Evidence for Coronary Artery Calcification Screening in the Early Detection of Coronary Artery Disease and Implications of Screening in Developing Countries

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ABSTRACT

Coronary artery disease (CAD) has become the biggest threat to population health all over the world. Although developed countries have witnessed a decline in CAD-related mortality in recent decades, developing countries are still experiencing steadily increasing CAD morbidity and mortality. Coronary artery calcification (CAC) is found to be a risk factor of CAD, and the use of CAC scanning may better predict CAD and improve evaluation and diagnosis of CAD. We review the major studies from developing countries investigating the prevalence and severity of CAC, the relationship of CAC and other conventional risk factors, the diagnostic accuracy of CAC computed tomography in relation to coronary angiography, and the predictive value of CAC scanning for future CAD events. Last, we summarize the recommendations on CAC scanning from several developing countries and propose future research topics about CAC.

Coronary artery calcification (CAC) is indicated by calcium deposits in the coronary artery wall and is a component of atherosclerosis and coronary artery disease (CAD) [1–5]. CAC is quantified by either multidetector computed tomography (CT) or electron beam CT, and there are several methods of calculating the CAC score, although the Agatston method is most commonly used clinically [6–9]. During past decades, numerous cohort studies and a few clinical trials have demonstrated that CAC score is significantly and independently associated with cardiovascular disease (CVD) events. The CAC scan has become an established, rapid, and noninvasive measure of subclinical atherosclerosis and has been suggested in the evaluation of subclinical disease and CVD risk in several guidelines. The pros and cons of CAC scanning are shown in Table 1, and a brief comparison with other tests for subclinical disease and risk assessment is shown in Table 2. In this review, we focus specifically on reviewing the research involving CAC screening in asymptomatic patients in developing countries and related guidelines for CAC screening as a risk predictor. We also review the strengths and limitations of CAC screening as applied to developing countries.

BURDEN OF CVD IN DEVELOPING COUNTRIES

Cardiovascular disease (CVD) is the leading cause of death throughout the world. Each year, CVD causes 17 million deaths globally, accounting for nearly one-half of noncommunicable disease–related deaths and 30% of all-cause deaths [10]. Nearly 80% of CVD-related deaths (14 million) occur in low- and middle-income countries. CVD is the most frequent cause of death in most of these countries. CVD deaths usually happen at an earlier age and during the productive decades of life in developing countries, in contrast to developed countries, where the CVD-related death usually occurs later in life [11,12]. During the years 1990 to 2020, expected increases in coronary heart disease rates alone are projected to be 137% in men and 120% in women in developing countries, compared with 60% and 30% in developed countries [13].

Another measure of disease burden, the disability-adjusted life-year, indicates the severity of CVD in most developing countries [12,14]. The rank of CVD in disability-adjusted life-years rose from 5 to 4 from the years 2000 to 2011 in low-income countries, from 4 to 2 in lower-middle-income countries, and remained 1 in upper- and middle-income countries [15]. CVD also confers a heavy financial burden in low- and middle-income countries. Noncommunicable diseases including CVD and diabetes are estimated to reduce gross domestic product by up to 6.77% in low- and middle-income countries [12]. Over the period from 2011 to 2025, the cumulative lost output in low- and middle-income countries associated with CVD is projected to be U.S. $3.76 trillion [16].

Instead of a decline in CVD mortality rates in some developed counties, the majority of developing countries have entered a third epidemic transition phase—a phase of degenerative and human-made diseases, in which CVD morbidity, mortality, and risk factors increase continuously [12,17,18]. Due to rapid industrialization and urbanization, related CVD risk factors such as tobacco use, unhealthy diet, and a sedentary life-style have increased accordingly [19]. In addition, a lack of early detection, prevention, and intervention strategies also impedes reductions in CVD and CVD-related deaths in developing countries [20].

