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Coronary Computed Tomography Angiography as a Screening Tool for the Detection of Occult Coronary Artery Disease in Asymptomatic Individuals

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Objectives The purpose of this study was to evaluate the prevalence of occult coronary artery disease (CAD) with coronary computed tomography angiography (CTA) to characterize plaque composition and to evaluate the potential of this new technology to impact risk stratification in asymptomatic middle-aged subjects.

Background There is a paucity of information regarding the role of CTA for the detection of occult CAD in asymptomatic individuals.

Methods We consecutively enrolled 1,000 middle-aged asymptomatic subjects (age 50 ± 9 years, 63% men) who underwent CTA (64-slice multidetector row computed tomography) as part of a general health evaluation.

Results Atherosclerotic plaques were identified in 215 (22%, 2 ± 1 segments/subject) individuals; 40 individuals (4%) had only noncalcified plaques. Fifty-two (5%) subjects had significant (≥50%) diameter stenosis and 21 (2%) had severe (≥75%) stenosis. Thirteen (25%) and 30 (58%) subjects with significant stenosis were classified into National Cholesterol Education Program low-risk and mild coronary calcification (coronary artery calcium scores <100), respectively. Midterm follow-up (17 ± 2 months) revealed 15 cardiac events only in those with CAD on CTA: 1 unstable angina requiring hospital stay and 14 revascularization procedures. Most (87%) events occurred within 90 days of index CTA.

Conclusions The prevalence of occult CAD in apparently healthy individuals was not negligible, although their midterm prognosis was good. CTA has a potential to provide a better insight about the occult CAD in this population. However, on the basis of our results and considering present radiation exposure data, we cannot recommend that CTA be used as a screening tool for this population at this point. (Subclinical COronary Atherosclerosis Updated With Coronary cT Angiography [SCOUT Study]; NCT00431860) (J Am Coll Cardiol 2008;52:357–65) © 2008 by the American College of Cardiology Foundation

A large proportion of patients with sudden cardiac death or nonfatal myocardial infarction do not experience prior symptoms of chest pain or exertional dyspnea, emphasizing the importance of early detection and treatment of underlying subclinical coronary atherosclerosis (1). Cardiovascular prevention algorithms based on traditional risk factors for coronary artery disease (CAD) often underestimate event risk, especially in women and in young individuals (2,3).

Evidence supporting the use of noninvasive imaging tests to screen for CAD is gradually accumulating. The identification and quantification of coronary artery calcium (CAC), a marker of subclinical atherosclerosis, provides incremental prognostic information in addition to the assessment of conventional risk factors (4,5). However, CAC does not represent the whole spectrum of atherosclerosis and has a limitation to diagnose obstructive CAD (6).

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With the advent of multi-slice computed tomography technology, coronary computed tomography angiography (CTA) has the potential to provide comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque. Despite the absence of evidence,

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Abbreviations and Acronyms

CAC = coronary artery calcium
CACS = coronary artery calcium score(s)
CAD = coronary artery disease
CAG = coronary angiography
CHD = coronary heart disease
CTA = computed tomography angiography
LAD = left anterior descending artery
MDCT = multidetector row computed tomography
NCEP = National Cholesterol Education Program
PCI = percutaneous coronary intervention

the use of CTA as a screening tool has been already initiated, not only through physician decision-making but through the mechanism of self-referral (7,8).

To date, there is a paucity of data regarding the prevalence and characteristics of CAD in asymptomatic subjects and any potential role of CTA to screen these asymptomatic individuals for occult disease. In this study, first, we evaluated the prevalence of subclinical coronary atherosclerosis and outlined coronary plaque composition in a group of asymptomatic apparently healthy South Korean individuals with CTA, and second, we tried to identify whether CTA has the potential to identify individuals at risk more accurately than conventional risk stratification methods.

Methods

Study population. We retrospectively enrolled 1,074 consecutive South Korean individuals who had undergone CTA evaluation with 64-slice multidetector row computed tomography (MDCT) for general routine health evaluation in Seoul National University Bundang Hospital (SNUBH) from December 2005 and May 2006. We excluded 74 subjects who had chest pain or discomfort before enrollment without a previous diagnostic workup to rule out CAD (n = 3), a history of myocardial infarction/angina (n = 25), history of percutaneous coronary intervention (PCI) (n = 1), age under 35 or over 75 years old (n = 39), or insufficient medical records (n = 6). As a result, a total of 1,000 self-referred middle-aged asymptomatic subjects were finally enrolled. The institutional review board approved the study protocol, and all patients gave written, informed consent.

