

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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*Circulation* 2005;111;3236-3241; originally published online Jun 13, 2005;

DOI: 10.1161/CIRCULATIONAHA.104.489781

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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## Calcium Concentration of Individual Coronary Calcified Plaques as Measured by Multidetector Row Computed Tomography

Fabian Moselewski, BS; Christopher J. O'Donnell, MD, MPH; Stephan Achenbach, MD; Maros Ferencik, MD, PhD; Joe Massaro, PhD; Ann Nguyen, MD; Ricardo C. Cury, MD; Suhny Abbara, MD; Ik-Kyung Jang, MD, PhD; Thomas J. Brady, MD; Udo Hoffmann, MD

**Background**—Characteristics of individual calcified plaques, especially calcium concentration (CC), may provide incremental value to global calcium scores in the assessment of plaque burden and risk of coronary events and evaluation of therapeutic intervention. In this study, therefore, we assessed the characteristics of individual calcified plaques and their relationship to other parameters derived from CT analysis of coronary calcium in a community-based cross-sectional cohort.

**Methods and Results**—Coronary artery calcium (CAC) was analyzed in 612 participants of the Framingham Heart Study (third-generation and offspring cohorts) using prospectively ECG-triggered multidetector CT. We determined the CC, Agatston score, calcified volume, and mineral mass of individual calcified plaques in each subject. Heterogeneity of CC was defined as the standard deviation of CC of all individual calcified plaques in a subject. CAC was detected in 274 of 605 subjects. After excluding 57 subjects (21%) because of motion artifacts, we identified a total of 956 calcified coronary plaques in 217 subjects (74 women, 143 men; mean age,  $57.1 \pm 10.8$  years) with detectable CAC and no image artifacts. CC of individual calcified plaques was independent of subject age ( $P=0.76$ ) and sex ( $197.8 \pm 74.8$  versus  $183.6 \pm 52.8$  mg/cm<sup>3</sup> for men versus women;  $P=0.21$ ). Among a subgroup of 125 subjects with multiple ( $\geq 3$ ) individual calcified plaques, CC was heterogeneous within individual subjects (mean SD of CC,  $43.6 \pm 23.1$  mg/cm<sup>3</sup>). The degree of heterogeneity of CC in these subjects was independent of age ( $P=0.60$ ), sex ( $P=0.99$ ), and number of plaques ( $P=0.06$ ).

**Conclusions**—The CC of individual calcified plaques is independent of age and sex but heterogeneous within a subject, which may reflect that the pathological process of calcified plaque formation and progression is the same in men and women regardless of age. CC may have incremental value to global calcium scores in the assessment of plaque burden and risk of coronary events and the evaluation of therapeutic intervention. Further studies are warranted to confirm that individual plaque analysis is preferable to global CAC scores to evaluate progression of atherosclerosis and to assess whether individual plaque analysis may be complementary to global CAC measures to assess coronary event risk. (*Circulation*. 2005;111:3236-3241.)

**Key Words:** aging ■ atherosclerosis ■ calcification, physiologic ■ coronary disease ■ tomography

Computed tomography (CT) scanners with high spatial and temporal resolution allow reliable detection and quantification of coronary artery calcium (CAC).<sup>1-3</sup> Global measurements of CAC such as Agatston Score (AS) and calcified plaque volume (CV) have been used to estimate plaque burden<sup>4,5</sup> and to predict the risk for subsequent coronary events<sup>6-9</sup> in longitudinal studies. A small but growing number of serial CT studies using electron-beam CT (EBCT) technology have begun to examine plaque progression using global CAC measurements.<sup>10-15</sup> Although the AS

was developed using EBCT, numerous multidetector CT (MDCT) studies have used similar algorithms to measure AS.<sup>1,16-18</sup>

Use of a calibration phantom during CT imaging permits calculation of the calcium concentration (CC) of individual calcified plaques. The mean CC within a calcified plaque (mg/cm<sup>3</sup>) can be calculated from the measurement of the mean CT attenuation in calcified plaques using the relationship of the CT attenuation in calcium phantoms with known concentrations of calcium.<sup>19</sup>

Received July 8, 2004; revision received January 20, 2005; accepted February 18, 2005.

