Calcium Scoring

4

Jongmin Lee

Contents

Abstract

Coronary artery calcium (CAC) is calcium compound deposited within atherosclerotic plaque along its aging. The amount of the calcium is known to be proportional to the whole plaque burden in the subject. Based on this acknowledgment, the quantitative amount of CAC has been applied in clinical field as an indicator for cardiovascular event risk. Among several methods to score the CAC, Agatston score has been widely used in research and practice as a representative scoring method. To stratify cardiovascular risk, CAC score was stratified by the score or percentile within a corresponding cohort by age and gender. In spite of controversy, the CAC scoring methods were validated to be feasible in clinical routine practice. The certain facts about the CAC are that the CAC score predicts CAD risk of intermediate- and high-risk populations; zero CAC score suggests very low risk of CAD unless other risk factors are associated; faster CAC score increase suggests higher risk of CAD; ethnic and sexual differences exist; CAC score is not for diagnosing CAD but for cardiovascular risk assessment.

Abbreviations

AS	Agatston score
CAC	Coronary artery calcium
CAD	Coronary artery disease
CaHA	Calcium hydroxyapatite
CCS	Calcium coverage score
EBCT	Electron-beam CT
HU	Hounsfield units
MS	Mass score
VS	Volume score

J. Lee
Department of Radiology, Kyungpook National University and Hospital, Daegu, Republic of Korea
e-mail: jonglee@knu.ac.kr

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4.1 Concept of CAC

- Calcium compound deposited within atherosclerotic plaque.
- The calcium volume suggests atherosclerotic plaque volume in coronary artery [1].
- Quantitative calcium volume evaluation (CAC score) can predict the extent of coronary atherosclerotic disease and its clinical risks [2].

4.2 Scoring Methods

- The first quantification method for CAC was suggested by Agatston using electron-beam CT (EBCT) [3].
- Besides scoring methods, the reference standard is important for practical application.

4.2.1 Agatston Score [3]

- Scanning protocol is suggested for standardization of image quality.

Parameters	Conditions
Prospective data acquisition	At 80 % of R-R interval
Tube voltage	130 kVp
Tube current	(630 mA)
Slice thickness	(3 mm)
Acquisition time	(100 ms)
Contrast enhancement	None

The values in parentheses, original protocol for EBCT, which can be adjustable by scanners

- Coronary artery calcium should be identified by analyzers with classifying branches.
- Calcium area segmentation is semiautomatic using threshold technique, higher than 130 Hounsfield units (HU) and larger than single pixel.
- The density of calcium area is stratified as "density factor" based on peak HU in two-dimensional ROI.

Density factors	Hounsfield units
1	130–199
2	200–299
3	300–399
4	Over 400

- Agatston score (AS) is a global sum of products by calcium areas, density factors, and slice thickness.

$$\mathrm{AS} = \sum_{x=1}^{n} \left(\frac{A_x \cdot D_x \cdot \mathrm{SL}}{3} \right)$$

x, serial number of ROIs; A, area of ROIs; D, density factor; SL, slice thickness

4.2.2 Volume Score [4]

- The volume score (VS) was invented to overcome drawbacks of AS such as nonlinear measurement of HU (density factors) and complexity of measurement.
- Scanning protocol and threshold value for segmentation are same as AS.
- The VS is acquired as a global sum of ROI volumes.

$$\mathrm{VS} = \sum_{x=1}^{n} \left(A_x \cdot \mathrm{SL} \right)$$

- The reproducibility of examination is higher by VS than by AS.
- However, AS has greater reference standard criteria.

4.2.3 Mass Score [5]

- Instead of adopting indirect parameters, the mass score (MS) was designed for more direct assessment of calcium mass.
- Scanning field includes calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, CaHA] phantoms as reference standard materials.
- Initially, the HUs of CaHA phantoms are measured in corresponding images. Based on real calcium density in the phantoms, density-HU plotting with a linear fitting equation is possible.

$$\mathrm{HU} = a \cdot [\mathrm{CaHA}] + b$$

[*CaHA*], calcium densities in CaHA phantoms

- Since the calcium mass is a product of calcium density and its volume, the MS can be acquired from the fitting equation and the volume of ROIs.

$$\mathrm{MS} = \sum_{x=1}^{n} \left[\left(\frac{\mathrm{HU}_x - b}{a} \right) \cdot A_x \cdot \mathrm{SL} \right]$$

- The strength of MS is the consistency of measured values throughout different scanning environments.
- The MS is the most accurate and reproducible technique for CAC quantification.
- Drawbacks of the MS are the complexity of assessment and lack of reference standard criteria for clinical application.

