Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 12, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.12.035

EXPEDITED REVIEWS

Clinical Outcomes After Both Coronary Calcium Scanning and Exercise Myocardial Perfusion Scintigraphy

Alan Rozanski, MD, FACC,* Heidi Gransar, MS,† Nathan D. Wong, PHD, FACC,‡ Leslee J. Shaw, PHD,† Romalisa Miranda-Peats, MPH,† Donna Polk, MD,† Sean W. Hayes, MD,† John D. Friedman, MD, MPH, FACC,† Daniel S. Berman, MD, FACC†

New York, New York; and Los Angeles and Irvine, California

Objectives The purpose of this work was to assess the prognosis in patients undergoing both coronary artery calcium (CAC) scanning and exercise myocardial perfusion scintigraphy (MPS).

Background Whereas the prognostic effectiveness of MPS is well established, recent studies indicate that quantification of CAC also predicts cardiac outcomes. However, prognostic information is not yet available upon which to guide the management of patients who have had both tests.

Methods We assessed the frequency of cardiac death and myocardial infarction over a mean follow-up of 32 ± 16 months in 1,153 patients undergoing both CAC scanning and MPS. Results were compared with those from a referent cohort of 9,308 patients who had earlier undergone MPS only.

Results The frequency of myocardial ischemia rose with increasing CAC scores ($p < 0.001$), but ischemia was present in only 64 patients. Among the 1,089 nonischemic patients, of which only 3 (0.3%) underwent early revascularization, the annualized cardiac event rate was <1% in all CAC subgroups, including those with CAC scores >1,000. Kaplan-Meier analysis revealed similarly low cardiac event rates among nonischemic patients with CAC scores >1,000 and nonischemic patients with Bayesian coronary artery disease likelihood ≥85%. Late myocardial revascularization rates were also similar in these 2 groups.

Conclusions Among patients with nonischemic MPS studies, high CAC scores do not confer an increased risk for cardiac events. Thus, although patients with high CAC scores may be considered for intensive medical therapy to prevent future coronary artery disease events, a normal MPS study in such patients suggests no need for more aggressive interventions. (J Am Coll Cardiol 2007;49:1352–61) © 2007 by the American College of Cardiology Foundation

The clinical management of patients suspected of having angiographically significant coronary artery disease (ASCAD) is often aided by the performance of stress tests, such as myocardial perfusion scintigraphy (MPS). For instance, because a normal exercise MPS study reliably signifies a low annualized risk of major cardiac events among patients with even a high Bayesian pre-MPS likelihood of ASCAD (1), it is generally reasonable to employ conservative medical management when such patients are nonischemic. By contrast, because the likelihood of cardiac events increases exponentially according to the magnitude of ischemia (2), patients with moderate-to-severe ischemia generally deserve aggressive interventions. These robust prognostic associations help account for the current ubiquitous use of cardiac stress testing in clinical practice.

Recently, coronary artery calcium (CAC) scanning has been advocated as a new method for risk stratifying patients at intermediate risk for ASCAD. Atherosclerotic lesions are frequently associated with the presence of calcium (3,4), which can be accurately detected using computed tomography and quantified according to calcium (5), volume (6), and percentile calcium scores (7). Measurements of CAC have been shown to predict the underlying magnitude of atherosclerotic burden (8–10), the frequency of stress-induced myocardial ischemia (11,12), and the likelihood of future cardiac events in longitudinal studies (13–18). To date, however, this newer method of

From the *Department of Medicine, St. Luke's Roosevelt Hospital, New York, New York; †Departments of Imaging and Medicine and the Burns and Allen Research Institute, Cedars-Sinai Medical Center, and the Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California; and the ‡Heart Disease Prevention Program, University of California, Irvine, California. This study was supported by a grant from The Eisner Foundation, Los Angeles, California.

Manuscript received August 22, 2006; revised manuscript received November 22, 2006, accepted December 8, 2006.

risk stratification has not been compared directly to cardiac stress testing for prognostic purposes. Thus, there is as yet no information to guide physicians in their clinical assessment and subsequent management of patients who have undergone both forms of testing. Perhaps most puzzling may be the following question: do high CAC scores, an indicator of increased long-term risk, still confirm an increased likelihood of future cardiac events in patients with nonischemic MPS studies, an indicator of low risk? To address this issue, we undertook a study that compares 3-year outcomes among patients undergoing both exercise MPS and CAC scanning.

