ORIGINAL RESEARCH

Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification

Ammar Sarwar, MD,* Leslee J. Shaw, PHD,† Michael D. Shapiro, DO,*
Ron Blankstein, MD,* Udo Hoffman, MD, MPH,* Ricardo C. Cury, MD,*
Suhny Abbara, MD,* Thomas J. Brady, MD,* Matthew J. Budoff, MD,‡
Roger S. Blumenthal, MD,§ Khurram Nasir, MD, MPH*§‖

Boston, Massachusetts; Atlanta, Georgia; Los Angeles, California; and Baltimore, Maryland

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

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.

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

plot was also created for symptomatic patient reports. Noted in this plot, there was 1 study exhibiting an extreme measure, possibly reflecting publication bias (5). For the symptomatic series, the classic fail-safe number of missing studies that would bring the p value to >alpha = 0.01 was only 26.

The positive and negative predictive value and 95% CI for significant CAD were calculated for each study and for a summary weighted (proportional to the sample size) measure.

Individual and summary odds ratios and 95% CIs were calculated for the frequency of ischemia in patients with no CAC and CAC >0. For patients with no ischemia in the zero-CAC group, a single case was added to allow for calculation of the odds ratio. The test for heterogeneity was significant (Q statistic = 54, p < 0.0001), with exclusion of the He and Rozanski series suggesting more homogeneous results (Q statistic = 5, p = 0.18).

RESULTS

Prognosis in asymptomatic adults. Table 1 compares 13 studies assessing the relationship of CAC with adverse cardiovascular outcomes consisting of 71,595 *asymptomatic* patients (65% men) (11–23). In this cohort, 29,312 patients (41%) did not have any evidence of CAC (range 22% to 80% of total patients per study). These patients were followed for 32 to 102 months (mean 50 months) for the occurrence of cardiovascular events. Overall, 154 of 29,312 patients (0.47%) without CAC had a cardiovascular event during follow-up, as compared with 1,749 of 42,283 patients (4.14%) with CAC. The cumulative relative risk ratio was 0.15 (95% CI: 0.11 to 0.21, p < 0.001) (Fig. 1).

Prognosis in symptomatic adults. There are 7 studies assessing the prognostic value of CAC in the *symptomatic* population (Table 2) (5,24–29). Overall, these studies included a total of 3,924 symptomatic patients (60% men), of whom 921 patients (23%) did not have any evidence of CAC. These patients were followed up for 30 to 84 months (mean 42 months). Overall, 17 of 921 patients (1.8%) without CAC had a cardiovascular event during follow-up compared with 270 of 3,003 patients (8.99%) with CAC. The cumulative relative risk ratio was 0.09 (95% CI: 0.04 to 0.20, p < 0.0001) (Fig. 2).

Diagnostic accuracy of CAC for stenosis on invasive angiography. Quantification of CAC has also been extensively studied (30–47) for its ability to predict significant CAD as determined by ICA (Table 3).

There were 18 studies from 1992 to 2007 in which a total of 10,355 symptomatic patients suspected of CAD underwent CAC testing, as well as ICA. Overall, 5,805 of these patients (56%) had a significant coronary stenosis (defined as >50%) on ICA. In this cohort, 1,941 patients (20%) had no CAC (range 12% to 36% of total patients per study). Overall, only 131 of 5,805 patients (2%) with significant CAD did not have detectable CAC. Pooled data revealed that the presence of calcium had a sensitivity, specificity, negative predictive value, and positive predictive value of 98%, 40%, 93% and 68%, respectively, for the prediction of a significant coronary stenosis. The summary negative predictive value was 92% (95% CI: 88% to 95%, p < 0.0001) (Fig. 3). The summary positive predictive value was 68% (95% CI: 64% to 72%, p < 0.0001) (Fig. 3).

Diagnostic accuracy of CAC for myocardial ischemia. Eight studies (29,48–54) evaluated CAC in patients undergoing stress myocardial perfusion imaging (Table 4). A total of 535 of 3,717 patients (14%) were found to have abnormal myocardial perfusion. In patients without CAC, 67 of 973 (7%) had evidence of ischemia, whereas in patients with CAC (n = 2,744), 486 patients (13%) had evidence of ischemia. The cumulative odds ratio for ischemia was 0.086 (95% CI: 0.024 to 0.311, p < 0.0001) (Fig. 4).

