Journal of the American College of Cardiology Vol. 56, No. 20, 2010

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.06.038

STATE-OF-THE-ART PAPER

Coronary Artery Calcium Progression: An Important Clinical Measurement?

A Review of Published Reports

John W. McEvoy, MB,* Michael J. Blaha, MD, MPH,* Andrew P. DeFilippis, MD, MSc,* Matthew J. Budoff, MD,† Khurram Nasir, MD, MPH,*‡ Roger S. Blumenthal, MD,* Steven R. Jones, MD*

Baltimore, Maryland; Torrance, California; and New Haven, Connecticut

Baseline coronary artery calcification (CAC) accurately identifies coronary atherosclerosis and might improve prediction of future cardiac events. Serial assessment of CAC scores has been proposed for monitoring atherosclerosis progression and for assessing the effectiveness of medical therapies aimed at reducing cardiac risk. However, whether knowledge of progression of CAC scores over time further improves risk prediction is unclear. Several trials relating medical therapies to CAC progression have been performed without any formal guidelines on the definition of CAC progression and how it is best quantified. We conducted a comprehensive review of published reports on CAC progression. Increased CAC progression is associated with many known cardiac risk factors. We found that CAC progression correlates with worsening atherosclerosis and may facilitate prediction of future cardiac events. These findings support the notion that slowing CAC progression with therapeutic interventions might provide prognostic benefit. However, despite promising early data, such interventions (most notably with statin therapy) have not been shown to slow the progression of CAC in any randomized controlled trial to date, outside of post hoc subgroup analyses. Thus, routine quantification of CAC progression cannot currently be recommended in clinical practice. First, standards of how CAC progression should be defined and assessed need to be developed. In addition, there remains a need for further studies analyzing the effect of other cardiac therapies on CAC progression and cardiac outcomes. (J Am Coll Cardiol 2010;56:1613–22) © 2010 by the American College of Cardiology Foundation

Atherosclerosis is a dynamic process, as demonstrated by studies documenting both plaque progression and regression (1). Coronary artery calcification (CAC) is characteristic of atherosclerosis (2) and should also be considered a dynamic process subject to influence by environmental factors and therapeutic interventions.

Baseline measures of CAC, as quantified by cardiac computed tomography (CT), have been shown to predict future cardiovascular events in multiple populations (3). This has led to a Class IIb recommendation by the American Heart Association (AHA) for the use of CAC quantification in intermediate risk patients to improve risk assessment (4). However, no formal recommendations exist regarding the clinical use of CAC progression.

From the *Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland; †Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor–University of California at Los Angeles, Torrance, California; and the ‡Section of Cardiovascular Medicine, Yale University, New Haven, Connecticut. Dr. DeFilippis is supported by a National Research Service Award (NRSA) Training Grant (T32-HL-07227). Dr. Budoff is on the Speakers' Bureau of GE. Dr. Jones has received research grant support from Atherotech and served as a consultant to Abbott Pharmaceuticals. All other authors have reported that they have no relationships to disclose.

Manuscript received November 24, 2009; revised manuscript received June 14, 2010, accepted June 15, 2010.

CAC progression has the potential to better capture temporal exposure to risk factors as compared with a baseline CAC score. For example, baseline CAC can be thought of as a single point on an atherosclerosis versus time curve, whereas progression correlates with the slope of that curve. Thus, CAC progression may also be more predictive of future coronary heart disease events than any current traditional risk factors, all of which are static clinical parameters. Similarly, although baseline CAC might reflect prior coronary atherosclerotic plaque burden, CAC progression might provide insight into ongoing current disease activity.

In this report, we focus on CAC progression rather than baseline assessment of CAC. We review the pathophysiologic understanding of CAC progression, the influence of clinical parameters on CAC progression, and treatment strategies aimed at slowing this progression. Recommendations for quantifying CAC progression and identifying areas in need of future research are also discussed.

Pathophysiology of CAC Progression

In brief, the presence of subintimal coronary calcification is characteristic of atherosclerosis (Fig. 1) (5). The AHA

Abbreviations and Acronyms

AHA = American Heart Association
AU = Agatston unit
CAC = coronary artery calcification
CRP = C-reactive protein
CT = computed tomography
CVS = calcium volume score
EBCT = electron beam computed tomography
LDL-C = low-density lipoprotein cholesterol
MDCT = multidetector computed tomography
RCT = randomized controlled trial

endorses a usual pattern of atherosclerosis progression in which coronary calcification appears in type 5 lesions (fibroatheroma) downstream from type IV lesions (formed atheroma). This occurs as a consequence of type-4 lesion instability and rupture, with subsequent calcification as part of the healing process (Fig. 1) (6). This process has some resemblance to bone formation (7,8). The formation of calcification in healing plaques has led to speculation that local CAC progression might correlate with progression of noncalcified plaque to more pathologically stable calcified plaque. For instance, acute coronary syndromes are associated with a relative lack of calcium in the culprit stenoses compared with stenoses of patients with stable angina (9). However, despite the potential local stability of CAC plaque, experimental studies suggest that intimal calcification might itself induce further inflammation and calcification in a positive feedback loop, driving CAC progression further in patients with positive baseline CAC (10).

Measuring CAC Progression

Two modes of cardiac CT can be employed for CAC quantification, electron beam computed tomography (EBCT) and multidetector computed tomography (MDCT). Electron beam computed tomography allows faster imaging by moving the X-ray source-point electronically rather than mechanically. Advantages of MDCT are its higher spatial resolution and cheaper cost. To achieve level 2 certification in cardiac CT, one must complete at least 2 months of training and have performed a minimum of 50 cases and interpreted a minimum of 150 cases (11).