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TABLE 1. Pros and cons of CAC scanning by computed tomography in lower- and middle- income countries

Pros	Cons
Provides greatest added risk prediction above global risk assessment	Requires special equipment (scanner) not routinely available in many underserved areas
Reproducible	Modest radiation, making it unsuitable for population-wide screening
Automated and standardized scoring process and software	Not generally reimbursable by health insurance, requiring cash payment
Only noninvasive method of detecting coronary atherosclerosis	Does not detect where tight coronary lesions may be present
Score strongly correlates with overall coronary atherosclerotic burden	Modest cost, depending on region/country

STUDIES OF CAC IN DEVELOPING COUNTRIES

Significant studies of CAC in developing countries have involved large samples of patients, depending on international collaboration (e.g., Israel, Korea, Brazil), and/or are have focused on specific national populations (e.g., China, India). Cohort studies are less common than are cross-sectional studies due to the difficulty of obtaining follow-up and/or bias in the ascertainment of subsequent CVD events. Cross-sectional studies have included the investigation of CAC prevalence and severity.

In one multinational study, researchers from Brazil compared CAC prevalence across Brazilian, Portuguese, and U.S. white populations [21]. The prevalences of CAC were 20% and 12% in Portuguese men and women, respectively, compared with 54% and 38% in their Brazilian counterparts and 67% and 41% and in their U.S. counterparts. The mean ± SD CAC score burden was 33 ± 221 among Portuguese patients, 128 ± 401 among Brazilian patients, and 144 ± 408 among U.S. patients. The significantly different CAC prevalence and burden among them imply an environmental impact on CAC because Brazilian participants were mostly Portuguese descendants and shared a gene pool similar to that of Portuguese whites. Another investigation of CAC prevalence from Korea comparing 5,239 asymptomatic Korean patients over 30 years of age showed that men had a fourfold greater risk for any CAC compared with Korean women, and that women, like those in developed countries, had a 10-year time lag in developing CAC. In addition, CAC increases according to age and Framingham risk score [22]. These findings on the patterns of CAC distribution (by sex or age) are similar to those from previous Western studies. Other cross-sectional studies have included the examination of the accuracy of CAC scanning in the detection of CAD compared with gold-standard coronary angiography. In a study from India of CAC scanning accuracy in relation to coronary angiography at three cut points of CAC scores (0, 100, and 400), there was high sensitivity (95%) when CAC was 0, and perfect specificity (100%) at the other extreme of 400 [23].

Longitudinal studies examining the prognostic value of CAC scanning in developing countries have been done as substudies (or ancillary studies) of data from larger clinical trials. In INSIGHT (International Nifedipine Study: Intervention as Goal for Hypertension Therapy) [24], a prospective, randomized, double-blind trial from Europe and Israel involving patients aged 55 to 80 years with hypertension, CAC predicted short- and long-term CVD events

TABLE 2. Comparison of subclinical cardiovascular screening/biomarker tests

Test	Strength of Recommendation for Risk Assessment	Potential for Availability in LMIC	Cost of Equipment	Cost per Test	Ease of Interpretation
CAC from CT scanning	+++	+	+++	+++	+++
Carotid IMT	++*	++	++	++	++
Ankle-brachial index	+++	+++	+	+	+++
Endothelial function/brachial artery reactivity	No current recommendations	+	++	+	+
Hs-CRP	+++	+++	+	+	+++
Global risk scoring	+++	+++	+++	+++	+++

CAC, coronary artery calcification score; CT, computed tomography; IMT, intima-media thickness; LMIC, left main stem of the internal carotid artery; Hs-CRP, high-sensitivity C-reactive protein.

*Most guidelines have recommended carotid IMT for risk stratification except for the most recent American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk [10].

in 446 and 423 patients, respectively, in the subset from Israel [25,26]. One study from China, enrolling 4,425 participants with a median follow-up of 3 years, found significant variation in major adverse cardiovascular events among different CAC strata [27]. Compared with participants with a CAC score of 0, the hazard ratios for severe major adverse cardiovascular events were 6.90, 8.33, and 20.97 in those with CAC scores of 1 to 100, 101 to 400, and >400, respectively. The *c*-statistic was increased from 0.71 to 0.82 when the CAC score was added to standard risk factors and was further increased to 0.93 when coronary CT angiography (CTA) was included.

