5 Assessment of Cardiovascular Calcium: Interpretation, Prognostic Value, and Relationship to Lipids and Other Cardiovascular Risk Factors

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Abstract

Coronary artery calcium scanning has proven to be the most powerful predictor of cardiac risk in the primary prevention population, far exceeding conventional risk factors in prognostic value. It has also proven superior to all markers of inflammation, ankle brachial index, carotid intima-media thickness and flow mediated vasodilation. Its most accepted application is in the intermediate risk cohort, with an outcome based net reclassification index of the Framingham Risk Score exceeding 50 %. Application to young patients with a family history of premature coronary disease and to all diabetics older than 40 years of age is also appropriate.

Keywords

Coronary artery calcium • Primary prevention • Coronary artery disease • Risk factors • Risk prediction • Atherosclerosis

Cardiac risk assessment has traditionally been based on conventional risk factors; the shortcomings of this approach are all too often highlighted by major cardiac events occurring in presumably low-risk people. The annual presentation of 650,000 previously asymptomatic patients with an acute coronary event as the initial manifestation of coronary artery disease (CAD) [1] is a testimony to the failure of our current risk assessment model. Consequently, there has been a focus on markers of subclinical atherosclerosis that may be utilized for risk assessment of individuals, rather than extrapolating from risk factors that reflect trends in large groups of patients in epidemiologic studies. The most powerful of these subclinical markers is coronary artery calcium (CAC).

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Background

CAC is pathognomonic for atherosclerosis [2–4]. Mönckeberg's calcific medial sclerosis does not occur in the coronary arteries [5]; atherosclerosis is the only vascular disease known to be associated with coronary calcification. Calcium phosphate (in the hydroxyapatite form) and cholesterol accumulate in atherosclerotic lesions. Circulating proteins that are normally associated with bone remodeling play an important role in coronary calcification, and arterial calcium in atherosclerosis is a regulated active process similar to bone formation, rather than a passive precipitation of calcium phosphate crystals [6–9]. Rumberger et al. [10] demonstrated that the total area of coronary artery calcification is highly correlated ($r=0.9$) in a linear fashion with the total area of coronary artery plaque on a segmental, individual, and whole coronary artery system basis (Fig. 5.1), and the areas of coronary calcification comprise approximately one fifth that of the associated coronary plaque. Additionally, there were plaque areas without associated coronary calcium, suggesting that there may be a coronary plaque size

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most commonly associated with coronary calcium but, in the smaller plaques, the calcium is either not present or is undetectable.

Intravascular ultrasound [11, 12] measures of combined calcified and non-calcified plaque confirm the strong relationship (Fig. 5.2).

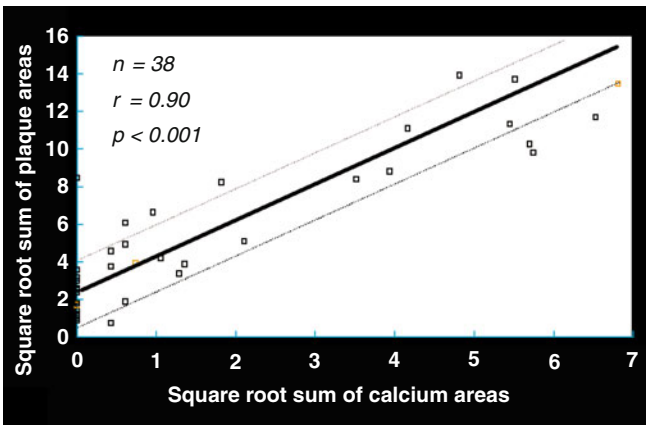

Fig. 5.1 Correlation between calcified and total plaque burden in histopathologic coronary artery specimens (Reproduced from Rumberger et al. [10], with permission from Wolters Kluwer Health)

Methodology

Technical

In the beginning, the data substantiating the importance of CAC were derived through the use of electron beam tomography (EBT), utilizing a rotating electron beam to acquire prospectively triggered, tomographic 100-ms X-ray images at 3 mm intervals in the space of a 30- to 40-s breathhold. The multidetector computed tomography (MDCT) technology has replaced EBT and employs a rotating gantry with a special X-ray tube and variable number of detectors (from 4 to 320), with 75–375-ms images at 0.5,1.5, 2.0, or 3.0 mm intervals, depending on the protocol and manufacturer.

Scoring

The presence of CAC is sequentially quantified through the entire epicardial coronary system. Coronary calcium is defined as a lesion above a threshold of 130 Hounsfield units (which range from −1000 (air), through 0 (water), and up to +1000 (dense cortical bone)), with an area of three or more adjacent pixels (at least 1 mm^2). The original calcium score

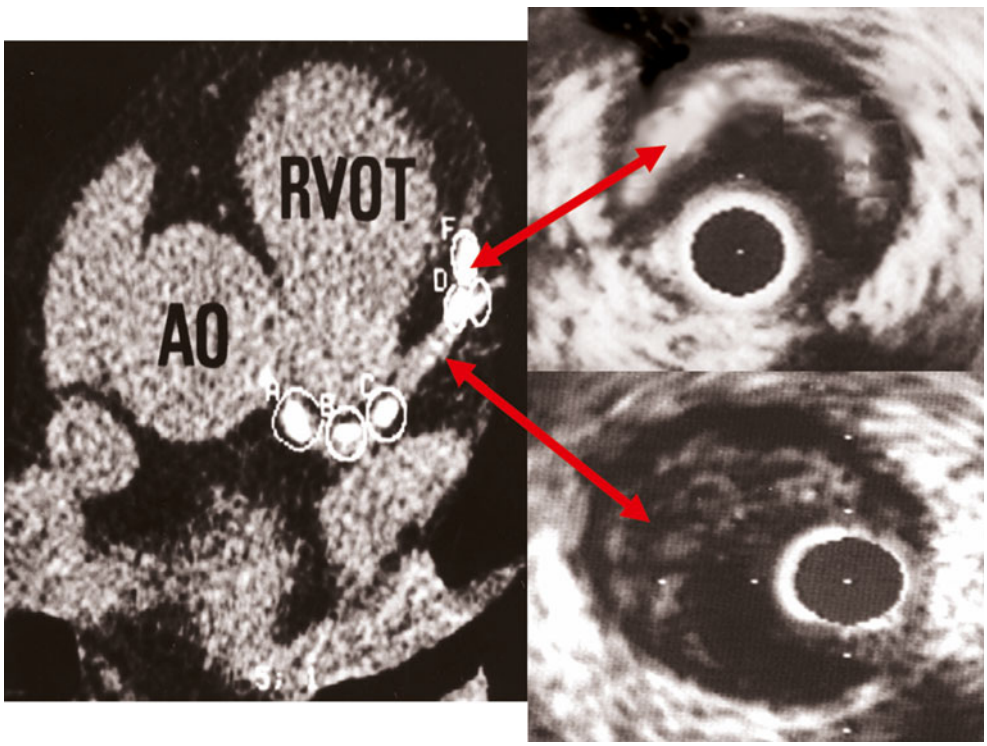

Fig. 5.2 Coronary artery calcium scan (*left*) demonstrating areas of extensive calcification corresponding to heavily calcified plaque on intravascular ultrasound (*upper right*), and less extensive calcification corresponding to less heavily calcified plaque on intravascular ultrasound (*lower right*), *AO* aorta, *RVOT* right ventricular outflow tract

developed by Agatston et al. [13] is determined by the product of the calcified plaque area and maximum calcium lesion density (from 1 to 4 based upon Hounsfield units). Standardized categories for the calcium score have been developed with scores of 0 indicating absence of calcified plaque, 1–10 considered minimal, 11–100 mild, 101–400 moderate, and >400 severe. Examples are shown in Fig. 5.1. The calcium volume score [14] is a more reproducible parameter that is independent of calcium density and may be the parameter of choice for serial studies to track progression or regression of atherosclerosis, but is rarely used. Phantom-based calcium mass scores are applicable to any CT scanner [15], but are never clinically used. Examples of CAC scans are shown in Fig. 5.3.

Epidemiology

By comparing a person's calcium score to others of the same age and gender through the use of large databases of asymptomatic subjects, a *calcium percentile* is generated [16]. This is an index of the prematurity of atherosclerosis; for example, a 50-year-old man in the 76th percentile has more plaque than 75 % but less plaque than 24 % of asymptomatic 50-year-old men. Although there is an increasing incidence of coronary calcification with increasing age, this simply parallels the development of coronary atherosclerosis.