Risk factor assessment and stratification. Basic demographic data was acquired from a database maintained by the SNUBH Health Promotion Center. All individuals were asked whether they had chest pain or equivalent symptoms according to a Rose angina questionnaire (9). Medical history of myocardial infarction, angina, hypertension, stroke, diabetes mellitus, family history of premature CHD (CHD in male first-degree relative age <55 years; CHD in female first-degree relative age <65 years), current medication profile, smoking, and social status were systematically acquired. Body weight, height, and blood pressure were also measured during their visit. Hypertension was defined as a self-reported history of hypertension and/or use of antihypertensive medication or a blood pressure ≥140/90 mm Hg. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting plasma glucose, glycated hemoglobin, blood urea nitrogen, and serum creatinine level were measured after at least a 12-h fasting period on the same day of the study. Diabetes was defined as a self-reported history of diabetes and/or receiving antidiabetic treatment or a fasting plasma glucose ≥126 mg/dl. Serum C-reactive protein was measured by latex agglutination with an auto-analyzer (Toshiba-200 FR, Tokyo, Japan). Framingham risk scores, as used by National Cholesterol Education Program (NCEP) guidelines, were calculated (10).

All subjects were assigned to 3 different risk groups according to the revised NCEP guidelines: high-risk (coronary heart disease [CHD], CHD risk equivalents, or 10-year risk >20%), moderate-risk (more than 2 risk factors and 10-year risk ≤20%), and low-risk group (0 to 1 risk factor) (10).

Data acquisition. Patients with a heart rate >70 beats/min received intravenous esmolol, 10 to 30 mg (Jeil Pharm. Co., Ltd., Seoul, Korea), before MDCT imaging. The CTA was performed with the use of a 64-slice MDCT scanner (Brilliance 64, Philips Medical Systems, Best, the Netherlands). A standard scanning protocol was applied, with 64 × 0.625 mm section collimation, 420-ms rotation time, 120-kV tube voltage, 800-mA tube current. All scans were performed with electrocardiogram-gated dose modulation. A bolus of 80 ml Iomeprol (Iomeron 400, Bracco, Milan, Italy) was intravenously injected (4 ml/s) followed by a 50-ml saline chaser.

A region of interest was placed in the descending thoracic aorta, and image acquisition was automatically initiated once a selected threshold (150 Hounsfield units [HU]) had been reached with bolus tracking. The patient's electrocardiogram was simultaneously recorded to allow for retrospective segmental data reconstruction. Images were initially reconstructed at mid-diastolic phase (75% of R-R interval) of the cardiac cycle. Additional reconstructions were performed if motion artifacts were present. The mean radiation exposure of CTA was 13.21 ± 0.82 mSv (13.21 ± 0.83 mSv for men and 13.33 ± 0.79 mSv for women).

Image analysis. All scans were analyzed independently by 2 experienced radiologists (S.I.C. 5 years; E.J.C. 3 years) who were blinded to the clinical information with a 3-dimensional workstation (Brilliance, Philips Medical Systems, Best, the Netherlands). After making independent evaluations, a consensus interpretation was arrived at to obtain a final MDCT diagnosis. Each lesion was identified with a multiplanar reconstruction technique and maximum intensity projection of short-axis, 2-chamber, and 4-chamber views. We analyzed plaque characteristics on a per-segment basis according to the modified American Heart Association classification (11). Image quality was evaluated on a per-segment basis and classified as good (no artifact), adequate (defined as the presence of image-degrading artifacts but feasible for evaluation with a moderate confidence), or poor

(the presence of image-degrading artifacts and feasible for evaluation only with a low confidence).

The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the maximal stenotic site and compared with the mean value of proximal and distal reference site. If the image was adequate or poor quality, coronary segments were visually scored for the grading of coronary artery stenosis. The severity of diameter stenosis was graded as normal-appearing (0% to 24%), mild (25% to 49%), moderate (50% to 74%), and severe (≥75%) narrowing (12). A stenosis more than 50% and 75% was defined as significant and severe, respectively.

Plaques were defined as structures >1 mm^2 within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques occupied by calcified tissue more than 50% of the plaque area (density >130 HU in native scans) were classified as calcified, plaques with <50% calcium were classified as mixed, and plaques without any calcium were classified as noncalcified lesions (13).

Coronary artery calcium scores (CACS) were measured with the scoring system previously described by Agatston et al. (14,15). Participants, on the basis of the CACS, were categorized in the following manner: no, 0; mild, 0.1 to 100; moderate, 100.1 to 400; and severe calcification, >400.