ETHNIC DIFFERENCES IN THE PREVALENCE AND DISTRIBUTION OF CAC

Most studies comparing the ethnic differences in CAC have been limited to those conducted in the United States and have compared the prevalence of CAC in ethnic groups living in similar social and natural environments. It has been shown that African Americans have the lowest prevalence and extent of CAC, with a relative risk (RR) for the presence of CAC ranging from 0.39 to 0.78, compared to whites [28–34]. The lower prevalence of subclinical disease as measured by CAC is paradoxical to the high prevalences of CVD and coronary heart disease (CHD) among blacks, presumably due to the high rates of other risk factors, particularly hypertension, which can contribute to hypertensive heart disease that is not specifically atherosclerotic in nature and therefore would not result in a higher CAC score [35]. Other ethnic groups have shown lower CAC prevalences compared with that in whites (RRs: Hispanic, 0.68 to 0.85; Asian, 0.64 to 0.92) [30–34]. Similarly, it was found in MESA (Multi-Ethnic Study of Atherosclerosis) [34] that the likelihood of CAC among those with an Agatston score >0 was greatest among whites, followed by Chinese (77% that of whites; 95% CI: 62% to 96%), Hispanics (74%; 95% CI: 61% to 90%), and blacks (69%; 95% CI: 59% to 80%).

South Asians have been observed to have a twofold higher risk for CHD-related mortality compared with whites. The MASALA (Mediators of Atherosclerosis in South Asians Living in America) study extended the comparisons from MESA to U.S. patients of South Asian origin (of Indian, Pakistani, Bangladeshi, Nepali, and Sri Lankan ancestry) and found that the prevalence and CAC burden in South Asians was similar to that in U.S. whites but higher than in those of other ethnicities [36]. Studies comparing CAC scores in South Asians with those in whites have found that there may be a greater severity of subclinical disease after the age of 50 years [37]. In addition, in a small-scale CTA study comparing the prevalence of coronary artery stenosis in British men of South Asian origin with that in European white men, South Asian men had greater coronary artery stenosis (left anterior descending coronary artery) despite similar CAC scores, suggested that South Asians may have narrower arteries and that there may be ethnic differences in vascular remodeling [38]. Finally, the LOLIPOP-PIC (London Life Sciences Population) study [39] measured CAC in a population of 2,369 asymptomatic Asian Indians and European whites and measured silent ischemia using magnetic resonance imaging. Despite known twofold higher event rates in South Asians, Jain et al. [39] did not find greater silent ischemia in Asian Indians compared with European whites.

Studies of the ethnic variation of CAC done outside of the United States are quite limited. These data are sometimes unable to be used for statistical comparisons with other races/countries due to the different inclusion criteria and influence of other risk factors. Table 3 lists studies conducted in other countries, the data from some of which are compared with data from the United States or other Western countries [21,22,37,40–45]. It can be concluded from the data mentioned earlier that women in all observed ethnic groups have a significantly lower prevalence and extent of CAC. Two studies have indicated a time lag of approximately 10 years in women compared with men with regard to the development of CAC [22,43]. It is also universally agreed that CAC prevalence increases with age in both sexes, but that as both men and women age, the between-sex difference in CAC prevalence becomes smaller [46].

A controversial finding in these studies was that the high prevalence of CAC did not always show parallel trends of CVD prevalence among different ethnicities, which might be explained by variations in other risk factors and comorbidities [21,39,40]. Table 4 shows the relationship of CAC and other risk factors across several key international studies among different ethnic groups [21–23,40,43,47–49]. Listed are both conventional and novel risk factors and their relationship to CAC. Age and sex usually have the strongest correlation with CAC, whereas other conventional risk factors do not always show a significant association. Some novel risk factors have been found to be related to CAC, but only in some populations. Inflammation measures, such as C-reactive protein and leukocyte count; peripheral artery disease measures, including ankle-brachial index; and lipid measures, such as lipoprotein (a), were all found to be related to CAC across several populations [47,50–55]. These findings help to better understand the pathology of CAC development and progression. Other measures such as serum bilirubin and serum uric acid have also been studied [56–59]. In addition, CAC has consistently been found to be positively associated with the number of risk factors in several studies [42,49]. Some investigators have explored the relationship between the metabolic syndromes and CAC. The more metabolic-syndrome risk factors present, the greater the risk for and extent of CAC [43,60,61].

