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ORIGINAL RESEARCH

Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification

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OBJECTIVES In this study, we systematically assessed the diagnostic and prognostic value of absence of coronary artery calcification (CAC) in asymptomatic and symptomatic individuals.

BACKGROUND Presence of CAC is a well-established marker of coronary plaque burden and is associated with a higher risk of adverse cardiovascular outcomes. Absence of CAC has been suggested to be associated with a very low risk of significant coronary artery disease, as well as minimal risk of future events.

METHODS We searched online databases (e.g., PubMed and MEDLINE) for original research articles published in English between January 1990 and March 2008 examining the diagnostic and prognostic utility of CAC.

RESULTS A systematic review of published articles revealed 49 studies that fulfilled our criteria for inclusion. These included 13 studies assessing the relationship of CAC with adverse cardiovascular outcomes in 64,873 asymptomatic patients. In this cohort, 146 of 25,903 patients without CAC (0.56%) had a cardiovascular event during a mean follow-up period of 51 months. In the 7 studies assessing the prognostic value of CAC in a symptomatic population, 1.80% of patients without CAC had a cardiovascular event. Overall, 18 studies demonstrated that the presence of any CAC had a pooled sensitivity and negative predictive value of 98% and 93%, respectively, for detection of significant coronary artery disease on invasive coronary angiography. In 4,870 individuals undergoing myocardial perfusion and CAC testing, in the absence of CAC, only 6% demonstrated any sign of ischemia. Finally, 3 studies demonstrated that absence of CAC had a negative predictive value of 99% for ruling out acute coronary syndrome.

CONCLUSIONS On the basis of our review of more than 85,000 patients, we conclude that the absence of CAC is associated with a very low risk of future cardiovascular events, with modest incremental value of other diagnostic tests in this very low-risk group. (J Am Coll Cardiol Img 2009;2:675–88) © 2009 by the American College of Cardiology Foundation

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The evaluation of coronary artery calcium (CAC) has undergone dramatic evolution over the past few decades. Published studies range from initial descriptions in histology studies (1,2) to cross-sectional and longitudinal studies using cine fluoroscopy (3,4), electron beam computed tomography (5), and multidetector computed tomography (6). There have been recommendations for examining the presence of CAC in the context of mass scores (7) and volume scores (8), as well as scores based on area of calcified plaque and attenuation (Agatston score) (9). The quantification of CAC has been further complicated by studies that recommend different categories of CAC extent, such as quartiles (10) or age- and sex-specific percentiles (11), for optimal risk stratification.

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ACS = acute coronary syndromes

AHA = American Heart Association

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

ICA = invasive coronary angiography

LDL = low-density lipoprotein

MPS = myocardial perfusion scans

Therefore, the purpose of this review was to provide a "back to the basics" approach examining the clinical, diagnostic, and prognostic significance of the *absence* of CAC. We examined published reports for the relevance of the absence of CAC in the context of 3 major categories: 1) its prognostic utility in categorizing both asymptomatic and symptomatic patients according to their risk for adverse events; 2) its relationship with the presence or absence of significant coronary artery stenosis by invasive coronary angiography; and 3) the degree of myocardial ischemia detected in those with the absence of CAC.

METHODS

We searched the MEDLINE database for studies published in the English language between January 1990 and March 2008, assessing CAC using either multidetector computed tomography or electron beam computed tomography in adult populations of both sexes. The search was performed using various permutations of the following search terms: "electron beam computed tomography," "multidetector computed tomography," "coronary artery calcium," "coronary artery calcification," "invasive coronary angiography," and "myocardial perfusion imaging." Additional references were found by reviewing bibliographies from identified articles. Individual articles had to meet the following criteria to be included: 1) articles examining the relationship between CAC and adverse cardiovascular events in asymptomatic individuals; only studies that prospectively enrolled asymptomatic patients and had a follow-up >1 year for cardiovascular events were included. Authors of articles that did not contain data on patients without CAC were contacted for more information. 2) Articles examining the relationship between CAC and adverse cardiovascular events in symptomatic individuals. 3) Articles examining the relationship between CAC and invasive coronary angiography (ICA) and defining a significant stenosis as >50% coronary luminal narrowing. 4) Articles comparing the incidence of myocardial perfusion abnormalities with the extent of CAC. 5) Articles reporting the ability of CAC to predict acute coronary syndromes. We contacted authors of studies in which the incidence of coronary artery disease (CAD) in patients without CAC was not reported or could not be calculated.

Statistical analysis. Based on the 2 × 2 event data for patients with no CAC and CAC >0, individual and summary Mantel-Haenszel relative risk ratios and 95% confidence intervals (CIs) were calculated (Comprehensive Meta-Analysis, version 2.2, Biostat, Englewood, New Jersey). For this analysis, a cumulative relative risk ratio was displayed in a Forest plot. Although duplicate series were included in the plot, the summary risk ratio was calculated using only the latter series. For reports showing no events in patients with 0 CAC, 1 event was added so that the relative risk ratio could be calculated. The test for heterogeneity for asymptomatic patients was significant (Q statistic = 26, p = 0.001); however, inclusion of studies published after 2004 revealed greater homogeneity in study results (Q statistic = 6, p = 0.19). Presentation of the data with and without publications before 2004, however, did not change the results noted herein. A funnel plot was created to estimate publication bias and is included in the online version of this article. For asymptomatic individuals, a review of this plot reveals that 4 series with results outside the precision lines may suggest publication bias, including Greenland (17), Shemesh (16), Raggi (11), and Wong (13), all with sample sizes <1,030. For asymptomatic individuals, the classic fail-safe number of missing studies that would bring the p value to >alpha = 0.05 was 1,354; if the alpha is changed to 0.01, the number of studies missing that would bring the p value >alpha was 779. The test for heterogeneity in symptomatic patients was nonsignificant (Q statistic = 4, p = 0.50), suggesting that pooling of these reports was appropriate. A funnel