Differential Prognostic Value of Coronary Computed Tomography Angiography in Relation to Exercise Electrocardiography in Asymptomatic Subjects

Sang-Eun Lee, MD[1], Iksung Cho, MD[1], Geu-Ru Hong, MD, PhD[1],
Hyuk-Jae Chang, MD, PhD[1,2], Ji Min Sung, PhD[3], In-Jeong Cho, MD[1],
Chi Young Shim, MD, PhD[1], Byoung Wook Choi, MD, PhD[4], and Namsik Chung, MD, PhD[1]

[1]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea
[2]Severance Biomedical Science Institute, Yonsei University Health System, Seoul, Korea
[3]Department of Research Affairs, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea
[4]Division of Radiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea

Background: To explore the prognostic performance of coronary computed tomography angiography (CCTA) and exercise electrocardiography (XECG) in asymptomatic subjects.

Methods: We retrospectively enrolled 812 (59 ± 9 years, 60.8% male) asymptomatic subjects who underwent CCTA and XECG concurrently from 2003 through 2009. Subjects were followed-up for major adverse cardiac events (MACE) including cardiac death, nonfatal myocardial infarction, unstable angina, and revascularization after 90 days from index CCTA.

Results: The prevalence of occult coronary artery disease (CAD) detected by CCTA was 17.5% and 120 subjects (14.8%) had positive XECG. During a mean follow-up of 37 ± 16 months, nine subjects experienced MACE. In multivariable Cox-regression analysis, only the presence of CAD by CCTA independently predicted future MACE (p = 0.002). Moreover, CAD by CCTA improved the predictive value when added to a clinical risk factor model using the likelihood ratio test (p < 0.001). Notably, the prognostic value of CCTA persisted in the moderate-to-high-risk group as classified by the Duke treadmill score (p = 0.040), but not in the low-risk group (p = 0.991).

Conclusion: CCTA provides incremental prognostic benefit over and above XECG in an asymptomatic population, especially for those in a moderate-to-high-risk group as classified by the Duke treadmill score. Risk stratification using XECG may prove valuable for identifying asymptomatic subjects who can benefit from CCTA.

KEY WORDS: Coronary artery disease · Coronary computed tomography angiography · Exercise electrocardiography · Asymptomatic population.

Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in developed countries.[1] Moreover, major CAD events such as sudden cardiac death, myocardial infarction (MI), or unstable angina, are often the first manifestation of CAD in patients who did not experience symptoms

in the past.[2] Thus, identification of asymptomatic subjects without known CAD who are at high risk of adverse events might help better guide the use of risk-reduction therapies.[3]

Currently, exercise electrocardiography (XECG) is the most frequently used tool for the initial assessment of CAD in daily practice. XECG is often recommended in symptomatic patients who present with an intermediate pretest probability of CAD,[4] though it has also been considered for cardiovascular risk assessment among intermediate-risk asymptomatic adults.[5] Despite this, ST-segment changes in XECG displays poor sensitivity and specificity for the detection of CAD,[6] and also has limited prognostic value.[7,8] Further still, XECG is not effective in identifying CAD in asymptomatic subjects as it is not capable of detecting the presence of atherosclerosis in the absence of flow-limiting stenosis.[9] To this end, coronary artery computed tomography angiography (CCTA), which enables direct anatomic visualization of CAD irrespective of coronary flow limitation, might serve as a more sensible modality for the detection of CAD, at least in this patient group.

The incremental value of CCTA findings over and above XECG in patients with suspected CAD has been documented elsewhere.[10] In this paper, CCTA discriminated future risk of major adverse cardiac events (MACE) independent of XECG results.[10] To date, however, limited data exists that substantiates the prognostic value and clinical utility of CCTA beyond traditional strategies of CAD evaluation in the asymptomatic population.[11-15] The present study is based on subgroup analysis of previous report database using same population which was excluded in the analysis.[10] This study sought to evaluate the prognostic value of CCTA and identify XECG parameters that may discriminate specific groups who might benefit from CCTA results in an asymptomatic population.

METHODS

A total 3944 subjects were consecutively enrolled and underwent both CCTA and XECG within 90 days at Severance Cardiovascular Hospital from May 2003 through April 2009 without any other cardiovascular testing. Subjects were excluded who: 1) had chest pain (n = 2389) or angina equivalent symptoms including dyspnea on exertion (n = 378); 2) were younger than 30 years of age (n = 65); 3) had a prior history of MI, coronary revascularization, or cardiac transplantation (n = 28); 4) had an inadequate XECG (154 subjects); 5) had uninterpretable coronary CCTA results (n = 117); or 6) had undergone CCTA and XECG more than 90 days apart (1 patient). Hence, a total of 812 asymptomatic subjects comprised the final analysis herein.

