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Carotid Intima–Media Thickness and Carotid Plaques Improves Prediction of Obstructive Angiographic Coronary Artery Disease in Women

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Abstract

Does carotid intima–media thickness (cIMT), a surrogate marker of cardiovascular events, have predictive incremental value over established risk factors for stable coronary artery disease (CAD)? Prospective study of 300 patients, with suspected stable CAD, admitted for an elective coronary angiography and carotid ultrasound. The CAD patients had a higher cIMT, which showed a modest predictive accuracy for CAD (area under the receiver–operating characteristic curve 0.638, 95% confidence interval 0.576-0.701, $P < .001$). The cIMT was an independent predictor of CAD, together with age, gender, and diabetes. C-statistic for CAD prediction by traditional risk factors was not significantly different from a model that included cIMT, carotid plaque presence, or both. However, in women, it was significantly increased by the addition of cIMT or carotid plaque presence. Although cIMT cannot be used as a sole indicator of CAD, it should be considered in the panel of investigations that is requested, particularly in women who are candidates for coronary angiography.

Keywords

carotid intima–media thickness, coronary artery disease, cardiovascular risk prediction

Introduction

Cardiovascular diseases are the leading cause of death in developed countries.[1] They are also a major problem in Portugal, not only as far as coronary artery disease (CAD) is concerned but also in terms of stroke, the incidence of which is among the highest in the world.[2] In fact, in developed countries, the most common cardiovascular disease is CAD, which is also the leading cause of death in all the European Union with the exception of Greece, the former Yugoslav Republic of Macedonia and Portugal, where it is stroke.[2] It is thus important to identify patients at risk of developing cardiovascular events to enable preventive interventions and promote lifestyle modifications. Traditional risk prediction scores have proven very useful in identifying persons at risk of coronary heart disease, but such tools have limitations. Carotid intima–media thickness (cIMT) is a well-described surrogate marker for cardiovascular disease that it is easily obtained by a noninvasive test and increased cIMT has been associated with prevalent and incident CAD and stroke.[3-6] Furthermore, plaque presence, which has been shown to be associated with coronary heart disease independent of cIMT measurement in several studies, seems to improve risk prediction.[7,8] However, most studies addressed the relationship between cIMT and acute cardiovascular events in the follow-up.[5,6] Fewer studies analyzed the relationship between cIMT and angiographic coronary artery disease—a stable end point with different pathopysiological mechanisms.

In the present study, we aimed to investigate the relationship between cIMT and angiographic CAD in patients evaluated by coronary angiography for suspected CAD. We intended to provide more information to help answer two important questions. Is cIMT evaluation useful in clinical practice? Does it help to define indications for coronary angiography?

Population and Methods

The present study is an observational and cross-sectional study, with prospective inclusion of patients admitted for an elective coronary angiography with suspected CAD (with stable angina and/or with documented ischemia on noninvasive tests). All patients had an age $\geq$18 years. Patients with previous acute coronary syndromes, myocardial revascularization

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procedure, valvular heart disease, congenital heart disease, or cardiomyopathy were excluded. The local institutional ethics committee approved the study, and all patients gave their written informed consent.

Blood pressure (BP) was measured on several occasions during hospital stay and hypertension was defined by a previous diagnosis of hypertension or the presence of systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg (mean of 2 consecutive measurements). Patients that smoked during the previous 6 months were classified as smokers and were self-reported. Diabetes was recorded by patient history, raised glucose (fasting level $\geq$126 mg/dL), or use of specific therapies.

A venous blood sample was drawn after a 12-hour overnight fast. All the samples were analyzed at the central laboratory of the hospital. Serum glucose, total cholesterol, and triglycerides were determined using automatic standard routine enzymatic methods. High-density lipoprotein (HDL) cholesterol was determined after specific precipitation. Low-density lipoprotein (LDL) cholesterol was determined by Friedewald formula.