CAC in detection of acute coronary syndromes in the emergency department. Three studies outlined the utility of CAC scanning for risk stratification of patients with suspicion of acute coronary syndromes (ACS) (Table 5) (24,55,56). These studies evaluated 431 patients complaining of acute chest pain with negative troponins and equivocal electrocardiographic findings. The cohort consisted of 48% men (mean age 51.4 years). There were only 2 of 183 patients (1.1%) without any CAC who were diagnosed with an ACS. Of the 248 patients with a positive CAC score, 77 (31%) were found to have an ACS. Overall, a positive CAC score had 99% sensitivity, 57% specificity, 24% positive predictive value, and 99% negative predictive value for the evaluation of ACS. The Mantel-Haenszel relative risk ratio for ACS was 0.07 (95% CI: 0.026 to 0.187, p < 0.00001) with absence of CAC.
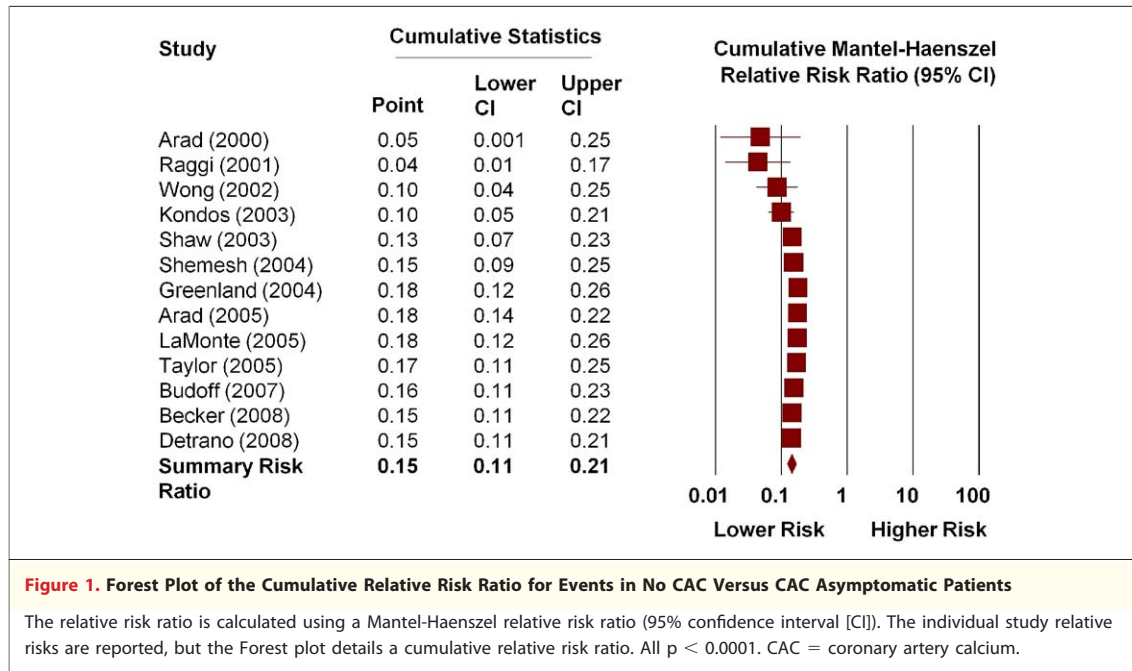
DISCUSSION

Overall, our review of the published data revealed that the absence of CAC translates into a low risk

Table 1. Studies Examining the Prognosis of Asymptomatic Patients on the Basis of Their Coronary Artery Calcium Scores

Author/Year (Ref. #)	Total Population	Type of Population	Scanner Type/ Slice Thickness	Men (%)	Prevalence, n (%) CAC = 0	Prevalence, n (%) CAC >0	Mean Follow-up (Months)	% Age Lost to Follow-Up	Definition of Events	Events, n (%) CAC = 0	Events, n (%) CAC >0
Arad et al./2000 (12)	1,173	Self referred	EBCT/3 mm	71	623 (53)	550 (47)	43	0.4	Cardiac death (3), myocardial infarction (15), revascularization (21)	2 (0.32)	37 (6.72)
Raggi et al./2001 (11)	676	PCP referred	EBCT/3 mm	50	319 (47)	357 (53)	32	N/A	Cardiac death (9), myocardial infarction (21)	1 (0.31)	29 (4.77)
Wong et al./2002 (13)	926	Self referred	EBCT/3 mm	79	398 (43)	528 (57)	40	N/A	Myocardial infarction (6), revascularization (20), stroke (2)	4 (1.01)	24 (6.12)
Kondos et al./2003 (14)	5,635	Self referred	EBCT/3 mm	74	1,816 (32)	3,819 (78)	37	36	Cardiac death (21), myocardial infarction (37), revascularization (166)	11 (0.61)	213 (5.58)
Shaw et al./2003 (15)	10,377	PCP referred	EBCT/3 mm	60	5,067 (49)	5,310 (51)	60	0	All-cause death (249)	39 (0.77)	210 (3.95)
Shemesh et al./2004 (16)	446	High-risk hypertensives	MDCT/N/A	48	152 (34)	294 (66)	45	0	Cardiac death (2), myocardial infarction (16), revascularization (14), stroke (15)	6 (3.95)	41 (13.95)
Greenland et al./2004 (17)	1,029	Self referred	EBCT/6 mm	90	316 (31)	713 (69)	102	12.5	Cardiac death (68), myocardial infarction (16)	14 (4.43)	70 (9.82)
Arad et al./2005 (18)	4,903	Population-based cohort	EBCT/3 mm	65	1,504 (31)	3,399 (69)	52	6	Cardiac death (40), revascularization (59), peripheral disease (13), stroke (7)	8 (0.53)	119 (3.50)
LaMonte et al./2005 (19)	10,746	Self and PCP referred	EBCT/3 mm	64	2,692 (25)	8,054 (75)	42	30	Cardiac death (19), myocardial infarction (62), revascularization (206)	15 (0.56)	272 (3.38)
Taylor et al./2005 (20)	1,983	Army population	EBCT/3 mm	82	1,591 (80)	392 (10)	36	0.8	Cardiac death, myocardial infarction, unstable angina	2 (0.13)	7 (1.79)
Budoff et al./2007 (21)	25,253	PCP referred	EBCT/3 mm	54	11,046 (44)	14,207 (56)	82	0	All-cause death (511)	44 (0.40)	466 (3.28)
Becker et al./2008 (22)	1,726	PCP referred	EBCT/3 mm	59	379 (22)	1,347 (78)	40	0	Cardiac death (66), myocardial infarction (114)	0 (0.00)	180 (13.36)
Detrano et al./2008 (23)	6,722	Population-based cohort (MESA)	EBCT/3 mm	47	3,409 (51)	3,313 (49)	44	0.5	Cardiac death (17), myocardial infarction (72)	8 (0.23)	81 (2.45)
Pooled	71,595			65	29,312 (41)	42,283 (59)	50			154 (0.47)	1,749 (4.14)

CAC = coronary artery calcium; EBCT = electron beam computed tomography; MDCT = multidetector computed tomography; MESA = Multi-Ethnic Study of Atherosclerosis; PCP = primary care physician.

