Coronary Artery Calcium Scoring

Sanjay Mehra, MD, Hossein Movahed, MD, Assad Movahed, MD

Department of Cardiovascular Sciences, East Carolina University Brody School of Medicine, Greenville, NC

Numerous clinical studies have shown that coronary artery calcium scoring provides substantial incremental risk prediction beyond conventional coronary risk factors for coronary heart disease events. About half of all patients with coronary artery disease (CAD) present initially with unexpected myocardial infarction or sudden death. Early identification of this subgroup of patients is vital for institution of intensive, early preventive measures to decrease morbidity and mortality due to CAD.
[Rev Cardiovasc Med. *2011;12(2):e94-e103 doi: 10.3909/ricm0566*]

Key words: Coronary artery calcium score • Coronary artery disease • Risk stratification • Metabolic syndrome • Multidetector computed tomography

Coronary artery disease (CAD) is the leading cause of mortality in both men and women in the United States. According to estimates, the annual incidence for a first myocardial infarction (MI) is 610,000 and for recurrent MI is 325,000. In 2006, one of every six deaths in the United States was attributed to coronary heart disease (CHD). The National Ambulatory Medical Survey data show that patients with a primary diagnosis of CHD comprised approximately 79.7 million visits to physician offices, emergency departments, and outpatient clinics. By American Heart Association computation, inpatient cardiovascular procedures and surgeries have increased by 33% from 1996 to 2006. The estimated direct and indirect cost of CHD for 2010 is $177.1 billion.[1] Due to the enormous economic burden, in addition to the morbidity and mortality associated with CAD, various studies have been undertaken to identify a diagnostic test that could risk stratify patients for the presence or absence of CAD, especially in those who are at intermediate to high risk according to other

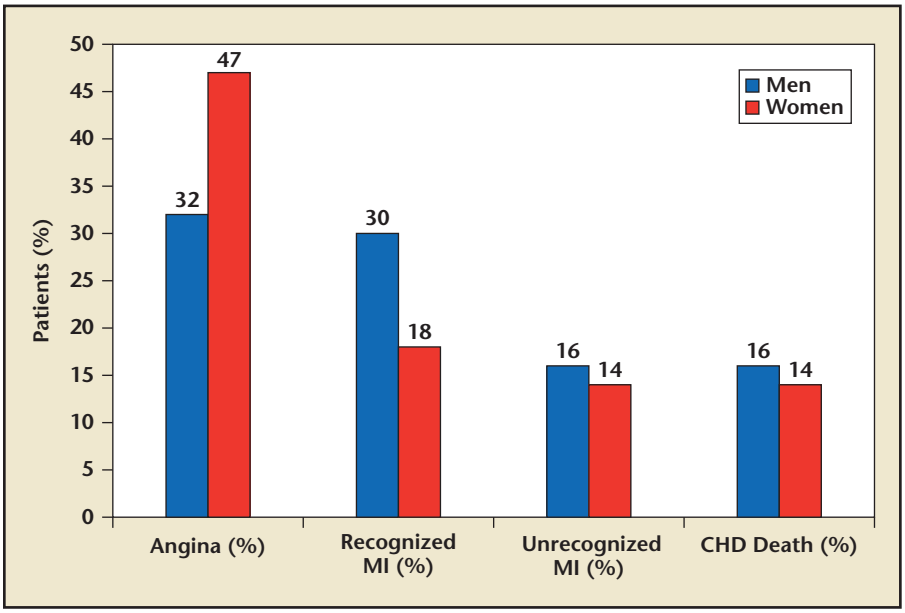


Figure 1. *Initial presentation in patients diagnosed with CHD. CHD, coronary heart disease; MI, myocardial infarction. Adapted with permission from Murabito JM et al.*[42]

scales, such as the Framingham Risk Assessment score (FRS). Approximately 50% of patients with clinical CAD present initially with an unexpected MI or sudden death (Figure 1). Identifying this group of asymptomatic patients is critical because intensive preventive interventions in such patients might avert sudden and unexpected outcomes of CAD.[2-4]

Coronary Artery Calcium Measurement

Recent studies have recommended coronary artery calcium (CAC) measurement as a noninvasive test to risk stratify asymptomatic patients into low-, intermediate-, or high-risk groups. Absence of CAC has been found to be associated with a very low risk of future cardiovascular events in symptomatic as well as asymptomatic individuals.[5,6] Numerous trials have shown the value of calcium scoring over traditional risk factor assessment. The intermediate-risk group identified by various traditional risk assessment models constitutes a dilemma to physicians and the presence of a high coronary calcium score in this group necessarily alters clinical decision making in favor of more aggressive risk modification.

A normal coronary artery should have no calcifications. The correlation of CAC and the presence of atherosclerosis has been demonstrated by various histopathologic studies. There also appears to be a modest relationship between the extent of coronary artery calcification and the severity of luminal stenosis.[7-11]

Numerous studies have shown plaque burden to be a better determinant of future coronary events. Myocardial perfusion scintigraphy (MPS) and stress echocardiography are invaluable in diagnosis of obstructive coronary disease, but cannot be used to estimate total plaque burden. Noncontrast cardiac computed tomography (CT) imaging serves as an anatomic, noninvasive test to visualize presence of calcified plaque.[12-14] Contrast multislice cardiac CT angiography can detect calcified plaques, noncalcified plaques, and mixed plaques.

Numerous trials have shown the value of calcium scoring over traditional risk factor assessment.