CAC scanning in CAD diagnosis

The presence of CAC indicates subclinical CAD and is associated with a greater progression of atherosclerosis. Therefore, CAC scanning with CT can be of benefit in the

TABLE 3. Prevalence and burden of CAC among countries worldwide

Study	Target Population	Reference Population	CAC Prevalence, Men/Women (%)	CAC Burden, Men/Women (Mean Score)	Comparison With Other Countries
Santos et al. [21]	Brazilian living in Brazil (most have Portuguese ancestry) Portuguese living in Portuguese	U.S. (95% whites and 5% other races)	54/38 20/12	128* 33*	CAC prevalence parallels to CVD death rates in 3 countries.
Park et al. [22]	Korean living in Korea	U.S.	40.5/19.3	N/A	Korean subjects seemed to have lower median CAC score than U.S.
Koulaouzidis et al. [37]	South Asian (India, Pakistan, Sri Lanka, Nepal and Bangladesh) living in U.K.	Caucasians living in U.K.	54.5*	156*	South Asian have similar CAC prevalence but significantly higher mean CAC score.
Dakik et al. [40]	Lebanese living in Lebanon	U.S. (80% whites and 20% other races)	N/A	167/97	Similar Prevalence of CAC but lower CVD morbidity than U.S.
Chia et al. [41]	Malays living in Singapore Indian living in Singapore	Chinese living in Singapore	46.8* 45.7*	190.2* 206.8*	CAC prevalence is similar among three ethnics, which cannot explain the higher MI rates in Malays and Indians.
Wasnik et al. [42]	Indian living in India		39.8/25.3	14.9/12.9	
Cao et al. [43]	Chinese living in Beijing		42/26	N/A	
Huang et al. [44]	Chinese living in Beijing (north city) Chinese living in Shanghai (south city) Chinese living in Guangzhou (south city)		N/A N/A N/A	185.5* 70.8* 52.1*	CAC burdens moderately parallel with coronary heart disease mortality in three cities.
Çelenk et al. [45]	Turkish living in Turkey		33.6/16.9	N/A	

CAC, coronary artery calcification score; N/A, not available.
*Data are not gender specific.

early detection of CAD before the onset of clinical symptoms. Numerous studies have been done both in developed and developing countries to test the sensitivity, specificity, positive predictive value, and negative predictive value of different CAC score cut points in relation to coronary angiography. Some of the results are listed in Table 5 [23,62–67]. As a screening method, the presence of CAC (with a score of 0 as the cut point) has a high sensitivity and a negative predictive value, whereas at the other extreme, in which CAC is high, such as >400, CAC scanning has a high specificity and a positive predictive value, which virtually confirms the presence of CAD [23]. Some studies have also calculated the area under the curve (AUC) for CAC scanning alone or in combination with CTA. The optimal cut point of CAC score can also be determined for maximal diagnostic accuracy [63,66].

TABLE 4. Conventional risk factors of CAC, by population (people native to their country of residence)

Risk Factor	Brazilian [21]	Korean [22]	Indian [23]	Lebanese [40]	Turkish [47,48]	Chinese [43,49]
Age	Y	Y	N	Y	Y	Y
Sex	Y	Y	N	Y	N/A	Y
Smoking habit	N	N/A	N	Y (in men)	Y	Y
HTN/SBP	Y	Y	N	N	Y	Y
Hyperlipidemia	Y	N	N/A	Y	Y	Y
Diabetes/HbA_{1c}	Y	Y	N	Y (in men)	Y	Y
Obesity/BMI	N/A	Y	N/A	Y (in men)	N/A	Y
Family history	N/A	N/A	N	N	N	Y

BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; HTN, hypertension; N, nonsignificant relationship; N/A, not available; SBP, systolic blood pressure; Y, significant relationship.

