DOI: 10.1111/j.1540-8175.2011.01407.x

Echocardiography

ECHO ROUNDS Section Editor: Edmund Kenneth Kerut, M.D.

Coronary Risk Assessment and Arterial Age Calculation Using Coronary Artery Calcium Scoring and the Framingham Risk Score

Edmund Kenneth Kerut, M.D.

Heart Clinic of Louisiana, Marrero, Louisiana

(Echocardiography 2011;28:686-693)

Key words: coronary artery calcium score, coronary age, diabetes mellitus, Framingham, lifetime risk, radiation

Accounting for one in five deaths, coronary artery disease (CAD) is the leading cause of death among Americans.[1] Risk assessment for future coronary events is important in management of patients who have no symptoms of cardiovascular disease (primary prevention). The European Prospective Cardiovascular Münster (PROCAM) Study and Systemic Coronary Risk Evaluation (SCORE), along with the American Framingham Heart Study are used to assess risk clinically.[2–4] These studies have made available methods for calculation of an individual's risk for a future cardiovascular event.[5–7]

Traditional Cardiovascular Risk Assessment:

A Framingham Risk Score (FRS) for future ten-year risk of coronary "hard" events (myocardial infarction or coronary death) is calculated (FRS Calculator) using the following risk factors: chronological age, gender, total cholesterol, HDL cholesterol, smoking history, systolic blood pressure, and current use of hypertension medications.[7] However, several important risk factors, including metabolic syndrome, obesity and family history are not included in this FRS calculation. The FRS categorizes coronary risk into: *Low Risk* (0% – 10%), *Intermediate Risk* (10% – 20%), and *High Risk* (>20%) for myocardial infarction or coronary death over the ensuing ten years.

In addition to the above, the category Intermediate Risk may be further subdivided into *Moderate Risk* and *Moderately High Risk*. Moderate Risk involves those patients deemed FRS Low Risk, but with two or more "risk factors," and Moderately High Risk involves those patients FRS Intermediate Risk with two or more "risk factors." Those risk factors for this "subclassification" are cigarette smoking, hypertension (140/90 mmHg or on therapy), low HDL (<40 mg/dL), family history of early heart disease (father or brother <55 years old, mother or sister <65 years old), and age (45 or older males, 55 or older females). For those with an HDL 60 mg/dL or higher, subtract one risk factor.[8]

Dependent on the category into which a patient falls, aggressiveness of therapeutic lifestyle changes (TLC)[9] and lipid lowering goals are as recommended by the National Cholesterol Education Program Adult Treatment Panel III Guidelines (Table I).[8]

Risk Assessment Using Coronary Artery Calcium Measurement:

Risk factors used for calculating the FRS, except for age, which is an indicator of increasing plaque burden through time, are believed to be causes of coronary disease. While these directly contribute to the atherosclerotic process, they are not atherosclerosis per se.

The likelihood of a patient having a coronary "hard" event is related to the total plaque burden in the coronary arteries.[10–12] As opposed to coronary risk factors, coronary artery calcium (CAC) is coronary artery atherosclerosis, as atherosclerosis is the only known disease process that is associated with CAC.[13,14] Also, the extent of CAC is related to the degree of atherosclerosis,[11,12,15] representing about one fifth of the total plaque burden (four-fifths of atherosclerotic plaque is noncalcified).[16,17] Therefore the "amount" of CAC in a coronary tree is proportional to total plaque burden.

While CAC is pathognomonic for coronary atherosclerosis, it is not specific for obstructive coronary disease, as both obstructive and nonobstructive disease is partly composed of calcified

Address for correspondence and reprint requests: Edmund Kenneth Kerut, M.D., Heart Clinic of Louisiana, 1111 Medical Center Blvd, Suite N613, Marrero, LA 70072. Fax: 504-349-6621; E-mail: kenkerut@pol.net

TABLE I

ATP III Recommendations for TLC and Drug Therapy Based on Risk Category.[8]

Risk Category	LDL Goal	Initiate TLC	Consider Drug Therapy
High	<100 mg/dL*	≥100 mg/dL	≥100 mg/dL†
Moderately high	<130 mg/dL	≥130 mg/dL	≥130 mg/dL‡
Moderate	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Low	<160 mg/dL	≥160 mg/dL	≥190 mg/dL§