The median number of days between coronary CCTA and XECG was 7 days (interquartile range: 1 to 14 days). Clinical indications of CCTA and XECG were subjects with clinical risk factors (n = 468), subjects undergoing general health evaluation (n = 223), preoperative evaluation for non-cardiac surgery (n = 30), or subjects with abnormal resting

electrocardiography (ECG) (n = 91). Clinical data including conventional risk factors for CAD (e.g., hypertension, diabetes mellitus, current cigarette smoking, and dyslipidemia) were collected at the time of the index visit. Hypertension was defined as a mean systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or both, a previously established diagnosis of hypertension, or current use of anti-hypertensive medications. Diabetes mellitus was defined as HbA1c ≥ 6.5%, or current use of insulin or anti-diabetic medications, and dyslipidemia was defined as a fasting total cholesterol of 220 mg per 100 mL or more, fasting triglycerides of 150 mg per 100 mL or greater, or a history of lipid-lowering therapy. Current smoking was defined as using tobacco in the previous six months. Appropriate institutional review committee approval and informed consent were obtained. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

CCTA PROTOCOL AND IMAGE ANALYSIS

Data acquisition and image analysis were carried out as described previously.[16] In brief, two types of CT system configurations were used: 1) a 64-slice CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) using retrospective ECG gating with tube current modulation from 2003 through 2009 and 2) a 64-row CT scanner (LightSpeed VCT XT, GE Healthcare, Milwaukee, WI, USA) using a prospectively ECG-gated axial technique from 2008 through 2009. Image reconstruction was performed on the scanner's workstation using commercially available software (Wizard, Siemens Medical Solutions, or GEAW, GE Healthcare). Two experienced cardiac radiologists who were masked to the XECG results of each patient evaluated the CCTA analysis. In case of a disagreement, a joint reading was performed to reach a consensus.

Lesions were classified by the maximal luminal diameter stenosis observed on any plane. The presence of obstructive CAD was defined as at least one plaque causing ≥ 50% luminal diameter stenosis in a major coronary artery. The extent of CAD was classified as the number of obstructive vessels (i.e., ≥ 50%) as follows: no obstructive CAD, 1-vessel disease (VD), 2-VD, and 3-VD. The severity of CAD was classified into 4 categories according to the degree of stenosis:[5] normal (absence of CAD), mild (1% to 39% luminal narrowing), moderate (40% to 69% luminal narrowing); and severe (≥ 70% luminal narrowing) stenosis.

XECG PROTOCOL

A symptom-limited exercise treadmill test was performed according to the Bruce protocol.[17] During the exercise stress test, symptom status, heart rhythm, blood pressure, exercise time (minutes) and exercise workload defined using metabolic equivalents of task (METs) were recorded. As an example for

the latter, one MET was defined as the energy expended by sitting quietly, which is equivalent to a body oxygen consumption of approximately 3.5 mL per kilogram of body weight per minute for an average adult.[9)17)18)]

A 12-lead ECG was obtained per minute, and a 3-lead ECG for heart rhythm was monitored continuously. Indications for terminating the exercise test were as previously described.[19)] With regards to the XECG dataset, results of the stress test were classified as positive when the ST segment appeared horizontal or reported a down-sloping depression ≥ 1 mm for 60 to 80 ms after the end of the QRS complex.[13)] Inadequate stress tests of subjects who had not reached the reference standards established for age, sex, and weight were excluded from analysis. The Duke treadmill score (DTS) was obtained from the duration of exercise in minutes, the maximum ST-segment deviation in millimeters, and the exercise angina index.[20)] The angina index was defined as follows: 0, if there was no exercise angina; 1, if the subject had non-limiting exercise angina; and 2, if the exercise is terminated by angina.[20)] Subjects were then divided into two groups using previously defined categories based on the DTS as follows: moderate-to-high-risk (≤ + 4), and low-risk (≥ + 5).[9)]

FOLLOW-UP

Clinical follow-up data were collected via review of electronic medical records and telephone contact by dedicated physicians or research nurses who were both masked to the CCTA and XECG results. The primary endpoint in this study was the occurrence of MACE, defined as cardiac death, nonfatal MI, unstable angina requiring hospitalization, and revascularization either by percutaneous coronary intervention or coronary artery bypass graft after 90 days of the index test. Coronary revascularizations occurring within 90 days after the index test were not included in the analyses to exclude any test-driven procedure from being considered as a MACE.[21-23)]

STATISTICAL METHODS

Discrete variables are presented as numbers (with proportions), and continuous variables are expressed as mean ± standard deviation or median with interquartile range, as appropriate. Differences between continuous variables were analyzed by independent t-test, and those between categorical variables were analyzed by the chi square test or Fisher exact test, as appropriate. Cumulative event rates as a function of time were calculated using Kaplan-Meier survival analysis for XECG results and CCTA-diagnosed CAD. A multivariate Cox proportional hazards model reporting hazard ratios (HRs) with 95% confidence intervals (95% CIs) was employed to assess the association of XECG and CCTA results with MACE (p values for χ^2 according to the likelihood-ratio test are also presented). A time-dependent receiver operating characteristic (ROC) curve was constructed to compare the global concordance probability between clinical risk factors (i.e., base model) versus clinical risk factors plus CAD detected by CCTA model. A p value less than 0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SPSS version 15 software (SPSS Inc., Chicago, IL, USA) and R software version 3.20.