A CAC of 0 or a high CAC score is valuable in ruling out or confirming CAD. However, the diagnostic efficacy of a low to intermediate CAC score is often questioned, mainly because of the existence of noncalcific plaque. Even in patients with a CAC score of 0, noncalcific plaque and obstructive atherosclerosis can exist in both asymptomatic and symptomatic patients [68–70], whereas calcified plaque often indicates prolonged disease duration and a trend of disease stabilization, suggesting more of a chronic condition. This rationale is consistent with epidemiological findings that a low CAC score is related to young age and unstable and acute CAD events [71].

Predictive value of CAC score in CVD risk assessment

Well-designed, large-population, and longitudinal investigations containing data sufficient for examining

TABLE 5. Diagnostic accuracy of CAC CT scanning compared with coronary angiography

Study	Year	Population*	Sample Size	Cut Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Shrivastava et al. [23]	2003	Indian	388	0	95.5	78.9	94.9	81.1	N/A
				100	75.6	94.7	98.3	51.3	
				400	23.1	100.0	100.0	241.0	
Shemesh et al. [62]	1995	Israeli	160	0	91.0	52.0	N/A	N/A	N/A
Javadrashid et al. [63]	2010	Iran	158	0	N/A	N/A	92.8	83.8	0.83
				7.7†	86.0	71	N/A	N/A	
Mendoza et al. [64]	2010	Cuban	150	6.5 (mm^3)†‡	98.7	71.7	N/A	N/A	0.88
Trevethan-Cravioto et al. [65]	2011	Mexican	64	0	87.5	92.8	N/A	98.1	0.90
Peng et al. [66]	2012	Chinese	189	250	42.9	96.9	98.5	26.4	0.71
Won et al. [67]	2014	Korean with T2DM	328	33.0†	83.0	81.0	30.0	98	0.853

AUC, area under the curve; CAC, coronary artery calcification score; CT, computed tomography; N/A, not available; NVP, negative predictive value; PPV, positive predictive value.
*All subjects are native to their country of residence.
†Optimal cut point according to *c*-statistic result.
‡Calcium volume is used for CAC measurement.

the predictive value of CAC and CVD event rates are relatively rare in developing countries. We therefore present the results from several cohort studies globally with both hazard ratios and *c*-statistics (Table 6 [25,27,72–74]). Overall, all studies except one from Korea showed incident CVD event rates to vary significantly across different CAC strata after adjustment for other clinical risk factors. The absence of a significant relationship in the study by Park et al. [73] may have been due to the addition of coronary stenosis to the multivariate model. The AUC of CAC has ranged from 0.62 to 0.81 across all studies. Some studies have also examined the incremental value of CAC after adding it to conventional risk models and observed significant improvement in AUC over that with conventional risk factors [25,27,74,75].

When CT scanning and CTA have been compared in predicting CVD events, it has been shown that CAC score does not add incremental value to CTA test results [75]. However, conclusions on whether CTA provides incremental information over CAC score are controversial. Although the researchers from Brazil and Korea have found nonsignificant increases in AUC when adding CTA to models with CAC score [76,77], the findings from China showed that AUC increased from 0.82 to 0.93 ($p < 0.001$) [27].