Table 5.1 shows coronary calcification incidence in an unselected patient population of men and women [17]. The amount of CAC in women is similar to that in men a decade

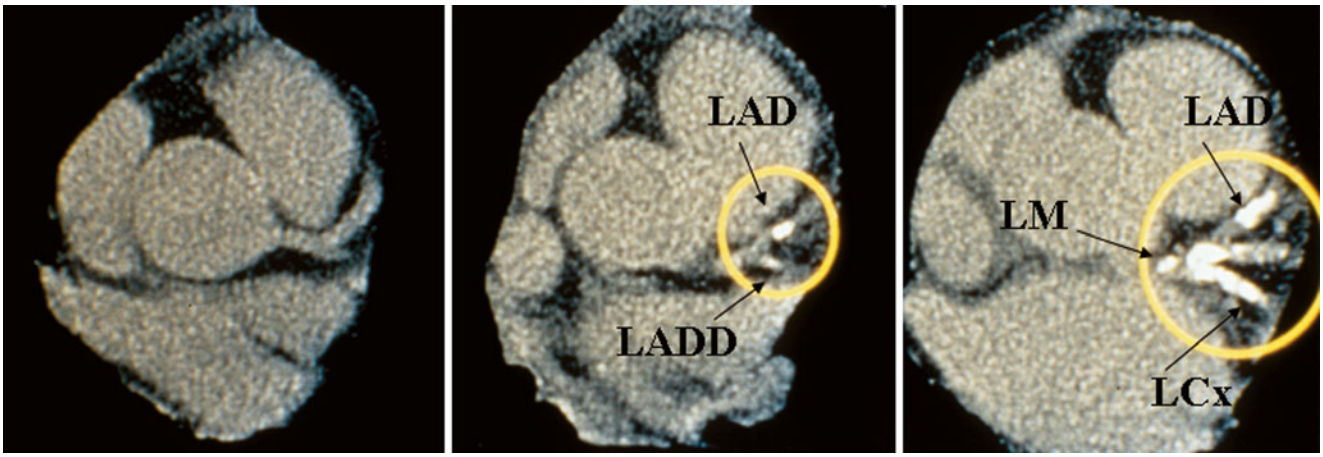

Fig. 5.3 Examples of coronary artery calcium scans. *Left* normal without CAC. *Center* moderate CAC involving the left anterior descending (*LAD*) and circumflex (*LCx*) coronary arteries. *Right* extensive CAC involving the left main (*LM*), anterior descending, and circumflex coronary arteries, *LADD* left anterior descending diagonal branch

Table 5.1 Calcium percentile database for asymptomatic men and women: coronary calcium scores as a function of patient age at the time of examination

Percentiles	40–45 years	46–50 years	51–55 years	56–60 years	61–65 years	66–70 years	71–75 years
Men (n = 28,250)							
10	0	0	0	1	1	3	3
25	0	1	2	5	12	30	69
50	2	3	15	54	117	166	350
75	11	36	110	229	386	538	844
90	69	151	346	588	933	1151	1650
Women (n = 14,540)							
10	0	0	0	0	0	0	0
25	0	0	0	0	0	1	4
50	0	0	1	1	3	25	51
75	1	2	6	22	68	148	231
90	4	21	61	127	208	327	698

younger, paralleling the 10-year lag in women of the development of clinical atherosclerosis.

Useful though these current nomograms are, variations according to ethnicity have been described, and data regarding these variations are still being collected and separated. In earlier studies, Blacks were noted to have either lower [18, 19] or similar [20, 21] amounts of CAC as Caucasians of the same age; Hispanics had less CAC than Caucasians [18]. In the more recent Multi-Ethnic Study of Atherosclerosis (MESA) of 6110 asymptomatic patients with 53 % female and an average age of 62 years, men had greater calcium levels than women, and calcium amount and prevalence continually increased with increasing age [22]. In men, Caucasians and Hispanics were the first and second highest respectively; Blacks were lowest at the younger ages, and Chinese were lowest at the older ages. In women, whites were highest, Chinese and Black were intermediate, and Hispanics were the lowest except for Chinese in the oldest age group. Thus, predictive indices should be extrapolated to non-whites with caution. However, MESA demonstrated very strong CAC predictive for all groups [23].

Younger patients with a family history of premature CAD have significantly higher CAC scores than similar aged individuals without this risk factor, particularly if there is a sibling history of premature CAD [24]. In MESA, the odds ratios for the presence of CAC independent of all risk factors in those with compared to those without a family history of premature CAD were 2.74 with premature CAD in both a parent and a sibling, 2.06 in a sibling alone, and 1.52 in a parent alone [25].

Radiation

The vast majority of CAC scanning is performed on MDCT scanners. The radiation exposure should not exceed 1.0 mSv [26]. Iterative reconstruction techniques that decrease noise will lead to even lower radiation exposure. Appropriate perspective is obtained by comparing this exposure to the 0.75 mSv of the annual mammographic examination recommended for women 45 years and older.

Coronary Artery Calcium and Obstructive Disease

Incidence

The relationship of CAC to obstructive disease has been extensively investigated, and was misunderstood by the 2000 ACC/AHA Consensus Document on EBT [27], which focused on the low specificity as a critical flaw. While the presence of CAC is nearly 100 % specific for atherosclerosis, it is not specific for obstructive disease since both obstructive and non-obstructive lesions have calcification present in the intima. Comparisons with pathology specimens have shown that the degree of luminal narrowing is weakly correlated with the amount of calcification on a site-by-site basis [28–30], whereas the likelihood of significant obstruction increases with the total CAC score [4, 31, 32]. Shavelle et al. [33] reported a 96 % sensitivity and 47 % specificity for a calcium score >0, with a relative risk for obstructive disease of 4.5, compared to a 76 % sensitivity and 60 % specificity for treadmill testing, with a relative risk of 1.7. Bielak et al. [34] noted a sensitivity and specificity of 99.1 % and 38.6 % for a calcium score >0. However, when corrected for verification bias, the specificity improved to 72.4 %, without loss of sensitivity (97 %). The likelihood ratio for obstruction ranged from 0.03–0.07 in men and women ≥50 years of age for 0 scores to 12.85 for scores >200. In the <50 years cohort, the likelihood ratios ranged from 0.1–0.29 for 0 scores to 54–189 for scores >100.

Rumberger et al. [35] demonstrated that higher calcium scores are associated with a greater specificity for obstructive disease at the expense of sensitivity; for example, a threshold score of 368 was 95 % specific for the presence of obstructive CAD. In 1764 persons undergoing angiography, the sensitivity and negative predictive value in men and women were >99 % [36]; a score of 0 virtually excluded patients with obstructive CAD. In a separate study of 1851 patients undergoing CAC scanning and angiography [37], CAC scanning by EBT in conjunction with pretest probability of disease derived by a combination of age, gender, and risk factors, facilitated prediction of the severity and extent of angiographically significant CAD in symptomatic patients.

In a recent meta-analysis of 10,355 symptomatic patients who underwent cardiac catheterization and CAC, 0 CAC was noted in 1941. Significant obstructive disease, defined as >50 % diameter stenosis, was noted in 5805 (56 %). For CAC >0 and the presence of >50 % diameter stenosis, the following were reported: sensitivity 98 %, specificity 40 %, positive predictive value 68 %, and negative predictive value 93 % [38].

Prognostic Studies in Symptomatic Patients

The prognostic value of extensive CAC (>1000) in symptomatic males with established advanced CAD was demonstrated in a 5-year follow-up study of 150 patients [39]. More recently, in a meta-analysis of 3924 symptomatic patients with a 3.5 year follow up, the cardiac event rate was

2.6 %/year in those with CAC >0 and 0.5 %/year in 0 CAC patients [38]. However, in this era of coronary computed tomographic angiography (CCTA), CAC alone is not justified in the symptomatic population; CCTA will identify the noncalcified plaque and obstructive disease that may be noted in these patients, even with 0 CAC.

Clarification

Despite the apparently reasonable specificities, which are similar to those of stress testing, it must be understood that the purpose of CAC scanning is not to detect obstructive disease and, therefore, it is inappropriate to even use "specificity" in the context of obstruction. Rather, its purpose is to detect subclinical atherosclerosis in its early stages, for which it is virtually 100 % specific.

CAC in Asymptomatic Patients

Key Prognostic Studies in Primary Prevention and Comparisons with Standard Risk Factor Paradigms

The utility of CAC for risk evaluation in the asymptomatic primary prevention population is dependent on prognostic studies documenting the relative risk conferred by calcified plaque quantitation compared to conventional risk factors. Raggi et al. [40] demonstrated, in 632 asymptomatic patients followed for 32 months, an annualized event rate of 0.1 %/year in patients with 0 scores, compared to 2.1 %/year with scores of 1–99, 4.1 %/year with scores of 100–400, and 4.8 %/year with scores >400. Thus, the annualized event rates associated with coronary calcium were in the range considered to warrant secondary prevention classification by the Framingham Risk Score (Fig. 5.4).

The odds ratio conferred by a calcium percentile >75 % was 21.5 times greater than for the lowest 25 %, compared to an odds ratio of 7 for the highest versus lowest quartiles of National Cholesterol Education Program (NCEP) risk factors (Fig. 5.5).

Wong et al. [41], in 926 asymptomatic patients followed for 3.3 years, noted a relative risk of 8 for scores >270, after adjusting for age, gender, hypertension, high cholesterol, smoking, and diabetes. Arad et al. [42], in 1132 subjects followed for 3.6 years, reported odds ratios of 14.3–20.2 for scores ranging from >80 to >600; these were 3–7 times greater than for the NCEP risk factors. In a retrospective analysis of 5635 asymptomatic, predominantly low to moderate risk, largely middle-aged patients followed for 37 ± 12 months, Kondos et al. [43] found that the presence of any CAC by EBT was associated with a relative risk for events of 10.5, compared to 1.98 and 1.4 for diabetes and smoking, respectively. In women, only CAC was linked to events, with a relative risk of 2.6; risk factors were not related. The presence of CAC provided prognostic information incremental to age and other risk factors.