CAC Versus Traditional Risk Factor Assessment

The St. Francis Heart Study attempted to determine the prognostic accuracy of electron beam tomography (EBT) scanning of the coronary arteries, and the relationship of coronary calcification to standard coronary disease risk factors and C-reactive protein, in predicting atherosclerotic cardiovascular disease (ASCVD) events in apparently healthy middle-aged subjects. The study involved EBT scanning of 4903 asymptomatic individuals aged 50 to 70 years who were then followed for ASCVD events. The relative risk for ASCVD events was 9.6 (95% confidence interval [CI], 6.7-13.7) among individuals with a CAC threshold $\geq$ 100 compared with individuals with a CAC threshold $<$ 100. CAC score (CACS) was found to be superior in predicting ASCVD events and actually predicted CAD events independently of standard risk factors and C-reactive protein (P = .004). CAC scoring also enhanced stratification of individuals falling into the Framingham categories of low, intermediate, and high risk ($P < .0001$).[15]

Polonsky and colleagues[16] demonstrated that inclusion of CACS in a predictive model based on traditional risk factors significantly improved the prediction of future CHD events. Participants from the Multi-Ethnic Study of Atherosclerosis (MESA) trial were subject to two

models for risk stratification. Model 1 was based on traditional risk factors including age, sex, tobacco use, systolic blood pressure, use of antihypertensive medications, total and high-density lipoprotein cholesterol, and race/ethnicity. Model 2 included CACS along with these risk factors. Using model 1 the area under the receiver operating characteristic curve for prediction of CHD events was 0.76 (95% CI, 0.72-0.79) and this increased to 0.81 (95% CI, 0.78-0.84; $P < .001$) using model 2. A total of 69% of the study population was classified into either highest- or lowest-risk categories using traditional risk factors, which increased to 77% when including CACS. This resulted in an additional 23% of those who experienced events to be reclassified as high risk, and an additional 13% of those who did not have events were reclassified as low risk.[16]

Sarwar and associates[6] reviewed more than 85,000 subjects participating in 49 studies to study the diagnostic and prognostic value of the absence of CAC in symptomatic and asymptomatic patients. In the asymptomatic group, the incidence of adverse cardiovascular events was 0.47% in more than 29,000 subjects with a CAC = 0 and 4.14% in subjects with CAC > 0. In the symptomatic group 1.8% of the subjects with CAC = 0 had a cardiovascular event in contrast to 8.99% of subjects with CAC > 0. The authors also reviewed 18 studies to compare the diagnostic potential of CACS with invasive coronary angiography (ICA). Results showed a sensitivity of 98% and specificity of 40%, with a negative predictive value of 93% for detection of significant CAD.[6]

CAC Versus ICA

ICA has been regarded as the gold standard for the diagnosis of CAD. It is estimated that approximately 1.5 million diagnostic ICAs are performed annually in the United States; 25% to 40% of individuals referred for elective ICA are found to have no significant coronary artery lesions. According to the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project estimates, mean hospital charges for a diagnostic coronary catheterization are $31,181, with an in-hospital death rate of 0.79%.[17-19] CAC scoring compares favorably with ICA as it is a rapid and simple method that requires no patient preparation, involves lower radiation exposure as compared with ICA and MPS, is reproducible, and requires no iodine contrast. According to the American Association of Physicists in Medicine Task Group 23 report, typical radiation exposure during CAC CT is 1 to 3 mSv, compared with 5 to 10 mSv during a diagnostic coronary angiogram, and 35 to 40 mSv during a ^{201}Tl myocardial perfusion scan.[20]

CAC scoring compares favorably with ICA as it is a rapid and simple method that requires no patient preparation, involves lower radiation exposure as compared with ICA and MPS, is reproducible, and requires no iodine contrast.

CACS Versus MPS

Rozanski and colleagues[21] assessed the frequency of cardiac death and MI over a mean follow-up of 32 ± 16 months in 1153 patients undergoing both CAC scanning and MPS. The frequency of myocardial ischemia rose with increasing CACS ($P < .001$).

Chang and associates[22] sought to study the relationship between CACS and single-photon emission computed tomography (SPECT) results in predicting cardiac events. A total of 1126 asymptomatic subjects with no known cardiovascular disease (CVD) underwent CACS determination by EBT and stress SPECT imaging within a median of 56 days. Primary events were cardiac death, nonfatal MI, and coronary revascularization with bypass surgery or percutaneous approach. Secondary events included events of all-cause mortality and nonfatal MI. Median follow-up was 6.9 years. FRS was found to be low in 16.2%, intermediate in 77.9%, and high in 5.9% of patients. Abnormal SPECT results were observed in 13% of subjects, out of whom 14% had a fixed defect, 62% had a partially reversible defect, and 24% had a completely reversible defect. Figures 2 and 3 show the observed relationship between traditional risk factor scoring (FRS) with CACS severity and SPECT results in the study population.

It was observed that out of 83.2% of subjects with a normal SPECT scan, 78.3% were in the intermediate risk category, and 4.9% were in the high-risk category per FRS. Also observed was that the prevalence of abnormal SPECT increased with increasing CACS ($P < .001$). Subjects with a CACS ≤ 100 had less than 2% prevalence of abnormal SPECT and this prevalence increased to 9.8% in those with a CACS between 101 and 400, and to 31% in those with a CACS > 400 ($P < .001$). Similarly, prevalence of early revascularization procedures in study subjects increased with increasing CACS, with a prevalence of 0% in those with a CACS ≤ 100 to a prevalence of 3% in subjects with a CACS > 400.

Increasing CACS and the presence and extent of abnormal SPECT scans represent an increased risk of total cardiac events and all-cause death/MI. The total and all-cause death/MI event rates were low, at < 1% and < 0.5%, respectively, in subjects with a