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Guest Editor for this article was Robert O. Bonow, MD.

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.104.489781

The measurement of individual plaques for serial calcium measurements was proposed more than a decade ago<sup>20</sup>; however, there is no information available about the characteristics of individual calcified plaques, and their relationship to global CAC scores is unknown.

It is likely that the pathological process of plaque formation and progression, including calcification, is the same in men and women regardless of age. Individual lesions have similar characteristics, likely based on the particular stage of atherosclerosis within the plaque. Histopathological studies demonstrate that multiple types of coronary atherosclerotic plaque containing calcifications can be found within an individual.<sup>21,22</sup> According to the current AHA classification, CAC is present in 2 types of coronary atherosclerotic plaques: type IVa (atheroma), often in the form of large cholesterol crystals and microcalcifications, and type Vb (fibrocalcific lesions), largely calcified with thick fibrous caps.<sup>23</sup> Measurement of the CC of individual calcified plaques may enable detection of differences in plaque composition among individual calcified plaques within subjects and could be complementary to global CAC measures in the assessment of coronary event risk. In addition, a parameter of CAC that does not change as a function of age and sex would potentially enable assessment of CAC in individual lesions across subjects in epidemiological studies without the need for stratifying by age and sex.

Previous studies have used global measurements of CAC to assess CAC progression.<sup>10,13–15,24,25</sup> However, individual calcified plaques at different stages of atherosclerotic plaque development within a subject may progress inhomogeneously and respond differently to risk factor alteration. Thus, global CAC scores may not accurately reflect actual changes in CAC, and measurements of individual plaques may be preferable to global CAC scores as a way to evaluate progression or regression of atherosclerosis in serial studies such as treatment studies involving lipid-lowering or anti-inflammatory agents.

In the present study, therefore, we assessed the value of the CC measurement of individual calcified plaques, its relationship to other parameters derived from CT analysis of coronary calcium, and the potential role of CC to assess plaque progression in response to therapeutic intervention in a community-based cross-sectional study.

## Methods

We analyzed data from 612 consecutive participants (226 women, 386 men) from the Framingham Heart Study who underwent prospectively ECG-triggered MDCT scans of the heart for the detection of CAC. Participants in this study were drawn from the offspring cohort and the third-generation cohort, consisting of children of the offspring. Men <40 years of age and women <45 years of age, as well as women with definite or possible pregnancy, were excluded from participation to minimize radiation exposure for young research subjects at overall low likelihood for CAC. The study was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written consent.

### CAC Imaging Protocol

Subjects were imaged on an 8-slice MDCT scanner (LightSpeed Ultra, General Electric) with ECG triggering during an individual

inspiratory breathhold (typically 18 seconds) using sequential data acquisition. Before the scan, a test breathhold was performed to ensure compliance.

Scans were prospectively initiated at 50% of the RR interval, which has been used widely for MDCT-based measurements of CAC and has been shown to provide the best average image quality for MDCT-based data acquisition.<sup>17</sup> Forty-eight contiguous 2.5-mm-thick slices [120 kV(p); 320 and 400 mA for <220 and >220 lb body weight, respectively; gantry rotation time, 500 ms; temporal resolution, 330 ms] were acquired. The effective radiation exposure was 1.0 to 1.25 mSv for 320 and 400 mA, respectively. Each scan was acquired with a quantitative CT calibration phantom (Image Analysis) positioned underneath the subject, with the long axis of the phantom parallel to the subject's spine.

### CAC Measurements

All CT scans were analyzed for the presence of CAC on an offline workstation (Aquarius, Terarecon). A calcified lesion was defined as an area of  $\geq 3$  connected pixels with a CT attenuation >130 HU applying 3D connectivity criteria (6 points).

For each lesion, the CV, CC, AS, and mineral mass (MM) were determined as follows.