*Optional goal of <70 mg/dL.
†If baseline LDL is <100 mg/dL lipid lowering drug therapy is an option to achieve at least a 30–40% LDL reduction.
‡With LDL 100–129 mg/dL consider lipid lowering drug therapy to achieve an LDL < 100 mg/dL.
§For an LDL 160–189 mg/dL, lipid lowering drug therapy is optional.

plaque. In addition, the location of CAC within the coronary tree only weakly correlates with that site having obstructive disease.[18,19] The probability of significant obstructive disease somewhere within the coronary vascular bed increases however, as the amount of CAC within the coronary vessels increases.[13,20,21]

Detection of CAC has become a method of evaluating a patient for risk of a coronary event. While an increased amount of coronary calcium may not be indicative of any significant obstructive coronary stenosis, it is associated with an increased risk of future "hard" coronary events by its reflection of total coronary atherosclerotic "burden."[16,22,23]

Several studies have reported prospectively collected registries of initially asymptomatic patients after obtaining a baseline CAC Score.[24–29] Most reported studies use the Agatston Scoring method.[30] This method was first described in 1990 as a method of quantification of CAC using ultrafast computed tomography (CT). A CAC Score (reported in Agatston Units) of zero is desirable, 1–10 "minimal," 11–100 "mild," 101–399 "moderate," and ≥400 "severe."[31]

These prospective reports suggest that for the ensuing 3–5 years, any amount of detected CAC increases risk of cardiac "hard" events (myocardial infarction or coronary death) by four times, when compared to patients with no detectable coronary calcium. Those without detected calcium have a very low risk (0.11–0.4%) over the same time period.[32–34]

Risk based on CAC Score may be further refined, as there is a direct relationship of increasing CAC Score with increasing cardiac risk. A CAC Score of from 1 to 112 increases risk by ~2× (compared to a CAC Score of 0), 100–400 by ~4×, 400–1,000 by ~5×, and >1,000 by ~7×.[32] In addition, measurement of CAC Score improves cardiac risk assessment independently and above that provided by standard risk measures.[24,27,35,36] As CAC is atherosclerosis and traditional risk factors are "markers" for the likelihood of developing disease; it is understandable how one's CAC Score is an independent predictor of future coronary events.[37,38]

CAC Scoring Best in Intermediate FRS Group:

CAC Score measurements in FRS Low-Risk groups generally do not alter prediction of cardiovascular outcomes.[25,26] Even if a Low-Risk patient has a high CAC Score, likelihood of coronary events remains low.[25] Likewise, patients deemed FRS High-Risk generally do not benefit from CAC Score measurements.[32] A low CAC Score will not significantly lower CV risk in patients in the FRS High-Risk category.[39]

Patients classified as Intermediate Risk by the FRS often will be "reclassified" to a higher risk group when CAC Score is added to risk assessment.[22,32] It may be justifiable to treat these patients more aggressively, as a CAC Score >300 is associated with increased rates of hard coronary events.[25] Similarly, in asymptomatic patients a high CAC Score is more predictive of ensuing CV events than marked perfusion defects by nuclear stress testing.[40] Alternatively, a CAC Score of zero may change these patients to a Low-Risk group.[32,24–26]

Zero or Very Low CAC Scores:

A CAC Score of zero is associated with a very low risk of a coronary event in the ensuing few years, regardless the number of coronary risk factors.[33,41,42] A long-term registry up to twelve years duration demonstrated a mortality of 0.4%.[43] Similarly, pooled data of over 16,000 patients with a CAC Score of zero had an estimated 10-year event rate of 0.3% (0.027% per year).[33]

The Multi-Ethnic Study of Atherosclerosis (MESA) Study found only 8 of 3,409 subjects with a zero CAC had a major cardiac event at a mean of 3.8 years follow-up.[44] Despite the low risk of subsequent events, another study found age, smoking, diabetes mellitus, and family history of heart disease as significant predictors of mortality in patients with a CAC Score of zero.

Smoking and diabetes mellitus were found to be the highest predictors.[45] These two risk factors were also associated with an increased likelihood of developing CAC during follow-up CAC scans.[46]

In distinction to asymptomatic patients, in a cohort of symptomatic patients with chest pain, the incidence of obstructive CAD in the setting of a CAC Score of zero was significant (7.2% incidence). Coronary obstruction was caused by noncalcified atherosclerotic disease.[47]

In asymptomatic patients with a "low" CAC Score (CAC Score 1–10) there is a more than twofold increased risk of CV events[43] and all cause death[45] compared to those with a CAC Score of zero.

