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Value of CACS Compared With ETT and Myocardial Perfusion Imaging for Predicting Long-Term Cardiac Outcome in Asymptomatic and Symptomatic Patients at Low Risk for Coronary Disease

Clinical Implications in a Multimodality Imaging World

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ABSTRACT

OBJECTIVES This prospective, observational study in 988 asymptomatic or symptomatic low-risk patients without prior coronary artery disease was conducted to define the relative value of coronary artery calcium score (CACS), exercise treadmill testing (ETT), and stress myocardial perfusion single-photon emission computed tomography (SPECT) variables in predicting long-term risk stratification.

BACKGROUND CACS, ETT, and stress myocardial perfusion SPECT results predict patients' outcome. There are currently no data comparing their relative value in long-term risk stratification.

METHODS Patients were stratified by Framingham risk score (FRS), with a median follow-up of 6.9 years. *Cardiac events* were defined as a composite of cardiac death, nonfatal myocardial infarction, and the need for coronary revascularization. Most patients (87%) were considered appropriate candidates for functional testing as defined by current appropriate use criteria.

RESULTS The long-term cardiac event rate was 11.2% (1.6% per year). Multivariate risk predictors in all patients and in the appropriate use cohort were abnormal SPECT (hazard ratio [HR]: 1.83 and 1.99), ETT ischemia (HR: 1.70 and 1.76), decreasing exercise capacity (HR: 1.11 and 1.17), decreasing Duke treadmill score (HR: 1.07 for both), and CACS severity (HR: 1.29 for both), respectively. Throughout the 10-year follow-up, CACS improved risk prediction, with event rates ranging from 0.6% per year (CACS ≤10) to 3.7% per year (CACS >400) ($p < 0.0001$). CACS also improved risk prediction in all patients, in the appropriate use cohort and among those with low-risk ETT and SPECT results (all, $p < 0.001$). Area under the receiver-operating characteristic curve was increased when CACS variables (from 0.63 to 0.70; $p = 0.01$) but not ETT variables (from 0.63 to 0.65) were added to FRS. Moreover, net reclassification improvement was significantly increased when CACS was added to FRS + functional variables in all patients and in the appropriate use cohort (both, $p < 0.0001$).

CONCLUSIONS CACS significantly improved long-term risk stratification beyond FRS, ETT, and SPECT results across the spectrum of clinical risk and importantly even among those who are currently considered appropriate candidates for functional testing or have low-risk functional test results. Our findings support CACS as a first-line test over ETT or SPECT for accurately assessing long-term risk in such patients. (J Am Coll Cardiol Img 2015;8:134–44) © 2015 by the American College of Cardiology Foundation.

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The coronary artery calcium score (CACS) severity has been reported to predict patients' cardiac outcomes (1,2), and CACS is considered an appropriate test in asymptomatic patients at intermediate to high clinical risk for coronary artery disease (CAD) (3,4). Likewise, exercise treadmill testing (ETT), performed with or without cardiac imaging, identifies those at high or low risk for mortality on the basis of the presence of stress-induced ischemia (5), peak exercise capacity (in metabolic equivalents of task [METs]) (6,7), and Duke treadmill score (DTS) (7,8). Current guidelines (3,9) and appropriate use criteria (4) support both ETT and stress myocardial perfusion single-photon emission computed tomography (SPECT) for evaluating risk in selected asymptomatic patients with risk factors for CAD. However, there are no studies addressing which of these tests offer the most benefit in CAD detection and long-term risk stratification.

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The purpose of this study was to examine the relative value of CACS, ETT, and SPECT in predicting long-term risk stratification in a large cohort of generally asymptomatic patients who had all tests performed within a close temporal period and who were followed up for up to a decade.

METHODS

STUDY POPULATION. This substudy analyzed data from a previously published prospective, observational follow-up trial in 1,175 predominantly middle-aged (40 to 65 years) men and women who had both CACS and stress SPECT performed for clinically indicated reasons (10). All patients had risk factors for, but no history of, CAD. The substudy included 988 patients (84%) who were stressed with ETT during SPECT (10). CACS was performed as the first-line test in 84% and SPECT in 16% of patients who were either asymptomatic (71% and 13%, respectively) or who had atypical chest pain (13% and 3%, respectively). No one had coronary revascularization performed between tests (median, 47 days), but 10 did so <60 days after testing. The overall results did not differ with the inclusion or exclusion of these 10 patients, and no statistical interaction was observed between SPECT and ETT variables on patients' outcome (all, $p > 0.20$). Testing sequence also had no effect on outcome on univariate ($p = 0.66$) or multivariate ($p = 0.69$) analysis. For these reasons, the data on all 988 patients are presented, of whom 946 (96%) had adequate follow-up.

ELECTRON BEAM COMPUTED TOMOGRAPHY. CACS assessment was performed using electron beam CT (Imatron C-150, Imatron, San Francisco, California). *Coronary artery calcification* was defined as a lesion of >130 Hounsfield units, with an area equal to 3 pixels. CACS was calculated using the standard Agatston criteria, and patients were classified as having normal (≤10), mild (11 to 100), moderate (101 to 400), or severe (>400) calcification (10). None of the patients underwent CT angiography as a part of their CACS procedure.

EXERCISE TREADMILL TESTING. Patients underwent symptom-limited ETT using the standard Bruce protocol. *Ischemia* was defined as ≥1 mm of ST-segment depression occurring >80 ms after the J point. ETT was interpreted by investigators blinded to the CACS and SPECT results. *High* and *low risk* were defined as the presence and absence of ischemia, respectively. DTS was calculated and classified as low (≥5), intermediate (4 to -10), or high (≤-11) risk (8). Risk on the basis of peak exercise capacity was classified as low (>8 METs), intermediate (5 to 8 METs), or high (<5 METs) (6).

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. SPECT was performed according to standard guidelines (10). Images were visually interpreted in all 3 standard projections, as previously reported, along with gated and raw image data to assess for study normalcy/abnormalcy and perfusion defect reversibility (10).

CLINICAL ASSESSMENT AND PATIENT FOLLOW-UP. Baseline demographic characteristics, symptom status, and medical history were prospectively recorded during interviews with experienced technical staff at the time of CACS testing. Patients were stratified, on the basis of standard FRS criteria, into categories of low (<6%), intermediate (6% to 20%), or high (>20%) 10-year risk for cardiac events (11). Because absolute cholesterol and blood pressure measurements were not available, we calculated the FRS using conservative definitions of *hyperlipidemia* (cholesterol 200 to 239 mg/dl) and *hypertension* (systolic blood pressure 140 to 159 mm Hg) as previously reported (10).

Follow-up was prospectively performed using questionnaires, telephone interviews, and review of medical records (median follow-up: 6.9 years; 25th to 75th percentile: 4.7 to 8.8 years), with events corroborated as previously reported (10). *Cardiac events* were defined as a composite of cardiac death, nonfatal myocardial infarction (MI), and the need for

ABBREVIATIONS AND ACRONYMS

AER = annualized event rate

AUC = area under the receiver-operating characteristic curve

CACS = coronary artery calcium score

DTS = Duke treadmill score

ETT = exercise treadmill test

FRS = Framingham risk score

IDI = integrated discrimination improvement

METs = metabolic equivalents of task

NRI = net reclassification improvement

SPECT = single-photon emission computed tomography