RESULTS

CLINICAL CHARACTERISTICS OF STUDY POPULATION

Overall, the study population consisted of 812 asymptomatic subjects (mean age 59 ± 9 years, 60.8% male) (Table 1). Subjects who had CAD determined by CCTA were older (62 ± 8 vs. 58 ± 9, $p < 0.001$) and comprised more male subjects (77.5% vs. 57.3%, $p < 0.001$) and history of diabetes mellitus (33.1% vs. 18.1%, $p < 0.001$) than subjects without CAD by CCTA. Subjects who had more than two clinical risk factors (i.e., hypertension, diabetes mellitus, dyslipidemia, and current smoking) composed 39.7% of the total study population (n = 322). Reasons for undergoing CCTA included subjects presenting with clinical risk factors (n = 468, 57.6%), part of a general health evaluation (n = 223, 27.5%), abnormal resting ECG (n = 91, 11.2%), or preoperative evaluation (n = 30, 3.7%).

XECG AND CCTA RESULTS

Among the study cohort, 120 subjects (14.8%) had a positive XECG result and 273 subjects (33.6%) were classified as moderate-to-high-risk according to DTS (Table 2). The proportion of positive XECG and value of METs did not differ between subjects with or without CAD by CCTA (all $p > 0.05$). In contrast, a higher number of subjects with CAD were classified into the moderate-to-high-risk group according to DTS,

Table 1. Baseline characteristics

	Total population (n = 812)	Patients with CAD in CCTA (n = 142)	Patients without CAD in CCTA (n = 670)	p value
Age, years	59 ± 9	62 ± 8	58 ± 9	< 0.001
Male, n (%)	494 (60.8)	110 (77.5)	384 (57.3)	< 0.001
Hypertension, n (%)	442 (55.1)	86 (60.6)	356 (53.1)	0.12
Diabetes mellitus, n (%)	168 (20.9)	47 (33.1)	121 (18.1)	< 0.001
Dyslipidemia, n (%)	344 (42.5)	60 (42.3)	284 (42.4)	> 0.99
Current smoking, n (%)	115 (14.2)	20 (14.1)	95 (14.2)	> 0.99

Data presented as number (percentage) or mean ± standard deviation. CAD: coronary artery disease, CCTA: coronary computed tomography angiography

which was significant (46.5% vs. 30.9%, p < 0.001). By CCTA, 142 subjects (17.5%) had obstructive CAD: 1-VD (n = 111, 13.7%), 2-VD (n = 28, 3.4%), or 3-VD (n = 3, 0.4%). In terms of the severity of CAD, subjects were classified as having mild (n = 271, 33.4%), moderate (n = 148, 18.2%), and severe (n = 30, 3.7%) CAD (Table 3). The overall agreement for subjects who had positive or negative results in both XECG and CCTA and between XECG and CCTA was 74.4% (576 out of 774 subjects, excluding subjects with equivocal XECG results). Most subjects with positive XECG results had no CAD as determined by CCTA (n = 92, 76.7%), while 6 subjects (5.0%) with positive XECG results had multi-VD (n = 6, 5.0%) or severe stenosis (n = 4, 3.3%) in CCTA.

For 92 patients with false positive XECG results, the mean age was 58 ± 8 years, and 42.4% were women, which showed no significant difference from total study population.

LONG-TERM CLINICAL OUTCOMES

During a mean follow-up of 37 ± 16 months, 9 subjects (1.1%) experienced MACE–all revascularization (Table 4). Patients identified to have CAD were regularly followed-up, and 4 of them underwent invasive coronary angiography within 90 days from CCTA. All 9 patients who experienced MACE underwent invasive coronary angiography due to new onset stable angina, and stenoses requiring revascularization were found during the procedure. The mean time to MACE was 20 ± 13 months. The incidence of MACE according to the results of XECG and CCTA is shown in Table 5. Most subjects who experienced MACE (n = 8) had CAD by CCTA and all revascularized lesions were previously identified by CCTA. There were only one patient with moderate CAD had positive XECG results (11.1%). According to DTS, five subjects were categorized into the moderate-to-high-risk group (n = 5, 55.6%), and all had moderate disease in index CCTA. Among eight subjects with negative XECG results who experienced MACE, 7 subjects had CAD and 5 had multi-VD by CCTA. In Kaplan-Meier survival curves, there was no difference according to either positive XECG results (log rank p = 0.76) or

Table 2. Results of XECG in relation to CCTA

	Total population (n = 812)	Patients with CAD in CCTA (n = 142)	Patients without CAD in CCTA (n = 670)	p value
Positive XECG, n (%)	120 (14.8)	28 (20.9)	92 (14.4)	0.07
METs, mean ± SD	14.0 ± 11.9	11.7 ± 1.8	12.0 ± 1.7	0.06
DTS, mean ± SD	5.8 ± 3.9	5.1 ± 4.2	5.9 ± 3.8	0.03
DTS, moderate to high risk, n (%)	273 (33.6)	66 (46.5)	207 (30.9)	< 0.001

Data presented as number (percentage) or mean ± SD. CAD: coronary artery disease, CCTA: coronary computed tomography angiography, DTS: Duke treadmill score, METs: metabolic equivalents of task, XECG: exercise electrocardiography, SD: standard deviation

