



Assessing Level of Agreement for Atherosclerotic Cardiovascular Disease Risk Categorization Between Coronary Artery Calcium Score and the American College of Cardiology/American Heart Association Cardiovascular Prevention Guidelines and the Potential Impact on Treatment Recommendations

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The 2013 American College of Cardiology/American Heart Association cardiovascular prevention guidelines use a new pooled cohort equation (PCE) to predict 10-year risk of atherosclerotic cardiovascular disease (ASCVD) events which form the basis of treatment recommendations. Coronary artery calcium score (CACs) has been proposed as a means to assess atherosclerotic risk. We sought to study the level of agreement in predicted ASCVD risk by CACS and PCE-calculated models and the potential impact on therapy of additional CACS testing. We studied 687 treatment naive, consecutive patients (mean age 53.5 years, 72% men) who had a CACS study at our institution. Clinical and imaging data were recorded. ASCVD risk was calculated using the published PCE-based algorithm. CACS-based risk was categorized by previously published recommendations. Risk stratification comparisons were made and level of agreement calculated. In the cohort, mean ASCVD PCE-calculated risk was $5.3 \pm 5.2\%$ and mean CACS was 80 ± 302 Agatston units (AU). Of the intermediate PCE-calculated risk (5% to <7.5%) cohort, 85% had CACS <100 AU. Of the cohort categorized as reasonable to treat per the ASCVD prevention guidelines, 40% had a CACS of 0 AU and an additional 44% had CACS >0 but <100 AU. The level of agreement between the new PCE model of ASCVD risk and demonstrable coronary artery calcium is low. CACS testing may be most beneficial in those with an intermediate risk of ASCVD (PCE-calculated risk of 5% to <7.5%) where, in approximately half of patients, CACS testing significantly refined risk assessment primarily into a very low-risk category. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;118:1480–1485)

Atherosclerotic cardiovascular disease (ASCVD) remains among the leading cause of death worldwide.¹ The American College of Cardiology (ACC)/American Heart Association (AHA) recently published updated guidelines on preventing ASCVD using a new multivariable risk equation to predict the 10-year risk for developing ASCVD in African-American and white men and women aged from 40 to 79 years.² The benefits of statin therapy in preventing ASCVD are well established, especially in secondary prevention.³ However, selection of patients who may benefit from therapy for primary prevention of ASCVD is more challenging.⁴ Since publication of the new guidelines, there has been considerable debate as whether the new pooled

cohort equation (PCE)—derived risk assessment accurately predicts the risk for ASCVD, therefore potentially recommending medications to patients in whom the benefit may not be as robust.^{5–7} The correlation and predictive value between coronary artery calcium score (CACs) and overall atherosclerotic burden has been well described.^{8–12} The updated ASCVD prevention guidelines noted that assessing coronary artery calcium (CAC) was most likely to be useful in improving risk assessment compared with other measures of subclinical cardiovascular disease,² particularly if a risk-based treatment decision is uncertain.¹³ In this study, we sought to (1) evaluate the level of agreement in predicted ASCVD risk by CAC score and PCE-calculated models and (2) examine the distribution of CAC severity within the therapy decision categories as per the new guidelines.

Methods

This is a retrospective cross-sectional study of a cohort of patients who had CAC scoring at the Cleveland Clinic Foundation between 2003 and 2011. The cohort was identified through an interrogation of the imaging data system, and data were collected through a retrospective chart review. The electronic medical records were reviewed to ascertain

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Table 1
Baseline characteristics

