum possible age was limited to 79 years. The 20 patients with diabetes mellitus (of the original 526) were excluded from the analysis.

Data Analysis

Software (Sigma Stat 3.0.1, SPSS, Chicago, Ill) was used for all analyses. Continuous variables were described by mean

(SD) values. Comparisons were performed using paired *t* tests with two-sided $\alpha = 0.05$. Advanced subclinical atherosclerosis was defined as CIMT 75th percentile or more for age, sex, and race as defined in the ARIC study.¹³ A clinically relevant change in predicted CVD risk was defined as a 5% or more change in predicted CVD after substituting chronologic age for vascular age. Forward stepwise and multiple logistic regression analyses were performed in the subset of individuals not using lipid-lowering therapy to identify predictors of advanced subclinical atherosclerosis and a clinically relevant change in predicted CVD risk using vascular age. For multiple logistic regression models, goodness of fit was described by the Hosmer-Lemeshow statistic.

RESULTS

Patients included 506 (287 men, 219 women) asymptomatic individuals (Table 1). The average chronologic age was 55.0 (7.4) years. Patients had an average of 2.3 (1.0) CVD risk factors (range: 0-6). The average composite CIMT was 0.788 (0.174) mm. Advanced subclinical atherosclerosis was present in 162 patients (32%). The mean vascular age was 61.8 (11.6) years ($P < .001$ compared with chronologic age). Substituting vascular age for chronologic increased the mean estimated 10-year CVD risk from 5.1% (4.8%) to 7.7% (7.3%) ($P < .001$).

Because almost half of the patients were using lipid-lowering therapy, which is not accounted for by Framingham risk estimates, these values may not accurately represent CVD risk, so the remainder of the analyses were restricted to the 261 patients (51.6%) who were not using lipid-lowering therapy (Table 1). The mean chronologic age of these patients was 54.9 (7.5) years. The average CIMT was 0.769 (0.180) mm. The prevalence of advanced subclinical atherosclerosis was 30% ($N = 77$). In a stepwise regression model, predictors of advanced subclinical atherosclerosis were systolic blood pressure ($P = .011$), total/high-density lipoprotein cholesterol ratio ($P = .033$), and decreasing age ($P = .039$). These predictors also were identified in a multiple logistic regression model ($P = .010$) (Table 2).

Among the patients not taking lipid-lowering therapy, the mean estimated 10-year CVD risk was 4.9% (4.7%). Using vascular age, the mean 10-year CVD risk increased to 6.9% (6.9%) ($P < .001$). There were 62 patients (23.8%) who had a change in CVD risk of 5% or more. In a stepwise regression model, predictors of a clinically relevant change in predicted CVD risk were systolic blood pressure ($P < .001$), total/high-density lipoprotein cholesterol ratio ($P < .001$), and male sex ($P < .001$). These predictors also were identified in a multiple logistic regression model ($P < .001$) (Table 3).

According to Adult Treatment Panel III, patients with zero or one risk factor are at low risk, which

Table 1 Patient characteristics

Continuous variables, mean, SD	Entire cohort	Patients not taking
	(N = 506)	lipid-lowering medication (N = 261)
Age, y	55.0 (7.4)	54.9 (7.5)
Risk factors, n	2.3 (1.0)	2.2 (1.1)
10-y Cardiovascular risk, %	5.1 (4.8)	4.9 (4.7)
Total/high-density lipoprotein cholesterol, ratio	3.8 (1.2)	3.91 (1.32)
Systolic blood pressure, mm Hg	127.7 (16.1)	126.6 (16.6)
Fasting glucose, mg/dL	81.9 (33.6)	78.5 (35.9)
Waist circumference, in	32.6 (11.9)	32.1 (11.3)
Body mass index, kg/m ²	26.8 (5.8)	25.9 (5.4)
Carotid intima-media thickness	0.788 (0.174)	0.769 (0.180)
Categorical variables, N (%)		
Male sex	287 (56.7)	140 (53.6)
Current smoker	32 (6.3)	15 (5.7)
Family history of cardiovascular disease	260 (51.4)	118 (45.2)
Metabolic syndrome	74 (14.6)	27 (10.3)
Use of lipid-lowering medication	261 (51.6)	0 (0.0)
Use of antihypertensive medication	82 (16.2)	39 (14.9)
Advanced subclinical atherosclerosis	162 (32.0)	77 (29.5)

Table 2 Predictors of advanced subclinical atherosclerosis (carotid artery intima media thickness \geq 75th percentile for age, race, and sex)

Variable	Odds ratio	95% Confidence interval		P	Standard error of estimate
Systolic blood pressure/ 10 mm Hg	1.30	1.08-1.56	.005	0.009	
Total/high-density lipoprotein cholesterol ratio/ 1 point	1.34	1.06-1.69	.013	0.118	
Age/10 y	0.63	0.41-0.97	.034	0.021	

N = 261 patients not taking lipid-lowering therapy. Goodness of fit = 11.35, $P = .182$.