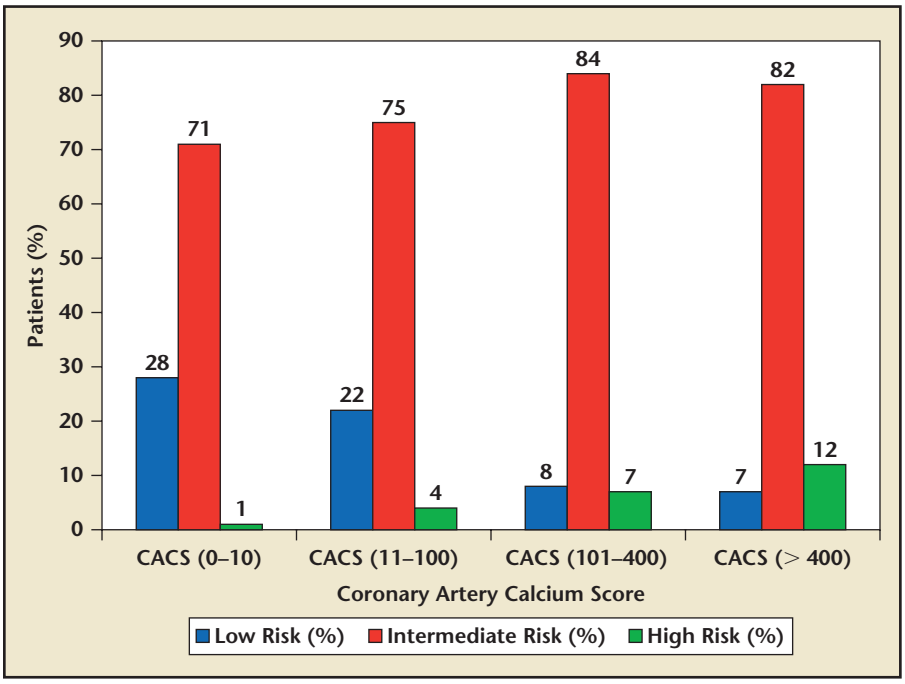
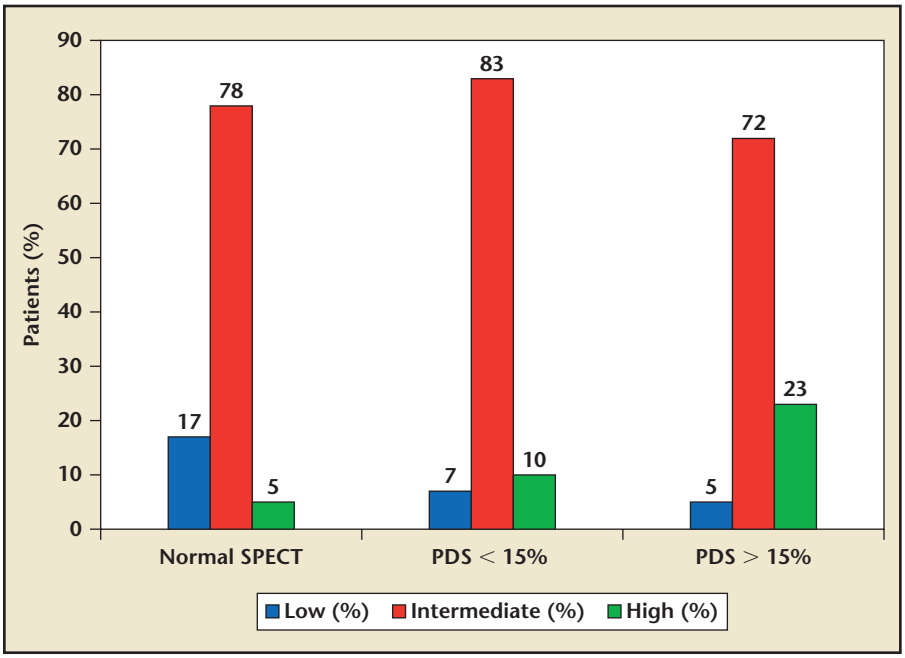


Figure 2. *Relationship between Framingham risk score (low, intermediate, and high) and coronary artery calcium score (CACS) severity. Adapted with permission from Chang SM et al.*[22]

Figure 3. *Relationship between Framingham risk score (low, intermediate, and high) and SPECT results. PDS, perfusion defect size; SPECT, single-photon emission computed tomography. Adapted with permission from Chang SM et al.*[22]



normal SPECT scan. However, even in these subjects, total cardiac and all-cause death/MI event rates increased significantly with increased CACS, with an annualized total cardiac event rate of 1.3% in those with a CACS of 101 to 400 and 2.97% in patients with a CACS $\geq$ 400. The annualized all-cause death/MI rates were 1.25% in subjects with normal SPECT scans and a CACS between 101 and 400, and 2.05% in those with a CACS $\geq$ 400.[22]

Racial Differences in CAC and Coronary Events

Sirineni and colleagues[23] used data from the MESA trial to predict the coronary age of individuals from four different ethnic groups: white, black, Hispanic, and Chinese. Analysis revealed the calculated 50th CACS percentile was highest for white patients of both sexes, with white males having the highest scores among all groups studied. Chinese subjects had the lowest CACS in both sexes and also overall.[23] Another study by Doherty and coworkers[24] enrolled 1375 asymptomatic but high-risk individuals based on risk factor analysis and calculations using the FRS algorithm. Digital subtraction fluoroscopy was used to calculate coronary calcium in all subjects, who were then followed annually. Traditional risk factors were also assessed at the time of digital subtraction fluoroscopy. Results revealed that prevalence of coronary calcium was 59.9% in white subjects and 35.5% in black subjects ($P < .0001$); however, despite a lower prevalence of coronary calcium, a higher percentage of black subjects suffered from a CHD endpoint (CHD death, nonfatal MI, new-onset angina, or performance of a revascularization procedure) than whites during the follow-up period (Figure 4).[24]

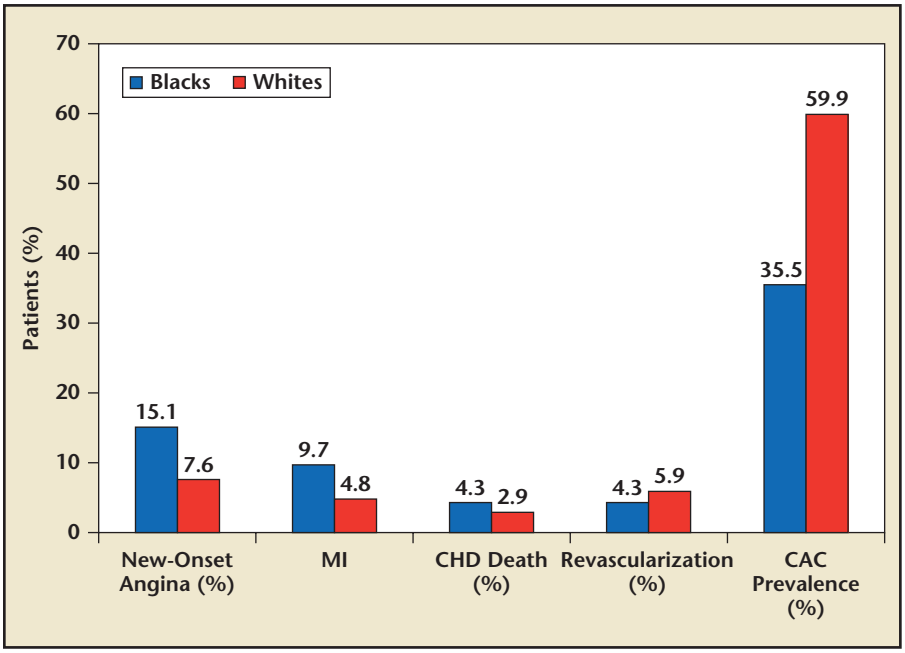


Figure 4. *Racial differences in prevalence of CAC and CHD endpoints. CAC, coronary artery calcium; CHD, coronary heart disease; MI, myocardial infarction. Adapted with permission from Doherty TM et al.*[24]