Midterm clinical outcome and secondary diagnostic tests. Follow-up data were obtained from medical records or telephone contact with trained personnel. Subjects were asked the occurrence of new chest pain, subsequent diagnostic test (i.e., single-photon emission computed tomography or coronary angiography [CAG] within 90 days after index CTA), and subsequent revascularization therapy (PCI or coronary artery bypass graft surgery) on the basis of index CTA or cardiac events. Cardiac events were defined as: cardiac death, nonfatal myocardial infarction, unstable angina requiring hospital stay, or revascularization therapy. Clinical follow-up (17 ± 2 months [range 12 to 21 months]) was available in 97.4% of cases.

Statistical analysis. Continuous variables are expressed as means ± SD, whereas categorical variables are presented as absolute values and percentages. Differences between continuous variables were analyzed by the unpaired Student *t* test and those between categorical variables by the chi-square test or Fisher exact test, as appropriate. We analyzed the relationship between age (quartiles) and indexes of CAD with chi-square testing for trend. Multiple logistic regression analysis (forward conditional) was employed to identify independent predictors of the presence of plaque, significant stenosis, and noncalcified plaque only on CTA. A p value of <0.05 was considered statistically significant, and all analyses were performed with SPSS 13.0 statistical package (SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics of asymptomatic population. The clinical characteristics of the population according to gender are listed in Table 1. The mean age of the study population was 50 ± 9 years (range 35 to 74 years), 63% were men, and the mean number of risk factors on the basis of NCEP guidelines was 1 ± 1 (range 0 to 4) with 2 or more risk factors observed in 41% of subjects.

CTA imaging. Image quality of coronary arteries was classified as good in 94%, adequate in 4%, and poor in 1% on a segmental basis. Reasons for poor image quality were motion artifact (55%, 121 of 219 segments), blooming artifact (29%, 64 of 219 segments), or low contrast-to-noise ratio (16%, 34 of 219 segments). Interobserver agreement for the degree of stenosis was 0.87, indicating very good agreement. Only vessels providing good image quality were considered for plaque analysis. Inter-observer agreement for the detection of any plaque/subject and plaque/segment were excellent (Cohen's kappa = 0.93 and 0.84, respectively), comparable to the previous study (16).

Subclinical coronary atherosclerosis—prevalence and characteristics of atherosclerotic plaques. Coronary calcifications were present in 175 of 1,000 (18%) patients (Fig. 1). Subsequent CTA revealed atherosclerotic plaques in 392 segments from 215 (22%) subjects (2 ± 1 segments/subject; range 1 to 6). Although mixed plaques emerged as the most frequent type of atherosclerotic plaque, noncalcified plaque was found in at least 1 coronary artery segment in 80 subjects (8%).

Fifty-two (5%) subjects had a significant stenosis on CTA, and 21 (40%) of them had severe stenosis (Table 2). Most of them had single-vessel disease (73%), and most of the significant lesions were located in the left anterior descending coronary artery (LAD) (85%). In 77% of subjects who had a significant stenosis, lesions were located on left main or proximal to mid-LAD.

The incidence of atherosclerotic plaques, significant stenosis, and moderate-to-severe coronary calcification increased with age (Fig. 2). In contrast, the proportion of noncalcified plaque in total plaques at each age quartile was lowest in the oldest one (46% vs. 53% vs. 39% vs. 21%, p for trend = 0.019).

Noncalcified plaques were the only manifestation of CAD in 40 subjects (4%, 1 ± 0.4 segments/subject; range 1 to 3 segments/subject). They were younger than the subjects with other types of plaques (51 ± 8 years vs. 56 ± 9 years, $p < 0.001$). Almost all (38, 95%) of them were classified into low and moderate risk group, and most of them were male (33, 83%). Their proportion and location of significant stenosis was not different from the subjects with other types of plaques: 10 (25%) subjects had significant stenosis on CTA, 5 (50%) of them had severe stenosis, and 70% (7) of lesions were located on left main or proximal to mid-LAD. Comparing within the subjects with 0 CACS (n = 825), those with noncalcified plaques only (n = 40) were older (51 ± 8 years vs. 48 ± 8 years, $p < 0.05$) and mostly male (83% vs. 57%, $p < 0.01$). Subgroup analysis within those with 0 CACS, 2% of men had significant stenosis, whereas no woman had significant stenosis.