#### CV Determination

CV was calculated for each calcified lesion by multiplying the number of voxels ( $V_n$ ) >130 HU with the voxel volume ( $V_v$ , mm<sup>3</sup>) using isotropic interpolation<sup>3</sup>:  $CV = V_n \times V_v$ .

#### CT Attenuation and CC

For each individual calcified plaque, the mean CT attenuation of all pixels within that plaque was determined. In a calibration phantom that contained 4 parallel cylinders corresponding to a water-equivalent compound (CT-Water) and 3 different concentrations of calcium hydroxyapatite (50, 100, 200 mg/cm<sup>3</sup>), the mean CT attenuation was also measured by placing standard regions of interest (2.0 cm<sup>2</sup>) in each of the 4 calibration inserts at the level of the left main coronary artery. The relationship between CT attenuation and CC in the calibration phantom was derived by regression analysis based on the association between CT attenuations and known CCs in a calibration phantom (see below).<sup>16,19</sup> The CC within each individual calcified plaque was then calculated from the known relation between CC and CT attenuation within the phantom.

The intercept and slope of regression line was determined from the following equation: CT attenuation (HU) = slope  $\times$  CC (mg/cm<sup>3</sup>) + intercept. From these values determined individually for each patient, the CC within a given calcified lesion was determined from the following formula:  $CC$  (mg/cm<sup>3</sup>) = (CT attenuation (HU) – intercept) / slope.

#### MM Determination

The MM was calculated as the product of CC and calcified plaque volume:  $MM$  (mg) =  $CC$  (mg/cm<sup>3</sup>)  $\times$  plaque volume (cm<sup>3</sup>).

#### AS Determination

The AS was calculated by multiplying the area of each lesion with a weighted CT attenuation score dependent on the maximal CT attenuation (HU) within the lesion as described elsewhere.<sup>27</sup> If an individual lesion appeared in >1 CT cross section, the AS values derived for each individual cross section were added to provide the AS of the lesion. Because the method for calculating the AS is similar for MDCT and EBCT,<sup>1,16–18</sup> we use the expression "AS" in this study. However, previous research has demonstrated that especially small lesions (AS <10) may have a different AS in EBCT than in MDCT because of differences in scanner specifications between the 2 modalities (ie, different temporal resolution, slice thickness, and tube current: 100 ms, 3 mm, and 625 mA for EBCT and 330 ms, 2.5 mm, and 300 mA for MDCT, respectively).<sup>18,28</sup>

In addition, traditional global measures of CAC were determined on a per-subject basis ( $CV_{\text{subject}}$ ,  $MM_{\text{subject}}$ , and  $AS_{\text{subject}}$ ) by summing the scores of individual lesions. The mean evaluation time was 10 minutes per patient.

**Descriptive Statistics of CAC Measurements in Individual Calcified Plaques and per Subject in 217 Subjects**

	CAC Measurements in Single Calcified Plaques (n=956)		CAC Measurements per Subject (n=217)	
	Mean±SD	Median (25th, 75th Percentiles)	Mean±SD	Median (25th, 75th Percentiles)
AS	33.6±76.2	10.9 (3.9, 32.5)	163.9±302.7	59.2 (21.0, 177.9)
CV, mm <sup>3</sup>	26.6±60.2	9.3 (4.1, 26.1)	111.5±186.8	43.1 (16.7, 123.7)
MM, mg	6.6±18.5	1.7 (0.6, 5.4)	25.6±52.0	8.8 (2.8, 26.4)
CC, mg/cm <sup>3</sup>	194.0±69.9	178.8 (150.8, 218.1)	...	...
CT-A, HU	220±78.8	203.5 (172.9, 249.3)	...	...

CT-A indicates CT attenuation.

**Statistical Methods**

Mean, SD, median, and 25th and 75th percentiles were calculated for the global measures of CAC and for individual calcified plaques. The heterogeneity of CC and CT attenuation of individual calcified plaques within a subject was calculated as the SD.