CAC in Patients With Diabetes and Patients With Metabolic Syndrome

Subjects with the metabolic syndrome (MetS) have insulin resistance, in addition to a cluster of cardiovascular risk factors, including hypertension, low high-density lipoprotein, elevated triglycerides, and obesity.[25] Diabetes is already recognized as a CAD equivalent. Subjects with MetS have also been demonstrated to have threefold greater risk for CHD and stroke and a fivefold greater risk for cardiovascular mortality.[26] Prevalence of CAC has already been shown by many studies to be sensitive in detecting clinical CAD in patients with type 1 diabetes. Wong and associates[27] enrolled 1823 subjects, of whom 15% had MetS and 8% were diabetic. Clinical characteristics were obtained followed by CAC scanning. Prevalence of CAC was highest among those with diabetes (67%), prevalence was 57% in those with MetS, and was 47% in those with neither condition ($P < .0001$).[27]

Raggi and coworkers[28] followed 10,377 asymptomatic subjects with no known CAD, who were referred for coronary calcium screening with EBT by their primary care physicians based on presence of established risk factors for atherosclerosis. Overall mortality, using Cox survival curves, was observed to be significantly greater in subjects with diabetes ($P < .0001$) than in those who were not diabetic. Also, mortality was seen to increase with rising CACS levels. Figure 5 illustrates 5-year survival in certain patient subsets who underwent EBT.[28] These studies reinforce the assumption that CAC measurement is a useful tool for risk stratification of patients with diabetes and MetS.

Prevalence of CAC has already been shown by many studies to be sensitive in detecting clinical CAD in patients with type 1 diabetes.

Taylor and associates[29] screened 1640 men between the ages of 40 and 50 years for CHD risk factors and CAC. Individuals were followed up annually by telephone and community-based initiation and persistence of aspirin and statin therapy were observed. Patients with CAC were significantly more likely to receive aspirin (53% vs 32.3%; $P < .001$) and to receive statins (48.5% vs 15.5%, $P < .001$) than those without CAC.

Progression of CAC

Min and colleagues[30] attempted to address temporal conversion of CAC and factors that might influence progression of CAC. Their study enrolled 422 patients with an initial CAC = 0, who were followed with CAC scanning annually until they reached a CAC > 0. Another cohort of 621 individuals who had at least two simultaneous CAC scans with one scan showing a CAC > 0 was also enrolled. Information about traditional CHD risk factors was collected from the study subjects. Figure 6 shows the conversion rate for subjects from CAC = 0 to CAC > 0.

Progression of CACS was observed in 80% of subjects with an initial CAC > 0 during a mean follow-up of 1.9 ± 1.1 years. The strongest independent predictor of CAC progression or conversion, in multivariate Cox regression, was found to be an initial CAC > 0 (hazard ratio, 14.96; 95% CI, 11.22-19.96; $P < .001$). Based on the study results, the conversion rate for an initial CAC scan with CAC = 0 was extremely low in the first 2 years. Another noticeable observation was that individuals with a higher baseline CACS had a higher rate of CAC increase during the follow-up period. Certain traditional CHD risk factors,

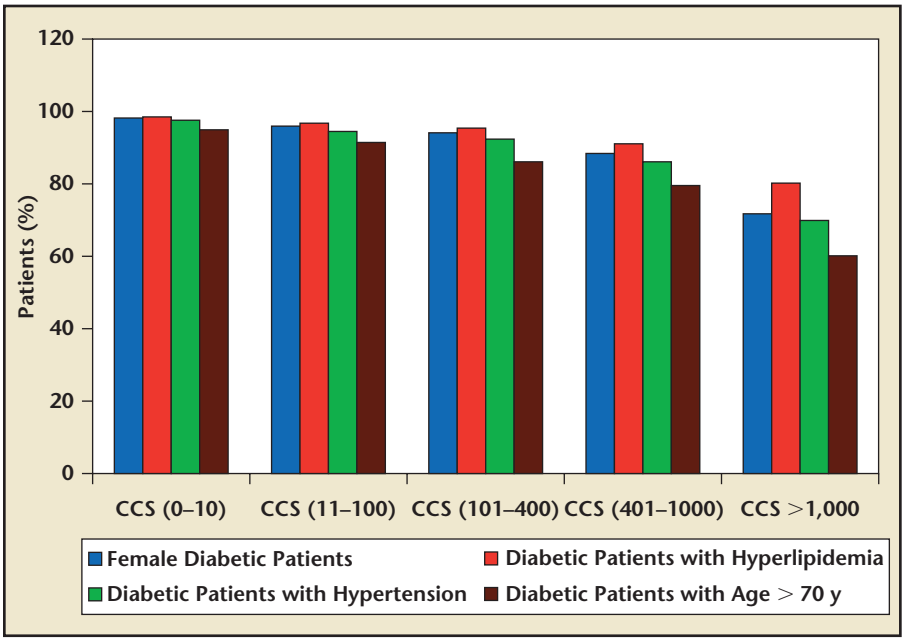
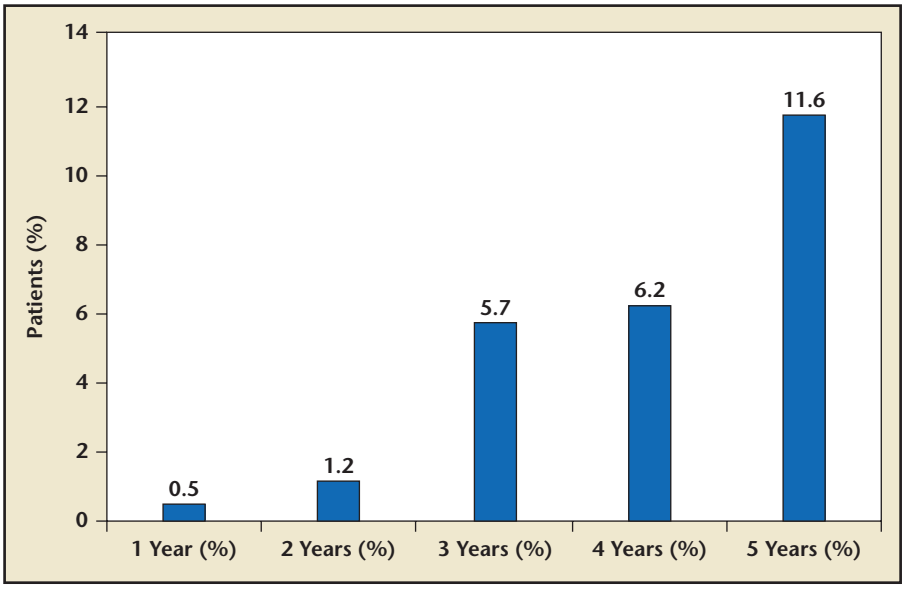