Shaw et al. [44] retrospectively analyzed 10,377 asymptomatic patients with a 5-year follow-up after an initial EBT evaluation. All-cause mortality increased proportional to CAC, which was an independent predictor of risk after adjusting for all of the Framingham risk factors ($p<0.001$). Superiority of CAC to conventional Framingham risk factor assessment was demonstrated by a significantly greater area under the ROC curves (0.73 versus 0.67, $p<0.001$).

Greenland et al. [45] analyzed a population-based study of 1461 prospectively followed, asymptomatic subjects who

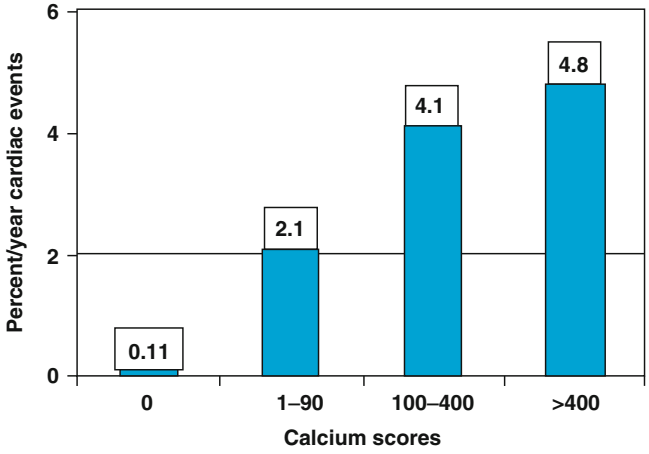

Fig. 5.4 Relationship of coronary artery calcium score to annual hard cardiac event rates in 632 asymptomatic patients undergoing EBT calcified plaque imaging. The solid line indicates the 2 %/year event rate consistent with secondary prevention risk

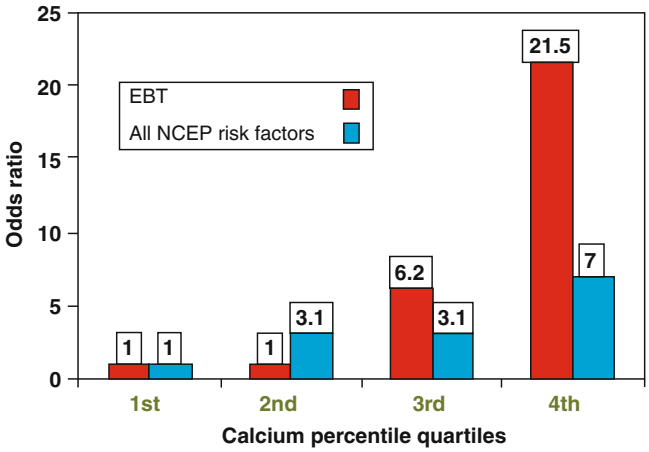

Fig. 5.5 Odds ratios of coronary artery calcium and NCEP risk factor quartiles for annual hard cardiac event rates in asymptomatic patients undergoing coronary artery calcium imaging

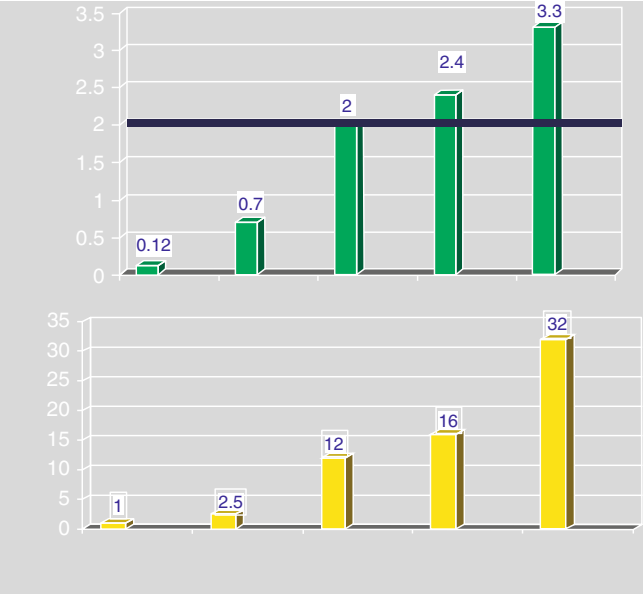

Fig. 5.6 Annual event rates and relative risks for cardiac events in 5585 asymptomatic patients at different levels of coronary artery calcium (St. Francis Heart Study). The solid line indicates the 2 %/year event rate consistent with secondary prevention risk

Table 5.2 Risk of coronary events associated with increasing coronary artery calcium after adjusting for standard risk factors in MESA

CAC	Annual rate	Events/no at risk	HR	P
0	0.11 %	15/3409	1.0	<0.001
1–100	0.59 %	39/1728	3.61	<0.001
101–300	1.43 %	41/752	7.73	<0.001
>300	2.87 %	67/833	9.67	<0.001
Doubling			1.26	<0.001

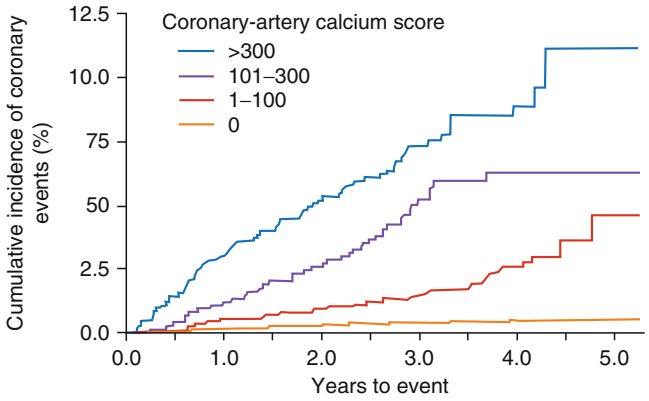

Fig. 5.7 Coronary events at different CAC levels in MESA

were predominantly moderate to high risk, and found that CAC scores >300 significantly added prognostic information to Framingham risk analysis in the 10–20 % Framingham risk category. The results of the St Francis Heart Study by Arad et al. [46] in a prospective, population-based study of 5585 asymptomatic, predominantly moderate- to moderately-high-risk men and women, mirrored previous retrospective studies [7, 18–20], and confirmed the higher event rates associated with increasing CAC scores. CAC scores >100 were associated with relative risks of from 12 to 32, and were secondary prevention equivalent, with event rates >2 %/year (Fig. 5.6). Incremental information over Framingham scores was documented with areas under the ROC curves of 0.81 for CAC and 0.71 for Framingham ($p<0.01$).

The prognostic significance of very high calcium scores was provided in a study of 98 asymptomatic patients with a CAC score >1000 who were followed for 17 months [47] during which 35 patients (36 %) suffered a hard cardiac event (myocardial infarction or cardiac death). The annualized event rate of 25 % refuted the erroneous concept that extensive calcified plaque may confer protection against plaque rupture and events.

In a younger cohort of 2000 asymptomatic Army personnel, Taylor et al. [48] demonstrated the powerful predictive value of CAC. There was a relative risk of 11.8 in patients with CAC >44 compared to those with 0 CAC, after correcting for the Framingham Risk Score. In a much more elderly population (71 years), Vliegenthart et al. found a hazard ratio of 4.6 for CAC 400–1000 compared to <100 after 3.3 years of follow up [49].

Subsequently, even more powerful data have emerged. Budoff et al. [50] in another all cause mortality study, with retrospective analysis of 25,203 asymptomatic patients after 6.8 years, found that CAC >400 was associated with a hazard ratio of 9.2. In the largest study using coronary calcium percentile rather than absolute scores, Becker et al. [51] in 1724 patients followed prospectively for 3.4 years, reported hazard ratios for CAC percentile >75 % versus 0 % of 6.8 for men and 7.9 for women. The area under the ROC curve for CAC percentile (0.81) was significantly superior to the Framingham (0.66), European Society of Cardiology (0.65), and PROCAM risk scores (0.63). Eighty two percent of patients who developed myocardial infarction or cardiac death were correctly classified as high risk by CAC percentile, compared to only 30 % by Framingham, 36 % by the European Society of Cardiology, and 32 % by PROCAM.

Perhaps the most important study is the Multiethnic Study of Atherosclerosis, an NHLBI sponsored prospective evaluation of 6814 patients followed for 3.8 years [23]. Compared to patients with 0 CAC, the hazard ratios for a coronary event were 7.73 for those with CAC 101–300, and 9.67 among participants for CAC >300 (P<0.001) (Table 5.2; Fig. 5.7).