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Table 1 Characteristics of CTA Study Group

Characteristics	Total (n = 1,000)	Male (n = 626)	Female (n = 374)
Age, yrs	49.7 ± 8.8	48.9 ± 8.4*	51.0 ± 9.3
BMI, kg/m^2	24.1 ± 2.7	24.8 ± 2.5*	23.0 ± 2.7
Systolic blood pressure, mm Hg	115.8 ± 14.2	117.6 ± 13.7*	112.8 ± 14.6
Diastolic blood pressure, mm Hg	74.3 ± 11.6	77.7 ± 10.3*	68.6 ± 11.5
Hypertension	246 (24.6)	177 (28.3)*	69 (18.4)
Diabetes mellitus	73 (7.3)	56 (8.9)*	17 (4.5)
Hypercholesterolemia	141 (14.1)	104 (16.6)*	37 (9.9)
History of stroke	12 (1.2)	5 (0.8)	7 (1.8)
Family history of premature CAD	129 (12.9)	83 (13.3)	46 (12.3)
Smoking	331 (33.3)	314 (50.2)*	17 (4.6)
Total cholesterol, mg/dl	204.8 ± 34.3	205.7 ± 32.9	203.4 ± 36.6
LDL cholesterol, mg/dl	118.0 ± 32.2	117.9 ± 31.5	118.1 ± 33.5
HDL cholesterol, mg/dl	60.1 ± 14.2	56.7 ± 12.8*	65.9 ± 14.6
Triglyceride, mg/dl	133.7 ± 89.9	155.8 ± 99.3*	96.8 ± 54.1
Fasting blood glucose, mg/dl	97.6 ± 24.8	100.7 ± 27.8*	92.3 ± 17.5
Glycated hemoglobin, %	5.8 ± 0.8	5.8 ± 0.8*	5.7 ± 0.7
BUN, mg/dl	13.1 ± 3.4	13.6 ± 3.5*	12.1 ± 3.1
Serum creatinine, mg/dl	1.1 ± 0.2	1.2 ± 0.1*	0.9 ± 0.1
CRP, mg/dl	0.13 ± 0.33	0.15 ± 0.38*	0.10 ± 0.21
FRS, average	5.2 ± 5.0	7.4 ± 5.2*	1.6 ± 1.3
NCEP-ATP III risk stratification			
High-risk group	102 (10.2)	75 (12.0)*	57 (7.2)
Moderate-risk group	341 (34.1)	290 (46.3)*	51 (13.6)
Low-risk group	557 (55.7)	261 (41.7)*	296 (79.1)
CACS (range)	17.6 ± 82.5 (0–1,151.4)	24.9 ± 101.2* (0–1,151.4)	5.3 ± 29.0 (0–313.5)

Data are expressed as n (%) and mean ± SD. *$p < 0.05$.

BMI = body mass index; BUN = blood urea nitrogen; CACS = coronary artery calcium score; CAD = coronary artery disease; CRP = C-reactive protein; CTA = computed tomography angiography; FRS = Framingham risk score; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP-ATP = National Cholesterol Education Program-Adult Treatment Program.

In univariate and multivariate analysis, most of conventional risk factors could not independently predict the presence of plaques, significant stenosis, and noncalcified plaques as the only manifestation of CAD on CTA (Table 3). Age (decade), male gender, and C-reactive protein were independent predictors for presence of any

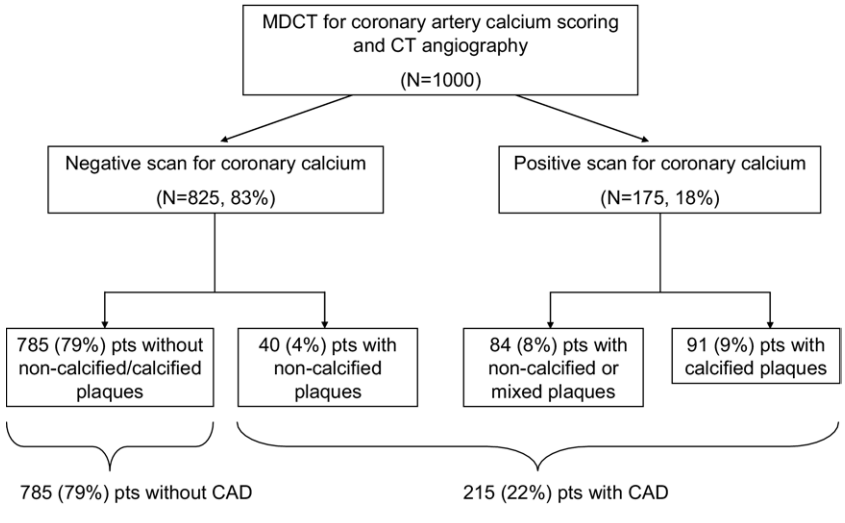

Figure 1 Study Population on the Basis of the Results of Coronary Artery Calcium Scoring and CT Angiography

CAD = coronary artery disease; CT = computed tomography; MDCT = multidetector row computed tomography; pts = patients.