Figure 5. *Comparing Cox proportional hazards 5-year survival in subsets of diabetic patients with relation to coronary calcium scores (CCS). Adapted with permission from Raggi P et al.*[28]

Figure 6. *Percentage of subjects converting from CAC = 0 to CAC > 0. CAC, coronary artery calcium. Adapted with permission from Min JK et al.*[30]



including age ($P = .001$ for age > 50), diabetes ($P = .001$), hypertension ($P = .021$), and smoking ($P < .001$), were found to be independently associated with incident CAC conversion among patients with CAC = 0.[30]

CAC in Risk Stratification of Renal Transplant Candidates

The Chronic Renal Failure (CRF) service at Instituto do Coração (São Paulo, Brazil) studied 97 CRF patients on hemodialysis who were being considered for renal transplantation; the objective was to compare the accuracy of multidetector computed tomography in the detection of obstructive CAD and to predict major adverse cardiovascular events in this patient population as compared with invasive coronary angiography. The mean Agatston score among study group members was 580.6 ± 1102.2; 14 subjects had a CAC = 0. Subjects with significant CAD on ICA were assessed for calcium scores. Of the 14 subjects with CAC = 0, 28% had ≥ 50% stenosis on ICA and only 14% had ≥ 70% stenosis on ICA. In subjects with a CAC between 400 and 999, approximately 80% had ≥ 50% stenosis and 40% had ≥ 70% stenosis on ICA. Thus, increasing calcium score in CRF patients represents an incremental increase in obstructive CAD. The calcium score obtained were also investigated at different cutoff levels as predictive of cardiovascular events; correlation between calcium score and events among CRF patients was significant for an Agatston score of 400, thus underlining its predictive potential for major adverse cardiovascular events in this subject population. Figure 7 shows the diagnostic accuracy of calcium score in this particular study.[31]

Effect of Treatment Strategies on CAC Progression

CAC scoring is a noninvasive measure of coronary atherosclerosis and its utility has been tested in various studies to determine whether it could serve as a reliable surrogate for clinically relevant endpoints such as MI and cardiovascular death. McCullough and Chinnaiyan[32] performed a literature search and analyzed data from 10 trials to compute the weighted

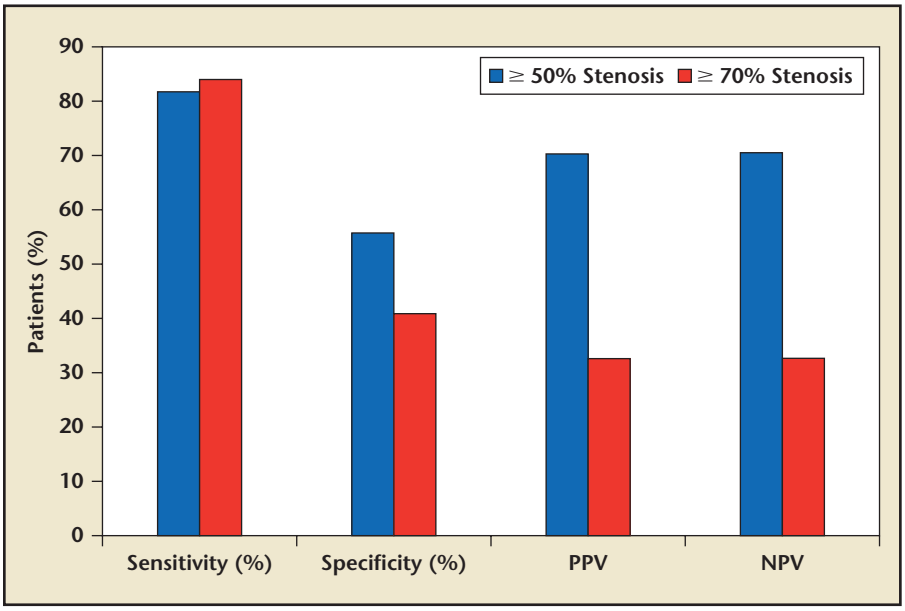


Figure 7. *Diagnostic accuracy of calcium score 75th percentile in the MESA study compared with invasive coronary angiography. MESA, Multi-Ethnic Study of Atherosclerosis; NPV, negative predictive value; PPV, positive predictive value. Adapted with permission from Rosário MA et al.*[31]

mean annualized rate of CAC progression for a variety of therapies tested in these trials. Five of the trials included subjects at risk for or with CVD and the other five were composed of subjects with chronic kidney disease (CKD). Therapies in the CVD group included statins, placebo, and antihypertensive drugs. In the CKD group, the main comparison was between sevelamer hydrochloride (a non–calcium-containing phosphate binder) and calcium-based binders.