Variable	Females (N = 193)		Males (N = 494)		Total (N = 687)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	54.4	7.8	53.2	7.6	53.5	7.7
Body Mass Index (kg/m ²)	25.4	4.8	28.1	4.2	27.3	4.5
Waist circumference (cm)	80.5	13.1	92.7	9.9	90.1	11.7
Systolic Blood Pressure (mmHg)	121.1	17.1	127.0	14.2	125.3	15.3
Total Cholesterol	217.1	35.7	204.2	35.9	207.8	36.3
High Density Lipoprotein- cholesterol (mg/dl)	73.4	19.0	54.2	14.9	59.6	18.3
Low Density Lipoprotein- cholesterol (mg/dl)	123.3	33.3	125.6	32.7	124.9	32.9
Triglycerides (mg/dl)	97.6	53.8	139.3	378.8	127.6	322.9
Pooled risk score (%)	2.9	3.5	6.3	5.4	5.3	5.2
Coronary Artery Calcium score	30.2	124.2	99.2	346.1	79.8	302.2
	Count	%	Count	%	Count	%
Hypertension	28	14.5%	85	17.2%	113	16.4%
Current Smoker	24	12.4%	40	8.1%	64	9.3%
Family History of Premature Coronary Artery Disease	33	17.1%	79	16.0%	112	16.3%
Pooled Risk Score						
<5%	167	86.5%	273	55.3%	440	64.0%
5%-7.49%	10	5.2%	81	16.4%	91	13.2%
≥7.5%	16	8.3%	140	28.3%	156	22.7%
Coronary Artery Calcium score						
0	137	71.0%	211	42.7%	348	50.7%
0.01-99	44	22.8%	191	38.7%	235	34.2%
100-299	6	3.1%	53	10.7%	59	8.6%
≥300	6	3.1%	39	7.9%	45	6.6%

their co-morbidities, lipid profile results, blood pressure, and lifestyle habits including smoking at the time of CAC testing. In an effort to model the population from which the PCE are derived and applied, we opted to exclude patients with a known history of ASCVD, type 2 diabetes mellitus, age 40 years or less, age greater than 75 years, and patients who were not African-American or white.² Furthermore, we excluded all patients on lipid-lowering therapy. This study was approved by the Institutional Review Board at the Cleveland Clinic Foundation.

Imaging was performed on a variety of scanner models over time, including standard 16-, 40-, and 64-slice scanners, dual-source scanners, and extended range single-source scanners from different vendors. Images were reconstructed at 3-mm slice thickness. Per institutional protocol, radiation exposure (dose-length product and effective radiation dose) was monitored in all patients and limited to as low as reasonably achievable; whenever possible, axial mode with prospective electrocardiographic triggering using a tube voltage of 120 kVp was used, and tube current was carefully selected on the basis of patient size, which models guidelines later recommended by the Society for Cardiovascular Computed Tomography.¹⁴ Scan length was limited to coverage of the heart only. Quantitative CAC scores were calculated using the method proposed by Agatston et al.¹⁵ If more than one CAC measurement was available for a participant during the study period, the initial measurement was used.

The 10-year risk for an ASCVD event was calculated using the published formula generated by the PCE set by the

2013 AHA/ACC Cardiovascular Risk Assessment guidelines.² These guidelines categorize patients into low (10-year ASCVD risk <5%), intermediate (10-year ASCVD risk <5% but <7.5%), and high (10-year ASCVD risk ≥7.5%) risk categories. The treatment algorithm to determine the need and type of treatment for ASCVD was based on these guidelines, which use the risk assessment as determined by the PCE.¹³ In summary, adults aged ≥21 years with a low-density lipoprotein-C (LDL-C) ≥190 mg/dl and adults with diabetes between the ages of 40 to 75 years should be treated with a high-intensity statin unless contraindicated (treatment category 1 [T1]); adults aged 40 to 75 years with an LDL-C of 70 to 189 mg/dl without clinical ASCVD or diabetes and an estimated 10-year ASVD risk ≥7.5% should also be treated with a moderate- or high-intensity statin (treatment category 2 [T2]); for adults aged 40 to 75 years with an LDL-C of 70 to 189 mg/dl without clinical ASCVD or diabetes and an estimated 10-year ASVD risk between 5% and 7.5%, it is reasonable to treat consider treatment with a moderate-intensity statin (treatment category 3 [T3]) and finally, for adults aged 40 to 75 years with an LDL-C of 70 to 189 mg/dl without clinical ASCVD or diabetes and an estimated 10-year ASVD risk <5%, routine statin treatment is not recommend unless supported by other factors (treatment not necessary [T4]).