Study	Cumulative Statistics			Cumulative Mantel-Haenszel Relative Risk Ratio (95% CI)
	Point	Lower CI	Upper CI	
Arad (2000)	0.05	0.001	0.25	
Raggi (2001)	0.04	0.01	0.17	
Wong (2002)	0.10	0.04	0.25	
Kondos (2003)	0.10	0.05	0.21	
Shaw (2003)	0.13	0.07	0.23	
Shemesh (2004)	0.15	0.09	0.25	
Greenland (2004)	0.18	0.12	0.26	
Arad (2005)	0.18	0.14	0.22	
LaMonte (2005)	0.18	0.12	0.26	
Taylor (2005)	0.17	0.11	0.25	
Budoff (2007)	0.16	0.11	0.23	
Becker (2008)	0.15	0.11	0.22	
Detrano (2008)	0.15	0.11	0.21	
Summary Risk Ratio	**0.15**	**0.11**	**0.21**	

Figure 1. Forest Plot of the Cumulative Relative Risk Ratio for Events in No CAC Versus CAC Asymptomatic Patients

The relative risk ratio is calculated using a Mantel-Haenszel relative risk ratio (95% confidence interval [CI]). The individual study relative risks are reported, but the Forest plot details a cumulative relative risk ratio. All p < 0.0001. CAC = coronary artery calcium.

for future events in both asymptomatic and symptomatic populations, a low probability of having a significant stenosis, a low incidence of abnormal myocardial perfusion, and a low likelihood of acute coronary syndrome. In summary, the absence of CAC identifies individuals at low risk for cardiovascular disease and cardiovascular events, thus precluding the need for further downstream testing and management.

Prognostic significance. ASYMPTOMATIC PATIENTS. A total of 13 studies examining the prognostic significance of CAC in asymptomatic individuals fit our criteria for inclusion. There were adverse cardiac events in an average of 0.47% (range 0 to 4.43%) of the total 29,312 individuals without evidence of CAC. Although 11 studies had event rates ≤1.01%, there were 2 studies that had extremely high event rates (3.95 and 4.43%) (16,17). When we examined these studies more carefully, the study with the highest event rates (4.43%) (17) applied an unconventional scanning protocol that employed a 6-mm slice thickness rather than the standard 3-mm collimation. It has been well established (57) that use of a larger slice thickness misses approximately one-third of calcified lesions. The effect of missing these lesions can result in misclassifying individuals as having no evidence of CAC. The other study with a higher event rate (3.95%) assessed 446 high-risk hypertensive patients from the INSIGHT (International Nifedipine Study Intervention as Goal for Hypertension Therapy) trial

(16). Nearly one-third of the events in this study were strokes. Hemorrhagic strokes related to hypertension might have elevated the number of events seen in individuals without CAC. Neither the nature of the strokes nor the number of patients with/without CAC who suffered a stroke was reported in the article.

Overall, despite the results of these 3 studies, our review indicates that the absence of CAC is associated with a very low overall risk of any event in asymptomatic individuals. Budoff et al. (21) demonstrated a similarly low risk for mortality (0.4%) in a follow-up extending up to 12 years, confirming the minimal long-term risk associated with absence of CAC in long-term follow-up.
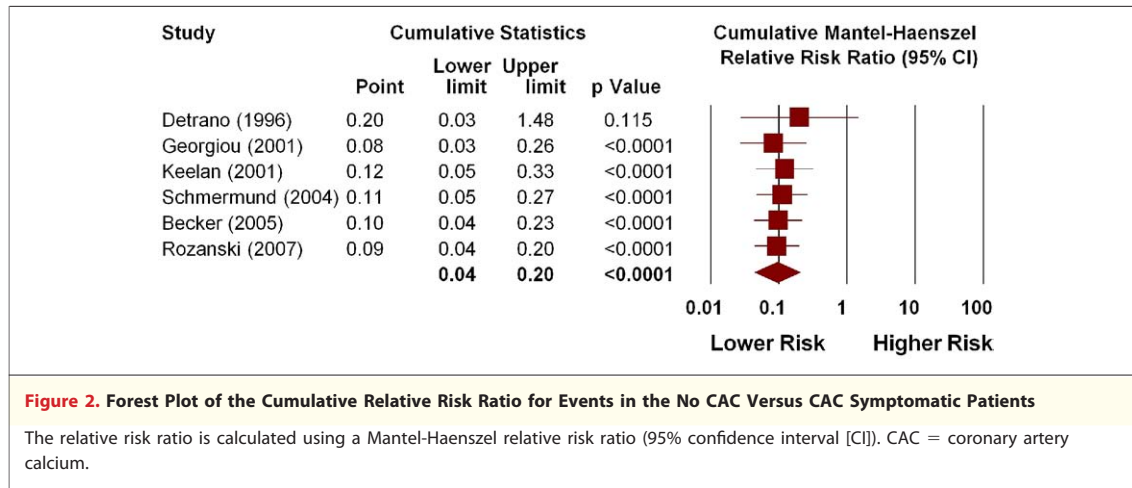
Another key question is how CAC compares with other noninvasive tests for subclinical atherosclerosis such as carotid intimal medial thickness, ankle-arm pressure index, and C-reactive protein. This question was examined recently (58) in a comparative review of subclinical atherosclerosis tests. The authors found that negative testing for subclinical atherosclerosis conveyed a low risk (<10%) regardless of the test considered. However, with respect to prognostic value in asymptomatic patients, the data on CAC seem to be the most robust in sheer size, diversity of populations, and duration of follow-up. Although other tests for subclinical atherosclerosis have the benefit of low

Table 2. Studies Examining the Prognosis of Patients Symptomatic for Coronary Artery Disease on the Basis of Their Coronary Artery Calcium Scores