Table 3. Results of CCTA in relation to DTS

Variables	Low risk group (DTS ≥ 5) (n = 539)	Moderate to high risk group (DTS ≤ 4) (n = 273)	p value
CCTA: extent of CAD			< 0.001
No obstructive CAD (n = 670, 82.5%)	463 (85.9%)	207 (75.8%)	
1-VD (n = 111, 13.7%)	62 (11.5%)	49 (17.9%)	
2-VD (n = 28, 3.4%)	14 (2.6%)	14 (5.1%)	
3-VD (n = 3, 0.4%)	0 (0.0%)	3 (1.1%)	
CCTA: severity of CAD			< 0.001
No stenosis (n = 363, 44.7%)	267 (49.5%)	96 (35.2%)	
Mild stenosis (n = 271, 33.4%)	177 (32.8%)	94 (34.4%)	
Moderate stenosis (n = 148, 18.2%)	74 (13.7%)	74 (27.1%)	
Severe stenosis (n = 30, 3.7%)	21 (3.9%)	9 (3.3%)	

CAD: coronary artery disease, CCTA: coronary computed tomography angiography, DTS: Duke treadmill score, VD: vessel disease

Table 4. Clinical outcomes in relation to the presence of CAD by CCTA

Clinical outcomes	Total population (n = 812)	Patients with CAD in CCTA (n = 142)	Patients without CAD in CCTA (n = 670)	p value
Follow-up duration, months	37 ± 16	35 ± 16	38 ± 16	0.06
MACE, n (%)	9 (1.1)*	8 (5.6)	1 (0.1)	< 0.001

Data presented as number (percentage) or mean ± standard deviation. *All MACE was revascularization. CAD: coronary artery disease, CCTA: coronary computed tomography angiography, MACE: major adverse cardiac events

DTS (log rank p = 0.16). However, CAD by CCTA appeared to discriminate the survival curve successfully (log rank $p <$ 0.001) (Fig. 1).

PROGNOSTIC UTILITY OF XECG AND CCTA

In multivariable Cox regression adjusting for age, sex, hypertension, diabetes mellitus, dyslipidemia, and current smoking, neither positive XECG results nor classification with DTS were associated with future MACE (all $p > 0.05$). However, the presence of CAD by CCTA was significantly associated with future MACE (HR: 27.05, 95% CI: 3.26–224.71, p = 0.002) (Table 6). Moreover, a positive XECG result and moderate-to-high-risk group by DTS also failed to predict future MACE according to the likelihood ratio test. Conversely,

in Table 6 CAD by CCTA had a significant predictive value when added to the clinical risk factor model in the likelihood ratio test ($p < 0.001$).

IDENTIFICATION OF PATIENT GROUPS WHO MAY BENEFIT FROM CCTA USING XECG PARAMETERS

In further analysis using parameters derived from XECG, we attempted to identify a specific population who might benefit from CCTA. When subjects were classified according to DTS, only CCTA had a predictive value in the moderate-to-high-risk group (HR: 11.39, 95% CI: 1.12–116.01, p = 0.04) in multivariable Cox regression that adjusted for clinical risk factors. Conversely, CCTA did not predict future MACE in the low-risk group derived from DTS ($p > 0.05$) (Fig. 2).

Table 5. Incidence of MACE according to XECG results and the presence of CAD by CCTA

	Results of XECG		DTS	
	Negative XECG (8/692, 1.16%)	Positive XECG (1/120, 0.83%)	Low risk group (DTS ≥ 5) (4/539, 0.74%)	Moderate to high risk group (DTS ≤ 4) (5/273, 1.83%)
Patients with CAD in CCTA (8/142, 5.63%)	7/114 (0.63%)	1/28 (3.57%)	3/76 (3.95%)	5/66 (7.58%)
Patients without CAD in CCTA (1/670, 0.15%)	1/578 (0.17%)	0/92 (0%)	1/463 (0.22%)	0/207 (0%)

CAD: coronary artery disease, CCTA: coronary computed tomography angiography, DTS: Duke treadmill score, MACE: major adverse cardiac events, XECG: exercise electrocardiography
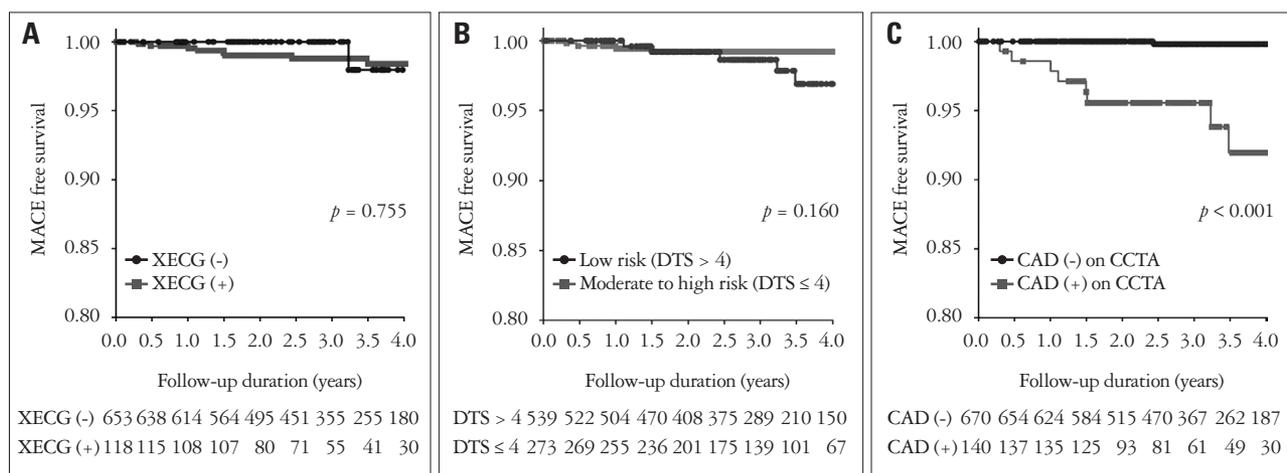