Coronary angiography was performed by the standard Judkins technique. The coronary angiograms were analyzed using QCA software, Cardiovascular Measurements System (QCA-CMS) version 6.0 (Medis Medical Imaging Systems, Leiden, The Netherlands) by a single operator blinded to the carotid ultrasound results. An automated edge detection algorithm determined vessel centerline and contour and absolute reference vessel and minimum lumen diameters were determined using the calibration factor. Percentage stenosis was calculated from minimum lumen diameter and a normal reference value obtained as an extrapolation of the proximal and distal segments surrounding the stenosis. Significant angiographic CAD was defined as stenosis of 50% or more in any coronary vessel. The severity of CAD was assessed by the Gensini score, a previously validated method.[9] The interclass correlation coefficients for intrareader reproducibility were 0.950 for Gensini score and 0.724 to 0.947 for vessel dimension (analyzed for different vessels), which suggests good agreement.

The carotid ultrasound procedure was performed with a Siemens Sonolite system and a 7.5-MHz linear array transducer. The cIMT was measured by a trained radiologist (blinded to the coronary angiographic result) at the distal common carotid artery (CCA; 1 cm proximal to dilation of the carotid bulb) at the far wall. The higher yield and superior reproducibility of measurement of the CCA IMT compared to internal carotid artery (ICA) and bulb IMT favor its use in the IMT measurements, and this was the segment chosen for the study. Manual measurements were taken and the value of both the right and the left side were obtained for analysis. The final cIMT was obtained as the maximum cIMT between both sides. Plaque was defined as a focal structure encroaching into the arterial lumen with a thickness that is more than 50% of the surrounding cIMT or more than 1.5 mm. The interclass correlation coefficients for intrareader and interreader reproducibility were 0.907 and 0.820, respectively, which also suggests good agreement.

Statistical Analysis

Statistical analysis was conducted using the PASW 18.0 program (SPSS Inc, Illinois, Chicago). Quantitative variables were described as mean and standard deviation or as median values and corresponding 25th and 75th percentiles for nonnormally distributed variables and qualitative variables as percentages. Student *t* test or Mann-Whitney *U* test was used for between-group comparisons of continuous variables (according to distribution characteristics), while the chi-square test was used for between-group comparisons of categorical variables. Gensini score and some laboratory variables were much skewed, and we performed a 10-based logarithmic transformation (Log) that was used in the subsequent analysis. Pearson correlation was done between cIMT and continuous variables. Bivariate logistic regression models were used to identify predictors of CAD. Multivariate logistic regression analysis (with CAD as the outcome variable) was performed to determine whether cIMT was an independent predictor of CAD. We used the area under the receiver–operating characteristic (AUC) curve analysis (or C-statistics) to evaluate predictive value for CAD of cIMT and to determine its best cutoff (maximizing the sum of sensitivity and specificity). Several risk prediction models were also considered: (1) established risk factors only, (2) established risk factors plus cIMT, (3) established risk factors plus carotid plaque, and (4) established risk factors plus cIMT plus carotid plaque. We described the AUC for each model to analyze the model predictive capacity.

Results

We included 300 patients in the study, with a mean age of 64 $\pm$ 9 years (aged 38-86 years), 59% males (Table 1). Significant CAD was present in 51.3% of patients, but it was significantly lower in females (35.8% vs 62.1%; $P < .001$). Patients with significant CAD were older, more frequently male and diabetic, had higher levels of blood glucose and triglycerides, and lower levels of HDL cholesterol (Table 1).

In our population, 88% of the patients had a noninvasive test positive for ischemia. However, even in this group of patients, the prevalence of significant CAD was low, particularly in females (Table 2).

Mean cIMT was 0.88 $\pm$ 0.33 mm, significantly higher in males (0.94 $\pm$ 0.35 vs 0.81 $\pm$ 0.29 mm; $P = .001$) and in patients with significant CAD (0.96 $\pm$ 0.35 vs 0.82 $\pm$ 0.29 mm; $P < .001$). Carotid plaques were present in 6.0% of patients.

The cIMT was associated with the number of diseased coronary vessels; however, the only significant difference was found between no diseased vessel and 1 diseased vessel (Figure 1). A more consistent association was found between cIMT and Gensini score, a CAD severity index ($r = .221$, $P < .001$).