To determine whether CC and CT attenuation of individual calcified plaques was dependent on CV, after taking into account the multiple observations per subject, we performed generalized estimating equation linear regression analysis; compound symmetry was assumed for the structure of the within-subject correlation. To compensate for partial volume effects, tests for age (categorized as <50, 51 to 70, and >70 years of age) and sex effects on natural logarithm of CC were performed using generalized estimating equation ANCOVA with the compound symmetry assumption, adjusting for natural logarithm of CV (natural logarithm transformation was used in statistical testing because of high skewness of the untransformed measures). To test whether heterogeneity of CC and CT attenuation was independent of the number of plaques per subject, we stratified our study population into subjects below and above the average number of calcified plaques (<7 versus ≥7 plaques) and performed a 2-sample *t* test on the log-transformed CC and CT attenuation heterogeneity to test for significant differences between the 2 groups. A value of *P*<0.05 was considered to indicate statistical significance for all tests.

**Results**

CAC was detected in 274 of 612 subjects (prevalence, 45%). Fifty-seven CT scans with motion artifacts were excluded from analysis. In the remaining 217 subjects (74 women, 143 men; mean age, 57.1±10.8 years), a total of 956 individual calcified plaques were analyzed (mean, 4.4 plaques per subject; range, 1 to 24). Baseline risk factor prevalence in this cohort included 40.1% for hypertension (defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or treatment), 36.8% for obesity (defined as body mass index >30 kg/m<sup>2</sup>), 13.6% for current cigarette smoking, and 11.7% for hypercholesterolemia (defined as total cholesterol >240 mg/dL or treatment). The per-subject and per-plaque measures of CAC for the 217 subjects are summarized in the Table. The following results were generated on the 217 subjects with detectable CAC.

**Plaque Size and CC**

We found a weak correlation between CC and CV of individual calcified plaques (*r*=0.34, *P*<0.01), indicating some remaining partial volume effects after calibration of CT attenuation. Thus, all subsequent statistical evaluations were corrected for CV.

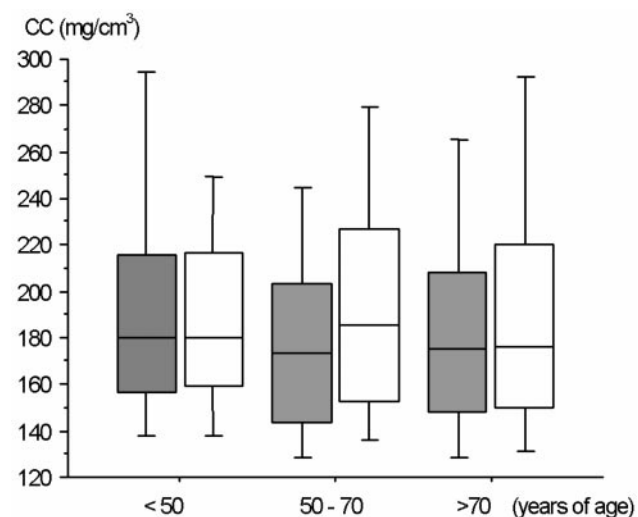
**Relation of CC and CT Attenuation of Individual Calcified Plaques to Age and Sex**

The mean CC was 194.0±69.9 mg/cm<sup>3</sup> (median, 178.8 mg/cm<sup>3</sup>; 25th and 75th percentiles, 150.8 and 218.1 mg/cm<sup>3</sup>,