CAC in Type 2 Diabetes Mellitus:

Diabetes mellitus may be considered a CAD equivalent.[48–50] As up to 80% of persons with diabetes will have a cardiovascular event, the National Cholesterol Education Panel Guidelines recommend that patients with diabetes be managed as a coronary heart disease risk equivalent, with treatment following Adult Treatment Panel III recommendations.[51]

As many patients with diabetes have increased risk of cardiovascular events in comparison to nondiabetics, there are a group of patients at low risk, and also a group at very high risk. These groups appear not to be distinguishable based on $HgBA_{1C}$ level, duration of diabetes, age, gender or other cardiovascular risk factors.[52] However, insulin resistance, blood pressure and cholesterol levels do appear to be independent risk factors for prediction of coronary events in these asymptomatic type 2 diabetics.[52–53]

The CAC Score is highly predictive of subsequent CV events in asymptomatic diabetics.[52,54,55] There is an increased incidence of CAC and also severity of CAC in diabetic patients and also those with the metabolic syndrome.[56,57] For every incremental increase in CAC Score, there is a larger increase in mortality for diabetic patients, compared to nondiabetics. However, diabetics with a CAC Score of zero have a similar good prognosis compared to nondiabetics with a CAC Score of zero.[54]

If a diabetic is already being treated maximally, then CAC Scoring is of little benefit. Diabetic patients that may benefit from CAC Scoring may include noncompliant patients (improved medical compliance when visualizing coronary calcium on CT scanning), and younger diabetic patients when choosing an age to begin intensive lipid lowering therapies.[55]

Coronary Age:

Several investigators have introduced the concept of "coronary age" as derived from a patient's CAC Score.[25,58–63] This CAC Score derived "coronary age" is then substituted for chronological age in the FRS calculation to refine determination of cardiovascular risk. In addition, this calculation of coronary age allows the patient to better understand "atherosclerotic burden" ("You are 52 years old, but your arteries are a vascular age of 65 years").

This method, as mentioned, is more predictive of cardiovascular events, when the coronary age is substituted for chronological age in the FRS calculation of risk.[61–63] There is, however, no predictive advantage to present CAC Score in relation to a patient's age, gender, or race. A patient's risk based on the CAC Score is the same, no matter the age, gender or ethnicity.[61,62]

Long Term "Lifetime" Cardiovascular Risk:

Absence of risk factors at age 50 years is associated with a very low lifetime risk for cardiovascular events (lifetime risk to 95 years old). There is a high lifetime risk in patients with intermediate or high risk factors at age 50 years.[64] Also, those with few risk factors in middle age have been found to have a better quality of life after $\sim$25 years of follow-up compared to those with intermediate or high risk factors.[65]

Individuals at age 50 years with $\geq$1 FRS risk factor have lifetime risk of 39–70% despite a 10-year risk of $<$ 10%.[64] Even looking over the relatively short-term future (3.75 year follow-up), MESA found in women classified as low risk by the FRS an increase in risk of sixfold those with any CAC compared to those with a CAC Score of zero. Those FRS Low-Risk females with a CAC Score of $\geq$300 had a marked increased risk of cardiovascular events (8.6%).[66]

Several clinical guidelines encourage evaluation of long-term (lifetime) cardiovascular risk, recognizing that many short-term risk patients (10-year risk) are at high-risk for the long-term.[67–69] Using risk factors of total cholesterol ($>$180 mg/dL), blood pressure ($\geq$120/$\geq$80 mm Hg), smoker, diabetes[64,70] many patients are classified as Low-Risk over ten years, but high risk over a lifetime. Over a lifetime, these risk factors are associated with a higher incidence of CAC and higher CAC Scores at baseline.

CAC Scores increase at a greater rate in patients with these risk factors.[70,71] From this, among patients $\leq$50 years old, two groups of short-term risk patients are identified: those who have a low lifetime cardiovascular risk, and those with a high lifetime cardiovascular risk. These groups are associated with correspondingly low and high "subclinical atherosclerosis" and also subsequent low and high rates of progression of atherosclerosis, as evidence by the CAC Score.[70]

Estimating a FRS 10-year risk as low may give the patient a feeling of security, when in fact this is not true over the course of a lifetime.[72]

Ionizing Radiation from the Coronary Artery Calcium Score:

Obtaining a CAC Score involves a CT and hence ionizing radiation.[73,74] Radiation absorption associated with measurement of a CAC Score is small but quantifiable, generally ranging from 0.9 mSv to 2.0 mSv. In comparison, the usual radiation dose of a chest x-ray is 0.02–0.1 mSv and CT chest about 7 mSv. For comparison, average environmental exposure yearly in the United States is about 3 mSv.[73–78]

Although medical procedures generally involve low radiation dose exposure, several investigators believe that a risk of cancer is present. Based on models derived from World War II atomic blast data the risk of cancer from 1 mSv would equate to cancer developing in one person out of 10,000. Other investigators, however, believe that cancer risk is nonexistent below radiation exposures less than 50–100 mSv.[79]

Coronary Artery Calcium Score and Implications for Therapeutic Intervention:

Performance of serial CAC Score calculations for following effects of therapy has yielded mixed results at best.[80] The first study of sequential scans (12–15 months apart) in asymptomatic patients (n = 149) involved intervening with a statin (CAC Score ≥30 baseline). Those treated with a statin had a average progression of ~5% with many showing regression. The untreated group progressed ~52%.[81] The next report demonstrated similar findings with statin therapy (n = 299 asymptomatic individuals) with progression over ~1 year of ~15% in treated and 39% in untreated patients.[82]

A large cohort of patients (n = 4,609) referred by primary physicians for CAC Score measurements with repeat screening was analyzed. With an average interscan time interval of 3.1 years, progression of CAC was significantly associated with mortality, independent of other traditional risk factors.[83] Similarly, the National Institutes of Health MESA Study has obtained a second CAC Score on a large cohort of patients, and is following for cardiovascular events. Results will not be ready until 2012 or 2013.[84]

The first prospective study involved asymptomatic patients (n = 66) with a CAC Score ≥ 20 and LDL cholesterol > 130 mg/dL. Follow-up scans (mean 14 months) was performed on no statin therapy. CAC Scores progressed at a rate of ~27% from the initial scan. All 66 patients were then treated with ceruvistatin 0.3 mg/day and a final scan performed (12 months later). CAC Scores subsequently regressed an average 3% (mean LDL values decreased from 152 mg/dL to 88 mg/dL with therapy).[85]

Four prospective, double-blinded, randomized trials in asymptomatic patients evaluated CAC Scores with statin intervention. All achieved a significant improvement in LDL lowering, but none found a statistically significant alteration of temporal progression of CAC Score.[80,86–89] The largest trial, the St. Francis Heart Study, did find a significant reduction in cardiovascular events, despite no significant change in CAC Score progression.[87] Further analysis did show that progression of CAC Score along with baseline CAC Scores was the strongest predictor of subsequent cardiovascular events in these baseline asymptomatic patients.[90]

Recent lipid lowering studies documented regression of carotid atherosclerosis using magnetic resonance imaging (MRI), with slowing of disease progression and a decrease in the amount of lipid-rich necrotic core.[91] Using intravascular ultrasound (IVUS), the ASTEROID trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (n = 349) used high dose statin therapy (40 mg rosuvastatin) to document significant reduction of atheroma burden in coronary arteries over 2 years.[92]

Cardiovascular progression of disease appears to result from accumulation of lipid and fibrotic materials. Likely, regression of disease involves removal of lipid and necrotic materials. Fibrous and calcified plaques are probably less likely to be removed by statins, once formed. Improvement in clinical outcomes probably is reflective of removal of this noncalcified plaque.[93]

While coronary artery calcium represents approximately 20% of total coronary atherosclerotic plaque burden, the CAC Score is a good predictor of risk of future coronary events. However, it may not serve as a good end-point for follow-up of lipid-lowering drug interventions.[16,17,80]

Special Population: Coronary Artery Calcium Scores in Patients with Renal Failure:

End-stage renal disease (ESRD) is associated with accelerated extraskeletal calcification including coronary artery calcification. Coronary artery calcification in patients without renal failure normally occurs in the vessel intima (innermost arterial layer), but with ESRD extensive calcification of vessel tunica media is noted.[94] CAC Scores in ESRD patients are much higher and progress at a faster rate than patients without renal failure (~100% increase over two years).[95,96] It is recommended that patients with ESRD on dialysis

be categorized as "highest risk," and therefore warrant aggressive coronary preventive therapy, with treatment goals the same as if obstructive coronary disease was evident.[97]