Table 5.3 Characteristics and risk ratio for follow-up studies using coronary artery calcium in asymptomatic persons

Author	N	Mean age (years)	Follow-up duration (years)	Calcium score cutoff	Comparator group for RR calculation	Relative risk ratio
Arad [42]	1173	53	3.6	CAC >160	CAC <160	20.2
Park [108]	967	67	6.4	CAC >142.1	CAC <3.7	4.9
Raggi [40]	632	52	2.7	Top quartile	Lowest quartile	13
Wong [41]	926	54	3.3	Top quartile (>270)	First quartile	8.8
Kondos [43]	5635	51	3.1	CAC	No CAC	10.5
Greenland [45]	1312	66	7.0	CAC >300	No CAC	3.9
Shaw [44]	10,377	53	5	CAC ≥400	CAC ≤10	8.4
Arad [46]	5585	59	4.3	CAC ≥100	CAC <100	10.7
Taylor [48]	2000	40–50	3.0	CAC >44	CAC = 0	11.8
Vliegenthart [49]	1795	71	3.3	CAC >1000	CAC < 100	8.3
Budoff [50]	25,503	56	6.8	CAC >400	CAC 0	9.2
Lagoski [53]	3601	45–84	3.75	CAC >0	CAC 0	6.5
Becker [51]	1726	57.7	3.4	CAC >400	CAC 0	6.8 men 7.9 women
Detrano [23]	6814	62.2	3.8	CAC >300	CAC 0	14.1
Erbel [55]	4487	45–75	5	>75th %	<25th %	11.1 men 3.2 women

CAC coronary artery calcium score

Among the four racial and ethnic groups (Caucasian, Chinese, Hispanic, Black), doubling the CAC increased risk of any coronary event by 18–39 %. The ROC curve areas were significantly higher ($p<0.001$) with the addition of CAC to standard risk factors. CAC was more predictive of coronary disease than carotid intima-media thickness; the hazard ratios per 1-SD increment increased 2.5-fold (95 % CI, 2.1–3.1) for CAC and 1.2-fold (95 % CI, 1.0–1.4) for IMT [52].

In the 2684 patients in the female component of MESA [53], Lagoski et al. reported a 6.5 hazard ratio for the 32 % with a CAC >0 versus the 68 % with 0 CAC, even though 90 % were low risk by Framingham. In an analysis of all cause mortality in 44,052 asymptomatic patients followed for 5.6 years [54], the deaths/1000 patient years were 7.48 for CAC >10, compared to 1.92 for CAC 1–10, and 0.87 for 0 CAC. Finally, in a meta-analysis of 64,873 patients followed for 4.2 years, the coronary event rate was 1 %/year for the 42,283 with CAC >0, compared to 0.13 %/year in the 25,903 patients with 0 CAC [38].

Finally, in the Heinz Nixdorf Recall Study [55], 4487 subjects without CAD were followed for 5 years. Low ATP III risk was noted in 51.5 %, while 28.8 % and 19.7 % were at intermediate and high risk, respectively. The prevalence of low (<100), intermediate (100–399) and high (≥400) CAC scores was 72.9 %, 16.8 % and 10.3 %, respectively ($p<0.0001$). The relative risk of CAC >75th vs ≤25th percentile was 11.1 ($p<0.0001$) for men and 3.2 ($p=0.006$) for women. Adding CAC to the ATP III categories improved the AUC from 0.602 to 0.727 in men and from 0.660 to 0.723 in women, and led to a reclassification of 77.1 % of intermediate risk individuals (62.9 % into low risk, and 14.1 % into high risk group). The relative risk associated with doubling of the CAC score was 1.32 (95 % CI: 1.20–1.45, $p<0.001$) in men and 1.25 (95 % CI: 1.11–1.42, $p<0.0001$) in women.

Table 5.4 Summary of CAC absolute event rates from 14,856 patients in five prospective studies

CAC	FRS risk	Ten years event rate
0	Very low	1.1–1.7 %
1–100	Low	2.3–5.9 %
100–400	Intermediate	12.8–16.4 %
>400	High	22.5–28.6 %
>1000	Very high	37 %

Abbreviations: *CAC* coronary artery calcium, *FRS* Framingham risk score

In all of these studies, receiver operator characteristic curves for CAC were superior to the Framingham Risk Score and the annual event rate for CAC >100–400 exceeded the coronary artery disease equivalent of >2 %/year. Table 5.3 summarizes the relative risk results of the largest published outcome studies.

Amalgamation of data from five large prospective randomized studies [23, 46, 49, 51, 55] yields 10 year event rates that can be translated into Framingham Risk Score equivalents (Table 5.4). CAC >400 is a CAD equivalent,

Table 5.5 Reclassification of FRS risk by CAC primary prevention outcome studies

Study	% reclassified	N	Age	Follow up (years)
MESA		5878	62.2	5.8
FRS 0–6 %	11.6 %			
FRS 6–20 %	54.4 %			
FRS >20 %	35.8 %			
NRI	25 %			
Heinz Nixdorf		4487	45–75	5.0
FRS <10 %	15.0 %			
FRS 10–20 %	65.6 %			
FRS >20 %	34.2 %			
Rotterdam		2028	69.6	9.2
FRS <10 %	12 %			
FRS 10–20 %	52 %			
FRS >20 %	34 %			
NRI	19 %			

Abbreviations: *CAC* coronary artery calcium, *FRS* Framingham risk score, *MESA* multiethnic study of atherosclerosis

with 10 year event rates exceeding 20 % in asymptomatic patients. The absence of calcified plaque conveys an extraordinarily low 10 year risk (1.1–1.7 %), irrespective of the number of risk factors [56].

Of critical importance is the net reclassification index (NRI) conferred by CAC in the asymptomatic population by three major prospective population based studies [23, 49, 55] (Table 5.5). The percentage of patients with FRS risk estimate correctly reclassified by CAC based on outcomes ranged from 52 to 65.6 % in the intermediate risk population, 34–35.8 % in the high risk group and 11.6–15 % in the low risk cohort, with NRI's for the entire study population from 19 to 25 %.

Zero Coronary Artery Calcium Scores

Individuals with zero CAC scores have not yet developed detectable, calcified coronary plaque but they may have fatty streaking and early stages of plaque. Non-calcified plaques are present in many young adults. Nonetheless, the event rate in patients with CAC score 0 is very low [40, 45, 46]. Raggi et al. [40] demonstrated an annual event rate of 0.11 % in asymptomatic subjects with 0 scores (amounting to a 10-year risk of only 1.1 %), and in the St Francis Heart Study [46], scores of 0 were associated with a 0.12 % annual event rate over the ensuing 4.3 years. Greenland et al. [45], in a higher-risk asymptomatic cohort, noted a higher annual event rate (0.62 %) with 0 CAC scores; a less sensitive CAC detection technique and marked ethnic heterogeneity may have contributed to their findings. In the definitive MESA study [23], 0 CAC was associated with a 0.11 % annual event rate. In a meta-analysis of 64,873 patients followed for 4.2 years [54], the coronary event rate was 0.13 %/year in the 25,903 patients with 0 CAC compared to 1 %/year for the 42,283 with CAC >0. In an analysis of all cause mortality in 44,052 asymptomatic patients followed for 5.6 years [54], the deaths/1000 patient years for the 19,898 with 0 CAC was 0.87, compared to 1.92 for CAC 1–10, and 7.48 for CAC >10.

While non-calcified, potentially "vulnerable" plaque is by definition not detected by CAC testing, CAC can identify the pool of higher-risk asymptomatic patients out of which will emerge approximately 95 % of the patients presenting each year with sudden death or an acute myocardial infarction (MI). While the culprit lesion contains calcified plaque in only 80 % of the acute events [57], of greater importance is the observation that exclusively soft, non-calcified plaque has been seen in only 5 % of acute ischemic syndromes in both younger and older populations [12, 58]. In a more recent meta-analysis [38], only 2 of 183 (1.1 %) 0 CAC patients were ultimately diagnosed with an acute coronary syndrome after presenting with acute chest pain, normal troponin, and equivocal EKG findings. CAC >0 had 99 % sensitivity, 57 % specificity, 24 % positive predictive value, and 99 % negative predictive value for ACS. Thus, while it is uncommon that a patient with an imminent acute ischemic syndrome would have had a 0 CAC score, further evaluation, particularly with CCTA, is mandatory.