The cohort was also categorized based on their CAC score, subjects were categorized into the following strata: low (0 or <100 Agatston units [AU]), intermediate (100 to 299 AU), and high (≥300 AU). The use of these cutpoints for categorization were based from the 2013 ACC/AHA

Table 2

Level of agreement between pooled cohort equations (PCEs) calculated risk and coronary artery calcium score (CACS) categories. Kappa = 0.23 ± 0.029

	PCE-calculated Risk Category			Total
	< 5%	5%-7.49%	≥7.5%	
Coronary Artery Calcium Score (CACS)				
0-99 AU				
Count	416	77	90	583
% within CACS category	71.4 %	13.2 %	15.4 %	100 %
% within PCE-risk category	94.5 %	84.6 %	57.7 %	84.9 %
100-299 AU				
Count	19	9	31	59
% within CACS category	32.2 %	15.3 %	52.5 %	100 %
% within PCE-risk category	4.3 %	9.9 %	19.9 %	8.6 %
≥ 300 AU				
Count	5	5	35	45
% within CACS category	11.1 %	11.1 %	77.8 %	100 %
% within PCE-risk category	1.1 %	5.5 %	22.4 %	6.6 %
Total				
Count	440	91	156	687
% within CACS category	64.0 %	13.2 %	22.7 %	100 %
% within PCE-risk category	100 %	100 %	100 %	100 %

cardiovascular risk guideline document which outlined the expert opinion thresholds for use of CACS when risk-based decisions regarding initiation of pharmacologic therapy are uncertain.² A CACS score of 300 AU or higher or ≥75th percentile or higher for age, gender, and ethnicity is considered high risk and supportive for initiation of statin therapy if additional factors need to be considered. The cutpoints within the guidelines are largely based on the published results of the South Bay Heart Watch study and the subsequent Multi-Ethnic Study of Atherosclerosis (MESA), which suggested that coronary calcium predicted coronary heart disease in a multiethnic American cohort.^{16,17} In the MESA study, in comparison to a CAC score of 0, those with a CAC score between 101 and 300 had an increased adjusted risk of a coronary event by a factor of 7.73 and those who had a CAC score >300 had an increased risk by a factor of 9.67.¹⁶

Continuous and categorical variables were described as means ± SD or counts and percentages, respectively. Cross tabulation of risk categories based on the PCE and CAC absolute values were performed to describe the number and percentage of subjects who were classified into potential treatment arms appropriately and potential implications on treatment. Comparisons between groups were done using the independent *t* test for continuous variables and chi-square test or Fisher's exact test, as applicable, for categorical ones. Agreement between the different risk scoring systems was calculated based on Cohen's Kappa coefficients. A value between 0.01 and 0.2 represents slight agreement, and a value between 0.21 and 0.4 represents fair agreement.¹⁸ Analyses were performed using SPSS, version 20.0 (IBM, Armonk, New York). *p* Value ≤0.05 was used to indicate significance of tests.

Results

A total of 687 patients eligible for the study were included in the analysis. The population was almost exclusively white

with only 12 black patients (1.7%). Table 1 presents the characteristics of our study cohort. Among our study population, 72% were men and the average age was 53.5 ± 7.7 years. The average CAC score was 79.8 ± 302 AU with men on average having a higher calcium score compared with women. The average 10-year risk for an ASCVD event as calculated by the ACC/AHA PCEs was 5.3 ± 5.2%. Sixty-four percent of the cohort was categorized as low risk (<5%) for 10-year ASCVD risk; 86.5% of women within the cohort compared with 55.3% of men. Conversely, 22.7% of subjects had high 10-year ASCVD risk as calculated by the ACC/AHA equations; again, a higher percentage of men than women in the cohort were considered having high predicted 10-year risk (28.3% vs 8.3%).

In terms of risk categorization, the overall agreement between the PCE-calculated risk and CACS-based categories showed a Kappa = 0.23 ± 0.029 indicating a low level of agreement (Table 2). Of the low-risk category by the PCE model, only 1.1% had CACS ≥300 (5 patients); the majority (94.5%) of low risk by PCE patients had CACS <100. Conversely, 57.7% of patients categorized as high risk by the PCE risk model had CACS between 0 and 99 (90 patients), whereas 22.4% of high-risk patients by PCE had CACS ≥300. Overall, although 65.6% of patients (451 patients) had concordant level of risk by the PCE model and CACS, 13.8% of patients (95 in total) had significant disagreement in level of predicted ASCVD risk between the PCE model and CACS (defined as being in the highest risk group by one risk assessment while being in the lowest risk group by the alternative risk assessment).