By receiver–operating curve analysis, we obtained a modest predictive capacity for CAD of isolated cIMT (AUC 0.638, 95% confidence interval [CI] 0.576-0.701; $P < .001$), with the best cutoff of 0.85 mm with a sensitivity of 63% and specificity of 64%. The same cutoff was obtained in both genders, however

Table 1. Characteristics of the Study Population and by Gender

Characteristics	Total Mean $\pm$ SD Median (IQR) %	CAD Mean $\pm$ SD Median (IQR) %	No CAD Mean $\pm$ SD Median (IQR) %	*P*
Age (years)	64.4 $\pm$ 9.2	66.2 $\pm$ 9.2	63.4 $\pm$ 9.9	.003
Male gender (%)	59	71	46	.001
Risk factors (%)				
Hypertension	79	87	84	.604
Hyperlipidemia	70	70	69	.957
Smoking	9	11	8	.398
Diabetes mellitus	23	29	16	.013
Laboratorial data				
Glucose (mg/dL)	100 (92-115)	104 (93-124)	97 (91-106)	.001
Total cholesterol (mg/dL)	181 (155-213)	182 (158-218)	177 (152-207)	.208
HDL-cholesterol (mg/dL)	43 (36-54)	41 (34-50)	47 (40-55)	<.001
LDL-cholesterol (mg/dL)	114 (93-136)	114 (97-141)	114 (89-133)	.141
Triglycerides (mg/dL)	97 (68-134)	100 (71-146)	93 (63-124)	.019

Abbreviations: SD, standard deviation; IQR, interquartile range; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Prevalence of Significant Coronary Artery Disease, Analyzing Only Patients With Positive Stress Tests and According to Gender

	Total, %	Males, %	Females, %	*P*
Positive treadmill test	49.3	60.7	30.8	.001
Positive nuclear test	54.3	65.2	41.4	.012
Any positive test	51.5	62.7	36.0	<.001

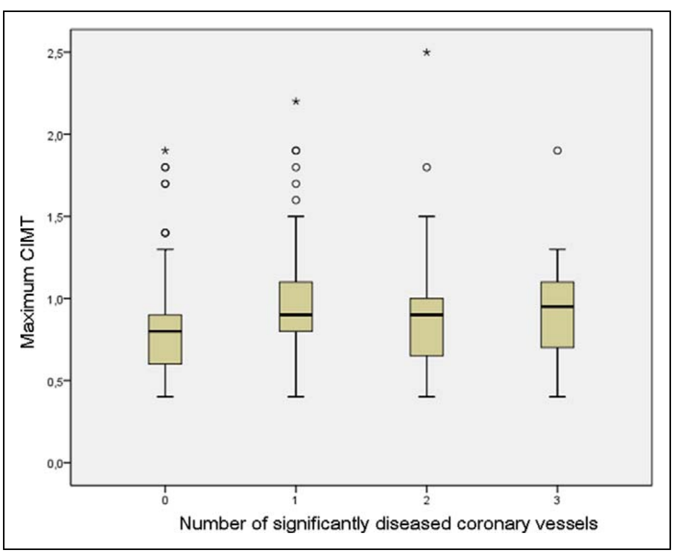

Figure 1. Carotid intima–media thickness according to the number of diseased coronary arteries ($P = .003$, post hoc analysis with the only significant difference between no-vessel and 1-vessel disease).

with a better AUC for women (Table 3). In a logistic regression model for CAD, cIMT was an independent predictor of CAD, as well as age, gender, and diabetes (Table 4). Even when cIMT was introduced in the model as a categorical value using the previous obtained cutoff, it remained as an independent predictor of CAD (odds ratio 2.26, 95% CI 1.36-3.75; $P = .002$).

To analyze the incremental value of cIMT and carotid plaques over established risk factors, we compared risk prediction models. We found that the AUC for traditional risk factor prediction of CAD was not significantly different from the model that included cIMT, carotid plaque presence, or both (Table 5). However, in women, it was substantially increased by the addition of cIMT or carotid plaque presence, and the combination of risk factors, cIMT, and plaque yielded the highest AUC.