There may be an association of CAC Score with cardiovascular disease and mortality in ESRD patients.[98,99] The Treat-to-Goal Study (n = 200) was a randomized trial comparing a calcium-free nonabsorbable polymer sevelamer to traditional calcium-based phosphate binders. Patients on dialysis for at least three years were studied at baseline, and then after 6 and 12 months of therapy. Despite similar serum phosphorus, calcium and parathyroid hormone levels, CAC Score progressed in the traditional calcium-based phosphate binder group, while there was no significant change in the sevelamer group. This difference was attributed to a lack of calcium overload induced by calcium-based phosphate binders.[100]

Summary:

CAD is the leading cause of death among Americans. Risk assessment for future coronary events is important in management of asymptomatic patients. The FHS categorizes an individual as Low, Intermediate or High-Risk for a coronary event over the ensuing ten years, based on risk factors (age, gender, total cholesterol, HDL cholesterol, smoking history, systolic blood pressure, and current use of hypertension medications). The likelihood of a patient having a coronary event is related to total plaque burden in the coronaries. Coronary artery calcium, found in the coronary intimal layer, represents about one-fifth of total plaque burden. It is coronary artery atherosclerosis, but is not necessarily luminal obstructive disease. The amount of coronary artery calcium detected by CT, using the Agatston Score, is predictive of an asymptomatic patient's risk of a future coronary event.

The CAC Score may be converted to a "coronary age." This calculated age is substituted for chronological age in the FRS Calculator to provide a more accurate risk of future coronary events. It appears that patients initially found to be an Intermediate FRS risk may benefit most from the CAC Score and use of the coronary age to further refine risk.

Coronary lifetime risk describes risk of a coronary event in asymptomatic individuals from middle age over the course of a lifetime. Many individuals at Low-Risk for the short-term (10 years) are at high lifetime risk. This may influence one's decision about use of lipid lowering therapies.

Calculation of a CAC Score is a radiological procedure using ionizing radiation, albeit a low dose ranging from 0.9 to 2.0 mSv. Using one model of effects from radiation exposure, approximately one individual in 10,000 would be expected to develop cancer from exposure to a dose of 1 mSv.

Lipid lowering therapy reduces coronary risk. It appears to reduce noncalcified plaque as detected by MRI and IVUS. Prospective studies measuring CAC Score have not uniformly shown a reduction in calcified plaque, therefore this methodology may not be a good way to sequentially follow results of lipid lowering therapies.

Patients with diabetes and also ESRD are coronary high-risk equivalents. Coronary artery calcium is more prevalent in these two disorders. A CAC Score in a diabetic patient represents a higher future risk than a nondiabetic individual with the same score, but a CAC Score of zero carries nearly the same low risk as a nondiabetic with a CAC Score of zero. ESRD patients have coronary calcium notably in the tunica media layer. There may be an association of CAC Score with coronary disease and mortality in ESRD patients. Treatment with calcium-free nonabsorbable phosphate binders has been noted to halt progression of coronary artery calcium.

It appears that measurement of the CAC Score may be of most benefit to individuals categorized by the FRS as Intermediate Risk. By substituting the "coronary age" for chronological age in the FRS Calculator, many of these individuals are recategorized as High-Risk, and should be more aggressively treated to reduce risk of future cardiovascular events.

References

1. Thom T, Haase N, Rosamond W, et al: American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85–e151.
2. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. *Circulation* 2002;105:310–315.
3. Conroy RM, Pyorala K, Fitzgerald AP, et al: Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003;24:987–1003.
4. Wilson PW, D'Agostino RB, Levy D, et al: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847.
5. International Task Force for the Prevention of Coronary Heart Disease. http://www.chd-taskforce.com/ Accessed January 8, 2011.
6. International Task Force for the Prevention of Coronary Heart Disease. http://www.chd-taskforce.com/ Accessed January 8, 2011.
7. Framingham Heart Study. Coronary heart disease (10-year risk). http://www.framinghamheartstudy.org/risk/coronary.html. Accessed January 8, 2011.
8. Grundy SM, Cleeman JI, Merz CN, et al: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004;110:227–239.