The distribution of CAC score categories within the treatment categories recommended by the guidelines is detailed in Figure 1. Among those within T1 (high-intensity statin therapy), 38.1% (8 patients) had a CAC score of 0. While among those within T2 (moderate-to-high intensity statin therapy), 15.6% (23 of 147 patients) had a CACS of 0, compared with 40.2% (33 of 82 patients) within the T3 (reasonable to treat) category who had a CACS of 0.

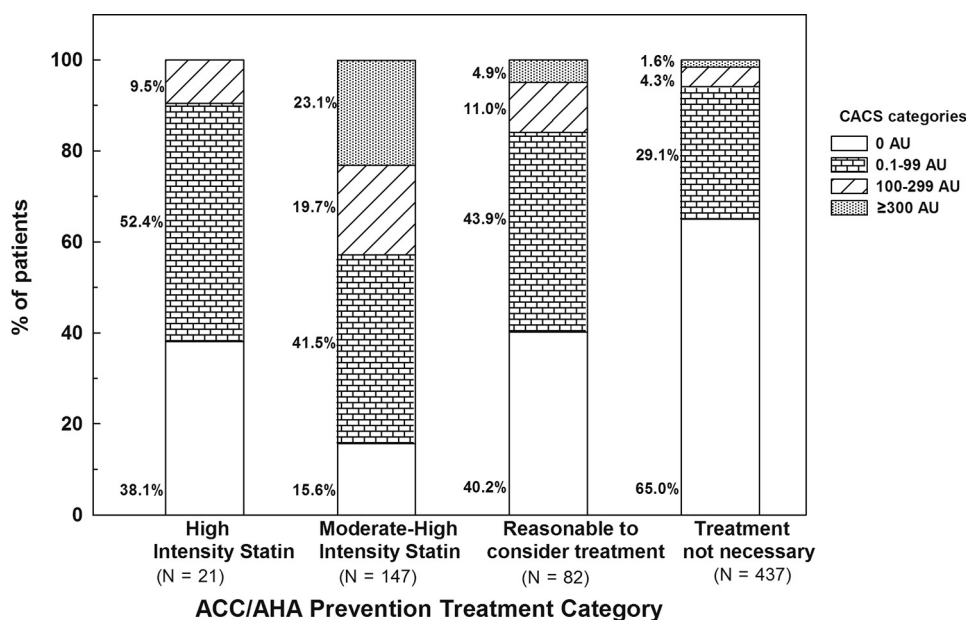


Figure 1. Coronary artery calcium and the American College of Cardiology/American Heart Association cardiovascular prevention treatment categories.

Although Figure 1 may suggest a U wave phenomenon with the highest percentage of the population with low CAC scores (0 and 0.1 to 99) in the T1 and T4 groups, we do not feel any definitive conclusion can be drawn from this due to the relatively low numbers in the T1 group. However, it is notable that in most of the patients in the T1 category who had a CACS of 0, the indication to treat was primarily driven by an LDL >190 mg/dl; these patients may be at an earlier stage of coronary atherosclerosis as evidenced by their median PCE risk score that was 3.9%.

In the total cohort, 9.3% (64 of 687 patients) who had a zero CAC score would be offered ASCVD-related therapy under the current guidelines; conversely, 3.7% (26 patients) who would not be offered ASCVD-related therapy by the guidelines had CACS \geq 100 AU.

Discussion

In this study, we found that the level of agreement between risk as calculated by the PCE and CACS was low in treatment naive patients. Within the “reasonable to treat” category, 40.2% of patients have a CAC score of 0 and 4.9% had CAC score \geq 300. This suggests that \sim 45% of subjects within this category may benefit from coronary calcium testing to clarify their risk for a significant cardiovascular event and whether they may benefit from cholesterol-lowering therapy.