Table 2 Results of CTA According to Gender

Characteristic, n (%)	Total (n = 1,000)	Male (n = 626)	Female (n = 374)
Any plaques	215 (21.5)	177 (28.3)*	38 (10.2)
Significant stenosis†	52 (5.2)	48 (7.7)*	4 (1.1)
Number of stenosed vessels‡			
1-vessel	38 (3.8)	35 (5.6)*	3 (0.8)
2-vessel§	11 (1.1)	11 (1.8)*	0 (0)
3-vessel§	3 (0.3)	2 (0.3)*	1 (0.3)
Maximal diameter stenosis			
0%–24%	896 (89.6)	540 (86.3)*	356 (95.2)
25%–49%	52 (5.2)	38 (6.1)	14 (3.7)
50%–74%	31 (3.1)	29 (4.6)*	2 (0.5)
75%–100%	21 (2.1)	19 (3.0)*	2 (0.5)
CACS			
0	825 (82.5)	482 (77.0)*	343 (91.7)
0.1–100	128 (12.8)	104 (16.6)*	24 (6.4)
100.1–400	37 (3.7)	30 (4.8)*	7 (1.9)
>400§	10 (1.0)	10 (1.6)*	0 (0)
Plaques (per-subject)			
No plaques	785 (78.5)	449 (71.7)*	336 (89.8)
Noncalcified plaque only	40 (4.0)	33 (5.3)*	7 (1.9)
Noncalcified or mixed plaque	84 (8.4)	67 (10.7)*	17 (4.5)
Calcified plaque	91 (9.1)	77 (12.3)*	14 (3.7)

*$p < 0.05$; †luminal diameter stenosis ≥50%; ‡diseased vessel having significant luminal diameter stenosis; §Fisher exact test was used.
CACS = coronary artery calcium score; CTA = computed tomography angiography.

plaque and noncalcified plaque only, whereas male gender and CAC category were independent predictors for significant stenosis.

Significant subclinical coronary atherosclerosis—relation with NCEP risk stratification and CACS according to ages. The prevalence of significant stenosis in low-, moderate-, and high-risk group were 2%, 7%, and 16%, respectively. Dividing those with significant stenosis according to ages reveals: young adults (age ≤55 years for male and age ≤65 years for female) had lower prevalence of significant stenosis compared with old adults (4% vs. 14%, $p < 0.001$), and younger adults (age ≤45 years for male and age ≤55 years for female) had extremely low prevalence of significant stenosis (0.9%).

However, 13 (25%) subjects with significant stenosis were classified into low risk, which was more pronounced in young adults than in older ones (31% vs. 17%) (Fig. 3A). Furthermore, two-thirds (n = 20) of young adults with significant stenosis had CACS lower than 100, and only 7% had CACS higher than 400, compared with 43% and 17% of old adults, respectively (Fig. 3B). Even stratifying the low-risk subjects combined with CACS (<100), 28% (8) and 13% (3) of the significant stenosis in young and older adults were missed, respectively.

Midterm outcome and secondary test of asymptomatic population according to CTA results. In those with CAD (n = 215), 15 subjects had cardiac events: no cardiac death, 1 unstable angina requiring hospital stay, and 14 revascularization procedures (13 in PCI and 1 in coronary artery bypass graft surgery). Most cardiac events (87%) (i.e., 13 revascularization procedures) occurred, on the basis of CTA results, within 90 days of index CTA except 1, which occurred for unstable angina without revascularization therapy. Thirty-one subjects (14%) underwent additional diagnostic testing on the basis of CTA results within 90 days of index CTA: myocardial single-photon emission computed tomography in 9 subjects (4%), CAG in 23 subjects (11%), and both tests in 1 subject (0.1%). As a consequence, 20 patients (2% of the total cohort) were confirmed to have a significant stenosis on the basis of the CAG. Severe stenosis was found in 16 patients (1.6% of the total cohort), 7 had multivessel disease, and 7 had single-vessel disease mostly in the proximal LAD (Fig. 4). In those with noncalcified plaque only (n = 40), 2 subjects (5%) had cardiac events: 1