Fig. 1. Kaplan-Meier survival curve of the MACE free survival according to results of XECG (A), risk stratification with DTS (B), and the presence of CAD on CCTA (C). MACE: major adverse cardiac events, XECG: exercise electrocardiography, DTS: Duke treadmill score, CAD: coronary artery disease, CCTA: coronary computed tomography angiography.

Table 6. Multivariate analysis-predictors of MACE (Cox proportional hazards regression model)

Model	Cox regression test adjusted with clinical risk factors*		Likelihood ratio test comparison with clinical risk factor alone model
	Hazard ratio (95% CI)	p value	p value
Moderate-high risk group by DTS[†]	2.17 (0.58–8.14)	0.25	0.25
Positive XECG result	0.70 (0.09–5.63)	0.73	0.48
CAD (+) on CCTA	27.05 (3.26–224.71)	0.002	< 0.001

*Clinical risk factors were adjusted with age, gender, hypertension, diabetes mellitus, dyslipidemia, and current smoking, [†]Patients were classified into moderate-high risk group or low risk group according to DTS. CI: confidence interval, CAD: coronary artery disease, CCTA: coronary computed tomography angiography, DTS: Duke treadmill score, MACE: major adverse cardiac events, XECG: exercise electrocardiography
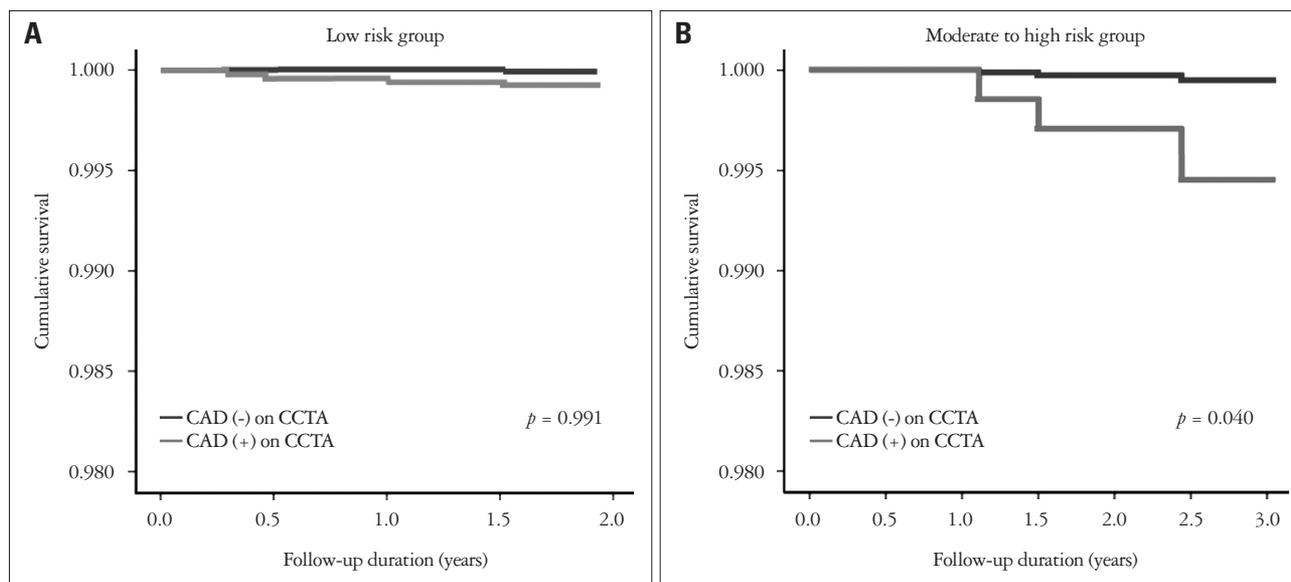
Fig. 2. Cox proportional hazard regression analysis for major adverse cardiac events according to the presence of CAD by CCTA in low risk group (A) and moderate to high risk group (B) classified with DTS – adjusted with age, gender, hypertension, diabetes mellitus, dyslipidemia, and current smoking. CAD: coronary artery disease, CCTA: coronary computed tomography angiography, DTS: Duke treadmill score.
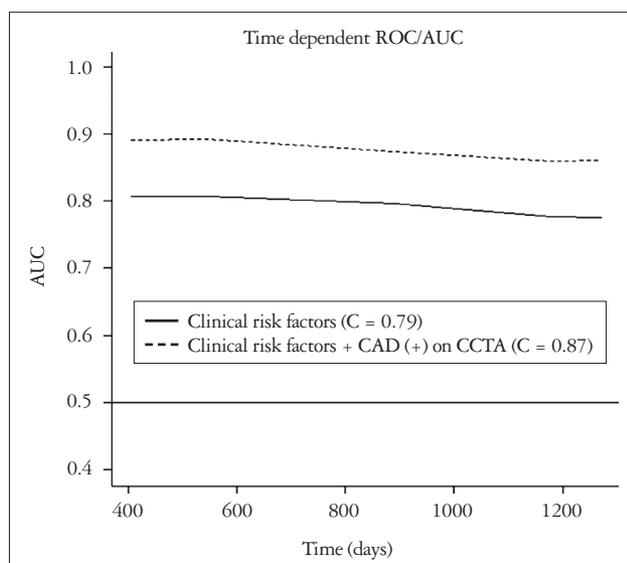