Figure 8 illustrates the values of baseline CACS as a mean in the treatment arm of these trials, along with subsequent follow-up CACS. In some trials the annualized rate of CAC progression was reported by the respective authors and in some cases McCullough and Chinnaiyan[32] extracted the values based on the baseline and follow-up CACS and duration of follow-up. Figure 9 shows the annualized CAC progression rates in the respective trials.

Results from the CVD group showed a baseline CACS of 391.5 (range, 108.0-563.0) and the mean weighted annualized CAC increase was 16.9%. Results from the CKD group yielded a mean weighted baseline CACS of 923.0 (range, 340.0-1712.0) and the mean weighted annualized CAC increase was 18.4%. Despite a differential treatment effect on the change in CAC, this analysis failed to show any vivid and consistent effect of a specific therapy on CACS progression.[32]

Prospective studies such as the Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression trial investigators (SALTIRE), the St. Francis Heart Study, and other recent observational studies have revealed that statin therapy does not result in regression of CAC. It is believed that statins may decrease overall plaque volume due to their effect on reduction of lipid core.[33] The Coronary Artery Calcification Treatment with Zocor (CATZ) trial[34] showed a decrease in low-density lipoprotein level by 42% in the active treatment group, but interestingly revealed a progression of CACS in the statin treatment group by 9% compared with 5% in the placebo group.

Role of Cardiac CT in Asia

The pattern of disease, demographic details, and the healthcare system in Asian countries differ vastly from those of the United States. Recently a working group formed by the Asian Society of Cardiovascular Imaging (ASCI)[35] rated the clinical indications for cardiac CT with reference to clinical practice in Asia. Out of 51 indications rated on a scale of 1 to 9, 33 were found to be appropriate (score, 7-9), 14 uncertain (score, 4-6), and 4 inappropriate (score, 1-3). Notably, ASCI rated the use of calcium score in patients placed in moderate- and high-risk groups by FRS as appropriate.[35]

Role of CAC Scoring in Coronary Risk Stratification

The Heinz Nixdorf Recall Study[36] enrolled 4129 subjects without overt CAD at baseline; traditional risk factors and CACS were measured. Subjects were risk stratified based on the FRS and National Cholesterol Education Panel Audit Treatment Panel III guidelines. Subsequently, subjects were reclassified based on their CACS and followed for 5 years; 93 primary endpoints were observed among 4129 subjects—31% were coronary deaths and 69% were nonfatal MIs. Subjects in the FRS intermediate-risk group with a low CACS had an event rate of only 1.4%, which was similar to those in the low FRS category. Similarly, the FRS intermediate-risk subjects with a high CAC had an event rate of 8.7%, which was comparable with the high FRS risk category. Thus, CAC scoring helped achieve high net reclassification

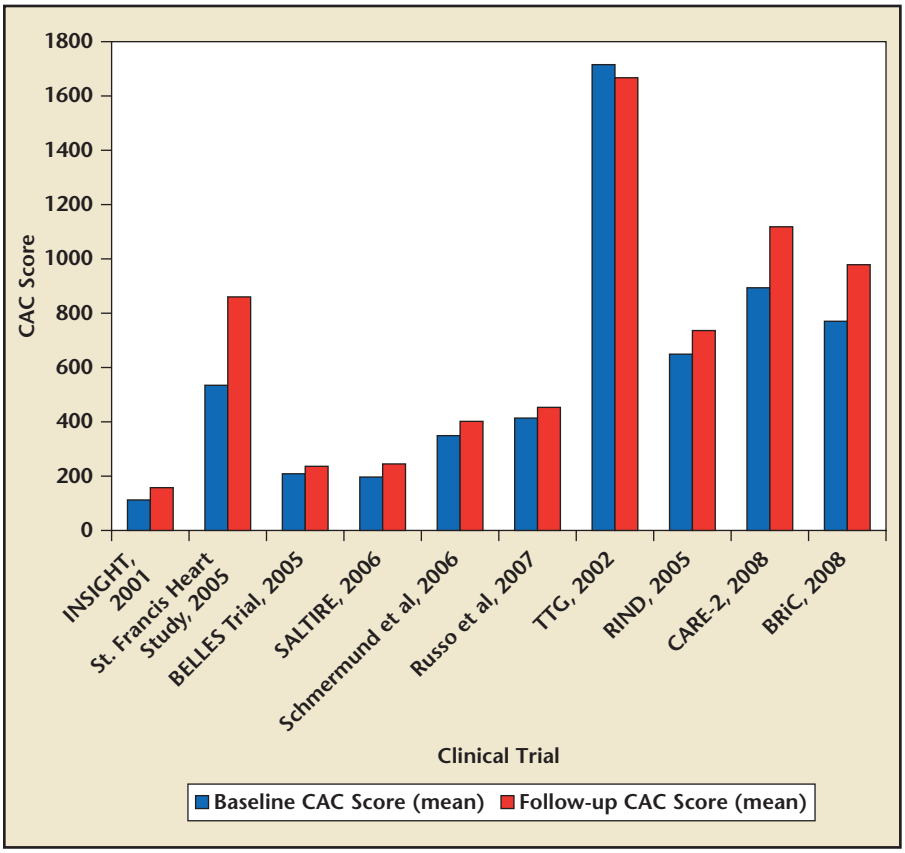


Figure 8. *Clinical trials measuring CAC score as an outcome in patients with CVD and CKD. Figures represent CAC scores in treatment arms. Trials in CVD group include INSIGHT,[43] St. Francis Heart Study,[44] BELLES Trial,[45] SALTIRE,[46] and Schmermund A et al.[47] Trials in the CKD group include Russo D et al,[48] TTG,[49] RIND,[50] CARE-2,[51] and BRiC.[52] BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning; BRiC, Bone Remodeling and Coronary Calcification; CAC, coronary artery calcium; CARE, Calcium Acetate Renagel Evaluation; CKD, chronic kidney disease; CVD, cardiovascular disease; INSIGHT, International Nifedipine Study: Intervention as Goal for Hypertension Therapy; RIND, Renagel in New Dialysis; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression; TTG, Treat to Goal Working Group. Adapted with permission from McCullough PA et al.[32]*

rates of 21.7% (and even as high as 30.6%) in subjects at intermediate risk as measured by traditional risk factors. However, caution is advised when applying CAC data to low-risk subjects because that may lead to unnecessary radiation exposure as well as an increase in cost. In the high-risk subjects with low CAC the event rates were low, but these subjects were found to be on risk-modifying therapy that could have affected the final event rate.[36]