CAC is defined as a hyper-attenuating lesion >130 Hounsfield units with an area of ≥3 pixels. Baseline CAC has been quantified by several methods. The Agatston unit (AU) score is calculated by multiplying the lesion area (mm^2) by a density factor (between 1 and 4) (12). Because of the stepwise nature of the density factor, changes in the Agatston score might not accurately capture changes in coronary calcium. In contrast to the AU, the calcium volume score (CVS) represents an actual volume of CAC and reduces variability between scans (13) (as does the CAC mass score [14]). The CVS might also have more biological plausibility, because an increase in Agatston score might represent an increase in plaque attenuation over time, not an increase in plaque size.

Progression can be quantified as absolute change in either AU or CVS score or as percentage relative change. However, there is no current standardization of how progression should be assessed and exactly what meaningful "progression" constitutes. For example, interscan variability means that simply classifying progression as any increase in CAC score might be inaccurate.

An original pilot study documented a "usual" CAC progression rate of 24% increase each year (15). This was a follow-up study of 88 patients (55% male) with a mean age of 46 years, a mean systolic blood pressure of 118 mm Hg, and mean total cholesterol of 197 mg/dl. Annual rates ranging from 20% to 30% have since been reported in patients at average Framingham risk in other studies (16,17).

CAC progression: methodology and variability. Measurement of CAC progression depends on accurate reproducibility of CAC scores (Table 1) (13,14,18–21). In general, interscan variability increases as levels of baseline CAC increase and can introduce a bias in the evaluation of CAC progression (18). Thus, measuring progression by change in absolute CAC can introduce an overestimation of the actual progression of atherosclerosis in subjects with high baseline CAC as compared with those with low baseline CAC. Using the percentage change in CAC has the opposite effect—overestimating the true progression of atherosclerosis in those with low baseline CAC. To illustrate, a score of 6 progressing to 9 is a relative increase of 50%, which is the same as for a score of 100 progressing to 150.

Reducing variability between scans is paramount to accurately quantify progression. Improved image acquisition and electrocardiographic gating (21) with EBCT has reduced the mean interscan variability to between 16% and 19% (22).

Mathematical transformations of the CVS have been attempted to further reduce variability. The logistic transformation has been used with some success (23). Hokanson et al. (18) found that the square root transformation of CVS provides a stable estimate of interscan variability across the range of baseline CAC. They suggested using a progression of square root–transformed CVS of ≥2.5 mm^3 to signify a significant change in CVS. A change of this magnitude is <1% likely to be due to interscan variability. Square root transformation can also be applied to AU but has not been studied in this regard.

Budoff et al. (24) found that the Hokanson method of CAC progression was the most accurate predictor of mortality ($p < 0.0001$) in 4,609 patients followed for a mean of 6 years after controlling for baseline CAC, age, sex, and follow-up time between scans.

Most of the aforementioned studies were performed with EBCT imaging, because MDCT initially suffered from increased variability due to reduced temporal resolution and retrospective gating (25). However, recent improvements in imaging protocols have decreased MDCT variability significantly, such that it now equates with EBCT (26).

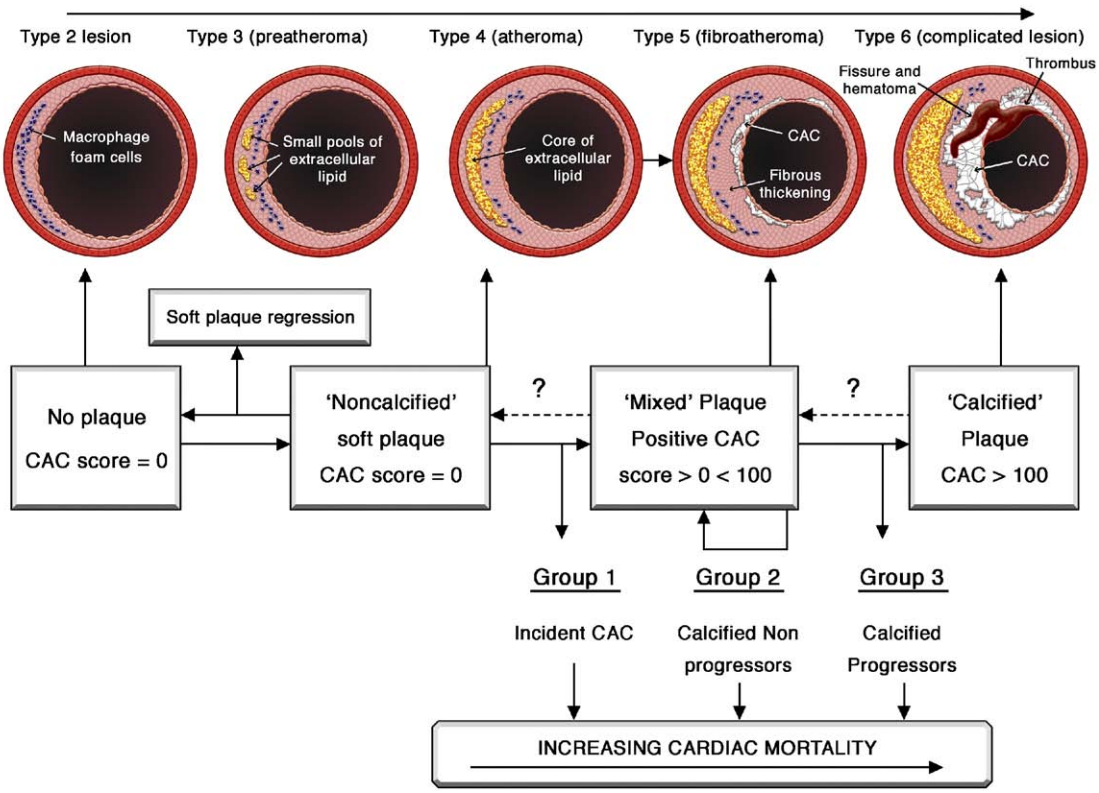

Figure 1 **Pathophysiology of CAC Progression**

Increasing coronary artery calcification (CAC) increases risk for future events. CAC progression occurs in 3 subgroups: 1) incident CAC; 2) calcified nonprogressors; and 3) CAC progressors. See the text for further details. The correlation of plaque type with CAC score in this figure is for descriptive purposes only, and the numbers are not part of any formal classification. Once calcification predominates in type 6 lesions they become known as type 7 "calcified" lesions.

