

Electron-Beam Tomography Coronary Calcium Scores Are Superior to Framingham Risk Variables for Predicting the Measured Proximal Stenosis Burden

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Previous studies of electron-beam tomography (EBT) have correlated coronary calcium scores with simplistic visual estimates of disease severity. In a clinical trial designed to evaluate 2 treatment strategies in coronary artery disease (CAD) patients with low levels of high-density lipoprotein cholesterol, we used quantitative coronary angiography to measure composite proximal stenosis burden from the baseline coronary angiogram and assessed the traditional Framingham risk variables in 146 patients. Stenosis burden is the sum, per patient, of percent stenosis for the worst lesion found in each of 9 standard proximal coronary segments. EBT estimates of coronary calcium (Agatston score, calcium volume score) were obtained for 115 of these patients. Stenosis burden was correlated with the calcium scores and risk variables. The best traditional correlates of stenosis burden were smoking status ($r = 0.31$, $p = 0.001$), prior myocardial infarction ($r = 0.24$, $p = 0.005$), body mass index ($r = 0.23$, $p = 0.005$), pack-years smoking ($r =$

0.20 , $p = 0.05$), and age ($r = 0.17$, $p = 0.04$). With adjustment for age, all these correlations improved (eg, body mass index \times age [$r = 0.28$, $p = 0.001$]). In addition, total cholesterol \times age ($r = 0.22$, $p = 0.008$), fibrinogen \times age ($r = 0.19$, $p = 0.03$), and systolic blood pressure \times age ($r = 0.18$, $p = 0.03$) became significant correlates. Spearman correlations of the calcium scores with stenosis burden were considerably greater (Agatston: $r = 0.62$, $p < 0.0001$; calcium volume: $r = 0.63$, $p < 0.0001$). In multivariate regression analysis, calcium score, body mass index, and history of myocardial infarction were independent correlates of stenosis burden ($R^2 = 0.45$). At a given point in time, the EBT coronary calcium scores are greatly superior to the Framingham risk factors in predicting the measured proximal stenosis burden. Agatston and calcium volume scores are comparably predictive of stenosis burden. ©2001 by Excerpta Medica, Inc.

Am J Cardiol 2001;88(suppl):23E-26E

Quantitative determination of coronary calcium by electron-beam tomography (EBT) has been shown to correlate well with the histologic burden of coronary atherosclerosis^{1,2} and with future cardiovascular risk,^{3,4} although the latter has been controversial.⁵ Because calcium may accumulate in nonobstructive atherosclerotic plaques, the calcium score is only moderately effective in predicting the likelihood and location of severe stenosis.^{6,7} A concern about the studies correlating stenosis severity with calcium score is that estimates of obstruction have typically

been made by the subjective visual method and often consider only whether the worst lesion in each of 3 major arteries is $>50\%$.^{6,8} In this article, we examine the relation of the Agatston coronary calcium score (or the calcium volume score) with the proximal coronary stenosis burden, measured from the angiogram by quantitative techniques. We compare this relation to that seen with the traditional Framingham risk variables.

METHODS

Patients: A total of 160 patients were enrolled in the High-density lipoprotein (HDL) Atherosclerosis Treatment Study (HATS), a 3-year placebo-controlled trial testing the effect of lipid-lowering therapy (simvastatin plus niacin), and/or antioxidant vitamins on progression of coronary stenosis and clinical cardiovascular events.⁹ Of these, 132 of 134 living in the Seattle area underwent coronary calcium determination by EBT at the Heartscan Seattle facility, within 3.9 ± 4.0 months of their baseline coronary angiogram. All patients had established coronary disease with prior myocardial infarction and/or angioplasty, and/or chest pain with positive exercise testing. All had moderate levels of low-density lipoprotein cholesterol (LDL-C)

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Supported by National Heart, Lung, and Blood Institute grant R01 HL49546, with drug supplies from Upsher-Smith Laboratories and Merck & Company, and in part by the Clinical Nutrition Research Unit (National Institutes of Health DK 35816). A portion of this study was performed in the Clinical Research Center (National Institutes of Health MOL 00037) at the University of Washington. Electron-beam computed tomography studies were supported by Imatron, Inc.

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(<145 mg/dL) and low levels of high-density lipoprotein cholesterol (HDL-C) (≤ 35 mg/dL for men and ≤ 40 for women). Mean age was 53; 13% were women; 15% were diabetic. The cohort considered in this article is the group of 146 patients who had near-simultaneous coronary arteriography and Framingham risk assessment, and the subset of 115 patients who also had coronary calcium assessment.