4.2.4 Other Scores

4.2.4.1 CAC Progression Rate [6]

- Based on the fact that CAC increasing speed is associated with the risk of CAD, CAC progression rate (R) is suggested.
- R reflects a percentile interval change of VS.

$$R = 100 \cdot e^{\left\{\frac{\Delta[\ln(VS)]}{T}\right\}-1}$$

T, time interval between examinations

- The R may be a useful marker for a subsequent monitoring of the coronary atherosclerotic burden in single subject.
- Drawbacks are the complexity of assessment and lack of the reference standard criteria.

4.2.4.2 Calcium Coverage Score [7]

- The calcium coverage score (CCS) is the percentage of coronary arteries affected by calcium.
- In a multiethnic large-scale cohort study, the CCS predicted cardiovascular events better than AS and MS.
- A drawback is insufficient clinical application results including reference standard criteria.

4.3 Clinical Significance of CAC

4.3.1 Cardiovascular Risk by Plaque Burden (Figs. 4.1, 4.2, 4.3, 4.4, and 4.5)

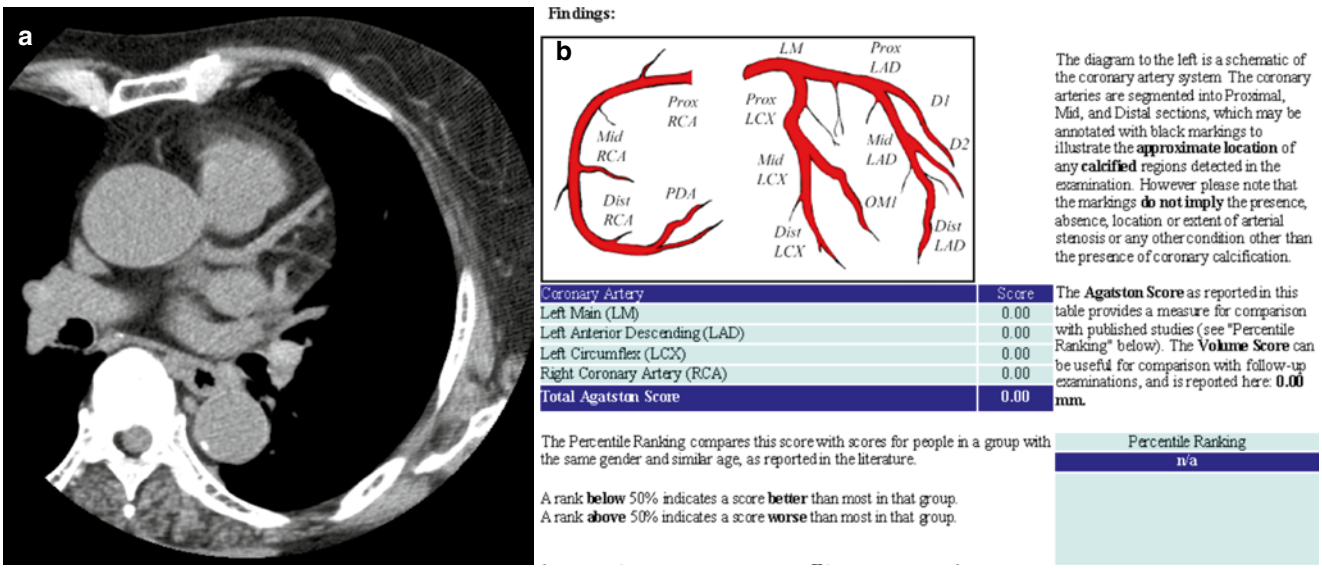

Fig. 4.1 A 72-year-old female. (**a**) Non-enhanced axial CT for calcium scoring shows no calcium in the coronary arteries. Small nodular calcification is noted in the descending aortic wall. (**b**) Total Agatston score is zero (From Hoff et al. [9])