Fig. 3. Time-dependent ROC curve analysis for prediction of MACE in moderate risk group classified with Duke treadmill score according to clinical risk factor model (solid line) and clinical risk factor plus CAD on CCTA model (dashed line). AUC: area under curve, CAD: coronary artery disease, CCTA: coronary computed tomography angiography, MACE: major adverse cardiac event, ROC: receiver operating characteristic.

In Fig. 3, when the time-dependent ROC curve analysis was drawn in the moderate-to-high-risk group, the presence of CAD provided additional prognostic value when combined with the clinical risk factor (i.e., base model) model (area under curve 0.79 vs. 0.87).

DISCUSSION

In the current study, the prognosis of asymptomatic middle-aged subjects who underwent CCTA and XECG was excel-

lent, despite the non-negligible prevalence of occult CAD (17.5%) in CCTA. In addition, CCTA provided a prognostic benefit over XECG in asymptomatic subjects, while risk assessment using DTS appeared useful for identifying asymptomatic subjects who might benefit from CCTA.

PROGNOSTIC VALUE OF XECG AND CCTA IN ASYMPTOMATIC POPULATION

Most often, XECG has been considered as the initial diagnostic assessment for subjects with suspected CAD and who are able to exercise due to its lower cost, and simplicity of its operation and interpretation.[17] Especially in asymptomatic subjects, XECG is the only recommended test that can be considered for cardiovascular risk assessment based on current guidelines.[5] However, there are non-negligible limitations of XECG including low sensitivity and specificity,[24][25] and its inability to detect the presence of an atherosclerotic plaque in the absence of impaired coronary flow.[7] As a consequence, the predictive value of XECG has been reported to be low.[26][27] To this end, the current study is fitting with previous studies, indicating that XECG has limited value in discriminating subjects who are at risk of future MACE.

CCTA VERSUS XECG AS AN INITIAL EVALUATION OF CAD IN ASYMPTOMATIC POPULATIONS

Along with its low sensitivity and specificity, the low prognostic value of XECG has given rise to controversy concerning the value of using XECG for "screening" asymptomatic populations. Therefore, as an alternative, CCTA has emerged as a novel diagnostic tool for the evaluation of possible CAD.[28-30] Recent studies have showed a higher sensitivity and specificity of CCTA in detecting CAD, which was superior

to XECG.[31)32)] Moreover, considering that most MACE are caused not only by flow-limiting coronary stenoses, but also by the atherosclerotic plaque burden which XECG cannot detect,[33)] the strategy of CCTA as a first-line test to exclude CAD and to replace invasive coronary angiography in symptomatic subjects has been suggested.[34)]

However, there is still limited data regarding the use of CCTA as a screening tool in the asymptomatic population, and the prognostic value of CCTA among such individuals is also not well known.[35)] Choi et al.[12)] evaluated the potential role of CCTA for risk stratification in 1000 middle-aged asymptomatic subjects who underwent CCTA as part of a general health evaluation and failed to report the positive value of CCTA as a screening tool. More recently, in the CONFIRM study, the additional risk-predictive benefit by CCTA was not clinically meaningful when compared to a risk model based upon coronary artery calcium scoring in individuals without chest pain.[35)] More recently, in the FACTOR-64 study,[36)] the use of CCTA to screen for CAD did not reduce the composite rate of MACE among asymptomatic subjects with type 1 or type 2 diabetes of at least 3 to 5 years' duration who were considered to be at high-risk of CAD. Hence, the current guidelines for the use of CCTA in the asymptomatic population propose that CCTA should not be recommended.[5)]

In this study, the use of CCTA showed clear prognostic benefit over XECG or clinical risk factors alone. Albeit, considering its relatively high cost, the use of iodinated contrast agents, and the present radiation exposure data,[37)] CCTA should not be recommended "routinely" in the asymptomatic population as a single screening tool. More evidence or additional parameters are clearly warranted to identify specific groups for the purpose of guiding clinical decisions on whether to utilize CCTA or not. Therefore, we advocate that XECG, the most widely used and accessible test, could be used as a discriminating tool in the present study.