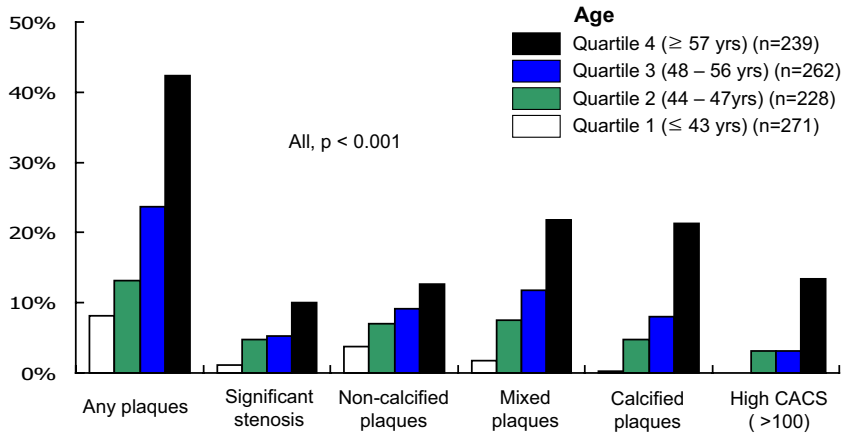

Figure 2 Coronary Artery Disease According to Age Quartiles

The incidence of atherosclerotic plaques, significant stenosis, and moderate-to-severe coronary calcification increased with age. CACS = coronary artery calcium scores.

Table 3 Predictors of Subclinical Coronary Atherosclerosis on CTA

	Any Plaque (n = 215)				Significant Stenosis (n = 52)				Noncalcified Plaque Only (n = 40)			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)
Age (decade)	<0.001	2.31 (1.95–2.74)	0.001	1.84 (1.28–2.64)	<0.001	2.00 (1.50–2.66)	—	—	0.196	1.24 (0.90–1.72)	0.001	1.84 (1.30–2.64)
Male gender	<0.001	3.49 (2.39–5.09)	0.001	4.26 (1.80–10.08)	<0.001	7.68 (2.75–21.48)	0.006	5.45 (1.62–18.35)	0.011	2.92 (1.28–6.66)	0.001	4.26 (1.80–10.08)
BMI, kg/m^2	<0.001	1.11 (1.05–1.17)	—	—	0.033	1.12 (1.01–1.24)	—	—	0.224	1.07 (0.96–1.21)	—	—
Systolic blood pressure, mm Hg	<0.001	1.03 (1.02–1.04)	—	—	0.003	1.03 (1.01–1.05)	—	—	0.830	1.00 (0.98–1.03)	—	—
Diastolic blood pressure, mm Hg	<0.001	1.03 (1.02–1.05)	—	—	0.014	1.03 (1.01–1.06)	—	—	0.109	1.02 (1.00–1.05)	—	—
Hypertension	<0.001	2.40 (1.74–3.32)	—	—	<0.001	2.80 (1.59–4.94)	—	—	0.753	1.13 (0.53–2.41)	—	—
Diabetes mellitus	<0.001	2.80 (1.71–4.58)	—	—	0.001	3.35 (1.60–6.98)	—	—	0.259	3.16 (0.43–23.4)	—	—
Smoking	0.025	1.43 (1.05–1.96)	—	—	0.010	2.09 (1.19–3.66)	—	—	0.816	1.08 (0.56–2.10)	—	—
Triglyceride, mg/dl	<0.001	1.00 (1.00–1.01)	—	—	0.005	1.00 (1.00–1.01)	—	—	0.856	1.00 (1.00–1.00)	—	—
Fasting blood glucose, mg/dl	<0.001	1.01 (1.01–1.02)	—	—	0.002	1.01 (1.00–1.02)	—	—	0.348	0.99 (0.98–1.01)	—	—
Glycated hemoglobin, %	<0.001	1.57 (1.31–1.88)	—	—	<0.001	1.66 (1.30–2.11)	—	—	0.196	0.68 (0.38–1.22)	—	—
BUN, mg/dl	<0.001	1.10 (1.05–1.15)	—	—	0.008	1.10 (1.03–1.19)	—	—	0.269	1.05 (0.96–1.15)	—	—
Serum creatinine, mg/dl	<0.001	10.87 (4.40–26.87)	—	—	0.001	11.87 (2.81–50.1)	—	—	0.051	4.80 (1.00–23.2)	—	—
FRS, average	<0.001	1.14 (1.11–1.18)	—	—	<0.001	1.15 (1.10–1.20)	—	—	0.322	1.03 (0.97–1.09)	—	—
CACS category†	—	—	—	—	<0.001	6.49 (4.50–9.35)	<0.001	5.91 (4.02–8.68)	—	—	—	—
CRP, mg/dl	0.001	2.61 (1.47–4.64)	0.007	3.33 (1.39–8.00)	0.302	1.34 (0.77–2.33)	—	—	0.014	1.81 (1.13–2.90)	0.007	3.33 (1.39–8.00)