Author/Year (Ref. #)	Total Population	Type of Population	Scanner Type/ Slice Thickness	Men (%)	Prevalence, n (%)		Mean Follow-up (Months)	% Age Lost to Follow-Up	Definition of Events	Events, n (%)	
					CAC = 0	CAC >0				CAC = 0	CAC >0
Detrano et al./1996 (5)	491	Referred for ICA	EBCT/3 mm	57	98 (20)	393 (80)	30	14	Cardiac death (13), myocardial infarction (8)	1 (1.02)	20 (5.09)
Georgiou et al./2001 (24)	192	Referred to emergency department for chest pain	EBCT/3 mm	54	76 (40)	116 (60)	50	8	Cardiac death (11), myocardial infarction (19), revascularization (13), hospitalizations (11), strokes (4)	2 (2.63)	56 (48.28)
Keelan et al./2001 (25)	288	Retrospective study, patients with EBCT and ICA	EBCT/3 mm	77	32 (11)	256 (89)	84	9	Cardiac death (N/A), myocardial infarction (N/A)	1 (3.13)	21 (8.20)
Schmermund et al./2004 (26)	255	Retrospective study, pts with recent onset of symptoms	EBCT/3 mm	71	62 (24)	193 (76)	42	15	Cardiac death (3), myocardial infarction (2), revascularization (35)	1 (1.60)	39 (20.21)
Becker et al./2005 (27)	924	Post ICA, no significant stenosis	MDCT	48	188 (20)	736 (80)	36	N/A	Cardiac death (28), myocardial infarction (50)	0 (0.00)	78 (11)
Rozanski et al./2007 (28)	1,153	PCP/self referred	EBCT/ MDCT 3/2.5 mm	74	252 (22)	901 (78)	32	3	Cardiac death and myocardial infarction (13), revascularizations >60 days (37)	1 (0.40)	49 (5.44)
Schenker et al./2008 (29)	621	Referred for stress PET on clinical grounds	MDCT/2.5 mm	40	213 (34)	408 (66)	17	0	Cardiac death (33), myocardial infarction (22)	11 (5.16)	44 (10.78)
Total	3,924			60	921 (23)	3,003 (76)	42			17 (1.80)	270 (8.99)

ACS = acute coronary syndromes; ICA = invasive coronary angiography; N/A = not applicable; PET = positron emission tomography; other abbreviations as in Table 1.

Figure 2. Forest Plot of the Cumulative Relative Risk Ratio for Events in the No CAC Versus CAC Symptomatic Patients

The relative risk ratio is calculated using a Mantel-Haenszel relative risk ratio (95% confidence interval [CI]). CAC = coronary artery calcium.

cost, higher reproducibility, and a better safety profile owing to the absence of radiation, none have shown any added benefit in prognostic value over traditional risk factors.

Despite its utility, it is important to assess whether the result of a negative CAC score would lead asymptomatic individuals to engage in less stringent adherence to preventive and therapeutic strategies. The results of a randomized controlled trial looking at this question suggest otherwise. O'Malley et al. (59) followed 459 young men for 1 year and found no difference in projected risk, and, more importantly, no change in behavior in those who were informed that they did not have evidence of CAC versus those who were found to have CAC. They concluded that the knowledge of a negative CAC score scan did not convey false reassurance resulting in adverse behavioral outcomes.

Another issue that must be closely examined is how often individuals without CAC should be assessed for development of atherosclerosis and who among these individuals may need early follow-up. A study examining progression rates of coronary calcification in 710 patients without CAC (60) reported that 62% of the cohort did not develop CAC in a period extending up to 5 years. In fact, only 2% developed a CAC score >50 (60). The investigators concluded that after an initial negative CAC scan, an individual can safely receive a follow-up scan up to 5 years later. Similarly, Kronmal et al. (61) reported from the MESA (Multiethnic Study on Atherosclerosis) study that only 16% of individuals without CAC developed CAC in a median follow-up of 41 months. This indicates that a negative CAC scan could save a patient from costly therapy over the course of 3 to 5 years and that these patients can be

followed simply with regular outpatient visits without the need for costly diagnostic imaging.

Although current guidelines do not recommend that preventive therapies such as lipid-lowering medications can be down-regulated in the absence of CAC (62), our data suggest that aggressive management in this cohort is not warranted if patients do not qualify according to National Cholesterol Education Program guidelines. For example, among individuals who are considered as intermediate Framingham risk, lipid-lowering medications are recommended only for low-density lipoprotein (LDL) cholesterol >160 mg/dl. In these scenarios, patients with LDL <160 mg/dl can be reassured of their risk without initiation of further pharmacotherapy. The results of our review provide an opportunity to introduce a robust model for providing treatment to deserving individuals in societies with finite resources. This would allow those with the absence of CAC to follow healthy lifestyle modifications with little or no medical therapy while focusing intense therapy on a smaller population of patients with an actual higher risk of events as demonstrated by increasing atherosclerotic burden.

SYMPTOMATIC PATIENTS. Along with the comprehensive literature on the prognostic utility of CAC in asymptomatic patients, a number of studies looked at similar parameters in a symptomatic population (Table 2). Although the prevalence of a CAC score of 0 was lower in symptomatic versus asymptomatic patients (23% vs. 40%), symptomatic patients without CAC also had a significantly lower event rate than those with CAC (1.8% vs. 8.99%). Although the prognostic data available on symptomatic patients are not as large as those on asymptomatic individuals, there is evidence that an ab-

Table 3. Studies Examining the Accuracy of Coronary Artery Calcium to Predict the Presence or Absence of Significant Coronary Artery Stenosis by Invasive Coronary Angiogram in Symptomatic Patients