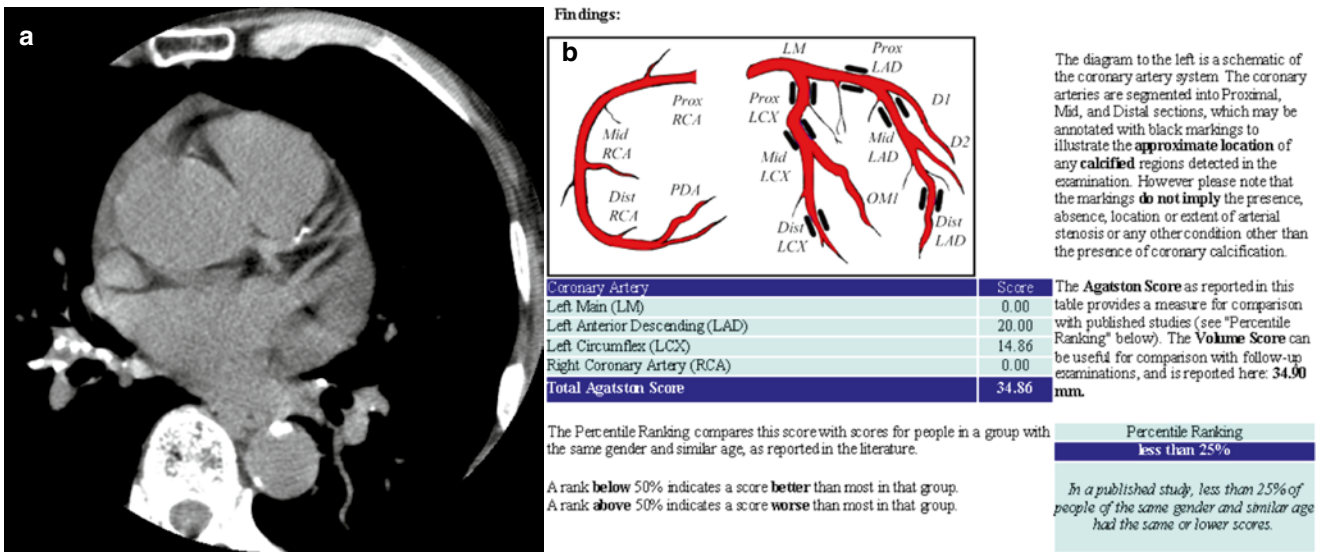

Fig. 4.2 A 77-year-old male. (**a**) Small calcific nodules are noted in the mid left anterior descending artery. Other calcific nodules are noted in the descending aortic wall and hilar lymph nodes. (**b**) Total Agatston score is 34.86, which means mild plaque burden. The subject is less than the 25th percentile in the same age and gender group (From Hoff et al. [9])