CAC screening in global guidelines

Three major groups have developed key CVD risk-assessment and prevention guidelines: 1) the World Health Organization, 2) the European Society of Cardiology, and 3) the American Heart Association jointly with the American College of Cardiology (AHA/ACC). The World Health Organization's Guidelines for Assessment and Management of Cardiovascular Risk [78] have been adopted by the majority of least-developed countries. Recommendations for CAC scanning are not included, probably because CAC scanning cannot serve as a conventional screening method in these countries. The European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012) [79] has been adopted by most

TABLE 6. Predictive value of CAC score in CVD risk assessment

Study	Population	Sample Size	Duration of Follow-Up	Endpoints	Hazard Ratio	AUC
Shemesh et al. [25]	Israeli with HTN	446	3.8 yrs	All CVD	12.76 (CAC >0 vs. CAC = 0)	0.75*
Hou et al. [27]	Chinese	4,425	1081 days	Severe CVD	7.18 (CAC 1–100 vs. CAC = 0)	0.82*
					9.21 (CAC 101–400 vs. CAC = 0)	
					22.22 (CAC >400 vs. CAC = 0)	
Yamamoto et al. [72]	Japanese	317	6 yrs	CVD death	2.98 (CAC >1000 vs. CAC 1–100)	0.72
				Severe CVD	2.14 (CAC >1000 vs. CAC 1–100)	0.62
Park et al. [73]	Korean	5,182	48 months	Severe CVD	1.000	N/A
Lau et al. [74]	Chinese with T2DM and low CVD risk	151	61 months	Atherosclerotic events	27.11 (CAC >40 vs. CAC ≤40)	0.81

AUC, area under the curve; CAC, coronary artery calcification score; CVD, cardiovascular disease; HTN, hypertension; N/A, not available; T2DM, type 2 diabetes mellitus.
*Combined model of CAC added to conventional risk factors.

European and some Middle Eastern countries, including Russia, Israel, and Turkey. These guidelines do provide a recommendation for CAC measurement (as well as other subclinical measures, including carotid intima-media thickness and ankle-brachial index) to refine risk estimation in intermediate-risk adults. The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [10] has been fully adopted by India and largely quoted by China. It provides a recommendation for the use of CAC scanning beyond global risk assessment when a treatment decision on the basis of the latter is uncertain. In addition, Brazil, Singapore, China, and Korea have developed their own guidelines including recommendations for CAC scanning [80—83]. Summarized below are four key points from the guidelines with respect to level of evidence, class of recommendation, target population, and contraindications.

1. Level of evidence. The guidelines from the ACC/AHA, the European Society of Cardiology, and Brazil all rate the level of evidence for CAC scanning as B (data derived from a single randomized clinical trial or large nonrandomized studies) [10,79,80]. Singapore's guidelines give an overall rating of 4 (expert onion) and a higher rating of 2++ (high-quality systematic reviews of case—control or cohort studies, high-quality case—control or cohort studies with a very low risk for confounding or bias and a high probability that the relationship is causal when CAC is applied in an intermediate-risk population), but most evidence comes from Western countries instead of from Singapore [81].
2. Class of recommendation. Guidelines from the ACC/AHA, the European Society of Cardiology, and Brazil give a Class IIa recommendation for CAC scanning [10,79,80]. Class IIa is generally regarded as a recommendation in which the procedure or test should be performed, but with less firm evidence in favor of the procedure. Singapore's guidelines give CAC scanning an overall recommendation grade of D, which is only on the basis of expert opinion and only recommended for use in selected populations (see "Target population" below) [81]. Cost issues and the unnecessary detection of CAD to initiate aggressive preventive therapies also contribute to the limited recommendation of CAC scanning in Singapore's guidelines.
3. Target population. Clinical consultation is necessary before imaging to identify risk factors and evaluate global risk for CVD (e.g., 10-year estimated risk such as by the Pooled Cohort risk algorithms, Systematic Coronary Risk Evaluation charts). CAC scanning is recommended for use in those patients falling into the intermediate-risk group on the basis of their own risk-evaluation model, or when the decision to initiate or intensify treatment is uncertain on the basis of global risk assessment as stipulated by the most recent 2013 ACC/AHA guidelines [10,79—82]. Earlier ACC/AHA guidelines for CVD risk assessment in asymptomatic patients, published in 2010, also recommended CAC screening for use in persons at intermediate risk or who had diabetes and were aged ≥40 years [84]. Brazil's guidelines suggest using CAC as one of the aggravating risk factors for the purpose of reclassification in patients who fall into the intermediate-risk group [80]. CAC scanning has also been moderately recommended for use in low-risk populations with other risk factors present (in Singapore) and in asymptomatic patients (in China) with a 10-year CVD risk of 6% to 10% [81,82]. In particular, the European guidelines include a recommendation for CAC scanning in patients who have a low risk score at a young age but who will switch to the high-risk group with age [79].
4. Contraindications of CAC screening. CAC scanning is not recommended for use in those patients with symptoms of or preexisting CVD in whom recommended treatment options are clear. Scanning is also not recommended for use in those at low risk (e.g., <10% 10-year risk for CHD) because this would expose a large segment of the population to scanning and the costs and radiation associated with it [85]. In addition, although there is evidence to suggest modest added prediction of progression of CAC for the prediction of CHD events over baseline CAC scores [86], there are no current guidelines either in developed, higher-income countries or in lower- and middle-income countries to support repeated CAC scanning. The value of CAC scanning is in the use of the baseline CAC scan in risk stratification, and the added cost and radiation of a repeated scan would not justify the modest added value of tracking the progression of CAC. Moreover, well established is the "warranty period" free of future CHD events in persons with a baseline CAC score of 0 [87].