Discussion

Our study showed a surprisingly low diagnostic yield of coronary angiography. However, recent registries point to the same results. In a 1992 report, between 9% and 36% of patients who underwent invasive angiography were found to have normal coronary arteries, but the findings were limited by varying definitions of normal and by different radiographic equipment.[10] Findings from the Coronary Artery Surgery Study showed that 18.8% of patients had nonobstructive CAD.[11] Data from the Society for Cardiac Angiography and Interventions (still more than 15 years old) showed that between 30% and 35% of patients had stenosis of less than 50%.[12] These data were obtained before the current increase in both noninvasive imaging and the use of cardiac catheterization and include a broad spectrum of patients undergoing angiography, including those with acute coronary syndromes and other emergency indications. Thus, the definition of the patient population is critical in placing our findings in context. The recently published CathPCI Registry of the National Cardiovascular Data Registry (NCDR), a large registry of clinical data and in-hospital outcome data associated with diagnostic cardiac catheterization and percutaneous coronary interventions collected from more than 800 US sites reported also a low diagnostic yield in patients

Table 3. Evaluation of cIMT Gender-Specific Cutoff Values for the Presence of Significant Coronary Artery Disease by ROC Curve Analysis

	Cutoff	Se	Sp	AUC	*P*	RR for CAD (95% CI)
Females	0.85 mm	64%	75%	0.715 (0.621-0.809)	<.001	5.16 (2.33-11.45)
Males	0.85 mm	63%	52%	0.557 (0.470-0.645)	.201	1.84 (0.99-3.41)

Abbreviations: ROC, receiver-operating curve; Se, sensitivity; Sp, specificity; AUC, area under curve; RR, relative risk; CAD, coronary artery disease; CI, confidence interval.

Table 4. Backward Multivariate Logistic Regression Model to Predict Coronary Artery Disease

	B	Wald	OR (95% CI)	*P*
Age	0.033	5.442	1.03 (1.01-1.06)	.020
Male gender	1.068	17.300	2.91 (1.76-4.81)	<.001
Diabetes	0.693	5.156	2.00 (1.10-3.64)	.023
cIMT	0.855	4.199	2.35 (1.04-5.33)	.040

Abbreviations: OR, odds ratio; CI, confidence interval; cMIT, carotid intima–media thickness.

without previously known CAD, with only a minority of patients with obstructive CAD (41.0%) similar to our results.[13] This registry represents contemporary clinical practice in the community. The NCDR registry also provides insights into patterns of noninvasive testing among patients undergoing diagnostic cardiac catheterization. Previous studies showed that only 41% of the patients underwent any stress testing before coronary angiography.[14] The NCDR registry showed that up to 84% of patients undergoing angiography had undergone a previous noninvasive diagnostic test and a positive result was recorded in 68.6% of all patients in the cohort.[13] Similar results were obtained in our population. The increased use of noninvasive testing to rule out ischemia prior to the procedure should result in more effective risk stratification of patients, allowing identification of those patients who would be most likely to benefit from cardiac catheterization and ideally reducing the use of invasive procedures in patients who do not have obstructive disease. Although certain demographic and clinical characteristics could be useful in determining the likelihood that obstructive CAD would be present, the incremental value of a positive result on a noninvasive test was however limited. In NCDR registry, although the association between a positive noninvasive test and the presence of obstructive CAD was significant, the effect of a positive noninvasive test on the ability of the model to predict the presence of obstructive CAD was limited with minimal increase in C-statistic.[13] It is also important to stress out that patients with chest pain and normal or nonobstructive coronary angiograms are predominantly women, and many have a prognosis that is not as benign as previously thought.[15] Assessment of endothelial function may help identify patients at risk of future cardiac events. Recent data suggest that ST-segment changes and myocardial reversible perfusion defects in patients with "normal" coronary arteries may be true myocardial ischemia likely related to atherosclerotic disease and not false-positive test results.[15]