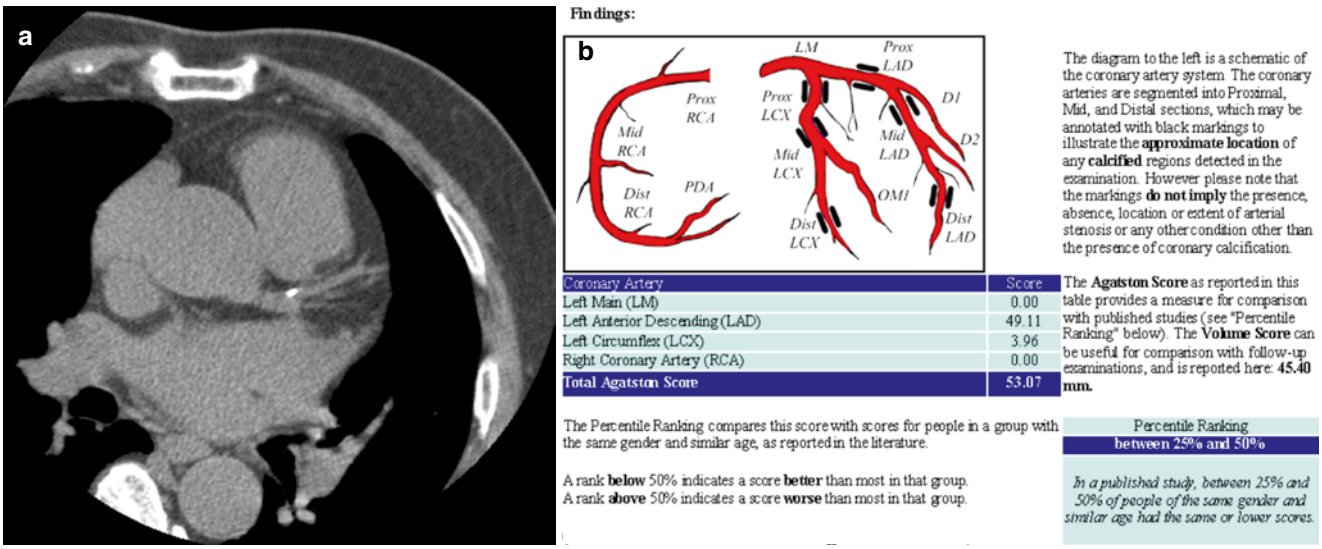

Fig. 4.3 A 69-year-old male. (**a**) Small nodular calcification is noted at the branching level of the left main coronary artery. (**b**) Total Agatston score is 53.07, which means mild plaque burden. Due to younger age than case 2, this subject is plotted between the 25th and 50th percentiles in the same age and gender group (From Hoff et al. [9])

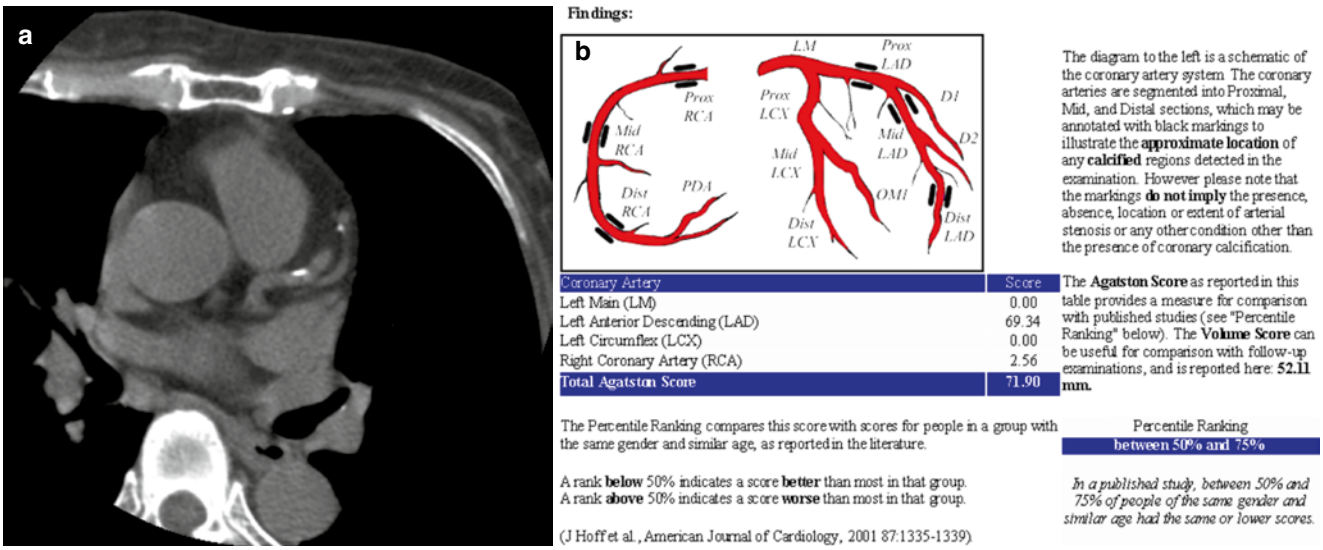

Fig. 4.4 A 71-year-old female. (**a**) Two calcific nodules are noted at the left anterior descending artery. (**b**) Total Agatston score is 71.90, which means mild plaque burden. Due to female gender, this subject is plotted between the 50th and 75th percentiles in the same age and gender group (From Hoff et al. [9])

- An initial meta-analysis-based guideline for CAC Agatston score focused on plaque burden and its clinical interpretation (Table 4.1) [8].
- Nonlinear stratification of Agatston score matched with plaque burden and its clinical interpretation.
- This guideline is simple to apply on routine practice.
- However, diversity of CAC score by sex and age was not considered.