Author/Year (Ref. #)	EBCT Reads Blinded to ICA Results	Total Patients	Scanner Type	Prevalence, n (%)			CAC + Stenosis +	CAC − Stenosis +	CAC + Stenosis −	CAC − Stenosis −	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
				CAC = 0	CAC >0	Significant Stenosis								
Breen et al./1992 (30)	Yes	100	EBCT	25 (25)	75 (75)	47 (47)	47	0	28	25	100	47	100	63
Fallavollita et al./1994 (31)	Yes	106	EBCT	30 (28)	76 (72)	59 (56)	50	9	26	21	85	45	70	66
Rumberger et al./1995 (32)	Yes	139	EBCT	30 (22)	109 (78)	65 (47)	64	1	45	29	99	39	97	59
Budoff et al./1996 (33)	N/A	710	EBCT	147 (21)	563 (79)	426 (60)	404	23	159	124	95	44	84	72
Baumgart et al./1997 (34)	Yes	57	EBCT	7 (12)	50 (88)	29 (51)	28	1	22	6	97	21	86	56
Budoff et al./1998 (35)	Yes	125	EBCT	45 (36)	80 (64)	73 (58)	71	1	9	44	99	83	98	89
Bielak et al./2000 (36)	Yes	213	EBCT	40 (19)	173 (81)	113 (53)	111	1	62	39	99	39	98	64
Yao et al./2000 (37)	Yes	64	EBCT	15 (23)	49 (77)	45 (70)	44	1	5	14	98	74	93	90
Shavelle et al./2000 (38)	Yes	97	EBCT	17 (18)	80 (82)	67 (69)	64	3	16	14	96	47	82	80
Haberl et al./2001 (39)	Yes	1,764	EBCT	249 (14)	1,515 (86)	935 (53)	935	5	580	244	100	30	98	62
Budoff et al./2002 (40)	Yes	1,851	EBCT	385 (21)	1,466 (79)	981 (53)	945	38	521	347	96	40	90	64
Hosoi et al./2002 (41)	Yes	282	EBCT	36 (13)	246 (87)	203 (72)	196	7	50	29	97	37	81	80
Budoff et al./2002 (42)	Yes	1,120	EBCT	277 (25)	843 (75)	672 (60)	653	19	190	258	97	58	93	77
Knez et al./2004 (43)	Yes	2,123	EBCT	334 (16)	1,789 (84)	1,253 (59)	1247	8	542	326	99	38	98	70
Haberl et al./2005 (44)	Yes	133	MSCT	25 (19)	108 (81)	53 (40)	45	8	63	17	85	21	68	42
Lau et al./2005 (45)	Yes	50	MSCT	6 (12)	44 (88)	30 (60)	29	1	15	5	97	25	83	66
Becker et al./2007 (46)	Yes	1347	MSCT	259 (19)	1,088 (81)	714 (53)	715	5	373	254	99	41	98	66
Leschka et al./2007 (47)	Yes	74	DSCT	14 (19)	60 (81)	36 (49)	36	0	24	14	100	37	100	60
Pooled data		10,355		1,941 (20)	8,414 (80)	56	5,684	131	2,730	1,810	98	40	93	68

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 1 and 2.
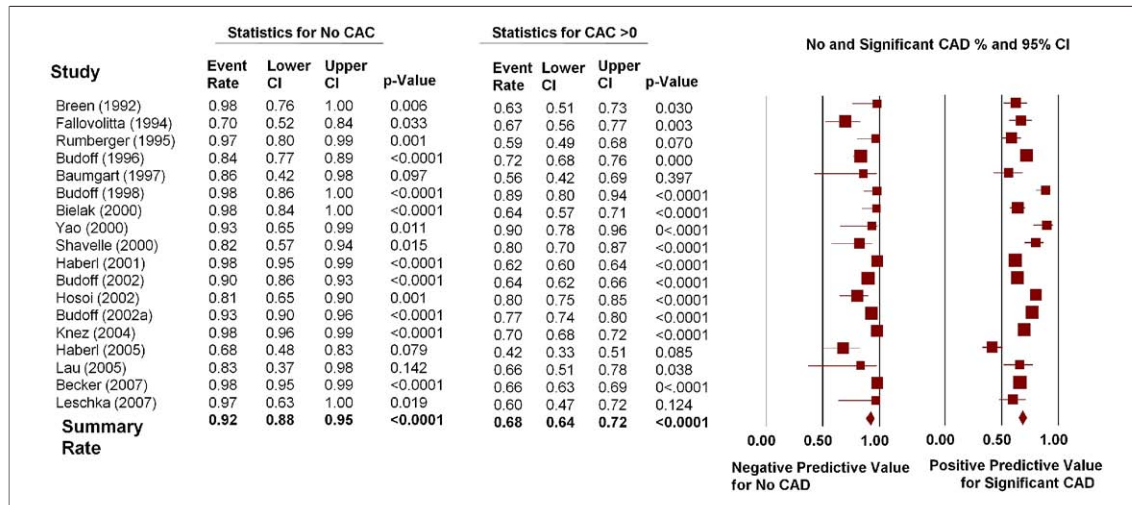
Figure 3. Negative and Positive Predictive Value of No CAC and CAC >0

Negative and positive predictive value of absence of detectable no CAC and CAC >0 for detection of significant coronary artery disease detected on invasive angiography, with summary statistics of 92% and 68%, respectively. CAC = coronary artery calcium; CAD = coronary artery disease; CI = confidence interval.

sence of CAC translates into a reduced risk for adverse events in this population. Further studies are needed to identify the true role of CAC in symptomatic individuals and how best to incorporate CAC information into the overall risk stratification algorithm in combination with other diagnostic tests, such as contrast-enhanced coronary computed tomography (CT) angiography and/or stress myocardial perfusion imaging.

Utility of CAC in ruling out significant CAD. Aside from the long-term prognostic value, our review reveals the potential of CAC scanning to serve as a gatekeeper for further diagnostic imaging for evaluation of coronary luminal patency. There were 18 studies comparing the diagnostic accuracy of Agatston scores with ICA to detect a significant (>50%) stenosis of the coronary lumen (Table 3).