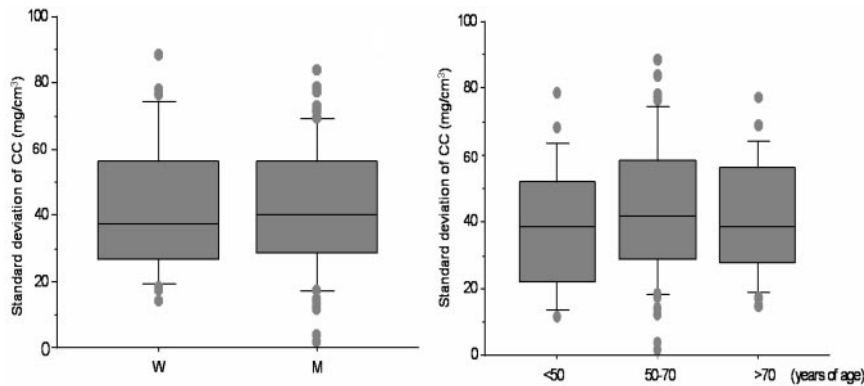
respectively). The CC was not significantly different among age groups in a comparison of 194 plaques in subjects ≤50 years of age, 560 plaques in subjects 51 to 70 years of age, and 202 plaques in subjects >70 years of age (196.8±91.9 versus 192.6±58.5 versus 194.9±74.6 mg/cm<sup>3</sup>, respectively; *P*=0.76). The CC was higher in male subjects but not significantly different between men and women (197.8±74.8 mg/cm<sup>3</sup> [n=703] versus 183.6±52.8 mg/cm<sup>3</sup> [n=253], respectively; *P*=0.21) (Figure 1). The results were similar for CT attenuation, which was not significantly different among age groups (*P*=0.81) and between men and women (*P*=0.91).

**Relation of AS, CV, and MM of Individual Calcified Plaques to Age and Sex**

Similar to CC, there were no differences between men and women in the values of individual calcified plaques for AS (34.3±71.6 versus 31.8±87.8, respectively; *P*=0.40), CV (26.9±55.0 versus 25.8±72.8 mm<sup>3</sup>; *P*=0.25), and MM (6.7±16.6 versus 6.2±22.8 mg/cm<sup>3</sup>; *P*=0.58). AS, CV, and MM were also not significantly different across age groups (*P*=0.18).



**Figure 1.** CC in individual calcified plaques. Box and whisker plot demonstrating association between CC and subject's age and sex (women, gray box; men, white box). Box contains values between 25th and 75th percentiles of CC (central line, median). Vertical lines represent 10th and 90th percentiles. CC was independent of age and sex.



**Figure 2.** Heterogeneity of CC among individual calcified plaques within 125 subjects with  $\geq 3$  individual calcified plaques stratified by sex (left) and age (right). Box and whisker plot (box, 25th and 75th percentiles; central line, median). Vertical lines represent 10th and 90th percentiles. There was no significant difference between women and men or age groups ( $P=0.99$ ,  $P=0.60$ , respectively).

### Relation of Global CAC Measures to Age and Sex

The values for  $AS_{\text{subject}}$ ,  $CV_{\text{subject}}$ , and  $MM_{\text{subject}}$  were higher in men than in women, but not significantly (for men and women,  $AS_{\text{subject}}$ ,  $196.6 \pm 357.6$  versus  $100.7 \pm 127.3$ ;  $CV_{\text{subject}}$ ,  $133.4 \pm 220.7$  versus  $69.2 \pm 75.7$ ; and  $MM_{\text{subject}}$ ,  $31.5 \pm 62.2$  versus  $14.2 \pm 16.5$  mg, respectively;  $P > 0.10$  for each comparison when based on the log-transformed data).  $AS_{\text{subject}}$ ,  $CV_{\text{subject}}$ , and  $MM_{\text{subject}}$  significantly increased across the 3 age groups (<50, 51 to 70, >70 years) as follows. The values for  $AS_{\text{subject}}$  were  $84.3 \pm 111.5$  versus  $167.1 \pm 275.2$  versus  $284.3 \pm 511.3$ , respectively ( $P < 0.01$ ); for  $CV_{\text{subject}}$ ,  $64.9 \pm 87.3$  versus  $120.7 \pm 208.5$  versus  $156.2 \pm 213.5$  ( $P < 0.01$ ); and for  $MM_{\text{subject}}$ ,  $13.9 \pm 19.6$  versus  $27.8 \pm 54.0$  versus  $37.5 \pm 74.7$  ( $P = 0.01$ ).