*Forward conditional multiple logistic regression analysis adjusting with age (decade), male gender, BMI, systolic blood pressure, diastolic blood pressure, hypertension, diabetes mellitus, smoking, triglyceride, fasting blood glucose, glycated hemoglobin, BUN, serum creatinine, FRS, CRP, and CACS category. †CACS category: 0, 0.1–100, 100.1–400, and >400.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

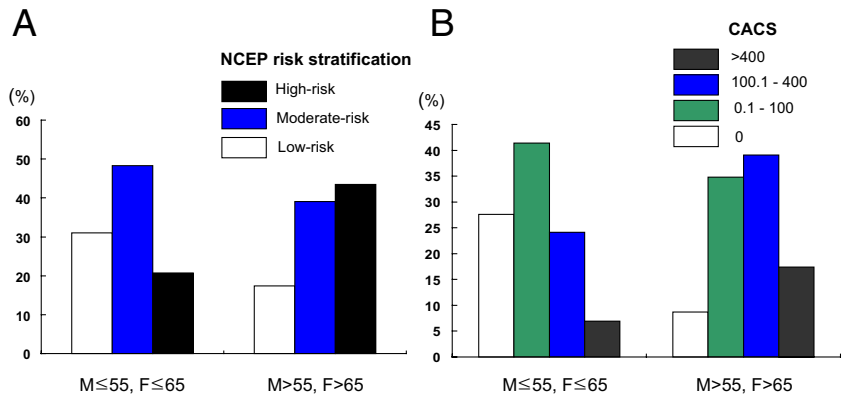

Figure 3 **Frequency of Significant Stenosis According to Age Groups**

Relationship with **(A)** National Cholesterol Education Program (NCEP) Risk Groups and **(B)** coronary artery calcium score (CACS). Young adults with significant stenosis were classified into low risk and low CACS more often than older adults.

unstable angina requiring hospital stay, and 1 revascularization procedure (PCI).

In those without CAD (n = 785; high-risk vs. moderate-risk vs. low-risk = 7% vs. 30% vs. 63%), there were no cardiac events during the follow-up period. Twenty-eight (4%) subjects complained of new chest pain after CTA evaluation; however, no further diagnostic test was performed on those subjects during the follow-up period.

Discussion

The main findings of the present study are the following: 1) a significant percentage of the population (22%) had evidence of occult CAD despite the absence of symptoms, and of those, 5% had at least 1 significant coronary artery stenosis; 2) in 4% of the subjects the presence of noncalcified plaques was the only manifestation of CAD; 3) 25% of subjects with significant stenosis were classified into low risk, which was more pronounced in young adults; and 4) individuals with a normal CTA had excellent clinical outcomes and underwent few additional diagnostic tests during mid-term follow-up, whereas those with CAD on CTA had all of the cardiac events and subsequent diagnostic tests.

Characteristics of subclinical coronary atherosclerosis—prevalence and plaque characteristics. Our knowledge with regard to the prevalence of occult CAD in asymptomatic individuals is limited. According to earlier observations, the prevalence of CAD confirmed by CAG in asymptomatic individuals is approximately 3% to 5% (17–19). Although CAG is generally accepted as the clinical gold standard for diagnosing the presence of CAD and plaque characterization in conjunction with intravascular ultrasound, it is difficult to use CAG as a screening test in asymptomatic subjects due to its highly invasive nature.

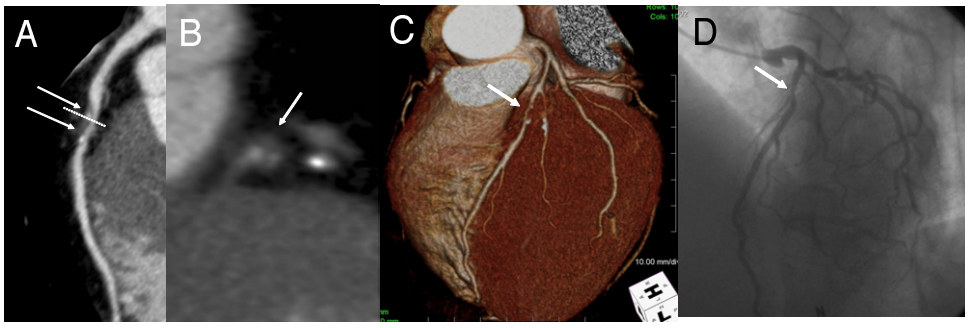

Figure 4 **Multidetector Row Computed Tomography and Coronary Angiography in a 49-Year-Old Male Subject**

Curved multiplanar imaging **(A)** shows significant lesion located in the left anterior descending artery demonstrated by multidetector row computed tomography **(arrows)**. Cross-sectional view **(B)** of **dashed line in A** demonstrates severe positive arterial remodeling of a mixed plaque. Volume-rendering imaging **(C)** shows severe discrete stenosis (degree of stenosis: 80%) located in the proximal left anterior descending artery **(arrow)**. Conventional angiography **(D)** reveals significant stenosis at corresponding area of left anterior descending artery **(arrow)**.