9. Lichtenstein AH, Appel LJ, Brands M. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82–96.
10. Schmermund A, Mohlenkamp S, Erbel R. Coronary artery calcium and its relationship to coronary artery disease. *Cardiol Clin* 2003;21:521–534.
11. Elkeles RS, Dunlop A, Thompson GR, et al: Coronary Calcification and predicted risk of coronary heart disease in asymptomatic men with hypercholesterolemia. *J Cardiovasc Risk* 2002;9:349–353.
12. Vliegenthart R, Oudkerk M, Song B, et al: Coronary calcification detected by electron-beam computed tomography and myocardial infaction. The Rotterdam coronary calcification study. *Eur Heart J* 2002;23:1596–1603.
13. Wexler L, Brundage B, Crouse J, et al: Coronary artery calcification: pathophysiology, epidemiology, image methods and clinical implications. A scientific statement from the American Heart Association. *Circulation* 1996;94:1175–1192.
14. Frink RJ, Achor RWP, OWN AL, et al: Significance of calcification of the coronary arteries. *Am J Cardiol* 1970;26:241–247.
15. Rumberger JA, Schwartz RS, Simons DB, et al: Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. *Am J Cardiol* 1994;73:1169–1173.
16. Rumberger JA, Simons DB, Fitzpatrick LA, et al: Coronary artery calcium areas by electron beam computed tomography and coronary atherosclerotic plaque area: A histopathologic correlative study. *Circulation* 1995;92:2157–2162.
17. Baumgart D, Schmermund A, Goerge G, et al: Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. *J Am Coll Cardiol* 1997;30:57–64.
18. Simons DB, Schwartz RS, Edwards WD, et al: Noninvasive definition of anatomic coronary disease by ultrafast computed tomographic scanning: A quantitative pathologic comparison study. *J Am Coll Cardiol* 1992;20:1118–1126.
19. Mautner GC, Mautner SL, Froelich J, et al: Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. *Radiology* 1994;192:619–623.
20. Budoff MJ, Georgiou 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.
21. Guerci AD, Spadaro LA, Popma JJ, et al: Electron beam tomography of the coronary arteries: relationship of coronary calcium score to arteriographic findings in asymptomatic and symptomatic adults. *Am J Cardiol* 1997;70:128–133.
22. Budoff MJ, Achenbach S, Blumenthal RS, et al: American Heart Association Committee on Cardiovascular Imaging and Intervention; American Heart Association Council on Cardiovascular Radiology and Intervention; American Heart Association Committee on Cardiac Imaging, Council on Clinical Cardiology. Assessment of coronary artery disease by cardiac computed tomography: A scientific statement. *Circulation* 2006;114:1761–1791.
23. O'Rourke RA, Brundage BH, Froelicher VF, et al: American College of Cardiology/American Heart Association Expert consensus document on electorn-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol* 2000;36:326–340.
24. Arad Y, Goodman KJ, Roth M, et al: Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerostic cardiovascular disease events: The St. Francis heart study. *J Am Coll Cardiol* 2005;46:158–165.
25. 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.
26. Kondos GT, Hoff JA, Sevrukov A, et al: Electron-beam tomography coronary artery calcium and cardiac events: A 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107:2571–2576.
27. 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;46:806–814.
28. LaMonte MJ, FitzGerald SJ, Chruch TS, et al: Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *Am J Epidemiol* 2005;162:421–429.
29. Detrano R, Carr JJ, Burke J, et al: Coronary calcium predicts near-term coronary heart disease events in major American ethnic groups: The multi-ethnic study of atherosclerosis. *J Am Coll Cardiol* 2007;49:101A.
30. Agatston AS, Janowitz WR, Hildner FJ, et al: Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
31. Rumberger JA, Brundage BH, Rader DJ, et al: Electron beam computed tomographic coronary calcium scanning: A review and guidelines for use in asymptomatic persons. *Mayo Clin Proc* 1999;74(3):243–252.
32. Greenland P, Bonow RO, Brundage BH, et al: ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA writing committee to update the 2000 expert consensus document on electron beam computed tomography). *J Am Coll Cardiol* 2007;49:378–402.
33. Shareghi S, Ahmadi N, Young E, et al: Prognostic significance of zero coronary calcium scores on cardiac computed tomography. *J Cardiovasc Comp Tomography* 2007;1:155–159.
34. Raggi P, Cooil B, Callister TQ: Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J* 2001;141:375–382.
35. Gopal A, Budoff MJ: Coronary calcium scanning. *Am Heart Hops J* 2006:4:43–50.

35a. Park R, Detrano F, Xiang M, et al: Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular event in nondiabetic individuals. *Circulation* 2002;106:2073–2077.