### Heterogeneity of CC and CT Attenuation of Individual Calcified Plaques Within Subjects With Multiple Plaques

The heterogeneity of CC within subjects was evaluated in a subgroup of 125 subjects with  $\geq 3$  individual calcified plaques (36 women, 89 men; mean age,  $59.1 \pm 10.9$  years; mean, 6.6 plaques per subject; range, 3 to 24). A total of 829 individual calcified plaques were analyzed. The mean heterogeneity of CC of individual calcified plaques within a subject was  $43.6 \pm 23.1$  mg/cm<sup>3</sup>. It was similar between men and women ( $P = 0.99$ ) and was not related to age ( $P = 0.60$ ) (Figure 2). The heterogeneity of CC in a subject was not significantly different between subjects above and below the mean number of plaques (heterogeneity with <7 versus  $\geq 7$  plaques,  $41.3 \pm 22.3$  versus  $47.8 \pm 24.0$ , respectively;  $P = 0.06$ ). The mean heterogeneity of CT attenuation of individual calcified plaques within a subject was  $50.8 \pm 25.2$  HU. It was similar between men and women ( $P = 0.62$ ) and was not related to age ( $P = 0.51$ ).

### Heterogeneity of AS, CV, and MM of Individual Calcified Plaques Within Subjects

The mean heterogeneity of AS, CV, and MM of individual calcified plaques within a subject was  $44.4 \pm 66$ ,  $34.7 \pm 53$  mm<sup>3</sup>, and  $9.5 \pm 17$  mg, respectively. The heterogeneity of AS, CV, and MM was not significantly different between subjects with <7 compared with  $\geq 7$  plaques ( $P = 0.29$ ,  $P = 0.37$ , and  $P = 0.38$  for AS, CV, and MM, respectively) and was independent of sex and age ( $P = 0.2$ ).

## Discussion

This is the first community-based study to systematically assess the CT-derived characteristics of individual calcified

plaques and their relationship to global CAC scores. In this study, we introduce the measurement of CC of individual plaques as a new marker of coronary calcification. Our results suggest that the mean CC, AS, CV, and MM of individual calcified plaques as opposed to global CAC measurements are similar in men and women across strata of increasing age. In addition, we demonstrated substantial heterogeneity of CC and other parameters of individual calcified plaques within subjects that were independent of age and sex.

Our finding that CC of individual lesions appears to be independent of age and sex is consistent with the notion that the pathological process of atherosclerotic plaque formation and progression, including calcification, is similar in men and women regardless of age. Thus, individual lesions have similar characteristics across age and sex, likely based on the stage of the plaque formation. Although our findings need to be confirmed in larger cohorts, they are remarkable in view of the range of ages and numbers of plaques in men and women in the study population and the fact that measurements accounted for multiple observations per subject. These results suggest that the CC of individual calcified plaques represents an additional marker of calcified coronary plaque that may provide additional value to global scores in assessing of plaque burden and risk of event and evaluation of therapeutic intervention. Although manual analysis of single plaques to determine the CC may be cumbersome in patients with advanced disease, dedicated software may permit faster semiautomatic per-lesion analysis of CC and its heterogeneity within a subject. The mean CT attenuation gave results parallel to CC. If confirmed in larger studies, this would greatly simplify the methodology and potentially allow it to be done on subjects without need for a phantom.

The risk of a coronary event (myocardial infarction, cardiac death) appears to be related primarily to the total extent of atherosclerosis and rises significantly above an AS of 100.<sup>6,9</sup> However, information on the composition of individual plaque such as CC may have additional value for risk stratification. It has been suggested, but not proven, that heavily calcified lesions (with high CC) may be more mature and stable than lesions with a lower CC. Thus, subjects with only heavily calcified lesions may be at lower risk for future coronary events than subjects with a preponderance of lesions with a low CC, despite a similar AS.<sup>29,30</sup> Our results suggest that further studies are warranted to test the hypothesis that

stratification of total plaque burden by CC may improve current assessment of coronary event risk based on global AS.