4.3.2 Cardiovascular Risk by Percentile Stratification (Figs. 4.1, 4.2, 4.3, 4.4, and 4.5)

- Based on multicenter large cohort prospective research, Agatston score distributions by age strata and genders were suggested as an interpretation guideline (Table 4.2) [9].

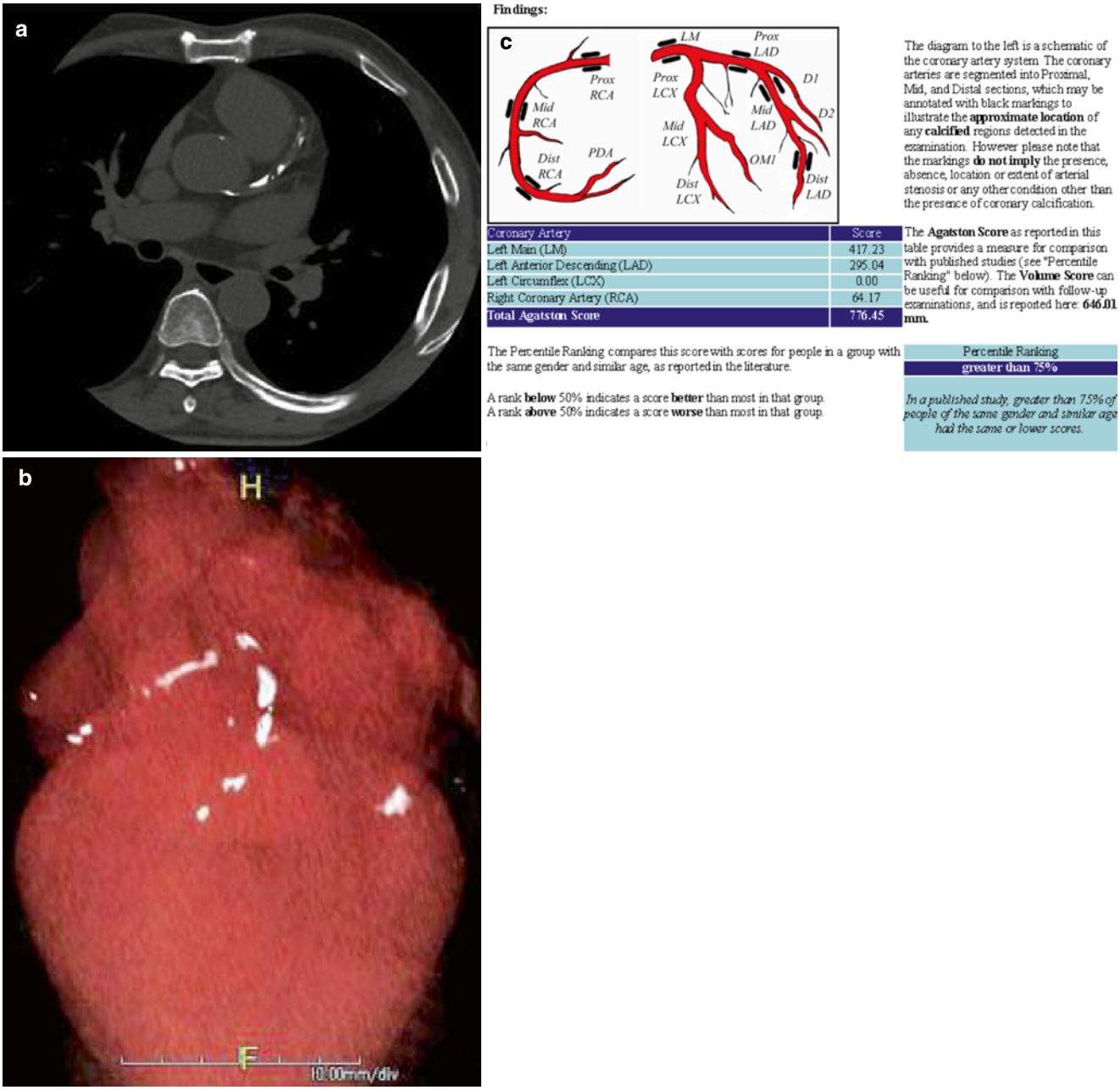

Fig. 4.5 A 61-year-old male with diabetes mellitus. (**a**) Diffuse calcification is noted from the orifice level of the left main coronary artery to the mid level of the left anterior descending artery. (**b**) Volume rendered 3-D image in 4-chamber orientation reveals heavy calcium in the left anterior descending and right coronary arteries. (**c**) Total Agatston score is 776.45, which means extensive plaque burden. This subject is stratified to higher than the 75th percentile in the same age and gender group. Stratification higher than the 75th percentile means high cardiovascular risk (From Hoff et al. [9])