CAC scoring results for triggering initiation or intensification of preventive therapies

Although some past guidelines have uniformly recommended preventive therapies such as statin therapy at specific CAC score cut points such as >100 [88], and there is evidence to support such a cut point above which the number needed to treat with a statin to prevent a CHD event is favorable and comparable to that of secondary prevention (e.g., ≤25) [89], the current ACC/AHA guidelines note that a CAC score of ≥300 or ≥75th percentile for age, sex, and ethnicity (a patient's percentile rank can be estimated by the MESA CAC calculator at www.mesa-nhlbi.org/CACReference.aspx) can be considered for upstaging a person's risk to better inform the treatment decision if uncertain on the basis of global risk assessment alone. It would appear that a similar approach should be considered for lower- and middle-income countries given that global risk scoring is inexpensive and generally more accessible, with CAC scanning (or other modalities of assessing the presence and extent of subclinical disease) reserved for further risk stratification when the treatment

decision is uncertain [10]. The guidelines from China, Brazil, and Singapore recommend that asymptomatic patients with intermediate CAD risk (estimated 10-year risk for coronary events: 10% to 20% [China and Singapore], 5% to 20% [Brazilian men], and 5% to 10% [Brazilian women]) be reclassified to a higher risk status on the basis of high CAC scores (>300 [China], >100 or age- and sex-specific >75% percentile [Brazil], no specific cut point [Singapore]), and that subsequent patient management may be modified [80–82].

SUMMARY

Research on the significance of CAC from developing countries is limited, but emerging studies have demonstrated its value. The potential for examining the long-term impact of screening on outcomes is great in countries such as China and India that have the ability to examine data from large samples of patients at a relatively low cost (e.g., per scan) and potentially to direct scarce health care resources using CAC to patients at higher risk for CVD. Most studies involving CAC screening have been done in Western countries at large medical centers and have involved self-referred patients who have paid for their scans, although large-scale, prospective studies such as MESA and CARDIA (Coronary Artery Risk Development in Young Adults) have utilized CAC scanning and have been funded by the National Institutes of Health in the United States. Studies in developing countries have generally been done in large cities. Thus, there might be selection bias that needs to be considered when examining the reported CAC distribution, severity, and relationship to events in these studies. Despite these limitations, these initial studies from developing countries have remarkably demonstrated conclusions (with regard to the epidemiology and prognosis associated with CAC) similar to those from developed countries. Although evidence is lacking, the cost-effectiveness of CAC screening may differ greatly between developed and developing countries. In developing countries, future research on CAC screening should focus on more generalized populations, including rural populations; longitudinal randomized trials should focus on how CAC scanning might change long-term outcomes; and cost-effectiveness assessments focused on CAC scanning should include the downstream cost of preventive therapies.

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