36. Vliegenthart R, Oudkerk M, Hofman A, et al: Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005;112:572–577.
37. 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.
38. Budoff MJ, Nasir K, McClelland RL, et al: Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles. *J Am Coll Cardiol* 2009;53:345–352.
39. Bonow RO: Should coronary calcium screening be used in cardiovascular prevention strategies? *N Engl J Med* 2009;361:990–997.

40. Wayhs R, Zelinger A, Raggi P: High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002;39:225–230.
41. Church TS, Levine BD, McGuire DK, et al: Coronary artery calcium score, risk factors, and incident coronary heart disease events. *Atherosclerosis* 2007;190(1):224–231.
42. Sarwar A, Shaw LJ, Shapiro MD, et al: Diagnostic and prognostic value of absence of coronary artery calcification. *J Am Coll Cardiol Img* 2009;2:675–688.
43. Budoff MJ, Shaw LJ, Liu ST, et al: Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007;49:1860–1870.
44. Detrano A, Guerci AAD, 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.
45. Blaha M, Budoff MJ, Shaw LJ, et al: Absence of coronary artery calcification and all-cause mortality. *J Am Coll Cardiol Img* 2009;2:692–700.
46. Kronmal RA, McClelland RL, Detrano R, et al: Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the multi-ethnic study of atherosclerosis (MESA). *Circulation* 2007;115:2722–2730.
47. Rubinshtein R, Gaspar T, Halon DA, et al: Prevalence and extent of obstructive coronary artery disease in patients with zero or low calcium score undergoing 64-slice cardiac multidetector computed tomography for evaluation of a chest pain syndrome. *Am J Cardiol* 2007;99:472–475.
48. Grundy SM, Benjamin IJ, Burke GL, et al: Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134–1146.
49. Prevalence of Asymptomatic Myocardial Ischaemia in Diabetic Subjects. *BMJ* 1990;301:92–95.
50. Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior Myocardial infarction. *N Engl J Med* 1998;339:229–234.
51. 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.
52. Elkeles RS, Godsland IF, Feher MD, et al: Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: The PREDICT study. *Eur Heart J* 2008;29:2244–2251.
53. Turner RC, Milns H, Neil HW, et al: United Kingdom prospective diabetes study group. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus United Kingdom Prospective Diabetes Study (UKPDS 23). *Br Med J* 1998;316:823–828.
54. Raggi P, Shaw LJ, Berman DS, et al: Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;43:1663–1669.
55. Budoff MJ. Not all diabetics are created equal (in cardiovascular risk). *Eur Heart J* 2008;29:2193–2194.
56. Narla V, Santos RD, Campbell CY, et al: Coronary artery calcification and inflammation according to various metabolic syndrome definitions. *J Cardiometab Syndr* 2009;4:33–39.
57. Ibebuogu UN, Ahmadi N, Hajsadeghi F: Measures of coronary artery calcification and association with the metabolic syndrome and diabetes. *J Cardiometab Syndr* 2009;4:6–11.
58. Schisterman E, Whitcomb BW: BMC medical imaging 2004;4:1–9.
59. Sirineni GKR, Raggi P, Shaw LJ, et al: Calculation of coronary age using calcium scores in multiple ethnicities. *Int J Cardiovasc Imaging* 2008;24:107–111.
60. Shaw LJ, Raggi P, Berman DS, et al: Coronary artery calcium as a measure of biologic age. *Atherosclerosis* 2006;188:112–119.
61. McClelland RL, Nasir K, Budoff M, et al: Arterial age as a function of coronary artery calcium (from the multiethnic study of atherosclerosis [MESA]). *Am J Cardiol* 2009;103:59–63.
62. Budoff MJ, Nasir K, McClelland RL, et al: Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles. *J Am Coll Cardiol* 2009;53:345–352.
63. Schiele F, Meneveau N: Are you as old as your arteries or as old as your coronary artery calcification score? *J Am Coll Cardiol* 2009;53:353–354.
64. Lloyd-Jones DM, Leip EP, Larson MG, et al: Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006;113:791–798.
65. Daviglus ML, Liu K, Pirzada A, et al: Favorable cardiovascular risk profile in middle age and health-related quality of life in older age. *Arch Intern Med* 2003;163:2460–2468.
66. Lakoski SG, Greenland P, Wong ND, et al: Coronary artery calcium scores and risk for cardiovascular events in women classified as low-risk by Framingham risk score. The multi-ethnic study of atherosclerosis (MESA). *Arch Intern Med* 2007;167(22):2437–2442.
67. 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.
68. McPherson R, Frohlich J, Fodor G, et al: Canadian cardiovascular society position statement: recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006:22:913–927.
69. Mosca L, Banka CL, Benjamin EJ, et al: Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;115:1481–1501.
70. Berry JD, Liu K, Folsom AR, et al: Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: The coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. *Circulation* 2009;119:382–389.
71. Loria CM, Liu K, Lewis CE, et al: Early adult risk factor levels and subsequent coronary artery calcification: The CARDIA study. *J Am Coll Cardiol* 2007;49:2013–2020.
72. Nambi V, Ballantyne CM: "Risky business" ten years is not a lifetime. *Circulation* 2009;119:362–364.
73. Brenner DJ, Hall EJ: Computed tomography—An increasing source of radiation exposure. *N Engl J Med* 2007;357(22):2277–2284.
74. Gerber TC, Kantor B, McCollough CH: Radiation dose and safety in cardiac computed tomography. *Cardiol Clin* 2009;27(4):665–677.
75. Kim KP, Einstein AJ, Berrington de et al: Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med* 2009;169:1188–1194.
76. U.S. Food and Drug Administration. What are the radiation risks from CT? http://www.fda.gov/RadiationEmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115329.htm. Accessed January 8, 2011.

