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].