Table 4. Studies Examining the Relationship Between Coronary Artery Calcium and Myocardial Ischemia

Author/Year (Ref. #)	Type of Population	Average Age (yrs)	Men (%)	Total Patients	Prevalence, n (%)			CAC + Ischemia + (%)	CAC − Ischemia + (%)
					CAC = 0	CAC >0	Abnormal Perfusion		
He et al./2000 (48)	87% asymptomatic	58	79	411	37 (9)	374 (91)	81 (20)	81 (22)	0 (0)
Yao et al./2004 (49)	Referred for SPECT on clinical basis	52	N/A	73	29 (40)	44 (60)	41 (56)	34 (77)	7 (24)
Berman et al./2004 (50)	61% PCP, referred 8%, self referred 31%, research study	58	73	1,195	250 (21)	945 (79)	76 (6)	72 (8)	4 (2)
Wong et al./2005 (51)	Referred for SPECT on clinical basis	58	33	1,043	282 (27)	761 (73)	77 (7)	71 (9)	6 (2)
Blumenthal et al./2006 (52)	Asymptomatic siblings of pts with known CAD	51	38	260	122 (47)	138 (53)	49 (19)	35 (25)	14 (11)
Budoff et al./2007 (53)	Scheduled for ICA	54	70	30	6 (20)	24 (80)	19 (63)	17 (71)	2 (33)
Esteves et al./2008 (54)	Referred for SPECT on clinical basis	62	39	84	34 (41)	50 (59)	13 (15)	13 (26)	0 (100)
Schenker et al./2008 (29)	Referred for PET on clinical basis	61	41	621	213 (34)	408 (66)	179 (29)	163 (40)	34 (16)
Total		57	47	3,717	973 (26)	2,744 (74)	535 (14)	486 (13)	67 (7)

CAD = coronary artery disease; SPECT = single-positron emission computed tomography; other abbreviations as in Tables 1 and 2.
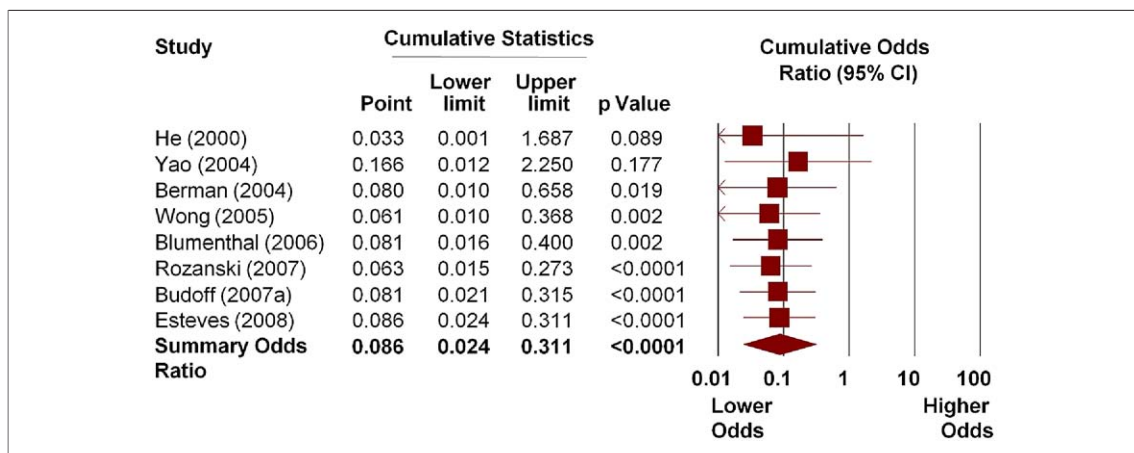
Figure 4. Forest Plot of the Cumulative Odds Ratio for Ischemia in Patients With No CAC Versus CAC Patients

The relative risk ratio is calculated using a Peto odds ratio (95% confidence interval [CI]), random effects model.

The presence of CAC was highly sensitive (98%) in predicting a luminal stenosis >50% in any coronary artery, although the specificity was low (40%). In fact, recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines also consider that "for the symptomatic patient, exclusion of measurable coronary calcium may be an effective filter before undertaking invasive diagnostic procedures or hospital admission" (62,63). Although absence of CAC is associated with a very low likelihood of significant CAD, approximately 2% of symptomatic individuals with significant CAD do not have evidence of CAC. These individuals (i.e., significant CAD without CAC) tend to be younger than 50 years of age (32,33,39,40,43,46). As a result, one must exercise caution when evaluating patients for potential CAD in the absence of CAC.

Recent advances in contrast-enhanced coronary CT angiography have allowed for higher accuracy in detection and exclusion of significant CAD, and thus the role of absence of CAC in this setting needs further assessment. Although the pooled sensitivity and specificity of CAC for detecting a

significant stenosis are 98% and 40%, respectively, the sensitivity and specificity of contrast-enhanced 64-slice CT are 97% and 90%, respectively (64). The most practical application would be using CT angiography in improving on the limited specificity of CAC for obstructive disease. Because the presence of CAC is often associated with nonobstructive disease, specificity for obstructive disease is reduced. The determination of significant stenotic disease with CT angiography in those with the presence of CAC will undoubtedly be useful to the clinician and patient.

However, it is important to keep in mind that approximately 2% of symptomatic patients with CAC may have underlying significant obstructive epicardial CAD, the significance of which is not entirely clear. As suggested by current ACC/AHA guidelines, absence of CAC can serve as a possible exclusion criterion for further cardiovascular risk testing, as the long-term prognosis of these patients is excellent.

Prevalence of myocardial ischemia in individuals without CAC. Although the absence of CAC shows exceptional ability for predicting the absence of a

Table 5. Studies Examining the Relationship Between Coronary Artery Calcium and Acute Coronary Syndrome in an Emergency Department Population

Author/Year (Ref. #)	Total Patients	Type of Scanner	Mean Age (yrs)	Men (%)	Prevalence CAC = 0	Prevalence CAC >0	CAC = 0 With ACS	CAC >0 With ACS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Laudon et al./1999 (58)	105	EBCT	48	54	59	46	0	14	100	63	30	100
McLaughlin et al./1999 (59)	134	EBCT	53	37	48	86	0	7	100	54	15	100
Georgiou et al./2001 (24)	192	EBCT	53	54	76	116	2	56	97	55	26	97
Total	431		51.4	48	183	248	2	77	99	57	24	99

Abbreviations as in Tables 1, 2, and 3.

significant stenosis, its ability to predict myocardial ischemia by myocardial perfusion scans (MPS) is also encouraging, although somewhat more modest. The negative predictive value of CAC for a perfusion abnormality was an average of 93% in 8 studies. More importantly, the 1 prognostic study simultaneously evaluating the prognostic value of both MPS and CAC scores (28) conclusively showed that the event risk of a person without CAC was extremely low regardless of whether they had ischemia. In fact none of the patients without CAC who had an abnormal MPS had an event, whereas a very low percentage of those without CAC and a normal MPS had an adverse outcome (0% vs. 0.2%, respectively). The recent ACC/American Society of Nuclear Cardiology appropriateness criteria state that a low calcium score (especially in the absence of CAC) precludes the need for MPS assessment (65).