Adherence to Therapeutic Interventions

With the exception of a single study flawed by insufficient power [59], CAC has been shown to have a positive effect on initiation of and adherence to medication and life style changes. In 505 asymptomatic patients, statin adherence 3.6 years after visualizing their CAC scan was 90 % in those with CAC >400 compared to 75 % for 100–399, 63 % for 1–99, and 44 % for 0 CAC ($p < 0.0001$) [60]. Similarly, in 980 asymptomatic subjects followed for 3 years, ASA initiation, dietary changes, and exercise increased significantly from those with 0 CAC (29 %, 33 %, 44 %, respectively) and was lowest (29 %) in those with CAC >400 (61 %, 67 %, 56 %, respectively [61]. Finally, after a 6 year follow up in 1640 asymptomatic subjects, the odds ratios for those with CAC >0 compared to 0 CAC for usage of statins, ASA, and statin + ASA were 3.53, 3.05 and 6.97, respectively [62]. In the Eisner (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial, 2137 asymptomatic patients were randomized to using CAC to guide treatment or employing usual care [63]. CAC directed care produced significant improvement in systolic blood pressure, LDL-C, weight and waist size compared to usual care, without an increase in downstream testing. Patients with CAC >400

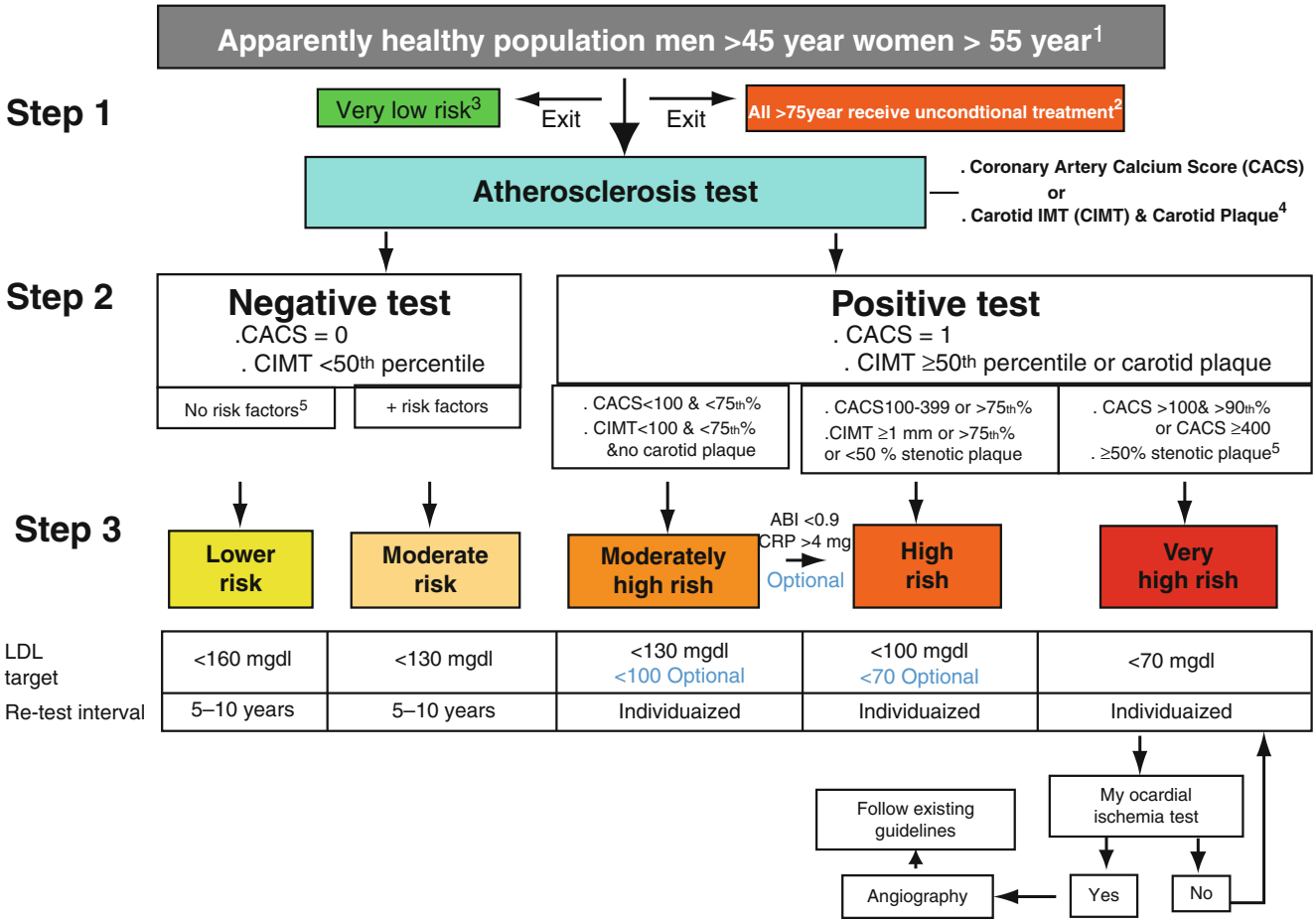

Fig. 5.8 The SHAPE guideline (Towards the National Screening for Heart Attack Prevention and Education Program)

had significantly greater improvement in all parameters than those with 0 CAC.

Coronary Artery Calcium and Guidelines

In 2006, the SHAPE guidelines (Fig. 5.8) recommended CAC or carotid intima-media thickening for all but the lowest risk asymptomatic men >45 years and women >55 years, with subsequent treatment based upon the amount of CAC [64].

The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults appropriately assigned a class IIa recommendation to CAC for evaluation of the asymptomatic intermediate-risk population and for all patients older than 40 with diabetes mellitus [65]. On the basis of flawed assumptions, the 2013 American College of Cardiology (ACC)/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [66] and the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [67] assigned CAC to a class IIb recommendation for low intermediate risk (<7.5 %), similar to the 2010 guidelines for low-intermediate risk (6–10 %, class IIb). CAC is now recommended when clinical decision making is unclear (by physician or patient), for those with risk <7.5 % and they state "assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment." This however does essentially exclude the intermediate risk population for which the NRI by CAC in three major population-based prospective outcome studies [23, 49, 55] has ranged from 52 to 66 % (see Table 5.3). The outcomes on which the 2013 guidelines were based were changed by the addition of stroke, for which the investigators believed there was not sufficient CAC data, even though the Heinz Nixdorf Recall Study of 4180 patients demonstrated hazard ratios of CAC for stroke to be similar to age, hypertension, and smoking (Table 5.6) [68]. Further, the MESA data shows CVD (including stroke) performs as well as CAD [69]. Erroneous cost and radiation exposure concerns were also used to justify the classification, despite the $100 CAC cost and the decrease in radiation to <1 mSv.

Table 5.6 Relationship between coronary artery calcium and events in asymptomatic diabetic patients

Study	n	Prevalence	Hazard ratio	AUC	Event rates/year
Wong [85]	1823	Any CAC			
		No DM: 53 %			
		DM: 73.5 %			
Becker [86]	716 DM	0 CAC: 15 %		CAC: 0.77 0	CAC: 0.2 %
		CAC >400: 42 %		FRS: 0.68	CAC >400:5.6 %
				UKPDS: 0.71	
				P<0.01	
Eikeles [87]	589 DM		Compared to CAC 0–10	CAC: 0.73	CAC <10: 0 %
			CAC >1000: 13.8	UKPDS: 0.63	
			CAC 401–1000: 8.4	P<0.03	
			CAC 101–400: 7.1		
			CAC 11–100: 4.0		
Anand [88]	510 DM	CAC <10: 53.7 %	Compared with CAC <100	CAC: 0.92	
			CAC >1000: 58	UKPDS: 0.74	
			CAC 401–1000: 41	FRS: 0.60	
			CAC 101–400: 10	P<0.001	
			CAC 0–100: 1		
Malik [89]	881 DM		Inc. CAC: 2.9–6.5	CAC + RF: 0.78–0.80	1.5 %
	4036 No DM		Inc. CAC: 2.6–9.5	RF: 0.72–0.73	0.5 %
				P<0.001	

Source: Wiley from Hecht and Narula [107]
AUC area under curve, *CAC* coronary artery calcium, *DM* diabetes mellitu, *FRS* Framingham risk score, *Inc*. increasing, *MetS* metabolic syndrome, *RF* risk factors, *UKPDS* UK prospective diabetes study

Correlation with Risk Factors

Correlation in Individual Patients with Conventional Risk Factors

Conventional risk factors do correlate with CAC [70–72], even though CAC is superior to conventional risk factors in predicting outcomes. There is a clear association of CAC with a premature family history of CAD, diabetes, and lipid values in large groups of patients. However, the difficulty equating risk factors with CAC in individual patients has been highlighted by the work of Hecht et al. in 930 consecutive primary prevention subjects undergoing EBT [71]. They found increasing likelihoods of CAC with increasing levels of low-density lipoprotein cholesterol (LDL-C) and decreasing levels of high-density lipoprotein cholesterol (HDL-C) in the population as a whole, but found no differences in the amount of plaque between groups and demonstrated a total lack of correlation in *individual* patients between the EBT calcium percentile and the levels of total, LDL- and HDL-cholesterol, total/HDL-cholesterol, triglycerides, lipoprotein(a) (Lp(a)), homocysteine, and LDL particle size.

Postmenopausal women presented a striking example of the inability of conventional risk analysis to predict the presence or absence of subclinical atherosclerosis [73]. There were no differences in any lipid parameters or in the Framingham Risk Scores between postmenopausal women with and without calcified plaque, rendering therapeutic decisions that are not plaque- imaging-based extremely problematic.

The very limited value of individual risk factors for risk prediction was illustrated by Nasir et al. [56] in 44,952 primary prevention patients followed for 5.6 years. The decrease in survival in 0 CAC subjects with increasing numbers of risk factors was trivial, declining from 99.7 % with no risk factors to 99.0 % with ≥3 risk factors. Patients with a CAC >400 and no risk factors had 7× the risk of 0 CAC patients with ≥3 risk factors (16.9 vs 2.7 events per 1000 patients years.