77. Fazel R, Krumholz HM, Wang Y, et al: Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009;361:849–857.
78. Lauer MS: Elements of danger—The case of medical imaging. *N Engl J Med* 2009;361:841–843.
79. Kerut EK, To F: Risk of low-level ionizing radiation from medical imaging procedures. *Echocardiography*, in press.
80. McCullough PA, Chinnaiyan KM: Annual progression of coronary calcification in trials of preventive therapies. *Arch Intern Med* 2009;169(22):2064–2070.
81. Callister TQ, Raggi P, Cooil B. Effects of HMG-CoA Reductase Inhibitors on Coronary Artery Disease. *N Engl J Med* 1998;339:1972–1977.
82. Budoff MJ, Lane KL, Bakhseshi H, et al: Rates of progression of coronary calcium by electron beam tomography. *Am J Cardiol* 2000;86:8–11.
83. Budoff MJ, Hokanson JE, Nasir K, et al: Progression of coronary artery calcium predicts all-cause mortality. *J Am Coll Cardiol Img* 2010;3:1229–1236.
84. Kronmal RA, McClelland RL, Detrano R, et al: Risk factors for the progression of coronary artery calcification in asymptomatic subjects—Results from the multi-ethnic study of atherosclerosis (MES). *Circulation* 2007;29:115:2722–2730.
85. Achenbach S, Ropers D, Pohle K, et al: Influence of lipid-lowering therapy on the progression of coronary artery calcification: A prospective evaluation. *Circulation* 2002;106:1077–1082.
86. Raggi P, Davidson M, Callister TQ, et al: Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic post-menopausal women: beyond endorsed lipid lowering with EBT scanning (BELLES). *Circulation* 2005;112(4):563–571.
87. 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(1):166–172.
88. Schmermund A, Achenbach S, Dudde T, et al: Effect of intensive versus standard lipd-lowering treament with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: A multicenter, randomized, double-blind trial. *Circulation* 2006;112(3):427–437.
89. 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 lipd-lowering treatment: A randomised controlled trial. *Heart* 2006;92(9):1207–1212.
90. 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.
91. Underhill HR, Yuan C, Zhao XQ, et al: Effect of Rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: A high-resolution magnetic resonance imaging trial. *Am Heart J* 2008;155:e581-e588.
92. Nissen SE, Nicholls SJ, Sipahi I, et al: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006;295:1556–1565.
93. Nicholls SJ. Rosuvastatin and progression of atherosclerosis: *Expert Rev Cardiovasc Therapy* 2008;6(7):925–933.
94. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res* 2004;95:560–567.
95. Braun J, Oldendorf M, Moshage W, et al: Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996;27:394–401.
96. Goodman WG, Goldin J, Kuizon BD, et al: Coronary artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478–1483.
97. Sarnak MJ, Levey AS, Schoolwerth AC, et al: Kidney disease as a risk factor for development of cardiovascular disease: A statement rom the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003;108:2154–2169.
98. Raggi P, Boulay A, Chasan-Taber S, et al: Cardiac calcification in adult hemodialysis patients. A link between end-state renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002;39:695–701.
99. Matsuoka M, Iseki K, Tamashiro M, et al: Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol* 2004;8:54–58.
100. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002;62:245–252.