Because most underlying plaques are nonstenotic and acute coronary events are caused by plaque rupture, the concept of using noninvasive imaging methods that permit detection, quantification, and possibly also characterization of coronary atherosclerotic plaques to carry out individualized risk stratification is intriguing.

Computed tomography technology can provide comprehensive information on CAD, such as lesion location, severity, and plaque characteristics (12,20–22). In our study, atherosclerotic plaques were identified in 22% of asymptomatic subjects; 18% of those with any plaque had only noncalcified plaques, whereas overall it was seen only in 4% of the total population. Even in the absence of symptoms, 52 (5%) subjects had significant (≥50%) diameter stenosis, and of those, 21 (40%) had severe (≥75%) stenosis. Interestingly, in 77% of subjects who had a significant stenosis and 61% (239) of plaques, lesions were located on the left main or proximal to mid-LAD. A previous study by Min et al. (23) demonstrated that the presence of left main or proximal LAD atherosclerotic disease as evidenced by CTA in symptomatic subjects is associated with a worse prognosis. Whether this association can be extrapolated to asymptomatic individuals remains to be seen.

Role of CTA in asymptomatic population: additional role to conventional NCEP risk stratification or CACS? Although specific algorithms based on the classical cardiovascular risk factors have been used to identify individuals at risk, they have limited predictive power for the development of cardiovascular events (24). In general, CAC does reflect plaque burden and therefore remains an unequivocal biomarker for the presence and extent of atherosclerotic disease (25). Coronary artery calcium provides incremental prognostic information over traditional risk factors and recently was proposed as an index parameter of routine screening especially among those with intermediate risk (26,27).

The NCEP III primary prevention guidelines on the basis of classical risk factors tend to underestimate the cardiovascular event risk in young adults (3). Furthermore, recent studies have demonstrated that 7% to 17% of symptomatic patients with a very low CACS have obstructive CAD and 6% of patients with an intermediate risk for having CAD had only noncalcified plaques (12,28). We found, in concordance with previous studies, that CTA could detect significant stenosis, especially in young adults, who might be misclassified by NCEP risk stratification, CACS, or combined but in only few percentages of individuals.

Impact of CTA on additional test and treatment, and the risk of radiation hazard. Although the American Heart Association and the American College of Cardiology have discouraged the use of MDCT as a screening procedure in asymptomatic subjects, mass-media and market forces have facilitated self-referral within the general public. In our study, 3% of asymptomatic individuals received at least 1 further diagnostic test on the basis of their CTA results and, finally, 1% of the total population received revascularization therapy due to significant stenosis on CAG. The triggering of more diagnostic studies, especially in this low-risk population, might introduce more risk than health benefit and could potentially increase overall health care expenditure.

The Food and Drug Administration announced that there is a small chance (1 in 2,000) of developing a fatal cancer due to a 10-mSv computed tomography study (29). On the basis of the recent BEIR-VII (Biological Effects of Ionizing Radiation) study, 64-slice MDCT is associated with a non-negligible risk of cancer, especially in women and in younger patients (30). In addition to outcomes data, questions relating to radiation exposure and cost-effectiveness also remain to be answered before CTA could be considered as a routine screening tool for occult CAD. However, with the advent of MDCT technology, the radiation dose for CTA could be minimized to the level of background radiation (<3 mSv) (31,32). Further studies using that technology will have to be done to assess the feasibility of using CTA as a screening tool.

Study limitations. All subjects in our study were self-referred, suggesting that selection bias might intervene. Also, because all subjects were drawn from the same ethnic background and geographical region, findings from this study should thus be cautiously applied. We excluded, similar to other studies, 5% of lesions of the coronary segments with impaired image quality from plaque analysis. However, with ongoing technological developments (i.e., dual-source computed tomography with improved temporal resolution or 256-slice computed tomography with faster scan time), we will expect that image quality will improve, permitting assessment of plaque morphology and composition.

Conclusions

The prevalence of CAD in asymptomatic individuals was not negligible, although their midterm prognosis was good. A number of individuals with occult CAD might be misclassified with conventional risk stratification algorithms. Computed tomography angiography has the potential to identify these patients, although its risks and benefits with regard to outcomes in asymptomatic individuals and its cost effectiveness remain to be seen.

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Key Words: arteriosclerosis ■ coronary angiography ■ coronary tomography ■ mass screening ■ X-ray computed.