Correlation with Novel Risk Factors

MESA extended the risk factor inferiority to more novel risk factors, including hs-CRP, carotid IMT, ankle bracial index, flow mediated vasodilation and family history of premature CAD, (Table 5.7). In 1330 intermediate risk patients followed for 7.6 years in the Multiethnic Study of Atherosclerosis, CAC had the highest HR and correctly reclassified 66 % of FRS predicted outcomes [69]. Similarly, in 1286 asymptomatic patients with a 4.1 year follow up, a combination of five blood biomarker risk factors, including hs-CRP, interleuk-6,

myeloperoxidase, beta natriuretic protein and plasminogen activator-1, did not significantly increase the FRS c-statistic. CAC, on the other hand, increased it from 0.73 to 0.84 ($p < 0.003$) [74].

The poor risk prediction performance of hs-CRP and its lack of correlation with CAC do not challenge the inflammatory aspects of the disease process. Rather, it emphasizes the greater value of evidence of the disease itself, namely CAC, compared to a risk marker, such as hs-CRP. Moreover, inflammation is the central commonality for a host of diseases characterized by higher incidences of both subclinical and clinical atherosclerosis (Fig. 5.9).

There is much less data regarding lipoprotein-associated phospholipase A2 (Lp-PLA2). In a nested case–control study among 266 CARDIA participants [75], Lp-PLA2 mass was significantly higher in subjects with CAC compared to those without CAC (OR 1.28). The numbers are too small to provide meaningful conclusions.

Table 5.7 Comparison of novel risk markers for improvement in cardiovascular risk assessment in 1330 intermediate-risk individuals

Marker	Multivariate HR	p	NRI vs FRS
ABI	0.79	.01	.036
Brachial FMD	0.82	.52	.024
CAC	2.60	<.001	.659
Carotid IMT	1.33	.13	.102
Family history	2.18	.001	.160
hs-CRP	1.26	.05	.079

Genetics

The lack of clear relationship between lipid levels and subclinical plaque in individual patients does not negate the atherogenic effect of these metabolic disorders. Rather, it highlights the variations in individual susceptibility to the atherogenic effects at a given plasma level, very likely mediated by as yet undetermined genetic factors. O'Donnell et al. [76], in an analysis of abdominal aortic calcium in 2151 patients in 1159 families in the Framingham Study, noted a heritability component accounting for up to 49 % of the variability in calcified plaque, and concluded that "AAC deposits are heritable atherosclerotic traits. A substantial portion of the variation is due to the additive effects of genes, which have yet to be characterized." Peyser et al. [77], analyzing coronary calcium in 698 patients in 302 families, found a variance of up to 48 % associated with additive polygenes after adjustment for covariates. They concluded that there is a: substantial genetic component for subclinical CAD variation . . . even after accounting for effects of genes acting through measured risk factors. These genes may act through other measurable risk factors or through novel pathways that have not or cannot be measured in vivo. Identification of such genes will provide a better basis for prevention and treatment of subclinical CAD.

Unfortunately, the single nucleotide polymorphism arena has not yet delivered any clinically concrete options.

The inevitable conclusion of the consistent lack of relationship between risk factors and disease and the superiority

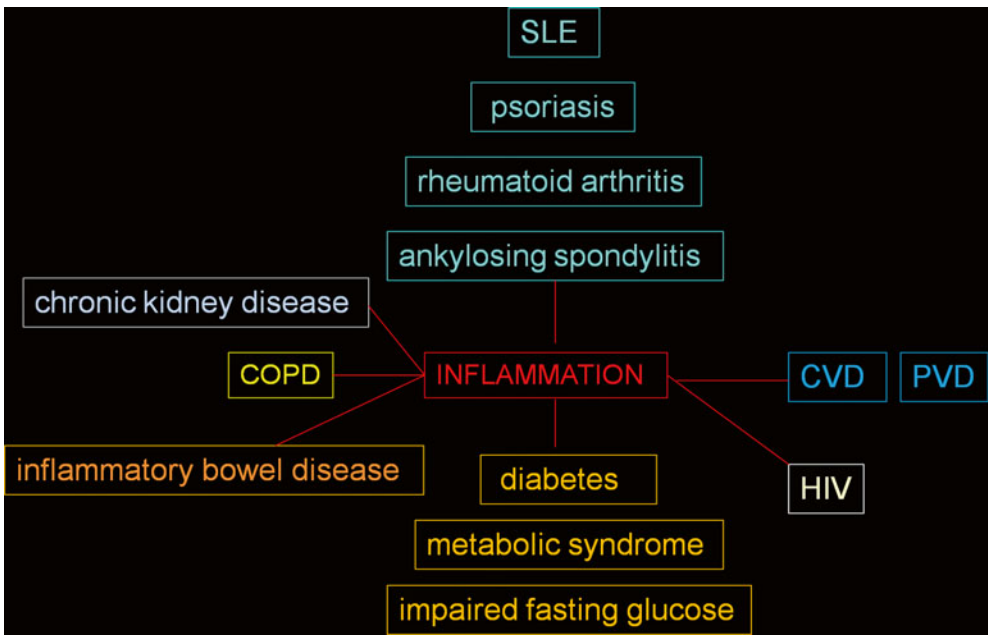

Fig. 5.9 Inflammatory diseases associated with a higher risk of coronary artery disease. *Abbreviations*: *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *HIV* human immunodeficiency virus, *PVD* peripheral vascular disease, *SLE* systemic lupus erythematosus

of CAC in individual patients was summarized by Hecht [78]: "*The most important role of risk factors may be to identify the modifiable targets of risk reduction in patients with risk already established by clinical events or significant CAC.*"

Clinical Applications

Patient Selection

Intermediate Risk

Hecht et al. [79] proposed recommendations for the application of CAC scanning (Table 5.8). The Framingham Risk Score [80], incorporating both age and gender, was recommended as the initial step in selecting the appropriate test populations. Asymptomatic patients in the National Cholesterol Education Adult Treatment Program III [81] classified 10–20 % Framingham 10-year risk category (intermediate risk) comprise the group that presents the greatest challenge to the treating physician, and are those in whom the application of CAC scoring is most appropriate; the CAC score can assist the physician in decisions regarding the initiation of statin therapy and lifestyle modifications. As previously noted, the NRI for this group ranges from 52 % to 66 %, with subsequent appropriate downgrading or upgrading of medical therapy for this majority of the intermediate risk group.

Lower Risk

Patients with less than 10 % Framingham risk may also benefit from CAC scoring to guide management decisions. For instance, most young patients with a family history of premature CAD will not have sufficient risk factors to even warrant Framingham scoring (lower NCEP risk) or will be in the moderate (1–10 % 10-year Framingham risk group), since family history, while an NCEP risk factor, does not contribute points to the Framingham score. In 222 young patients presenting with an MI as the first sign of CAD (mean age 50 years), Akosah et al. [82] demonstrated that 70 % were in these lesser risk categories and would not have been started on a statin using NCEP guidelines. Data from Schmermund et al. [12] and Pohle et al. [58] indicate that 95 % of acute MI patients would have been identified by CAC plaque imaging irrespective of age. On the basis of these observations, the use of CAC scoring should be considered in patients with a family history of premature CAD, irrespective of the FRS, as recommended by the 2009 CAC Appropriate Use Criteria [83]. Irrespective of family history, the NRI in the low risk population ranges from 11.6 to 16 %; approximately one of every eight low risk patients will miss the opportunity for recognition of their increased risk and upgrading of therapy in the absence of CAC scanning.

Higher Risk

With an NRI of 35 % for the FRS >20 % group, scanning of this cohort appears appropriate, with treatment and goals to be determined by the CAC level. Whether or not clinicians will consider downgrading intensity of treatment is quite problematic, since it is not guideline based.

Examples of risk transformation are shown in Figs. 5.10, 5.11, and 5.12. A 57-year old man with hypertension, total cholesterol 235 mg/dL, LDL-C 150 mg/dL, HDL-C 75 mg/dL, and a 10-year Framingham risk of 12 %, was referred for CAC scanning. The CAC score was 1872, in the >99th % for his age, placing him in the highest risk category with LDL-C treatment goal of <70 mg/dL (Fig. 5.10).