Quantitative coronary arteriography: At baseline catheterization, 5 views of the left coronary arteries and 3 of the right coronary artery were obtained after administration of 0.2 to 0.4 mg of sublingual nitroglycerine. A detailed coronary map was drawn, locating each lesion causing $\geq 20\%$ stenosis. Then, 2 to 6 cine frames were selected from the view(s) that best demonstrated each stenosis. The lesion causing the worst stenosis in each of the 9 standard proximal coronary segments was designated the "primary" lesion for that segment. The region of the selected image frame showing the lesion of interest was digitized at up to 4-fold optical and 2-fold digital magnification using a Sony SME 3500 digital cine projector (Sony Corporation of America, New York, NY) linked to a PowerMac 7100 computer (Apple Computer, Inc., Cupertino, CA) running a program developed and validated in our laboratory. This program contains NIH Image software, a public domain image processing and analysis program (developed at the Research Services Branch [RSB] of the National Institute of Mental Health [NIMH], part of the National Institutes of Health [NIH] in Bethesda, Maryland). The diameter of the lumen at the point of greatest local narrowing (minimum diameter) and nearby normal diameters were measured in millimeters, with an accuracy of 0.1 mm, with the catheter used as a scaling factor.¹⁰ The principal patient measure of disease was the sum (over the 9 proximal segments) of percent diameter stenosis (%S = $100 [1 - \text{minimum diameter/normal diameter}]$), for the worst lesion found in each segment.

Calcium scoring: A standard coronary calcium imaging protocol¹¹ was completed shortly after the baseline coronary angiogram for each of the 115 patients in this cohort. Then, 40 nonoverlapping 3-mm thick tomographic slices were acquired during a 30-second breath-hold, gated to the relatively motionless period of the cardiac cycle in late diastole. Images were analyzed at an AccuImage workstation (AccuImage Diagnostics Corporation, South San Francisco, CA). The Agatston calcium score and the calcium volume score were estimated using standard methods.^{4,11} Because the scores in these patients were heavily skewed into the 0 to 750 range, but also included scores up to 3,000, the distribution was clearly not normal, and the Spearman, nonparametric, correlation statistic was used.

Traditional Framingham risk factors: Noninvasive risk factors, identified in epidemiologic studies as predictive of future cardiac events,¹² which have also correlated with proximal coronary stenosis,¹³ were determined at baseline. These include age, gender,

systolic blood pressure, LDL-C, HDL-C, lipoprotein(a), fibrinogen, a history of diabetes, prior myocardial infarction, smoking status (never, prior, current), and pack-years of smoking. These risk variables, where appropriate, were adjusted linearly for age as an estimate of duration of risk-factor exposure. We combined individual risk factors in each patient to obtain a composite Framingham 10-year estimate of CAD risk.¹²

Statistical methods: Independent variables were the risk factors listed above and the 2 calcium scores. Univariate Pearson correlations of these independent variables with the proximal stenosis burden were computed using a standard statistical package; in cases in which the scatterplot was nonlinear, Spearman correlations were used. A multiple linear regression analysis was performed, including all risk variables having significant ($p < 0.05$) univariate correlation with baseline disease severity, plus the most highly correlated calcium variables.

RESULTS

Univariate analysis: TRADITIONAL RISK VARIABLES: Table 1 shows the coefficients of correlation and their statistical significance, in univariate association with proximal stenosis burden. Of the Framingham variables, smoking status, prior myocardial infarction, body mass index, pack-years, age, and lipoprotein (a) were the significant correlates. With linear age adjustment, all correlations improved, and systolic blood pressure, total cholesterol, LDL-C/HDL-C, and fibrinogen then became significant.

CALCIUM SCORES: Table 1 shows the correlation coefficients and their significance level for the 2 calcium scores. The Spearman correlation coefficients, $R = 0.62$ for Agatston score and 0.63 for the calcium volume score, are virtually identical and account for approximately 40% of the observed variance in measured proximal coronary stenosis burden. This relation is illustrated in Figure 1.

Multiple regression analysis: The variables showing significant univariate correlations with proximal stenosis burden were entered into a multiple linear regression model. The results of this analysis show that the dominant correlate ($p < 0.0001$) of proximal stenosis burden is the transformed calcium score (Agatston and calcium volume are virtually equivalent); however, body mass index and history of myocardial infarction also make independent and significant ($p = 0.007$ and $p = 0.01$, respectively) contributions to prediction of obstructive disease burden. Overall R^2 is 0.45 ; without the calcium score in the above model, R^2 is 0.10 .

DISCUSSION

This analysis shows that the Agatston and calcium volume score are equivalent in their relatively high correlation with proximal stenosis burden. These scores provide a method that is far superior to the assessment of traditional Framingham risk factors for prediction of this quantitative estimate of the severity of distributed obstructive disease. The multiple regres-

TABLE 1 Spearman Nonparametric Correlations, at Baseline, of Traditional Framingham Risk Variables and of Ca^{++} Scores with Measured Proximal Coronary Stenosis Burden