The Rotterdam study,[37] a population-based study of subjects with a mean age of 69.6 ± 6.2 years, has endorsed the same inference and shown that addition of CAC to the FRS model led to the reclassification of > 50% of study participants who had initially been placed in the intermediate risk category. The study suggested empirically derived cutoff values of 615 Agatston units, at which point individuals should be up-graded from intermediate to high risk, and 50 Agatston units, at which point individuals should be down-graded to low risk.[37]

Conclusions

CVD is among the leading causes of death in the adult population. Effective prevention to reduce the prevalence of atherosclerosis, such as lifestyle modification and medical therapy, is a logical approach. Risk stratification using history, physical examination, biomarkers, and tools such as the FRS can identify subsets of the general population at low or high risk, but a significant number of subjects remain at indeterminate risk. CT is a complementary tool for the quantification of atherosclerotic plaque burden. Coronary artery calcification occurs only in the setting of atherosclerosis. Total CACS is strongly associated with total atherosclerotic plaque burden. CACS is predictive of major cardiovascular events and can be used to further modify cardiovascular risk, especially in the intermediate-risk group. Subjects who fall into the intermediate-risk group who have high CACS should be referred for MPS; coronary angiography should be reserved for subjects with inducible myocardial ischemia on MPS. In asymptomatic subjects, the absence of CAC predicts an excellent survival, with 10-year cardiac event rates of approximately 1%, and can be used to emphasize lifestyle modifications rather than medical therapy. In contrast, increasing cardiac events are most associated with increasing CACS. Patients with increasing CACS should receive aggressive lifestyle modifications and medical therapy. The role of CACS has also been recognized in the 2010 American College of Cardiology Foundation/American Heart Association guidelines that recommend a class IIa indication for measurement of CACS in asymptomatic adults at intermediate risk (10%-20% 10-year risk) and a class IIb indication for measurement of CACS in adults at low to intermediate risk (6%-10% 10-year risk).[38-41] ■

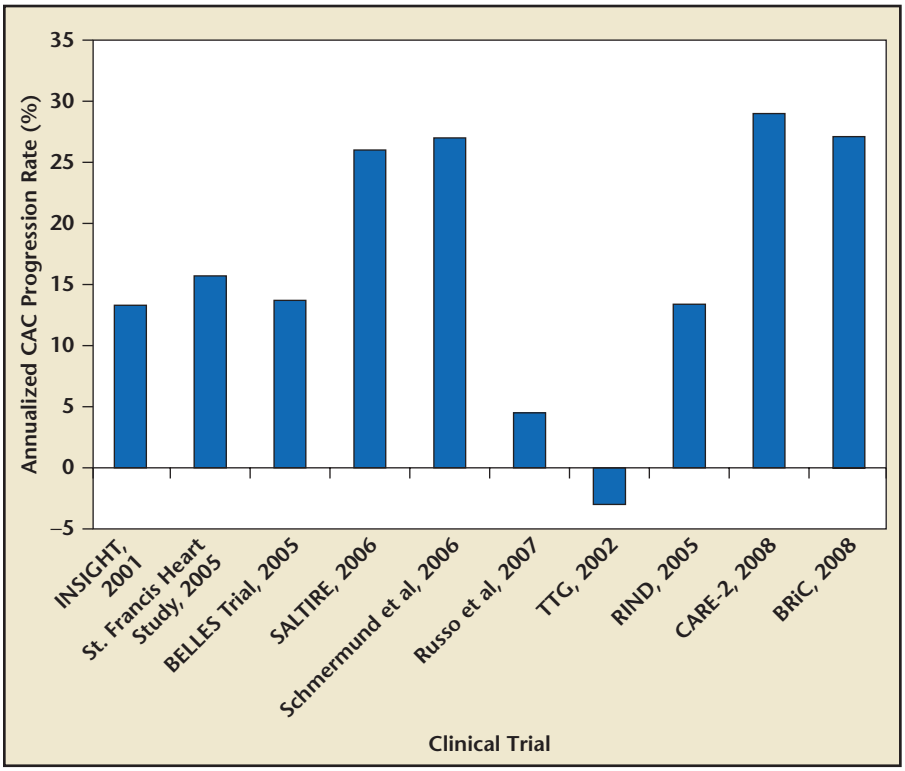


Figure 9. *Annualized CAC score progression rate in treatment arms of 10 clinical trials in patients with CVD and CKD. BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning; BRiC, Bone Remodeling and Coronary Calcification; CAC, coronary artery calcium; CARE, Calcium Acetate Renagel Evaluation; CKD, chronic kidney disease; CVD, cardiovascular disease; INSIGHT, International Nifedipine Study: Intervention as Goal for Hypertension Therapy; RIND, Renagel in New Dialysis; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression; TTG, Treat to Goal Working Group. Adapted with permission from McCullough PA et al.*[32]