Table 4.1 The interpretation guideline of Agatston score

Calcium score	Plaque burden	Clinical interpretation
0	None	Very low CVD risk
		Less than 5 % chance of presence of CAD
		A negative examination
1–10	Minimal	Significant CAD very unlikely
11–100	Mild	Likely mild or minimal coronary stenosis
101–400	Moderate	Moderate nonobstructive CAD highly likely
Over 400	Extensive	High likelihood of at least one significant coronary stenosis (>50 % diameter)

Table 4.2 Distributions of Agatston score by age strata and genders

	Age (years)								
Percentile	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	>74
Men									
25th	0	0	0	1	4	13	32	64	166
50th	1	1	3	15	48	113	180	310	473
75th	3	9	36	103	215	410	566	892	1,071
90th	14	59	154	332	554	994	1,299	1,774	1,982
Women									
25th	0	0	0	0	0	0	1	3	9
50th	0	0	0	0	1	3	24	52	75
75th	1	1	2	5	23	57	145	210	241
90th	3	4	22	55	121	193	410	631	709

- Since the age factor is stratified as decades, interpolated data can demonstrate percentile zone graph for practical application.
- This guideline reflects the diversity of CAC by genders and ages so that more practical application on clinical field is possible.
- Since the result display is intuitive, this guideline is equipped in most CAC analyzing tools.
- CAC score higher than the 75th percentile was reported to present higher cardiovascular risk than the score below the 25th percentile [10].

4.3.3 CAD Risk Per Patient

- The CAC scoring pursues an evaluation of cardiovascular risk in a target subject based on data from communities.
- Can we use CAC score to evaluate CAD per patient?
- Based on histological comparison, intraplaque calcium amount was reported to be proportional to the total plaque volume [11]. This means the positive CAC score can estimate total plaque burden per plaque and per patient.
- Through many reports supporting the relationship between CAC score and CAD severity per patient, some papers suggest cutoff values (AS 371 or 400) of CAC score for prediction of flow-limiting CAD per patient [12, 13].
- The regional distribution and specific patterns of calcium may suggest plaque features in per patient level. Shell-like and diffuse calcifications have higher relationship with significant stenosis and noncalcified plaque than nodular calcification [14].
- Yes, we can use CAC score to predict the severity of CAD in per patient level when the CAC score is high enough. In contrast, low to zero CAC score is limited to preclude the possibility of significant CAD generally.

4.3.4 Zero Calcium Score

- According to interpretation guidelines of CAC, a zero score means very low cardiovascular risk with the lowest percentiles in both male and female (Tables 4.1 and 4.2).
- However, no calcium is detected in uncalcified soft plaque, which is more important for acute coronary syndrome.
- Theoretically, CAC cannot reflect the risk of acute coronary syndrome, which is more fatal than stable angina.
- The clinical meaning of zero CAC score reaches a consensus, although some controversy continues until now [15].
- The zero CAC score virtually exclude cardiovascular risk more likely in subjects older than 50 years of age and subjects without other significant risk factors [16, 17].
- The zero CAC score implies very low cardiovascular risk in the intermediate term (around 3.5 years) [18].