Risk Variable	Mean Value (\pm SD)	Correlation with Σ %Sprox*	
		ρ	p Value
Framingham (n = 146)			
Age (yr)	53.3	0.17	0.04
Sex (0, 1)	13% F	0.11	0.19
MI history (0, 1)	55% MI	0.24	0.004
Framingham risk [†]	13.2% (7.2)	0.22	0.001
Smoking history (0, 1)	71% smokers	0.31	0.001
Pack-years smoking	21.3 (\pm 21.8)	0.20	0.05
BMI	29.3 (4.1)	0.23	0.005
BMI \times (age/53)		0.28	0.001
DM or IFG (0, 1)	15% DM, 10% IFG	0.04	0.6
SBP (mm Hg)	127 (14)	0.11	0.18
SBP \times (age/53)		0.18	0.03
TC	197 (32)	0.12	0.15
TC \times (age/53)		0.22	0.008
LDL-C/HDL-C	4.0 (1.0)	0.12	0.17
LDL-C/HDL-C \times (age/53)		0.20	0.02
Lp(a) (mg/dL)	27 (33)	0.17	0.04
Lp(a) \times (age/53)		0.18	0.03
Fibrinogen	363 (85)	0.12	0.17
Fibrinogen \times (age/53)		0.19	0.03
EBT coronary Ca^{++} scores (n = 115)			
Agatston score	471	0.62 [‡]	<0.0001
Ca^{++} volume score	420	0.63 [‡]	<0.0001

BMI = body mass index; DM = diabetes mellitus; EBT = electron-beam tomography; F = female; HDLC = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MI = myocardial infarction; SBP = systolic blood pressure; TC = total cholesterol.

* Σ %Sprox is the sum, per patient, of measured percent stenosis values for the worst lesion found in each of 9 standard proximal coronary segments.

[†]Ten-year risk of death or nonfatal MI in an asymptomatic population, based on composite of multiple traditional risk factors. Because of established coronary artery disease, this cohort has experienced a roughly 4% per year incidence of these events.

[‡]Because of skewed distributions, nonparametric Spearman correlations were performed.

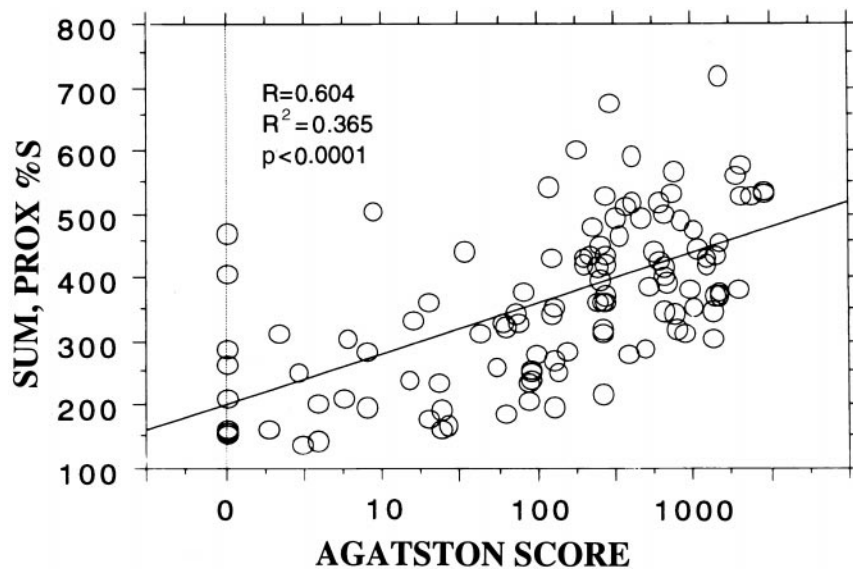


FIGURE 1. Coronary Ca^{++} : Electron beam tomography (EBT). Relation between the Agatston score and the proximal stenosis burden (SUM, PROX %S), as defined in the text and in Table 1. The Pearson correlation (R) is 0.604; the Spearman (nonparametric) correlation (R) is 0.620. The \log_{10} transform of the Agatston score provides a more nearly normal distribution for statistical analysis.

sion model explains 45% of the observed variability in proximal stenosis burden; if the contribution from calcium score is omitted, only 10% is explained. A similar study with 290 subjects, using visual coronary assessment, came to comparable conclusions.¹⁴

The above may, in part, be true because the angiographic estimate of stenosis and the calcium score reflect present conditions, whereas the current lipid, lipoprotein, and other risk variables may not reflect their mean lifelong exposure levels. The improvement in prediction of proximal stenosis burden by these risk factors, when age-adjusted, supports this concept.

CONCLUSION

We conclude that EBT-estimated coronary calcium provides a superior method for predicting overall proximal disease severity when compared with traditional Framingham risk assessments. This is the first use of a quantitative assessment of coronary stenosis burden for this purpose. Because composite severity of proximal vessel disease—often expressed as number (0 to 3) of >50% stenosed vessels—is highly predictive of cardiovascular event risk,¹⁵ then the EBT calcium score should prove superior to the Framingham risk variables in prediction of event risk. Indeed, this has been the case in several studies,^{3,4} although not all.⁵

Acknowledgment: The encouragement and assistance of David King in completing the calcium studies is greatly appreciated. We thank Heather Bruggman for preparation of the manuscript.

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