References

1. Heart Disease and Stroke Statistics—2010 Update. American Heart Association Web site. http://www.americanheart.org/downloadable/heart/1265665152970DS-3241%20HeartStrokeUpdate_2010.pdf. Accessed June 6, 2011.
2. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation*. 1998;97:596-601.
3. Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol*. 1985;5:141B-149B.
4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.
5. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2009;53:345-352.
6. Sarwar A, Show LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging*. 2009;2:675-688.
7. Rumberger JA, Simons DB, Fitzpatrick LA, et al. Coronary artery calcium area by electron beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. *Circulation*. 1995;92:2157-2162.
8. Mautner GC, Mautner SL, Froehlich J, et al. Coronary artery calcification: assessment with electron beam computed tomography and histomorphometric correlation. *Radiology*. 1994;192:619-623.
9. Rumberger JA, Sheedy PF, Breen JF, Schwartz RS. Electron beam computed tomography calcium score cutpoints and severity of associated angiographic luminal stenosis. *J Am Coll Cardiol*. 1997;29:1542-1548.
10. Bielak LF, Rumberger JA, Sheedy PF 2nd, et al. Probabilistic model for prediction of angiographically defined obstructive coronary artery disease using electron beam computed tomography calcium score strata. *Circulation*. 2000;102:380-385.
11. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenosis in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol*. 2001;37:451-457.
12. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med*. 2000;343:915-922.
13. Deanfield JE. Total ischemic burden in patients with coronary artery disease. *Cardiovasc Drugs Ther*. 1990;4(suppl 4):833-839.
14. Deedwania PC. Silent ischemia predicts poor outcome in high-risk healthy men. *J Am Coll Cardiol*. 2001;38:80-83.
15. Arad Y, Goodman KJ, Roth M, et al. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol*. 2005;46:158-165.
16. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303:1610-1616.

Main Points

- Coronary artery calcium (CAC) scoring provides substantial incremental risk prediction for coronary heart disease events in asymptomatic subjects beyond conventional coronary risk factors.
- Subjects in the intermediate-risk group as measured by convention risk assessment and high CAC scores should be approached more aggressively with regard to diagnostic imaging, lifestyle modifications, and medical therapy for dyslipidemia.
- The 2010 American College of Cardiology Foundation/American Heart Association guidelines for cardiovascular risk in asymptomatic adults assigned a class IIa indication for measurement of CAC for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10%-20% 10-year risk) and class IIb indication in asymptomatic adults at low to intermediate risk (6%-10% 10-year risk).

17. Heart Disease and Stroke Statistics—2007 Update: a Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69-e171.
18. Budoff MJ, Georgia D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation*. 1996;93: 898-904.
19. Kim WY, Danias PG, Stuber M, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med*. 2001;345:1863-1869.
20. American Association of Physicists in Medicine. The measurement, reporting, and management of radiation dose in CT. Report of AAPM Task Group 23 of the Diagnostic Imaging Council CT Committee. American Association of Physicists in Medicine Web site. http://aapm.org/pubs/reports/RPT_96.pdf. Accessed June 6, 2011.
21. Rozanski A, Gransar H, Wong ND, et al. Clinical outcomes after both coronary calcium scanning and exercise myocardial perfusion scintigraphy. *J Am Coll Cardiol*. 2007;49:1352-1361.
22. Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. *J Am Coll Cardiol*. 2009;54:1872-1882.
23. Sirineni GK, Raggi P, Shaw LJ, Stillman AE. Calculation of coronary age using calcium scores in multiple ethnicities. *Int J Cardiovasc Imaging*. 2008;24:107-111.
24. Doherty TM, Tang W, Detrano RC. Racial differences in the significance of coronary calcium in asymptomatic black and white subjects with coronary risk factors. *J Am Coll Cardiol*. 1999;34:787-794.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
26. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with metabolic syndrome. *Diabetes Care*. 2001; 24:683-689.
27. Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol*. 2003;41:1547-1553.
28. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43:1663-1669.
29. Taylor AJ, Bindeman J, Feuerstein I, et al. Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. *J Am Coll Cardiol*. 2008;51:1337-1341.
30. Min JK, Lin FY, Gidseg DS, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the "warranty period" for remaining normal? *J Am Coll Cardiol*. 2010;55:1110-1117.
31. Rosário MA, Lima JJ, Parga JR, et al. Coronary calcium score as predictor of stenosis and events in pretransplant renal chronic failure [in Portuguese]. *Arq Bras Cardiol*. 2010;94:236-243.
32. McCullough PA, Chinnaiyan KM. Annual progression of coronary calcification in trials of preventive therapies: a systematic review. *Arch Intern Med*. 2009;169:2064-2070.
33. Gill EA Jr. Does statin therapy affect the progression of atherosclerosis measured by a coronary calcium score? *Curr Atheroscler Rep*. 2010;12:83-87.
34. Terry JG, Carr JJ, Kouba EO, et al. Effect of simvastatin (80mg) on coronary and abdominal aortic arterial calcium (from the coronary artery calcification treatment with zocor [CATZ] study). *Am J Cardiol*. 2007;99:1714-1717.
35. Tsai IC, Choi BW, Chan C, et al; Asian Society of Cardiovascular Imaging Cardiac Computer Tomography and Cardiac Magnetic Resonance Imaging Guideline Working Group. ASCI 2010 appropriateness criteria for cardiac computed tomography: a report of the Asian Society of Cardiovascular Imaging Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging Guideline Working Group. *Int J Cardiovasc Imaging*. 2010;26:1-15.
36. Erbel R, Möhlenkamp S, Moebus S, et al; Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol*. 2010;56:1397-1406.
37. Elias-Smale SE, Proença RV, Koller MT, et al. Calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. *J Am Coll Cardiol*. 2010;56:1407-1414.
38. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336-1345.
39. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210-215.
40. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2007;167:2437-2442.
41. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol*. 2005;46:807-814.
42. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation. *Circulation*. 1993;88:2548-2555.
43. Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. *Hypertension*. 2001;37:1410-1413.
44. Arad Y, Spadaro LA, Roth M, et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol*. 2005;46:166-172.
45. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation*. 2005; 112:563-571.
46. Houslay ES, Cowell SJ, Prescott RJ, et al; Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression trial investigators. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomized controlled trial. *Heart*. 2006;92: 1207-1212.
47. Schmermund A, Achenbach S, Budde T, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. *Circulation*. 2006;113:427-437.
48. Russo D, Miranda I, Ruocco C, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int*. 2007;72:1255-1261.
49. Chertow GM, Burke SK, Raggi P; Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002; 62:245-252.
50. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*. 2005;68:1815-1824.
51. Qunibi W, Moustafa M, Muenz LR, et al; CARE-2 Investigators. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *Am J Kidney Dis*. 2008;51:952-965.
52. Barreto DV, Barreto Fde C, de Carvalho AB, et al. Phosphate binder impact on bone remodeling and coronary calcification—results from the BRiC study. *Nephron Clin Pract*. 2008; 110:c273-c283.