Thus, interscan variability by either modality is now below the expected annual rate of CAC progression (<20%) (15–17).

Other limitations of CAC progression application. Advances in CAC quantification methodology over time have hampered the comparison of datasets. This is due to varying methods of image acquisition (EBCT vs. MDCT) (23,27), varying cutoffs for a positive score (2 to 4 pixels of >130 Hounsfield units), varying score reports (Agatston vs. CVS) (23), and different timing of image acquisition within the cardiac cycle (80% of RR interval vs. 40%) (28). The use of different measures of "progression" (absolute change vs. relative change vs. transformed), which yield differing results, also complicates this issue. Standardized guidelines are necessary to guide research efforts and allow comparisons between studies in the field.

Measuring CAC progression also requires sequential CT scans, with a cumulative radiation exposure. Prior reports have raised concern about the excess risk of cancer with such an approach (29). However, such estimates will become outdated as current gating technology has reduced the radiation dose, with an achievable dose of <1 mSv/scan.

Table 1 **Variability of CAC: Baseline and Progression**

Baseline CAC		CAC Progression	
Measure	**Variability**	**Measure**	**Variability**
AU	Reference measure	Absolute change	Variability increases as baseline of absolute CAC increases (18)
CVS	32% reduced vs. AU (13,14) 9% reduced vs. AU (23)	Percentage change	Underestimates changes at higher levels of baseline CAC (19)
CAC mass	54% reduced vs. AU (14)	Log transformation	Variability still depends on the mean CVS (rho = −0.66, $p < 0.0001$) (18)
		Square root transformation (Hokanson)	Removes the relation between variability and the mean CVS (rho = 0.09, $p < 0.15$) (18)
		Regression method	Variance increases with increased mean CAC area (20)

AU = Agatston units; CAC = coronary artery calcification; CVS = calcium volume score.

This compares favorably with other cardiac imaging modalities used for risk stratification (>8 mSv for a sestamibi cardiac stress test).

The conscientious physician should also bear in mind that diagnosing an asymptomatic subclinical disease can raise anxiety and reduce future quality of life (30). Extracardiac "incidentalomas" are found in approximately 8% of cardiac CTs, and the ramifications of such findings are often unclear (31).

Clinical Determinants of CAC Progression

Studies relating clinical risk factors to CAC progression. Table 2 provides an overview of studies relating traditional cardiac risk factors to CAC progression (31–39). This table demonstrates that CAC progression has been related to all traditional risk factors but that the relationship is not always consistent between studies. This finding might be a reflection of baseline cohort demographics or the measure of CAC progression used.

These traditional risk factors interact together when influencing CAC progression. For example, Berry et al. (40) have shown that, even among 2,988 study participants with low 10-year risk of a cardiac event, those with a high lifetime risk had significantly greater annual CAC progression (22% vs. 15% in men; 9% vs. 5% in women) compared with those with a low lifetime risk.

Some studies have also analyzed the effect of emerging novel cardiac risk factors on CAC progression. Such novel markers associated with CAC progression include: C-reactive protein (CRP) (41), Cystatin-C (42), polymorphisms of the renin-angiotensin genes (43), and low adiponectin levels (44).

Imaging parameters. In addition to being representative of the pathophysiologic sum of prior cardiac risk factors, baseline CAC score by cardiac CT is itself one of the most consistent predictors of future CAC progression (45,46). Gopal et al. (47) demonstrated that 62% of individuals with zero CAC did not develop any calcification, whereas only 2% had CAC progression >50 AUs at follow-up of 5 years.

Other cardiac risk stratification imaging modalities have been studied with regard to their relationship with CAC progression. Notably, increased carotid intima-media thickness (48) by ultrasound (increasingly being used a surrogate in cardiac clinical trials) and baseline thoracic aortic calcium (49) (less relevant to practice, because this is calculated by cardiac CT at the same time that CAC is quantified) have also been correlated with CAC progression. The clinical relevance of these associations remains to be defined; for now they serve to highlight the systemic nature of atherosclerosis.

Clinical Implications of CAC Progression

Angiographic measures of atherosclerosis progression have been shown to predict clinical coronary events (50). However, these findings cannot be directly extrapolated to CAC progression, because calcification only forms part of the plaque seen at angiography (Fig. 1). Given that this calcified plaque might be more clinically stable (9), one might arrive at the conclusion that cardiac risk does not increase with CAC progression. However, this heuristic has been refuted by available data (51).

Alternatively, increased local coronary calcification might be associated with increased cardiac risk by its association with increased total plaque burden, including both noncalcified and mixed plaque subtypes (Fig. 1). Because less mature plaques calcify after they rupture and heal, new highly calcified lesions might represent a propensity for active atherosclerosis deposition and rupture throughout the coronary tree. Research also suggests that mixed plaques, which contain early calcification near the plaque shoulders, increase the propensity for plaque fracture (52).

This viewpoint has the support of emerging epidemiologic data. Shemesh et al. (53) found a higher annual progression rate (180% increased from baseline score) in patients who had coronary events compared with those who did not ($p < 0.05$). Another early retrospective study of 485 asymptomatic patients treated with statins found a relative risk of 17.2 for development of first myocardial infarction with CAC progression ≥15% (progressors) versus <15% (nonprogressors) over 3-year follow-up (54).