However, in 3 studies, a significantly higher prevalence of ischemia in patients without CAC was reported. One of these studies (52) showed that 11% of individuals without CAC had an abnormal MPS. This study was exclusively performed in siblings of those with premature CAD. Another study by Budoff et al. (53) examined a cohort of 30 individuals, with 70% of the subjects demonstrating a clinically significant stenosis. The investigators found 2 of 6 individuals (33%) without CAC to have ischemia on MPS. The results of this study are remarkably discordant with other studies, not only because of the study's small sample size but also because of the high prevalence of disease in this cohort.

ACS in individuals without CAC. The 3 studies evaluating the relationship between CAC and ACS reported a 99% sensitivity and 99% negative predictive value, which is comparable to that of contrast-enhanced coronary CT angiography (66,67). On the other hand, the specificity and positive predictive value was modest (57% and 24%, respectively). The total number of patients in each of these studies was too small to conclusively establish the role of CAC evaluation in the emergency department. The current state of published reports is certainly small and inconclusive with respect to this important clinical entity. Although CAC can serve as a useful marker for excluding ACS in patients presenting to the emergency department, further studies in larger cohorts need to be done to establish CAC's role in a clinical paradigm, especially in lieu of excellent depiction of not only coronary anatomy but also of left ventricular function with contrast-enhanced coronary CT angiography.

Study limitations. This is a systematic review of a large number of studies consisting of heterogeneous populations. Although the results of the vast majority of these studies are concordant, the results might not be generalizable to populations that were not examined by any of the preceding studies. It is also important to keep in mind that no information was available in a majority of the studies on the effect of the absence of CAC in various pre-test CHD risk settings. However, when we extrapolate the data over a range of asymptomatic and symptomatic patients, absence of CAC has generally demonstrated favorable prognostic value. This key question will need to be addressed in large population-based cohorts such as MESA. In addition, for studies examining the diagnostic accuracy of CAC to predict a significant stenosis by ICA, caregivers were blinded to CAC results in a majority of cases. However in 4 studies, the results of the ICA could have been driven by CAC scores (33,34,37,46).

CONCLUSIONS

On the basis of extensive evidence in published reports (in more than 85,000 patients), the absence of CAC identifies a group of asymptomatic and symptomatic individuals at a very low cardiovascular risk. As endorsed by current guidelines, these results should be considered strongly in current management algorithms for better utilization of health care resources.

Reprint requests and correspondence: Dr. Khurram Nasir, Division of Cardiology, Johns Hopkins University, Baltimore, Maryland 21287. *E-mail: knasir1@jhmi.edu.*

REFERENCES

1. Blankenhorn DH, Stern D. Calcification of the coronary arteries. Am J Roentgenol Radium Ther Nucl Med 1959;81:772–7.
2. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–62.
3. Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification. A report of 800 cases. Radiology 1980;137:609–16.
4. Detrano RC, Wong ND, Tang W, et al. Prognostic significance of cardiac cinefluoroscopy for coronary calcific deposits in asymptomatic high risk subjects. J Am Coll Cardiol 1994;24:354–8.

5. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285–90.

6. Becker CR, Kleffel T, Crispin A, et al. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. AJR Am J Roentgenol 2001;176:1295–8.

7. Hong C, Becker CR, Schoepf UJ, Ohnesorge B, Bruening R, Reiser MF. Coronary artery calcium: absolute quantification in nonenhanced and contrast-enhanced multi-detector row CT studies. Radiology 2002;223:474–80.

8. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998;208:807–14.

9. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.

10. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. Am J Cardiol 2000;86:495–8.

11. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. Am Heart J 2001;141:375–82.

12. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol 2000;36:1253–60.

13. Wong ND, Budoff MJ, Pio J, Detrano RC. Coronary calcium and cardiovascular event risk: evaluation by age- and sex-specific quartiles. Am Heart J 2002;143:456–9.

14. Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571–6.

15. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826–33.

16. Shemesh J, Morag-Koren N, Goldbourt U, et al. Coronary calcium by spiral computed tomography predicts cardiovascular events in high-risk hypertensive patients. J Hypertens 2004;22:605–10.

17. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–5.

18. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–65.

19. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421–9.

20. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005;46:807–14.

21. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.

22. Becker A, Leber A, Becker C, Knez A. Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. Am Heart J 2008;155:154–60.

23. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.

24. Georgiou D, Budoff MJ, Kaufer E, Kennedy JM, Lu B, Brundage BH. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. J Am Coll Cardiol 2001;38:105–10.

25. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 2001;104:412–7.

26. Schmermund A, Stang A, Mohlenkamp S, et al. Prognostic value of electron-beam computed tomography-derived coronary calcium scores compared with clinical parameters in patients evaluated for coronary artery disease. Prognostic value of EBCT in symptomatic patients. Z Kardiol 2004;93:696–705.

27. Becker A, Knez A, Becker C, et al. [Prediction of serious cardiovascular events by determining coronary artery calcification measured by multi-slice computed tomography]. Dtsch Med Wochenschr 2005;130:2433–8.

28. Rozanski A, Gransar H, Wong ND, et al. Clinical outcomes after both coronary calcium scanning and exercise myocardial perfusion scintigraphy. J Am Coll Cardiol 2007;49:1352–61.

29. Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. Circulation 2008;117:1693–700.

30. Breen JF, Sheedy PF, 2nd, Schwartz RS, et al. Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. Radiology 1992;185:435–9.