Our study confirmed the limited value of noninvasive tests, particularly in women. Thus, there is still need of an inexpensive and easily accessible test that would indicate the likelihood of CAD with reasonable high sensitivity and specificity. A meta-analysis of 8 trials on cIMT, including 37 197 asymptomatic individuals who were followed up for a mean of 5.5 years showed that a cIMT increment of 0.1 mm increased the risk of myocardial infarction by 10% to 15% and increased the risk of stroke by 13% to 18%, after adjusting for age and gender.[16] Moreover, the cIMT prediction for both events may be better in women than in men and the cIMT prediction may be better for stroke than for CAD when cIMT is measured in the CCA alone.[6] The fact that cIMT provides additional prognostic information to that of conventional risk factors is pivotal in discussing its clinical utility in primary prevention and was not supported by available data until recently. Since 2000, 7 guidelines or consensus statements recommended measuring cIMT and/or carotid plaque detection as clinical tools to assist cardiovascular disease risk prediction.[17] However, the US Preventive Services Task Force recently recommended against measurement of anatomical markers of atherosclerosis, including cIMT, basing its negative recommendation regarding the independent predictive value of cIMT for patients at intermediate CAD risk and concerns about this test's ability to reclassify such patients into lower or higher risk categories, therefore altering their clinical management.[18,19] The very recent report from the Atherosclerosis Risk in Communities (ARIC) study with >13 000 individuals provide the best evidence, to date, demonstrating the ability of carotid ultrasound data to improve CAD risk prediction.[20] They found that the AUC for established risk factor prediction of CAD events was significantly increased by the addition of increased cIMT or carotid plaque presence and that the combination of risk factors, cIMT, and plaque yielded the highest AUC. Thus, carotid ultrasound-based cIMT measurement and identification of plaque presence or absence improves CAD risk prediction and should be considered in the intermediate risk group.

These findings support the previous American Society of Echocardiography's recommendation of combining cIMT and carotid plaque data for optimal risk prediction.[17] In the ARIC report, although the increments in AUC achieved using the carotid ultrasound data may seem small, they are on the same order of magnitude as the individual contributions of smoking status and systolic BP and greater than the contributions of lipids, family history, and high-sensitivity C-reactive protein.[20]

Table 5. Predictive Value for Each Model[a]

	Model 1	Model 2	Model 3	Model 4
Overall				
AUC (95% CI)	0.701 (0.642-0.760)	0.709 (0.651-0.768)	0.707 (0.649-0.766)	0.709 (0.651-0.768)
P	.613	.001	.521	<.001
Males				
AUC (95% CI)	0.636 (0.551-0.720)	0.630 (0.547-0.719)	0.638 (0.554-0.723)	0.641 (0.557-0.725)
P	.920	.519	.532	.727
Females				
AUC (95% CI)	0.689 (0.591-0.788)	0.745 (0.656-0.834)	0.717 (0.621-0.812)	0.747 (0.658-0.836)
P	.552	.887	.383	.969

Abbreviations: cIMT, carotid intima–media thickness; CI, confidence interval; AUC, area under the curve.

[a] Risk prediction models: (1) established risk factors only; (2) established risk factors plus cIMT; (3) established risk factors plus carotid plaque; (4) established risk factors plus cIMT plus carotid plaque. *P* values derived using the Hosmer and Lemeshow test.

Indeed, after age and gender inclusion in predictive models, additional risk factors contribute little on an individual basis but are very important when considered together.[20]

In the past few years, several groups have shown that carotid plaque or plaque area are more closely related to CAD and is more strongly predictive of coronary events.[5,8,21-24] In fact, established coronary risk factors explain only 15% to 17% of cIMT but account for 52% of the carotid plaque area, suggesting that the carotid plaque area is more representative of atherosclerotic burden than cIMT.[25-27] Although highly intercorrelated, measurements of cIMT and plaque area probably reflect different biological aspects and stages in the development of atherosclerosis. Whereas plaque is the biological hallmark of atherosclerosis, reflecting subendothelial deposition of cholesterol as well as infiltration of inflammatory cells, a diffuse thickening of the intima–media layer may be caused by other pathogenic mechanisms. In this layer, 20% is made of the endothelial layer and subendothelial matrix, and the remaining 80% consists of smooth muscle cells.[27] Age-related arterial stiffness and hypertension increase the shear forces acting on the vessel surface, causing hyperplasia of the smooth muscle cells, explaining the association of cIMT with age and hypertension.[27] Increased cIMT therefore may not necessarily reflect the atherosclerotic process. On the other hand, plaque growth occurs longitudinally along the carotid axis of flow faster than it thickens, which may make plaque area more sensitive as a measure of atherosclerosis.[28]