Raggi et al. (55) related the occurrence of myocardial infarction with CAC progression in 817 asymptomatic subjects referred for sequential EBCT imaging (average interval 2 years). The yearly mean absolute CVS change in the 45 patients who had a myocardial infarction was 147, compared with 63 in those patients without events ($p < 0.001$).

The St. Francis Heart Study prospectively evaluated the prognostic accuracy of CAC progression in the prediction of cardiac events in 4,613 adults between 50 and 70 years of age. Follow-up was over 4.3 years, and events occurred in 119 subjects (2.6%). In those without a cardiac event the median increase in CAC score was 4 AU. In contrast, those with a cardiac event had a median progression of CAC score of 247 (51).

CAC Progression and Therapeutic Interventions

For descriptive purposes and to facilitate accurate research discourse, we propose a schema for CAC progression and the response of CAC to treatment that describes 3 subgroups (Fig. 1).

1. Incident CAC, defined as detectable CAC at the follow-up examination in a participant initially free of CAC (41).
2. Calcified nonprogressor, defined as an unchanged or reduced CAC score in participants with detectable CAC at baseline.
3. Calcified progressor, defined as an increase in CAC score in participants with detectable CAC at the initial exam-

Table 2 Cardiac Risk Factors Associated With CAC Progression

Study/First Author (Ref. #)	Study Details	Blood Pressure	Cholesterol	Age	Diabetes	FBG/HbA1c/MA/IR	Male Sex	Smoking	Ethnicity	Family History of CHD	Obesity/BMI	Metabolic Syndrome	Novel Markers
MESA (41)	n= 5,756 48% men Mean baseline age 62 yrs Baseline total cholesterol: NR (14% on Rx) Interval to follow-up CAC scan: 2.4 yrs Method: natural logarithm + 25 difference in AU*	✓	✓	✓	✓	✓ FBG, ✓ MA	✓	✓	✓ White	✓	✓	X	NR
ECAC (32)	n = 877 46% men Mean baseline age 56 yrs Baseline total cholesterol: NR Interval to follow-up CAC scan: 7.3 yrs Method: log change in CAC area*	✓	✓ LDL	✓	X	NR	✓	✓	NR	X	✓ Waist:hip	NR	✓ Genetic
Rancho Bernado (33,34)	n = 338 46% men Mean baseline age 68 yrs Baseline total cholesterol: 208 mg/dl Interval to follow-up CAC scan: 4.5 yrs Method: Hokanson*	✓	A	A	X	✓ FBG	A	A	NR	NR	✓ Abdominal obesity	✓ WHO	NR
Lee et al. (35)	n = 869 62% men Mean baseline age 66 yrs Baseline total cholesterol: 205 mg/dl Interval to follow-up CAC scan: 1 yr Method: Hokanson*	✓	✓	X	✓	✓ IR	X	X	✓ White	X	X	NR	X CRP
Costacou et al. (36)	n = 222 type 1 DM 47% men Mean baseline age 38 yrs Baseline total cholesterol: 190 mg/dl Interval to follow-up CAC scan: 4 yrs Method: Hokanson (AU)*	✓	✓	✓	A	✓ MA X A1c	X	X	NR	NR	✓	NR	NR
Anand et al. (37)	n = 398 type 2 DM 61% men Mean baseline age 52 yrs Baseline total cholesterol: 187 mg/dl Interval to follow-up CAC scan: 2.5 yrs Method: Hokanson (CVS)*	✓	X	✓	✓ DM duration	✓ A1c >7	✓	X	White	NR	✓ Waist:hip	NR	✓ IL-6 ✓ OPG X CRP
PREDICT (38)	n = 202 type 2 DM 68% men Mean baseline age 62 yrs Baseline total cholesterol: 187 mg/dl Interval to follow-up CAC scan: 4 yrs Method: CVS/AU annualized*	✓	X	✓	X DM duration	✓ MA	✓	X	NR	NR	X BMI ✓ Waist:hip	X	X CRP
South Bay Heart watch (39)	n = 828 88% men Mean baseline age 63 yrs Baseline total cholesterol: NR Interval to follow-up CAC scan: 7 yrs Method: log transformed AU*	X	HDL	✓	✓	NR	X	X	✓ White + Asian/ Pacific Islanders	NR	✓	NR	NR

*Method used to quantify CAC progression.

A = adjusted for in analysis; BMI = body mass index; CHD = coronary heart disease; CRP = C-reactive protein; DM = diabetes mellitus; ECAC = Epidemiology of Coronary Artery Calcification; FBG = fasting blood glucose; Hb = hemoglobin; HDL = high-density lipoprotein; IL = interleukin; IR = insulin resistance; LDL = low-density lipoprotein; MA = micro-albuminuria; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; OPG = osteoprotegerin; PREDICT = patients with renal impairment and diabetes undergoing computed tomography; WHO = World Health Organization definition for metabolic syndrome; X = not associated with CAC progression; ✓ = significantly associated with CAC progression; other abbreviations as in Table 1.

ination (41). This measure should account for interscan variability and be clinically meaningful. For example, Raggi et al. (54) suggested a ≥15%/year change in CVS; Hokanson et al. (18) suggest a difference of ≥2.5 mm^3 between the follow-up and baseline square root–transformed CVS.

Published reports relating to CAC progression and therapeutic interventions are best categorized into statin studies and nonstatin studies (Table 3) (17,54,56–69).

Statin Studies

Statins reduce clinical cardiac end points across a spectrum of patient populations (70). It seemed intuitive to early researchers that statins should reduce the progression of CAC. This was an attractive venture, because CAC quantification could be used as a surrogate for events, potentially reducing the number of patients needed to evaluate the effectiveness of an intervention. However, the enthusiasm promised by the results of early retrospective and prospective studies in this field (Table 3) did not bear fruit in randomized controlled trials (RCTs).

SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) randomized 102 patients to atorvastatin or placebo and assessed CAC progression over an average follow-up of 2 years. Despite a significant reduction in low-density lipoprotein cholesterol (LDL-C) and CRP levels, there was a nonsignificant increase in percentage CAC progression (26%/year with atorvastatin vs. 18%/year with placebo) (60). An RCT by Terry et al. (61) with 80 subjects also found no difference in CAC progression in those treated with 80 mg of simvastatin versus placebo over 12 months (9% vs. 5%).

Another double-blind RCT by Schmermund et al. (62) failed to show reduced progression of CAC in 366 asymptomatic patients randomized to either 10 or 80 mg of atorvastatin over 12 months. This was despite a 20% additional reduction in LDL-C in the 80-mg atorvastatin treatment group.

Although prior trials studied mostly men, 1 early study documented CAC progression in post-menopausal women (71). The BELLES (Beyond Endorsed Lipid Lowering with EBCT Scanning) study was an RCT of hyperlipidemic post-menopausal women randomized to atorvastatin 80 mg or pravastatin 40 mg. Most of the 4,739 screened were excluded for lipid levels below cutoff (63%) or baseline CVS <30 (42%). Of the 615 randomized, 475 received a follow-up EBCT at 1 year. Atorvastatin reduced LDL-C by 47%, whereas pravastatin reduced LDL-C by 25%. There was no significant difference in CVS progression after 12 months with an increase of 15% in the atorvastatin arm and an increase of 14% for pravastatin (63). This study was limited by lack of a placebo group.

Most CAC RCTs have compared LDL-C reduction with CAC progression. An inherent weakness in these trials is the use of surrogates for clinical events. There remains a need for studies to correlate statin treatment with both CAC progression and cardiac events. The St. Francis Heart Study is the only such trial to date. This was a double-blind RCT of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1,000 U daily versus matching placebos in 1,005 patients with coronary calcium scores at or above the 80th percentile for age and sex. Mean baseline LDL-C was 146 mg/dl, and CRP was 1.99 mg/l. Despite significant reductions in LDL over a treatment course of 4.3 years, there was no effect on CAC progression. There was a non-statistically significant 30% reduction in cardiac events in the overall cohort ($p = 0.08$). However, there was a significant 42% reduction in events in treated patients who had CAC >400 at baseline (8.7% vs. 15.0%, $p = 0.046$) (64), suggesting that these patients might be suitable candidates for future primary prevention statin-CAC trials in a fashion similar to a CRP ≥2 mg/l in JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) (72).

So, why have statins been unsuccessful in reducing CAC progression? The AHA model of atherosclerosis, where plaque evolves from a noncalcified lesion to a calcified one, is useful in conceptualizing the issue (Fig. 1). It is possible to induce regression of the noncalcified portion of plaque with statin therapy (1). Whether this is possible with the calcified portion of plaque is unknown. Animal models suggest that a reduction in LDL-C does not decrease the amount of plaque calcification at histology (73). Pathologically, statins have been shown to promote microcalcification, which might lead to CAC score increases even when total atherosclerosis is reduced on statin therapy (73,74). This argument is bolstered by Burgstahler et al. (75), who used MDCT to assess CAC progression in men treated with 20 mg/day of atorvastatin. They found no effect on CAC progression but did note a significant reduction in noncalcified plaque burden. Also, when statins reduce the soft lipid core of a calcified plaque, the density of the plaque and its Agatston calcium score might increase, whereas its volume might decrease.

This might explain why some of the early risk factor studies found an increased CAC progression rate with statin therapy (although a major confounder is that those receiving statins have a history of dyslipidemia) (41). It seems doubtful that the small increase in the incidence of diabetes (a risk factor associated with increased CAC progression) associated with statin use is playing a role (76).

It is also possible that statins need more time to affect the downstream process of calcium deposition. Inadequate statin intensity is an unlikely explanation for failure to reduce CAC progression, given the study by Hecht and Harman (59) of 182 patients followed over 1.2 years that failed to show a difference in CAC progression in those treated to an LDL-C <80 mg/dl compared with those with more liberal goals.

Finally, in the early observational studies, statin therapy might have introduced confounding if associated with better