Table 3 Predictors of 5% or more change in estimated 10-year cardiovascular risk using vascular age

Variable	Odds ratio	95% Confidence interval		P	Standard error of estimate
Systolic blood pressure/ 10 mm Hg	1.74	1.35-2.24	<.001	0.012	
Total/high-density lipoprotein cholesterol/1 point	1.82	1.38-2.42	<.001	0.143	
Male sex	6.20	2.65-14.53	<.001	0.434	

*N = 261 patients not taking lipid-lowering therapy. Goodness of fit = 12.25, $P = .140$.

corresponds to a 10-year CVD risk of less than 10%.¹² Patients with two or more risk factors and a 10-year CVD risk less than 10% are at moderate risk, those with 10-year CVD risk of 10% to 20% are at moderately high risk, and those with greater than

20% are at high risk.¹² In this study, 90% of patients with zero or one risk factor had a 10-year CVD risk of 5% or less, so a 10-year CVD risk of 5% or less was considered low risk. Moderate risk was defined as those with a 10-year CVD risk of 5% to less than 10%, and moderately high risk as those with a 10-year CVD risk of 10% to 20%. The 97 patients (37%) at moderate or moderately high risk had the most change in predicted risk using vascular age, with 56.7% changing risk classification (Figure). Of the 65 patients at moderate risk, 39 (60%) changed risk classification (15 decreased, 24 increased). Of the 32 patients at moderately high risk, 16 (50%) changed risk classification (7 decreased, 9 increased). As expected, only 12% of patients at low risk (19 of 160) changed classification. There only were 4 patients at high risk and two of them changed risk classification.

DISCUSSION

In this study, we demonstrated that measurement of CIMT in a clinical setting identifies individuals with advanced subclinical atherosclerosis. Furthermore, CIMT measurements and population-based percentiles can be integrated with existing risk stratification paradigms, resulting in clinically meaningful alterations in CVD risk estimates. Predictors of advanced subclinical atherosclerosis (CIMT \geq 75th percentile for age, race, and sex) were systolic blood pressure, the total/high-density lipoprotein cholesterol ratio, and decreasing age. Male sex predicted a greater than 5% change in predicted CVD risk, whereas age did not. Individuals at moderate or

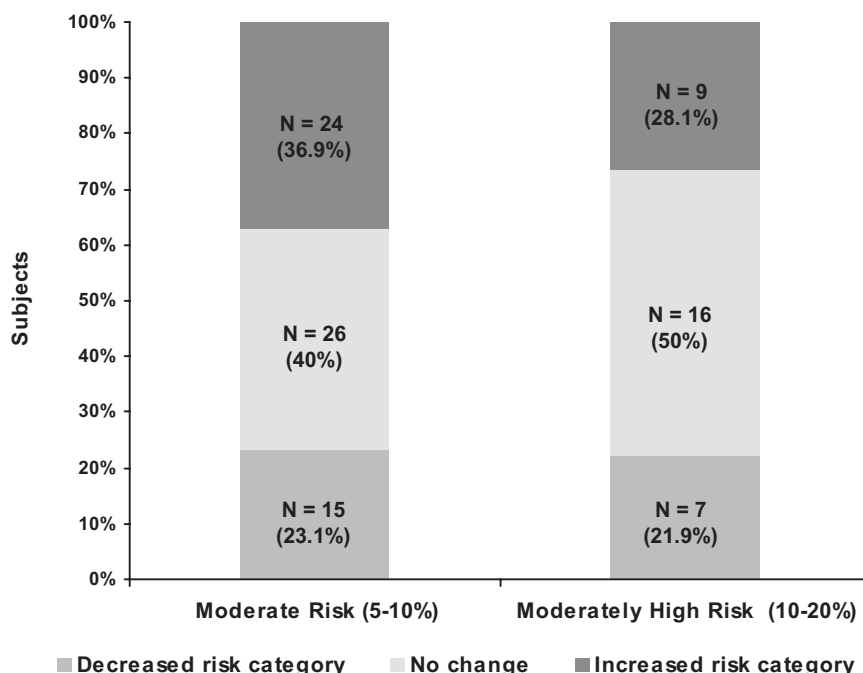


Figure Change in 10-year predicted cardiovascular disease risk categories based on carotid artery intima-media thickness-derived vascular age.

moderately high risk were most likely to change risk classifications.