Table 4.3 Prediction of coronary age based on Agatston score by ethnicity and gender

Ethnicity	Gender	Formulae	R^2
White	Male	$y=7\cdot10^{-12}\cdot x^5-10^{-8}\cdot x^4+6\cdot10^{-6}\cdot x^3-0.001\cdot x^2+0.248\cdot x+53.65$	0.998
	Female	$y=10^{-9}\cdot x^5-5\cdot10^{-7}\cdot x^4+8\cdot10^{-5}\cdot x^3-0.006\cdot x^2+0.376\cdot x+65.89$	0.999
Black	Male	$y=3\cdot10^{-6}\cdot x^{53}-0.001\cdot x^2+0.254\cdot x+62.64$	0.995
	Female	$y=2\cdot10^{-5}\cdot x^3-0.003\cdot x^2+0.321\cdot x+69.97$	0.999
Hispanic	Male	$y=3\cdot10^{-6}\cdot x^3-0.001\cdot x^2+0.243\cdot x+59.71$	0.998
	Female	$y=3\cdot10^{-5}\cdot x^3-0.004\cdot x^2+0.384\cdot x+70.94$	0.998
Chinese	Male	$y=7\cdot10^{-6}\cdot x^3-0.002\cdot x^2+0.444\cdot x+57.75$	0.999
	Female	$y=6\cdot10^{-6}\cdot x^3-0.001\cdot x^2+0.250\cdot x+66.50$	0.997

y coronary age, *x* Agatston score

- Based on specific conditions, the zero CAC score can be used as an indicator to preclude significant CAD.

4.3.5 CAC-Concordant Clinical Parameters

- Currently, the CAC score is regarded as a feasible independent marker for cardiovascular risk stratification.
- The CAC score is used as a reference standard or a major input factor for cardiovascular risk estimation during the other clinical studies.

4.3.5.1 Coronary Age [19]

- As a cardiovascular risk predictor, the "coronary age" was suggested by a large cohort study using MESA data.
- Based on the 50th percentile CAC score by ethnicity and gender, the coronary age is calculated as a polynomial function of Agatston score (Table 4.3).
- A true biological age of the subject's coronary artery as well as the degree of the coronary arterial damage during the subject's aging process.
- The coronary age can be applied to enhance patient's compliance to treatment of CAD and modification of one's lifestyle.

4.3.5.2 DM Mortality

- The National Cholesterol Education Program (NCEP) regards diabetes mellitus as a CAD equivalent condition due to its high incidence in diabetic group [20].
- The cardiovascular risk of the diabetics, especially asymptomatic patients, can be monitored using CAC score.
- In a large cohort study based on US National Death Registry, the all-cause mortality of the asymptomatic diabetics increased in proportion to Agatston score [21].
- Relative risk ratios for all-cause mortality in asymptomatic diabetic patients are 3.76, 1.76, 1.44, and 1.06 by hypertension, current smoking, CAC score, and age, respectively ($p<0.05$) [21].
- Combining with other hazardous variables, the diabetics can be monitored in a more strict way.

4.3.5.3 Cardiac Risk of Hypertensive Disease

- Left ventricular hypertrophy of the hypertensive suggests a high cardiovascular risk.
- In a hypertensive cohort, CAC score showed a significant correlation with the severity of left ventricular hypertrophy as well as its clinical marker, QT dispersion on ECG [22].
- Since CAC score is correlated with abnormal lipid profile and ascending aortic prominence, CAC score monitoring may be a comprehensive indicator of cardiovascular risk for hypertensive patients.

4.4 Appropriateness Criteria for CAC

4.4.1 AHA Criteria [23]

- When is CAC score appropriate for detection of CAD and risk assessment?

	Without	With
Asymptomatic patients		Low pretest-probability
		Family history of premature CAD
	Known CAD	Intermediate pretest-probability

The *CAD*, coronary heart disease

- When is CAC score inappropriate for detection of CAD and risk assessment?

	Without	With
Asymptomatic patients	Known CAD	Low pretest-probability

4.4.2 European Criteria [24]

- CAC score is a good predictor of cardiovascular events in intermediate-risk Caucasian population.
- Rapid CAC progression is associated with higher risk of events.
- A zero CAC score is associated with a very low prevalence of CAD.

4.4.3 ASCI Criteria [25]

- How is CAC scored in the coronary artery disease (CAD) risk assessment for the general population?

	Framingham risk score	Criteria
Asymptomatic subjects with	Low	Inappropriate
	Moderate	Appropriate
	High	Appropriate

4.5 Summary

- CAC score predicts CAD risk of intermediate- and high-risk populations.
- A zero score suggests very low risk of CAD unless other risk factors are associated.
- Faster CAC score increase suggests higher risk of CAD.
- Ethnic and sexual differences exist.
- CAC score is not for diagnosing CAD but for cardiovascular risk assessment.

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