CAC is a well-established surrogate for coronary atherosclerosis.¹⁹ Although there is certainly noncalcified plaque within the coronary tree, CAC has been shown in autopsy studies to correlate to overall coronary plaque burden and the frequency of a CAC of 0 with significant plaque is extremely uncommon.⁸ Furthermore, a large number of published studies have shown that CACS is an independent predictor for coronary heart disease,^{9–12,20} and that CACS is also able to reclassify low-to-intermediate risk

groups and certain subgroups, such as woman and younger patients, that may be classified as low risk by the Framingham Risk Score.^{17,21–23} Despite this work on reclassifying patients’ risk, the latest guidelines have limited recommending CAC testing only when a risk-based treatment decision is uncertain.^{2,19}

CAC testing may provide clinicians and patients with further evidence to justify starting or withholding therapy. It has been argued that the new risk assessment guidelines based on the PCE does not appear to lead to significantly better discrimination of cardiovascular events, especially among subgroups, than previous models and that utilization of absolute risk may result in overuse of pharmacologic agents.²⁴ Although the benefits of treatment with statins for prevention are well accepted within the scientific community and the patients at large, it is not uncommon to encounter subjects who for many reasons prefer to delay starting a long-term therapy. Our study suggests that coronary calcium scores can lead to more personalized risk assessment and preventive therapies, especially in the “reasonable to treat” category.

However, in an era with increasing scrutiny of the cost of medical imaging, concern over radiation exposure and the potential for generating further downstream testing for incidental noncardiac findings such as pulmonary nodules, recommending additional testing requires robust evidence of effectiveness. Through a cost-effectiveness analysis, Pletcher et al²⁵ showed that in the setting of low-cost, well-tolerated statins, CAC had only a limited role in asymptomatic patients. Conversely, Roberts et al²⁶ recently published their work using a Markov model showing that CAC testing was both effective and cost-saving as a risk stratification tool, especially if there are adverse effects of long-term statin use. Nasir et al suggest that CAC testing would likely have limited impact on decisions regarding statin therapy in those at the high and low end of risk. This

is supported by our data showing the largest impact on risk stratification in the “reasonable to treat” group.²⁷

Our study needs to be interpreted in the context of the recently published review of the MESA study.²⁷ Nasir et al evaluated the implications of a zero CACS in reclassifying patients into different treatment categories according to the current treatment guidelines in a similar study to our own. There are important similarities between the 2 studies: there was a similar proportion of patients with a zero CACS (58% vs 51% in our study) and an almost equivalent proportion of patients with a CACS of >0 (21% vs 22%) and >100 (4% in both studies) in whom treatment was not recommended. However, there are some significant differences between the 2 studies. Most notably, in our study, only 4.5% of patients had a CACS of 0 in whom moderate- or high-dose statin therapy was recommended versus 41% of patients in the MESA study. In our population, 41% of the total population had no coronary calcium and treatment was deemed not necessary compared with only 30% in the MESA trial. Therefore, there was less disparity between CACS and the current recommendations for statin therapy in our study compared with the MESA study. These findings are possibly explained by differences in the studied populations: the MESA cohort was older (59 vs 54 years in our study), had higher proportion of risk factors for coronary artery disease (CAD) including hypertension (41% vs 16%), diabetes (10%, excluded from our analysis), smoking (14% vs 9%) and a family history of CAD (38% vs 16%), and had differences in their lipid profiles including LDL (123 vs 125 mg/dl in our study), high-density lipoprotein (51 vs 60 mg/dl), and triglycerides (125 vs 128 mg/dl). The most important difference, however, may be racial. Our study included almost exclusively white patients while the MESA study, by its very design, had a wide racial mix with only 37.5% whites. Previous work from the MESA population has shown that whites tend to have more CAC than blacks, hispanics, and Asians even after adjusting for multiple potential confounding factors.²⁸ This comparison suggests that race needs to be considered when comparing risk models; further studies are required to clarify this interaction.

This study has limitations that should be acknowledged. The results should be interpreted in the context of being a retrospective study at a single tertiary care center and thus is not free from selection bias. Furthermore, the study is limited by additional referral bias for CAC testing in patients with a low-to-intermediate risk pretest probability for CAD. Since we only selected patients who modeled the demographics used by the PCE cohort, the results may not be generalizable to other populations, which is also a limitation of the PCE-calculated risk model. Given the lack of outcomes data for our patient population, we are unable to examine the natural history of CACS or PCE-derived risk calculations in this present study, thus the true ASCVD risk. Another potential limitation in our study may be CACS measurement variability; however, earlier studies have shown that there was low interscan and interobserver variability in CACS.²⁹

Disclosures

The authors have no conflicts of interest to disclose.

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