The observation that younger age predicted a higher CIMT than expected (based on age, sex, and race) likely is a result of referral bias. Physicians may have selectively referred patients who they believed were at higher than apparent risk because of measures not accounted for by the Framingham risk algorithm (eg, family history), new/emerging risk factors not measured in this study, or the presence or magnitude of risk factor abnormalities did not achieve thresholds to change therapy. A low apparent risk is directly associated with the patient age because age is the dominant determinant of Framingham 10-year CVD risk estimates, so a referral bias of low apparent risk (by Framingham risk estimation) but higher actual risk (based on CIMT) is more likely to occur in younger patients. Indeed, most of the patients in this study were at low risk based on Framingham scores, despite the high prevalence of multiple risk factors.

CIMT can be used to identify individuals at increased risk of future CVD events and those who have subclinical atherosclerosis. CIMT is strongly associated with prevalent and incident CVD.^{6,15-18} Because vascular age is derived from CIMT, CIMT can be used to predict advanced subclinical atherosclerosis and to modify 10-year CV risk assessment. Framingham risk calculations that are modified with vascular age generate considerably different risk assessments as compared with chronologic age. In

our experience, reporting a vascular age rather than a CIMT percentile helps facilitate communication to patients and health care professionals by providing a quantitative description of atherosclerotic burden and relative CVD risk.

Limitations

This is an observational study of patients referred to a CVD screening program. As discussed above, physicians refer patients for CIMT testing based on the presumption of greater than apparent risk, a bias that explains why lower age predicted a higher likelihood of advanced subclinical atherosclerosis and increased risk based on CIMT measurements. Almost all of the patients were white (>99%), reflecting local demographics. Although some findings may not be generalizable, the purpose of this study was to identify predictors of patients in whom CIMT measurement and determination of vascular age change CVD risk assessment in a clinical setting, such as the program described in this study. Because of the high prevalence of lipid-lowering therapy, predictive models were limited to individuals not taking these medications. In addition, vascular age is estimated by incorporating ultrasound image measurements into a predictive model with an expected median value that is based on chronologic age, race, and sex. This model has an inherent variance that is not present for an individual's chronologic age, so some of the change in risk classification observed in

this study may have been a result of chance. Finally, although this study showed changes in predicted risk using CIMT and vascular age calculation, improved outcomes cannot be demonstrated in an observational study such as this and would require longitudinal study.

Future Directions

Although recommended as a useful test in asymptomatic patients at intermediate risk for CVD, measurement of CIMT is not used widely, because scanning and measuring are time-consuming, and ways to integrate CIMT measurements with current risk-prediction paradigms have not been established. The vascular age construct is one such way to integrate CIMT measurements with Framingham CVD risk prediction models. Because submillimeter differences in CIMT have clinical relevance, rigorous training, ongoing quality assurance evaluation, and meticulous attention to detail are used to minimize errors in CIMT measurement. Semiautomated border detection algorithms eventually will make CIMT measurement faster, more reliable, and more suitable in an office setting.^{14,19} Furthermore, improved technology for 3-dimensional imaging will aid in image analysis and allow for complete reconstruction of the carotid artery and more sophisticated assessment of the vessel wall, including plaque characterization and assessment of compliance, in addition to measurement of CIMT.

Conclusions

Measurement of CIMT in a clinical setting can identify individuals with advanced subclinical atherosclerosis, resulting in clinically meaningful alterations in CVD risk estimates. In our institution, clinical predictors of advanced subclinical atherosclerosis included age, systolic blood pressure, and the total/high-density lipoprotein cholesterol ratio. Individuals at moderate or moderately high risk were most likely to change risk classifications. Prospective studies are needed to determine if patient treatment guided by CIMT measurements improves long-term CVD outcomes.

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