Figure 5.11a displays the CAC scan of a 41-year-old woman whose mother experienced a myocardial infarction at age 55. The total cholesterol was 188 mg/dL, LDL-C 112 mg/dL, HDL-C 50 mg/dL and triglycerides 132 mg/dL. She was in the 0–1 risk factor group in which a

Table 5.8 Recommendations for treatment in asymptomatic, NCEP classified moderately high-risk patients based upon CAC score

CAC score/percentile	Framingham risk group equivalent	LDL goal (mg/dL)	Drug therapy (mg/dL)
0	Lower risk; 0–1 risk factors; Framingham risk assessment not required	<160	≥190
			160–189: drug optional
1–10 and ≤75th %	Moderate risk; 2+risk factors (<10 % Framingham 10-year risk)	<130	≥160
11–100 and ≤75th %	Moderately high risk; 2+risk factors (10–20 % Framingham 10-year risk)	<130	≥130
			100–129: consider drug
101–400 or >75th %	High risk; CAD risk equivalent (>20 % Framingham 10-year risk)	<100 Optional goal <70	≥100
			<100: consider drug
>400 or >90th %	Highest risk[a]	<100 Optional goal <70	Any LDL level

[a]Based on CAC score; consider beta blockers

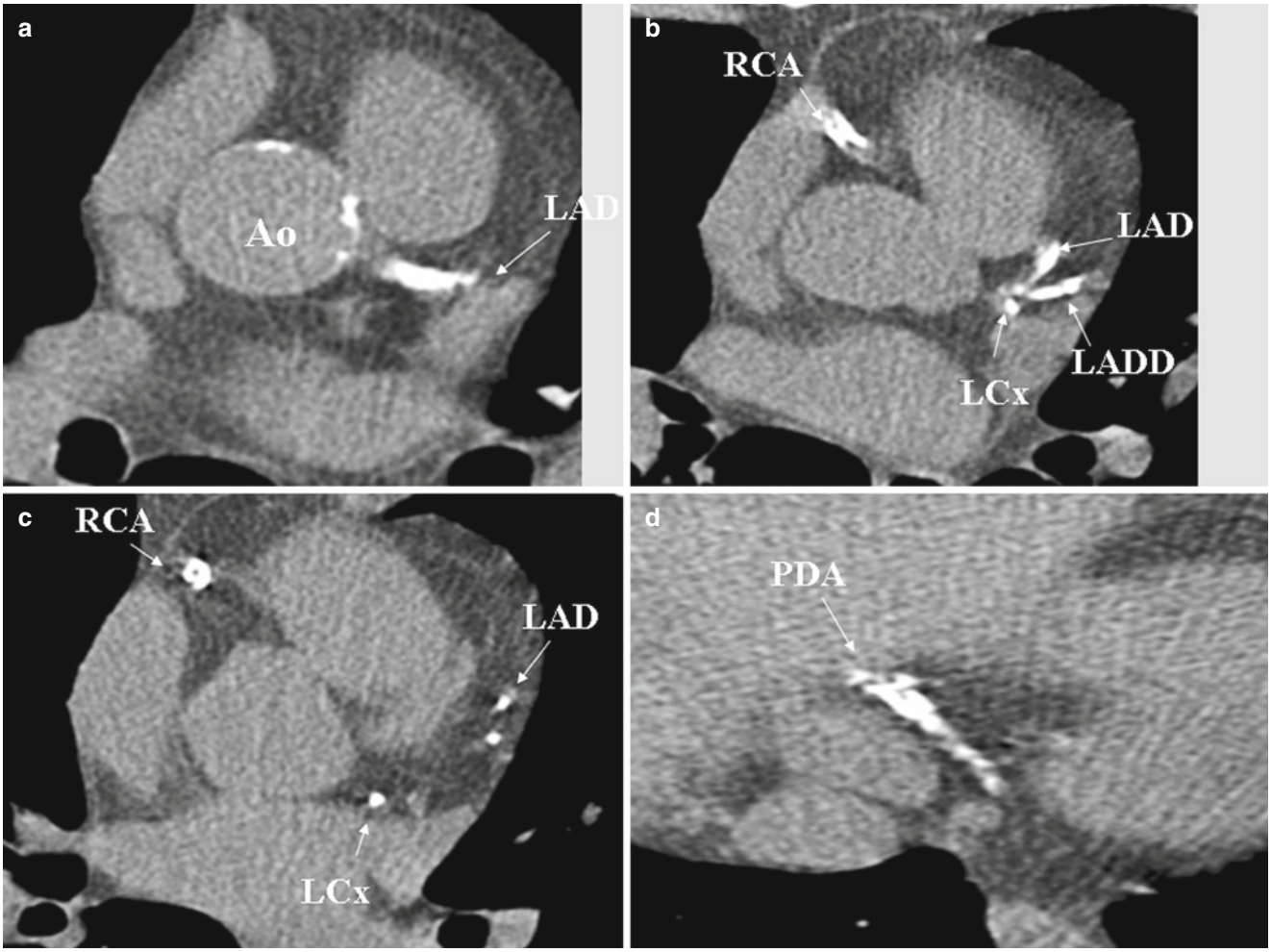

Fig. 5.10 A 57-year-old man with hypertension, total cholesterol 235 mg/dL, LDL-C 150 mg/dL, HDL-C 75 mg/dL, and a 10-year Framingham risk of 12 % referred for CAC scanning; CAC score was 1872, in the >99th percentile. Slices from base (**a**) through apex (**d**) reveal significant CAC in all coronary arteries and the ascending aorta. *Ao* aorta, *LAD* left anterior descending coronary artery, *LADD* diagonal branch of left anterior descending coronary artery, *LCx* left circumflex coronary artery, *PDA* posterior descending branch of right coronary artery, *RCA* right coronary artery

Framingham Risk Score need not be calculated. The CAC score was 110, in the left anterior descending (LAD) and diagonal branch, in the >99th percentile for her age, placing her in a high-risk category. She developed symptoms, underwent dual isotope nuclear stress testing (Fig. 5.11b), which revealed severe anteroseptal ischemia, followed by angiography and placement of a stent to treat a 95 % ostial LAD stenosis (Fig. 5.11c). Statin therapy was implemented to reduce the LDL-C to <70 mg/dL.

A 65- year-old male hypertensive smoker, with an LDL-C of 140 mg/dL and a 10-year Framingham risk of 25 %, was very reluctant to take a statin prescribed for his LDL-C. A CAC scan was performed (Fig. 5.12), which demonstrated total absence of calcified plaque, despite the presumed high risk. Therapeutic life changes, rather than statins, were recommended.

Other Applications

Diabetes

The 2010 ACC Guideline for Assessment of Risk in Asymptomatic Adults awarded CAC a Class IIa recommendation for all adults older than 40 with diabetes [65]. While the initial reasoning was to identify the high risk patients with CAC >400 for further evaluation to rule out obstructive disease, CAC prognostic data have challenged the ingrained concept of diabetes mellitus as a CAD disease equivalent. Patients with diabetes and CAC have higher risks than those without diabetes and similar CAC, but the absence of CAC conveys a similar low risk in both groups [84–90]. Therefore, the more appropriate rationale is for straightforward risk classification as with any other risk factor, allowing for the possibility of downgrading risk.