Methods

Study population. Two patients groups at Cedars-Sinai Medical Center (CSMC) were evaluated. The first group (the "CAC" group) consisted of 1,153 patients followed for ≥1 year after undergoing dual isotope exercise MPS and CAC scanning within 6 months of each other (mean of 24 ± 38 days), between April 1998 and January 2005. This CAC group included a mixed sample of 702 patients (61%) who were physician-referred for CAC scanning, 92 (8%) who were self-referred, and 359 (31%) who underwent scanning as part of an ongoing research protocol (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research Study). Coronary artery calcium scanning was performed before MPS in 517 (55%) patients and on the same day or after MPS in 636 (55%) patients. The second group (hereafter referred to as the "MPS" group) consisted of 9,308 patients followed for ≥1 year after undergoing MPS on a clinical basis between March 1991 and September 1999. Patients with known coronary artery disease (CAD), valvular disease, or known cardiomyopathy were excluded. This MPS referent group allowed us to investigate whether there is a parallel between the prognostic relationship between CAD likelihood values and MPS results and CAC values and MPS results, in light of data indicating that CAC increases patients' Bayesian likelihood for CAD (19). This research was approved by the CSMC Institutional Review Board, and all patients signed informed consent.

Stress testing and imaging protocol. Patients were injected intravenously at rest with thallium-201 (3 mCi to 4 mCi). After rest MPS, patients underwent symptom-limited Bruce protocol treadmill exercise testing, with a 20 mCi to 30 mCi dose of technetium-99m sestamibi injected at near maximal exercise, and MPS imaging was then repeated. The MPS studies were acquired using elliptical 180° orbits and standard energy windows (19). Scintigrams were assessed semiquantitatively by visual interpretation of 20 myocardial segments according to a 5-point score, and summed scores were compared at stress and rest (20). A summed difference score ≥4, corresponding to ≥5% of the myocardial segments with reversible defect (21), defined the presence of ischemia.

Calcium scanning. Scanning was performed using either electron beam (EBT) (Imatron C-150 or GE eSpeed, General Electric, Milwaukee, Wisconsin) (n = 934 patients) or multislice computed tomography (MSCT) (n = 219 patients), with acquisitions consisting of approximately 30 to 40 3-mm or 2.5-mm slices for the 2 tomographic systems, respectively (12). Foci of coronary artery calcification were identified and scored by an experienced technician, blinded to both patient characteristics and the MPS results, using semiautomatic commercial software on a NetraMD workstation (ScImage, Los Altos, California) by detection of at least 3 contiguous pixels (voxel size = 1.03 mm^3) of peak density ≥130 HU within a coronary artery, with scoring verified by an experienced imaging cardiologist. Coronary artery calcium scores were calculated according to the method of Agatston et al. (5), and age- and gender-adjusted CAC percentile scores were determined according to the database of Raggi et al. (7).

Likelihood of CAD. The likelihood of ASCAD, exclusive of the MPS results, was calculated for each patient based on the Bayesian analysis of patients' age, gender, risk factors, chest pain symptoms, and results of exercise electrocardiography according to a previously validated commercial software program (CADENZA, Advanced Heuistics, Bainbridge Island, Washington) (22).

Follow-up. Patients were followed for the occurrence of hard cardiac events, which included either the occurrence of cardiac death, as noted and confirmed by a review of death certificate and hospital chart or physician's record, or myocardial infarction, as evidenced by the appropriate combination of patients' signs and symptoms and enzyme elevations (23). In addition, we identified if patients underwent cardiac catheterization or coronary revascularization procedures (coronary bypass or percutaneous coronary interventions), and defined these as "early" if they occurred ≤60 days of noninvasive testing and "late" if they occurred >60 days after testing. The performance of late myocardial revascularization was a secondary end point in this study based on its use as a proxy variable for worsening clinical status (24). As previously described (25), initial patient follow-up was obtained by searching our hospital-based information system (WebVS) as well as the Social Security Death Index. Follow-up in the remaining patients was sought through a mailed questionnaire or a scripted telephone interview. To ascertain the cause of death, the information provided by WebVS and the death certificates obtained for all those who died in Los Angeles County were reviewed by 2 cardiologists blinded to subjects' clinical information. Death from

Abbreviations and Acronyms

ASCAD = angiographically significant coronary artery disease
CAC = coronary artery calcium
CAD = coronary artery disease
CSMC = Cedars-Sinai Medical Center
EBT = electron beam computed tomography
MPS = myocardial perfusion scintigraphy
MSCT = multislice computed tomography