Global CAC scores have been used to assess CAC progression but have rendered discordant results, specifically in the assessment of effects of risk factor modification, ie, lipid-lowering therapy.<sup>11,14,15,24</sup> Our results demonstrate heterogeneity of individual calcified plaques within a subject. Likely depending on the particular stage of atherosclerotic development within the plaque, these plaques may progress or respond to risk factor alteration in a heterogeneous fashion. Although global CAC scores cannot account for these differences, they may be identified using CC and other CT-derived measures of individual calcified plaques. Thus, individual plaque analysis may be preferable to global CAC scores as a way to evaluate progression or regression of atherosclerosis in serial studies such as treatment studies involving lipid-lowering or antiinflammatory agents. Notably, measurements of individual calcified plaques that combine information on volume and density such as AS and MM may fail to detect shrinking and condensing of a plaque, a pattern of plaque regression after statin treatment that has been described in animal (apolipoprotein E–Leiden mice) and human studies.<sup>31–33</sup> However, measurements of CC and volume of individual plaques would enable accurate detection of such changes.

### Study Limitations

Although consecutive subjects were enrolled in this study, the current study sample represented only a small sample of the >3000 Framingham Heart Study subjects we plan to image. Because of the relatively small sample size, a modest degree of heterogeneity of CC may not have been detected, particularly within subjects. Follow-up studies in larger sample sizes will enable better power to make generalizable population estimates of the distribution and CC of plaques in men and women. Furthermore, we excluded CT scans of 57 subjects because of motion artifacts. Because we performed a feasibility study on a new marker for CAC, we included only high-quality CT exams. Although it is possible with MDCT to use ECG-gated reconstruction (with variable reconstruction points in the cardiac cycle to improve the accuracy of calcium detection), we used ECG-triggered techniques in this study to minimize radiation exposure (1.0 versus 12.4 mSv)<sup>34</sup> in a population-based study cohort.

Further studies are necessary to determine the effect of image quality on CC of individual calcified plaques in larger numbers of subjects and to provide reproducibility data to assess measurement accuracy of single plaque measurements. Our methodology did not permit the analysis of separate regions of varying CC, which may be present in larger calcified plaques. The need for a calibration phantom may be a further limitation of this measurement. However, the use of CT scanner–based calibration (using a chest torso phantom) and potentially CT attenuation would simplify the assessment but needs further evaluation.

A final limitation is that this study analyzed cross-sectional data. Longitudinal studies are necessary to prove the incremental value of CC of individual calcified plaques over conventional CAC measures with respect to evaluation of

progression of CAC. Similarly, we did not perform any validation using modalities such as intravascular ultrasound or histology, although the different CCs most strongly imply different plaque composition.

### Conclusions

The CC within individual calcified plaques represents a new marker for CAC. We demonstrate that the CC of individual calcified plaques as opposed to global measures of CAC is independent of age and sex, reflecting the fact that the pathological process of plaque formation and progression, including calcification, is the same in men and women regardless of age. In addition, we demonstrate that the CC of individual calcified plaques is heterogeneous within subjects, reflecting the presence of atherosclerotic plaque at different stages of atherosclerotic development that may respond differently to risk factor alteration and may be more or less prone to plaque rupture. Further studies are warranted to confirm that individual plaque analysis is preferable to global CAC scores as a way to evaluate progression or regression of atherosclerosis in serial studies such as treatment studies involving lipid-lowering or antiinflammatory agents and to assess whether individual plaque analysis may be important and complementary to global CAC measures to assess coronary event risk.

### Acknowledgments

This work was supported by the NHLBI Framingham Heart Study (NIH/NHLBI Contract N01-HC-25195). F. Moselewski was supported by the Daniela und Juergen Westphal-Stiftung, Flensburg, Germany. Dr Achenbach was supported by Deutsche Forschungsgemeinschaft, Bonn, Germany.

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