Table 3 CAC Progression: Therapeutic Studies to Date

First Author/Study (Ref. #)	Study Type	Treatment Modality	Patients (n)	% Baseline CAC = 0; Mean Baseline CAC	Follow-Up, yrs	Baseline LDL and LDL After Treatment	Change in CAC Progression Rate (%)	Event Data
Statin studies								
Callister et al. (56)	Retrospective	Any statin vs. no statin	149	Unreported 750 CVS	1	Unreported baseline vs. LDL <120 mg/dl	45% reduced	No
Raggi et al. (44)	Retrospective	Any statin vs. no statin	495	0% 327 CVS	3	Mean LDL 118 mg/dl vs. 122 mg/dl (p = NS)	35% reduced	No
Budoff et al. (17)	Prospective	Any statin vs. no statin	131	27% 394 AU	2	Not reported	61% reduced	No
Budoff et al. (57)	Prospective diabetic only	Any statin vs. no statin	163	6% 651 AU	1	Not reported	50% reduced	No
Achenbach et al. (58)	Prospective	Cerivastatin vs. no statin	66	Unreported 155 CVS	2	Mean LDL from 164–107 mg/dl with statin	64% reduced	No
Hecht and Harman (59)	Prospective	Intensive statin Rx–LDL <80 mg/dl vs. liberal statin Rx	182	Unreported 450 AU	1	LDL 201–65 mg/dl with intensive Rx, 221–101 with liberal Rx	No change	No
SALTIRE (60)	RCT	Atorvastatin vs. placebo	102	24% 215 AU	2	Mean LDL from 135–67 mg/dl with statin	44% increased (p = NS)	No
Terry et al. (61)	RCT	Simvastatin vs. placebo	80	0% 650 AU	1	Mean LDL from 128–75 mg/dl with statin	No change	No
Schmermund et al. (62)	RCT	80 mg atorvastatin vs. 10 mg atorvastatin	366	Uunreported 450 AU	1	LDL from 106–87 mg/dl with 80 mg, no change with 10 mg	No change	No
BELLES (63)	RCT	80 mg atorvastatin vs. 40 mg pravastatin	475	0% (CVS <30 excluded) 235 CVS	1	LDL 175–92 mg/dl with atorvastatin, 173–129 mg/dl with pravastatin	No change	No
St. Francis Heart Study (64)	RCT	20 mg atorvastatin vs. placebo	1,005	Unreported 545 AU	4	LDL 146–98 mg/dl with statin	No change	Yes, no overall difference
Nonstatin studies								
Budoff et al. (65)	Prospective	Estrogen only HRT vs. no HRT/combined HRT	177	Unreported	1	Not reported	63% reduced with estrogen only HRT	No
Motro et al. (66)	RCT, subgroup	Nifedipine vs. amiloride/HCTZ	376	0% 110 AU	3	Not reported	50% reduced at 3 years	No
Budoff et al. (67)	RCT	Aged garlic extract vs. placebo	65	Unreported 320 CVS	1	LDL 105–90 mg/dl with Rx, no change with placebo	75% reduced	No
Chertow et al. (68)	RCT	Sevelamer vs. calcium-based phosphate binders	200	17% 1,418 AU	4	LDL 102–65 mg/dl with Rx, no change with calcium	75% reduced	Yes, mortality reduced 5.3/100 patient-yrs
Qunibi et al. (69)	RCT, nonblinded	Intensive LDL (<70 mg/dl) with statins + sevelamer vs. calcium PO4 binders	203	0% (CVS <30 excluded) 1,033 AU	1	LDL 108–62 mg/dl with sevelamer, 112–69 mg/dl with calcium	No change	No

BELLES = Beyond Endorsed Lipid Lowering with EBCT Scanning; HRT = hormone replacement therapy; LDL = low density lipoprotein; RCT = randomized control trial; Rx = treatment; SALTIRE = Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression; other abbreviations as in Table 1.

generalized cardiac care. The subsequent RCTs likely controlled for this possibility and might have ameliorated the effect seen. More studies evaluating the effect of other established cardiac preventive medications and their relationship to CAC progression and cardiac outcomes are needed.

Nonstatin Studies

There is a paucity of data on whether treating other cardiac risk factors can reduce CAC progression. In a subgroup of 201 patients from INSIGHT (International Nifedipine Study: Intervention as Goal for Hypertension Therapy), nifedipine demonstrated significant inhibition of coronary calcium progression over 3 years compared with amiloride/hydrochlorothiazide (40% vs. 78%, $p = 0.02$) (66). Similar encouraging results have been found with unopposed estrogen hormone replacement (65) and aged garlic extracts and supplements (67).

Cardiovascular mortality rates in dialysis patients are, on average, 30-fold higher than the general population (77). Bursztyn et al. (78) also found that, among high-risk hypertensive patients, even mild renal dysfunction is associated with faster CAC progression. Chertow et al. (68) found that, compared with calcium-based phosphate binders, sevelamer is associated with less progressive coronary calcification in hemodialysis patients at 1 year. Sevelamer is known to reduce LDL-C levels, independent of other medications. In a trial with concomitant intensive lowering of LDL-C levels for 1 year, hemodialysis patients treated with either calcium acetate plus atorvastatin versus sevelamer plus atorvastatin experienced similar progression of CAC (69).

Recommendations and Future Directions

There are currently no published guidelines for physicians or researchers who wish to quantify progression of subclinical atherosclerosis by CAC. The limited data to date suggest that CAC progression may be a more accurate predictor of future cardiac risk than baseline CAC alone (51). However, the clinical utility of this is unknown. No prospective comparison has been undertaken to evaluate therapy decisions based on serial CAC scanning versus baseline CAC scanning alone. Such a study would need to justify the repeat exposure to radiation needed to quantify progression.

Therefore, serial CAC quantification cannot be routinely recommended on the basis of current evidence. However, we believe it has considerable potential as a noninvasive measure of the progression of atherosclerosis and might have ongoing applicability to the study of interventions targeted at reducing this progression. Further research is needed to explore whether this potential can be fulfilled.

We recommend the transformed square root method of Hokanson for quantifying progression, because it minimizes both variability and the effect of the baseline score on progression. We recommend that CAC scores be reported by CVS, with or without Agatston scores, to facilitate universal comparisons of CAC progression by the Hokanson method across future trials.

Future directions in research include: prospectively studying the difference in predictive power between baseline CAC alone and CAC progression, further evaluating the effect of both traditional and novel cardiac risk factors on CAC progression to better understand their relationship to atherosclerosis, study of other established (nonstatin) cardiac medications to explore their relationship to CAC progression and cardiac outcomes, and studying the optimal time interval for measuring progression. With regard to the latter, Min et al. (46) have prospectively found that incident CAC occurs at low frequency before 4 years in those with baseline low to intermediate risk and 0-baseline CAC. The optimal time for retesting those with positive baseline CAC (CAC progressors) remains unknown, although this interval will likely be related to the severity of baseline CAC (46).

Conclusions

Progression of CAC is associated with multiple cardiac risk factors. In most observational studies, increased rates of CAC progression have been shown to increase the risk for future cardiac events. Despite this, there has been a lack of success in retarding CAC progression with statin therapy, underscoring the point that CAC progression might not equate exactly with pathologic atherosclerosis progression. Little is known of the clinical implications of decreasing CAC progression with therapy, and it is unclear whether decreased CAC progression can be achieved with currently available medications. The best measure of CAC progression seems to be the Hokanson method, but no prospective comparisons have been performed between the various measurement options. More prospective data are needed to further elucidate whether quantifying CAC progression can be recommended for cardiac risk stratification in clinical practice or can be used as a surrogate for clinical end points in future therapeutic trials.