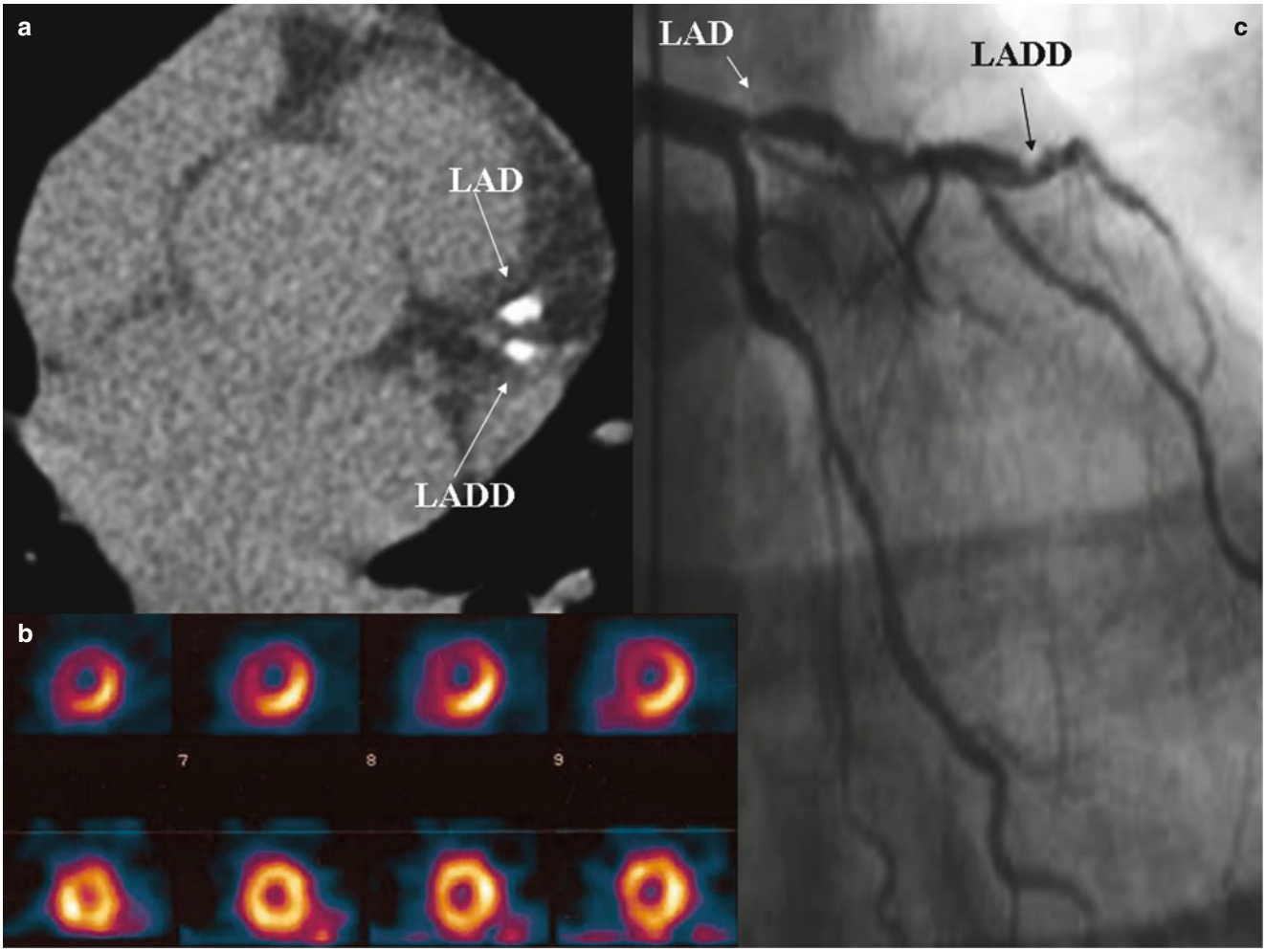

Fig. 5.11 A 41-year-old woman with a premature family history of CAD, total cholesterol 188 mg/dL, LDL-C 112 mg/dL, HDL-C 50 mg/dL, and triglycerides 132 mg/dL, in the lowest Framingham risk group. (**a**) CAC score of 110, in the left anterior descending and diagonal branch, in the >99th percentile. (**b**) Dual isotope nuclear stress testing revealing severe anteroseptal ischemia. (**c**) Angiography demonstrating 95 % ostial LAD stenosis and severe LADD disease. *LAD* left anterior descending coronary artery, *LADD* diagonal branch of left anterior descending coronary artery

Repeat Scanning

The use of serial CAC scanning to evaluate the progression of disease and the effects of therapy is a powerful emerging indication that will be covered in greater detail in Chap. 6. Asymptomatic patients with a 0 CAC score should not undergo repeat scanning for at least 4 years. The average time to conversion to a >0 CAC was 4.1 ± 0.9 years and the average score at the time of conversion was 19 ± 19 [91]. The repeat scanning interval in patients with >0 CAC is not data determined. Rather, logic dictates that the greater the concern, the shorter should be the interval. The low radiation dose makes repeat scanning less problematic.

Stress Testing

Since stress testing should only be performed in symptomatic patients, in whom CAC is not indicated, the interplay between the two is limited. Nonetheless, a combination of CAC and stress EKG has been advocated in symptomatic patients. However, coronary CTA is clearly the CT modality of choice, and will very likely replace stress testing as the first test in the evaluation of symptomatic patients [92].

In asymptomatic patients, post CAC stress testing is an issue, and the appropriateness of stress testing after CAC scanning is directly related to the CAC score. The data indicate that the incidence of abnormal nuclear stress testing is 1.3 %, 11.3 % and 35.2 % for CAC scores of <100,100–400

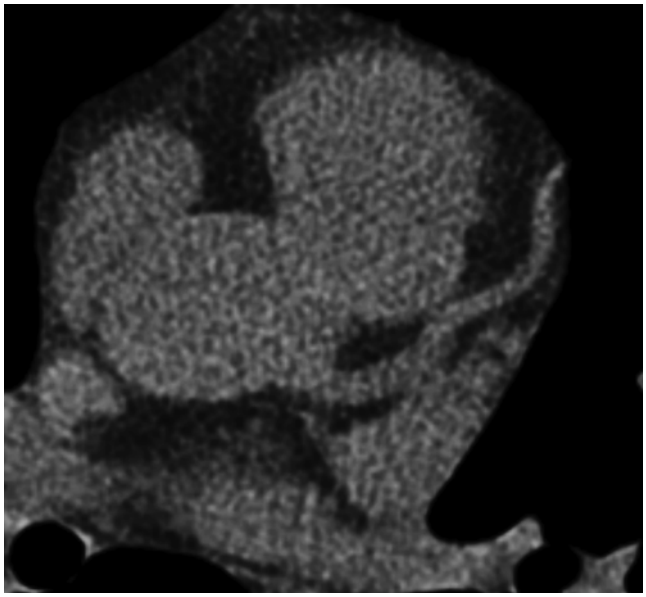

Fig. 5.12 A 65-year-old male hypertensive smoker, LDL-C of 140 mg/dL and a 10-year Framingham risk of 25 %. CAC scan demonstrated total absence of calcified plaque

and >400, respectively [93–97]. It is only in the >400 group that the pretest likelihood is sufficiently high to warrant further evaluation with functional testing. Coronary computed tomographic angiography is appropriate in patients with CAC <1000; higher CAC scores may preclude accurate evaluation. It is never appropriate to proceed directly to the catheterization laboratory from a CAC scan in asymptomatic patients.

Evaluation of incidental findings, particularly lung nodules, should follow standard radiology guidelines [98].

Cardiomyopathy

CAC may be used to differentiate ischemic from nonischemic cardiomyopathies. Budoff et al. [99] demonstrated in 120 patients with heart failure of unknown etiology that the presence of CAC was associated with a 99 % sensitivity for ischemic cardiomyopathy. Nonetheless, coronary CTA has replaced CAC for this indication.

Emergency Department Chest Pain Evaluation

Emergency department triage of chest pain patients by CAC has been totally supplanted by CCTA. Several early studies demonstrated potential application of CAC to the ED. Laudon et al. [100] reported on 105 patients. Of the 46 with positive scores (>0), 14 had abnormal follow-up inpatient testing. Of the 59 with 0 calcium scores, stress evaluation and/or coronary arteriography were normal in the 54 who underwent further testing and all were free of cardiac events 4 months later (100 % negative predictive value). Georgiou et al. [101] noted 41 cardiac events in 192 emergency room patients followed for 37 months; all but four were associated with calcium scores ≥4. However, CCTA data have clearly demonstrated a small (5 %) but finite incidence of obstructive disease in 0 CAC patients with chest pain [102], mandating performance of CCTA rather than CAC alone in this setting

Limitations

Frequently cited limitations of CAC are assuming much less importance. Radiation is no longer a significant issue as the absorbed radiation dose falls to the level of mammography. Unfortunately, irresponsible scare tactics have magnified public concern; education is needed to counter these negative effects. Cost has also become less of a concern as the price of CAC scanning has plummeted to ~ $100. "Incidentalomas" and their subsequent evaluation have generated negative sentiments. The frequency of clinically significant findings is 1.2 %, with indeterminate findings at 7.0 % [103]. The associated costs do not negatively impact the cost effectiveness of CAC [104]. Standard guidelines on how to handle these findings may reassure patients and physicians [98]. Patient anxiety related to CAC findings has also been cited as a negative. Anxiety is not an intended consequence but a certain amount is appropriate and inevitable when informed of increased cardiac risk, and may motivate increased adherence. On the other hand, for those with high anxiety of early ASCVD based on a severe family history or a high calculated ASCVD risk score, concern can often be calmed when reclassified toward significantly less risk by CAC. The most persistent criticism is the lack of randomized controlled trials that demonstrate improved patient outcomes through the use of CAC. The appropriate response notes that there "… is a double standard that demands randomized controlled (outcome) trials for CAC screening while ignoring their necessity for every other technology…. It is incumbent on the cardiology community to temper the inflexible need for randomized trials with the reality of 565,000 patients presenting with myocardial infarctions annually as their first symptoms, 95 % of whom could be identified as at high risk by CAC screening and aggressively treated to significantly reduce events [105]."

Conclusions

The validation of CAC scanning as a risk assessment tool may well represent one of the most significant advances in the history of preventive medicine. It offers the possibility of accurately identifying the vast majority of patients destined to suffer acute cardiac events, and, in so doing, should allow for substantial reduction of cardiovascular mortality and morbidity by increasingly effective pharmacologic and lifestyle therapy of the underlying disease process.

It is appropriate to conclude by quoting Dr. Scott Grundy [106]:

The power of imaging for detecting subclinical atherosclerosis to predict future ASCVD events is increasingly being recognized. Imaging has at least three virtues. It individualizes risk assessment beyond use of age, which is a less reliable surrogate for atherosclerosis burden; it provides an integrated assessment of the lifetime exposure to risk factors; and it identifies individuals who are susceptible to developing atherosclerosis beyond established risk factors. Also of importance, in the absence of detectable atherosclerosis, short-term risk appears to be very low. Thus, for primary prevention, a recommendation could be established that detection of significant plaque burden is a preferred strategy for initiation of LDL-lowering drugs. With such a recommendation, major risk factors and emerging risk factors could be used as a guide for selecting subjects for imaging more than as a primary guide for therapy. Once subclinical atherosclerosis is detected, intensity of drug therapy could be adjusted for plaque burden. This 2-step approach to risk assessment could provide a solution to the dilemma of patient selection for cholesterol-lowering drugs in primary prevention. In addition, it could be applied to all population subgroups. It could also be useful as a guide to low-dose aspirin prophylaxis and cholesterol-lowering therapy.

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