XECG AS RISK STRATIFICATION TOOL FOR IDENTIFICATION OF PATIENT GROUP WHO CAN BENEFIT FROM CCTA

A major reason why previous studies have failed to find sufficient evidence for recommending CCTA as a screening tool in the asymptomatic population is the lack of novel approaches for identifying specific groups that may actually benefit from CCTA. In this aspect, the identification of potential subjects who could benefit from CCTA using more traditional methods is critical when considering the potential harm of CCTA. In this study, DTS with XECG successfully identified a patient group that can benefit from CCTA. CCTA had a discriminative value only in the moderate-to-high-risk group assessed with DTS, but not in the low-risk group. This finding is in line with recent studies which showed that the prognostic value of XECG in the asymptomatic population derives not from electrocardiographic ischemia but from fitness-related

variables.[27)38)] Moreover, the identification of ischemia using exercise echocardiogram was also useful only in subjects with moderate risk DTS in one study.[39)]

Therefore, the strategy of combining CCTA with DTS could be used to augment predictability of MACE in the asymptomatic population. By simultaneously using XECG and DTS as a "gatekeeper" of CCTA, the incidence of unpredicted first major CAD events as an initial manifestation may likely be attenuated in subjects with moderate-risk DTS, while potentially avoiding any "unnecessary" CCTA in the low-risk group. The fact that all revascularized lesions were same lesions identified by CCTA also may indicate that more thorough surveillance is warranted with patients with CAD by CCTA. When considering the risk of radiation exposure and use of contrast materials in CCTA, future comprehensive studies are warranted to demonstrate the safer and clinically efficient method to diagnose CAD and to predict future risk of cardiac events in asymptomatic subjects without known CAD.

STUDY LIMITATIONS

This study was retrospectively conducted and therefore may have been influenced by unobserved confounders and selection or referral biases, or both. In addition, the effect of post-test medical treatments or risk factor control was not considered. Although we included only revascularizations more than 90 days after CCTA as outcome events, revascularizations according to the index test may have been included, and the low number of study events resulted in the wide 95% CIs. Finally, the fact that all MACEs were revascularization and about 44% of MACE was occurred in patients with low risk in DTS may lower the impact of the CCTA and DTS.

In conclusion, we demonstrated the prognostic value of CCTA in conjunction with XECG in this study. CCTA provided incremental prognostic benefit over and above XECG in this asymptomatic population, especially for those in the moderate-to-high-risk group as classified by DTS. Risk stratification using XECG may prove valuable for identifying asymptomatic subjects who might benefit from CCTA.

REFERENCES

1. Gibbons RJ, Jones DW, Gardner TJ, Goldstein LB, Moller JH, Yancy CW; American Heart Association. *The American Heart Association's 2008 statement of principles for healthcare reform. Circulation* 2008;118:2209-18.
2. Christopher Jones R, Pothier CE, Blackstone EH, Lauer MS. *Prognostic importance of presenting symptoms in patients undergoing exercise testing for evaluation of known or suspected coronary disease. Am J Med* 2004;117:380-9.

3. O'Malley PG, Redberg RF. *Risk refinement, reclassification, and treatment thresholds in primary prevention of cardiovascular disease: incremental progress but significant gaps remain. Arch Intern Med 2010;170:1602-3.*

4. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. *2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012; 60:e44-164.*

5. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW; American College of Cardiology Foundation; American Heart Association. *2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50-103.*

6. Detrano R, Gianrossi R, Froelicher V. *The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis 1989;32:173-206.*

7. Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. *Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. JAMA 2004;292:1462-8.*

8. Goraya TY, Jacobsen SJ, Pellikka PA, Miller TD, Khan A, Weston SA, Gersh BJ, Roger VL. *Prognostic value of treadmill exercise testing in elderly persons. Ann Intern Med 2000;132:862-70.*

9. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. *Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849-53.*

10. Cho I, Shim J, Chang HJ, Sung JM, Hong Y, Shim H, Kim YJ, Choi BW, Min JK, Kim JY, Shim CY, Hong GR, Chung N. *Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol 2012;60:2205-15.*

11. Cho I, Min HS, Chun EJ, Park SK, Choi Y, Blumenthal RS, Rivera JJ, Nasir K, Kim YJ, Sohn DW, Oh BH, Park YB, Chang HJ. *Coronary atherosclerosis detected by coronary CT angiography in asymptomatic subjects with early chronic kidney disease. Atherosclerosis 2010;208:406-11.*

12. Choi EK, Choi SI, Rivera JJ, Nasir K, Chang SA, Chun EJ, Kim HK, Choi DJ, Blumenthal RS, Chang HJ. *Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. J Am Coll Cardiol 2008; 52:357-65.*

13. Djaberi R, Schuijf JD, Boersma E, Kroft LJ, Pereira AM, Romijn JA, Scholte AJ, Jukema JW, Bax JJ. *Differences in atherosclerotic plaque burden and morphology between type 1 and 2 diabetes as assessed by mul-*

14. Nucifora G, Schuijf JD, van Werkhoven JM, Jukema JW, Djaberi R, Scholte AJ, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. *Prevalence of coronary artery disease across the Framingham risk categories: coronary artery calcium scoring and MSCT coronary angiography. J Nucl Cardiol 2009;16:368-75.*