Acknowledgment
The authors would like to thank Dr. Allen J. Taylor from the Cardiology Division of Washington Hospital Center for his thoughts and input in preparing this paper.

Reprint requests and correspondence: John W. McEvoy, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, 600 North Wolfe Street, Carnegie 568B, Baltimore, Maryland 21287. E-mail: jmcevoy1@jhmi.edu.

REFERENCES

1. 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;295:1556–65.
2. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical impli-

cations. A statement for health professionals from the American Heart Association Writing Group. Circulation 1996;94:1175–92.
3. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–5.
4. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol 2000;36:326–40.
5. Bostrom K. Insights into the mechanism of vascular calcification. Am J Cardiol 2001;88:20E–2E.
6. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol 1995;15:1512–31.
7. Fitzpatrick LA, Severson A, Edwards WD, Ingram RT. Diffuse calcification in human coronary arteries. Association of osteopontin with atherosclerosis. J Clin Invest 1994;94:1597–604.
8. Van Campenhout A, Golledge J. Osteoprotegerin, vascular calcification and atherosclerosis. Atherosclerosis 2009;204:321–9.
9. Beckman JA, Ganz J, Creager MA, Ganz P, Kinlay S. Relationship of clinical presentation and calcification of culprit coronary artery stenoses. Arterioscler Thromb Vasc Biol 2001;21:1618–22.
10. Nadra I, Mason JC, Philippidis P, et al. Proinflammatory activation of macrophages by basic calcium phosphate crystals via protein kinase C and MAP kinase pathways: a vicious cycle of inflammation and arterial calcification? Circ Res 2005;96:1248–56.
11. Thomas JD, Zoghbi WA, Beller GA, et al. ACCF 2008 training statement on multimodality noninvasive cardiovascular imaging: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training. J Am Coll Cardiol 2009;53:125–46.
12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
13. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998;208:807–14.
14. Hong C, Bae KT, Pilgram TK. Coronary artery calcium: accuracy and reproducibility of measurements with multi-detector row CT—assessment of effects of different thresholds and quantification methods. Radiology 2003;227:795–801.
15. Maher JE, Bielak LF, Raz JA, Sheedy PF II, Schwartz RS, Peyser PA. Progression of coronary artery calcification: a pilot study. Mayo Clin Proc 1999;74:347–55.
16. Schmermund A, Baumgart D, Mohlenkamp S, et al. Natural history and topographic pattern of progression of coronary calcification in symptomatic patients: an electron-beam CT study. Arterioscler Thromb Vasc Biol 2001;21:421–6.
17. Budoff MJ, Lane KL, Bakhsheshi H, et al. Rates of progression of coronary calcium by electron beam tomography. Am J Cardiol 2000;86:8–11.
18. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. AJR Am J Roentgenol 2004;182:1327–32.
19. Lu B, Budoff MJ, Zhuang N, et al. Causes of interscan variability of coronary artery calcium measurements at electron-beam CT. Acad Radiol 2002;9:654–61.
20. Bielak LF, Sheedy PF II, Peyser PA. Coronary artery calcification measured at electron-beam CT: agreement in dual scan runs and change over time. Radiology 2001;218:224–9.
21. Mao S, Bakhsheshi H, Lu B, Liu SC, Oudiz RJ, Budoff MJ. Effect of electrocardiogram triggering on reproducibility of coronary artery calcium scoring. Radiology 2001;220:707–11.
22. Budoff MJ, Raggi P. Coronary artery disease progression assessed by electron-beam computed tomography. Am J Cardiol 2001;88:46E–50E.
23. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility—MESA study. Radiology 2005;236:477–84.
24. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010. In press.
25. Budoff MJ, Mao S, Zalace CP, Bakhsheshi H, Oudiz RJ. Comparison of spiral and electron beam tomography in the evaluation of coronary calcification in asymptomatic persons. Int J Cardiol 2001;77:181–8.
26. Budoff MJ, McClelland RL, Chung H, et al. Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the Multi-Ethnic Study of Atherosclerosis. AJR Am J Roentgenol 2009;192:613–7.
27. Mao SS, Pal RS, McKay CR, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64-multidetector computed tomographic scanner. J Comput Assist Tomogr 2009;33:175–8.
28. Lu B, Zhuang N, Mao SS, et al. EKG-triggered CT data acquisition to reduce variability in coronary arterial calcium score. Radiology 2002;224:838–44.
29. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med 2009;169:1188–94.
30. Feldman W. How serious are the adverse effects of screening? J Gen Intern Med 1990;5 Suppl:S50–3.
31. Horton KM, Post WS, Blumenthal RS, Fishman EK. Prevalence of significant noncardiac findings on electron-beam computed tomography coronary artery calcium screening examinations. Circulation 2002;106:532–4.
32. Cassidy-Bushrow AE, Bielak LF, Sheedy PF II, et al. Coronary artery calcification progression is heritable. Circulation 2007;116:25–31.
33. Kramer CK, von Muhlen D, Gross JL, Barrett-Connor E. A prospective study of abdominal obesity and coronary artery calcium progression in older adults. J Clin Endocrinol Metab 2009;94:5039–44.
34. Kramer CK, von Muhlen D, Gross JL, Laughlin GA, Barrett-Connor E. Blood pressure and fasting plasma glucose rather than metabolic syndrome predict coronary artery calcium progression: the Rancho Bernardo Study. Diabetes Care 2009;32:141–6.
35. Lee KK, Fortmann SP, Fair JM, et al. Insulin resistance independently predicts the progression of coronary artery calcification. Am Heart J 2009;157:939–45.
36. Costacou T, Edmundowicz D, Prince C, Conway B, Orchard TJ. Progression of coronary artery calcium in type 1 diabetes mellitus. Am J Cardiol 2007;100:1543–7.
37. Anand DV, Lim E, Darko D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes role of glycemic control and inflammatory/vascular calcification markers. J Am Coll Cardiol 2007;50:2218–25.
38. Elkeles RS, Godsland IF, Rubens MB, Feher MD, Nugara F, Flather MD. The progress of coronary heart disease in Type 2 diabetes as measured by coronary calcium score from electron beam computed tomography (EBCT): the PREDICT study. Atherosclerosis 2008;197:777–83.
39. Kawakubo M, LaBree L, Xiang M, et al. Race-ethnic differences in the extent, prevalence, and progression of coronary calcium. Ethn Dis 2005;15:198–204.
40. 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;119:382–9.
41. 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;115:2722–30.
42. Maahs DM, Ogden LG, Kretowski A, et al. Serum cystatin C predicts progression of subclinical coronary atherosclerosis in individuals with type 1 diabetes. Diabetes 2007;56:2774–9.
43. Kretowski A, McFann K, Hokanson JE, et al. Polymorphisms of the renin-angiotensin system genes predict progression of subclinical coronary atherosclerosis. Diabetes 2007;56:863–71.
44. Maahs DM, Ogden LG, Kinney GL, et al. Low plasma adiponectin levels predict progression of coronary artery calcification. Circulation 2005;111:747–53.
45. Yoon HC, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: progression of coronary artery calcification in asymptomatic subjects. Radiology 2002;224:236–41.