31. Fallavollita JA, Brody AS, Bunnell IL, Kumar K, Canty JM Jr. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease. Comparison with angiography in patients < 50 years old. Circulation 1994;89:285–90.

32. Rumberger JA, Sheedy PF, 3rd, Breen JF, Schwartz RS. Coronary calcium, as determined by electron beam computed tomography, and coronary disease on arteriogram. Effect of patient's sex on diagnosis. Circulation 1995;91:1363–7.

33. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. Circulation 1996;93:898–904.

34. Baumgart D, Schmermund A, Goerge G, et al. Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. J Am Coll Cardiol 1997;30:57–64.

35. Budoff MJ, Shavelle DM, Lamont DH, et al. Usefulness of electron beam computed tomography scanning for distinguishing ischemic from nonischemic cardiomyopathy. J Am Coll Cardiol 1998;32:1173–8.

36. Bielak LF, Rumberger JA, Sheedy PF 2nd, Schwartz RS, Peyser PA. Probabilistic model for prediction of angiographically defined obstructive coronary artery disease using electron beam computed tomography calcium score strata. Circulation 2000;102:380–5.

37. Yao Z, Liu XJ, Shi RF, et al. A comparison of 99Tcm-MIBI myocardial SPET and electron beam computed tomography in the assessment of coronary artery disease in two different age groups. Nucl Med Commun 2000;21:43–8.

38. Shavelle DM, Budoff MJ, LaMont DH, Shavelle RM, Kennedy JM, Brundage BH. Exercise testing and electron beam computed tomography in the evaluation of coronary artery disease. J Am Coll Cardiol 2000;36:32–8.

39. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. J Am Coll Cardiol 2001;37:451–7.

40. Budoff MJ, Diamond GA, Raggi P, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. Circulation 2002;105:1791–6.

41. Hosoi M, Sato T, Yamagami K, et al. Impact of diabetes on coronary stenosis and coronary artery calcification detected by electron-beam computed tomography in symptomatic patients. Diabetes Care 2002;25:696–701.

42. Budoff MJ, Shokooh S, Shavelle RM, Kim HT, French WJ. Electron beam tomography and angiography: sex differences. Am Heart J 2002;143:877–82.

43. Knez A, Becker A, Leber A, et al. Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients. Am J Cardiol 2004;93:1150–2.

44. Haberl R, Tittus J, Bohme E, et al. Multislice spiral computed tomographic angiography of coronary arteries in patients with suspected coronary artery disease: an effective filter before catheter angiography? Am Heart J 2005;149:1112–9.

45. Lau GT, Ridley LJ, Schieb MC, et al. Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined. Radiology 2005;235:415–22.

46. Becker A, Leber A, White CW, Becker C, Reiser MF, Knez A. Multislice computed tomography for determination of coronary artery disease in a symptomatic patient population. Int J Cardiovasc Imaging 2007;23:361–7.

47. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. Heart 2008;94:1154–61.

48. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. Circulation 2000;101:244–51.

49. Yao ZM, Li W, Qu WY, Zhou C, He Q, Ji FS. Comparison of (99)mTc-methoxyisobutylisonitrile myocardial single-photon emission computed tomography and electron beam computed tomography for detecting coronary artery disease in patients with no myocardial infarction. Chin Med J (Engl) 2004;117:700–5.

50. Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. J Am Coll Cardiol 2004;44:923–30.

51. Wong ND, Rozanski A, Gransar H, et al. Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischemia among patients with subclinical atherosclerosis. Diabetes Care 2005;28:1445–50.

52. Blumenthal RS, Becker DM, Yanek LR, et al. Comparison of coronary calcium and stress myocardial perfusion imaging in apparently healthy siblings of individuals with premature coronary artery disease. Am J Cardiol 2006;97:328–33.

53. Budoff MJ, Rasouli ML, Shavelle DM, et al. Cardiac CT angiography (CTA) and nuclear myocardial perfusion imaging (MPI)—a comparison in detecting significant coronary artery disease. Acad Radiol 2007;14:252–7.

54. Esteves FP, Sanyal R, Santana CA, Shaw L, Raggi P. Potential impact of noncontrast computed tomography as gatekeeper for myocardial perfusion positron emission tomography in patients admitted to the chest pain unit. Am J Cardiol 2008;101:149–52.

55. Laudon DA, Vukov LF, Breen JF, Rumberger JA, Wollan PC, Sheedy PF 2nd. Use of electron-beam computed tomography in the evaluation of chest pain patients in the emergency department. Ann Emerg Med 1999;33:15–21.

56. McLaughlin VV, Balogh T, Rich S. Utility of electron beam computed tomography to stratify patients presenting to the emergency room with chest pain. Am J Cardiol 1999;84:327–8, A8.

57. Mao S, Child J, Carson S, Liu SC, Oudiz RJ, Budoff MJ. Sensitivity to detect small coronary artery calcium lesions with varying slice thickness using electron beam tomography. Invest Radiol 2003;38:183–7.

58. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. Eur Heart J 2007;28:2967–71.

59. O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial. JAMA 2003;289:2215–23.

60. Gopal A, Nasir K, Liu ST, Flores FR, Chen L, Budoff MJ. Coronary calcium progression rates with a zero initial score by electron beam tomography. Int J Cardiol 2007;117:227–31.

61. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–30.

62. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114:1761–91.

63. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). J Am Coll Cardiol. 2007;49:378–402.

64. Hamon M, Morello R, Riddell JW, Hamon M. Coronary arteries: diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography—meta-analysis. Radiology 2007;245:720–31.

65. Brindis RG, Douglas PS, Hendel RC, et al. ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association. J Am Coll Cardiol 2005;46:1587–605.

66. Hoffmann U, Nagurney JT, Mose>lewski F, et al. Coronary multi-detector computed tomography in the assessment of patients with acute chest pain. Circulation 2006;114:2251–60.

67. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol 2007;49:863–71.

► APPENDIX

For supplementary figures, please see the online version of this article.