15. Zeina AR, Odeh M, Rosenschein U, Zaid G, Barmeir E. *Coronary artery disease among asymptomatic diabetic and nondiabetic patients undergoing coronary computed tomography angiography. Coron Artery Dis 2008; 19:37-41.*

16. Kwon SW, Kim YJ, Shim J, Sung JM, Han ME, Kang DW, Kim JY, Choi BW, Chang HJ. *Coronary artery calcium scoring does not add prognostic value to standard 64-section CT angiography protocol in low-risk patients suspected of having coronary artery disease. Radiology 2011; 259:92-9.*

17. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. *ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40:1531-40.*

18. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. *Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.*

19. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD Jr, Winters WL, Yanowitz FG, Ritchie JL, Gibbons RJ, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. *ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30:260-311.*

20. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. *Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106:793-800.*

21. Hadamitzky M, Freissmuth B, Meyer T, Hein F, Kastrati A, Martinoff S, Schömig A, Hausleiter J. *Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. JACC Cardiovasc Imaging 2009;2:404-11.*

22. Hadamitzky M, Distler R, Meyer T, Hein F, Kastrati A, Martinoff S, Schömig A, Hausleiter J. *Prognostic value of coronary computed tomographic angiography in comparison with calcium scoring and clinical risk scores. Circ Cardiovasc Imaging 2011;4:16-23.*

23. Hachamovitch R, Nutter B, Hlatky MA, Shaw LJ, Ridner ML, Dorbala S, Beanlands RS, Chow BJ, Branscomb E, Chareonthaitawee P, Weigold WG, Voros S, Abbara S, Yasuda T, Jacobs JE, Lesser J, Berman DS, Thomson LE, Raman S, Heller GV, Schussheim A, Brunken R, Williams KA, Farkas S, Delbeke D, Schoepf UJ, Reichek N, Rabinowitz S, Sigman SR, Patterson R, Corn CR, White R, Kazerooni E, Corbett J, Bokhari S, Machac J, Guarneri E, Borges-Neto S, Millstine JW, Caldwell J, Arrighi J, Hoffmann U, Budoff M, Lima J, Johnson JR, Johnson B, Gaber M, Williams JA, Foster C, Hainer J, Di Carli MF; SPARC Investigators. *Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). J Am Coll Cardiol 2012;59:462-74.*

24. Gibson RS, Beller GA. *Should exercise electrocardiographic testing be re-*

placed by radioisotope methods? Cardiovasc Clin 1983;13:1-31.

25. Podrid PJ, Graboys TB, Lown B. *Prognosis of medically treated patients with coronary-artery disease with profound ST-segment depression during exercise testing. N Engl J Med 1981;305:1111-6.*

26. Froelicher VF Jr, Thomas MM, Pillow C, Lancaster MC. *Epidemiologic study of asymptomatic men screened by maximal treadmill testing for latent coronary artery disease. Am J Cardiol 1974;34:770-6.*

27. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, Blumenthal RS. *Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. JAMA 2003;290:1600-7.*

28. Li S, Liu J, Luo Y, Peng L, Ni Q, Wu H, Wang C, Chen L, Dong R, Zhu J. *Diagnostic accuracy of noninvasive coronary angiography with 320-slice computed tomography in the clinical routine: results from four-year clinical registry at a single center. Int J Cardiol 2013;168:5035-6.*

29. Chang HJ, Chung N. *Clinical perspective of coronary computed tomographic angiography in diagnosis of coronary artery disease. Circ J 2011;75: 246-52.*

30. Fujimoto S, Kondo T, Kodama T, Orihara T, Sugiyama J, Kondo M, Endo A, Fukazawa H, Nagaoka H, Oida A, Ikeda T, Yamazaki J, Takase S, Narula J. *Coronary computed tomography angiography-based coronary risk stratification in subjects presenting with no or atypical symptoms. Circ J 2012;76:2419-25.*

31. Dewey M, Dübel HP, Schink T, Baumann G, Hamm B. *Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease. Eur Heart J 2007;28: 2485-90.*

32. Dedic A, Genders TS, Ferket BS, Galema TW, Mollet NR, Moelker A, Hunink MG, de Feyter PJ, Nieman K. *Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology 2011;261:428-36.*

33. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. *Prog-*

nostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826-33.

34. Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, Serruys PW, Krestin GP, de Feyter PJ. *High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005;112:2318-23.*

35. Cho I, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Callister TQ, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Maffei E, Cademartiri F, Kaufmann P, Shaw LJ, Raff GL, Chinnaiyan KM, Villines TC, Cheng V, Nasir K, Gomez M, Min JK; CONFIRM Investigators. *Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation 2012;126:304-13.*

36. Muhlestein JB, Lappé DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL, Vavere AL, Anderson JL. *Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA 2014;312:2234-43.*

37. Jakobs TF, Becker CR, Ohnesorge B, Flohr T, Suess C, Schoepf UJ, Reiser MF. *Multislice helical CT of the heart with retrospective ECG gating: reduction of radiation exposure by ECG-controlled tube current modulation. Eur Radiol 2002;12:1081-6.*

38. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. *Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000;284:1392-8.*

39. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. *Prediction of mortality by exercise echocardiography: a strategy for combination with the duke treadmill score. Circulation 2001;103:2566-71.*