46. 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;55:1110–7.
47. Gopal A, Nasir K, Liu ST, Flores FR, Chen L, Budoff MJ. Coronary calcium progression rates with a zero initial score by electron beam tomography. Int J Cardiol 2007;117:227–31.
48. Taylor AJ, Bindeman J, Le TP, et al. Progression of calcified coronary atherosclerosis: relationship to coronary risk factors and carotid intima-media thickness. Atherosclerosis 2008;197:339–45.
49. Rivera JJ, Nasir K, Katz R, et al. Relationship of thoracic aortic calcium to coronary calcium and its progression (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol 1 2009;103: 1562–7.
50. Azen SP, Mack WJ, Cashin-Hemphill L, et al. Progression of coronary artery disease predicts clinical coronary events. Long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. Circulation 1996;93:34–41.
51. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–65.
52. Veress AI, Cornhill JF, Herderick EE, Thomas JD. Age-related development of atherosclerotic plaque stress: a population-based finite-element analysis. Coron Artery Dis 1998;9:13–9.
53. Shemesh J, Apter S, Stolero D, Itzchak Y, Motro M. Annual progression of coronary artery calcium by spiral computed tomography in hypertensive patients without myocardial ischemia but with prominent atherosclerotic risk factors, in patients with previous angina pectoris or healed acute myocardial infarction, and in patients with coronary events during follow-up. Am J Cardiol 2001;87:1395–7.
54. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24: 1272–7.
55. Raggi P, Cooil B, Shaw LJ, et al. Progression of coronary calcium on serial electron beam tomographic scanning is greater in patients with future myocardial infarction. Am J Cardiol 2003;92:827–9.
56. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. N Engl J Med 1998;339: 1972–8.
57. Budoff MJ, Yu D, Nasir K, et al. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005;149: 695–700.
58. 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;106:1077–82.
59. Hecht HS, Harman SM. Relation of aggressiveness of lipid-lowering treatment to changes in calcified plaque burden by electron beam tomography. Am J Cardiol 2003;92:334–6.
60. Houslay ES, Cowell SJ, Prescott RJ, et al. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. Heart 2006;92:1207–12.
61. Terry JG, Carr JJ, Kouba EO, et al. Effect of simvastatin (80 mg) on coronary and abdominal aortic arterial calcium (from the Coronary Artery calcification Treatment with Zocor [CATZ] study). Am J Cardiol 2007;99:1714–7.
62. 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: 427–37.
63. 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;112:563–71.
64. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. 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;46:166–72.
65. Budoff MJ, Chen GP, Hunter CJ, et al. Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography. J Womens Health (Larchmt) 2005;14:410–7.
66. Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. Hypertension 2001;37:1410–3.
67. Budoff MJ, Ahmadi N, Gul KM, et al. Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: a randomized clinical trial. Prev Med 2009;49:101–7.
68. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245–52.
69. Qunibi W, Moustafa M, Muenz LR, et al. 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;51:952–65.
70. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48:438–45.
71. Sutton-Tyrrell K, Kuller LH, Edmundowicz D, et al. Usefulness of electron beam tomography to detect progression of coronary and aortic calcium in middle-aged women. Am J Cardiol 1 2001;87:560–4.
72. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
73. Stary HC. The development of calcium deposits in atherosclerotic lesions and their persistence after lipid regression. Am J Cardiol 2001;88:16E–9E.
74. Wu B, Elmariah S, Kaplan FS, Cheng G, Mohler ER III. Paradoxical effects of statins on aortic valve myofibroblasts and osteoblasts: implications for end-stage valvular heart disease. Arterioscler Thromb Vasc Biol 2005;25:592–7.
75. Burgstahler C, Reimann A, Beck T, et al. Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the New Age II Pilot Study. Invest Radiol 2007;42:189–95.
76. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–42.
77. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9 Suppl:S16–23.
78. Bursztyn M, Motro M, Grossman E, Shemesh J. Accelerated coronary artery calcification in mildly reduced renal function of high-risk hypertensives: a 3-year prospective observation. J Hypertens 2003;21: 1953–9.

Key Words: atherosclerosis ■ cardiac CT ■ coronary artery calcium ■ progression ■ review.