The present study analyzed directly the relationship between carotid subclinical atherosclerosis and stable significant angiographic coronary artery disease. This end point is different from the most often studied end points since acute cardiovascular events are caused by unstable atherosclerotic plaques, with different pathophysiological mechanisms involved when compared to stable atherosclerotic plaques. Our results showed that cIMT is higher in patients with significant CAD than in patients without CAD. Regression analysis revealed that thickening of the mean intima–media complex more than 0.85 mm was predictive of significant CAD. As an isolated tool, its predictive capacity for CAD is, however, very modest but slightly better in women. We also found that although in the general population, it was not very helpful in increasing predictive capacity for CAD when added to a predictive model with conventional risk factors, in women there was a substantial incremental value of cIMT to predict significant CAD and that it was slightly better than carotid plaque. Therefore, cIMT value cannot be used as a sole indicator of CAD but needs to be considered in the panel of studies that is requested, particularly in women who are considered candidates for coronary angiography.

Both cIMT and carotid plaques seemed to have a more profound effect on improving risk prediction in women than in men, and the reason is not completely clear. The most likely explanation is that middle-aged women have a relatively low prevalence of atherosclerosis. For that reason, increased cIMT and plaque presence, which reflects a definite area of atherosclerosis, is more powerful in predicting CAD.

In conclusion, coronary angiography has a low diagnostic yield for significant CAD, particularly in women. In this group, noninvasive tests for risk stratification before coronary angiography also have severe limitations. In women, cIMT seems to be a useful risk stratification tool in association with conventional risk factors for CAD.

Limitations

Our study is a cross-sectional study, and as such, it is not possible to establish a causal relationship since no information from the follow-up was analyzed and individuals only underwent a single coronary angiogram and carotid ultrasound.

The present scanning protocol for cIMT measurement only focuses on the CCA due to difficulties in adequate evaluation of cIMT in the bulb and ICA. However, scanning of the remaining segments of the carotid arteries for plaques might be important to avoid missing "upstream" advanced atherosclerosis. In fact, we did not account for the potential difference between plaque presence in one artery alone versus in multiple arteries. It is possible that plaque presence in multiple carotid artery segments may be associated with higher risk. Very recent studies showed that cIMT measured solely in the far wall of the CCA is associated with incident stroke in unadjusted analysis, but this association became nonsignificant after adjustment for risk factors.[29,30] However, using measurements that included the carotid bifurcation, where there is a nonlaminar turbulent flow that favors atherosclerotic plaque development, it was associated with stroke but only in women.[30] This highlights the importance of segment-specific measurements as well as gender influence.

Manual assessment of cIMT is not optimally reproducible. There have been rapid advances in ultrasound technology resulting in greater consistency and resolution of images. Semiautomated edge-detection software to measure cIMT has been developed and has been found to be both accurate and reproducible. This technology might have yielded different results.

This is an angiographic study and as such, coronary plaque morphology was not directly assessed. Intravascular ultrasound allows cross-sectional imaging of coronary arteries and provides more comprehensive assessment of atherosclerotic plaque in vivo and this is considered the gold standard technique. With quantitative coronary angiography analysis, we measured reference diameter and percentage diameter stenosis. However, it has been previously described that this measurement might be misleading because patients with identical measurements in angiography might have different vessel volume and plaque volume when assessed by intravascular ultrasound. In fact, in some patients, vessels might have a compensatory enlargement to prevent building atheroma from encroaching in lumen, thereby concealing the presence of a lesion when angiography is performed.[31]

Declaration of Conflicting Interests

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