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Role of computed tomography screening for detection of coronary artery disease☆,☆☆

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ABSTRACT

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in Western populations, and the prediction and prevention of CAD is an inherent challenge facing current health care societies. Computed tomography (CT) has emerged as a noninvasive imaging tool in the field of cardiovascular disease. Notably, CT scanning for detection of coronary artery calcium (CAC) has proven useful in predicting adverse cardiovascular outcomes as well as early identification of CAD. In asymptomatic persons undergoing screening for CAD, CAC is well established as a surrogate of CAD risk and has demonstrated incremental benefit over and above traditional risk prediction tools. In addition, a zero CAC score has shown to reflect a substantially lower risk of CAD and may therefore be considered an important marker of CAD protection. Irrespective of screening in the asymptomatic population, CAC scanning has also displayed a beneficial role in the symptomatic population, specifically as gatekeeper in guiding further treatment decision making. Further still, the combination of alternative CT screening strategies such as CT screening for lung cancer with CAC scanning may hold particular promise as an effective screening approach by lowering overall health costs as well as limiting radiation exposure.

1. Introduction

Cardiovascular disease (CVD) remains the most prominent cause of morbidity and mortality in Western societies, accounting for approximately 17.3 million deaths per year, which are projected to rise substantially to more than 23.6 million by 2030. In the United States, the economic burden of CVD is immense, resulting in an estimated expenditure of US$320.1 billion in 2011 alone. Of further concern is that the total direct medical costs related to CVD are forecasted to reach around US$918 billion by 2030 [1].

The initial manifestation of coronary artery disease (CAD) is generally the presence of myocardial infarction or sudden cardiac death, particularly among asymptomatic individuals, thereby emphasizing the need for improved screening, prediction, and treatment approaches for subclinical coronary atherosclerosis [2]. To date, a potential pitfall of the classic cardiovascular risk assessment tools is their inability to identify more than 75% of asymptomatic individuals who experience future CAD events [3]. Indeed, the availability of an alternative modality capable of detecting significant subclinical atherosclerosis, while additionally targeting prevention of future cardiovascular events, would likely augment prognosis in asymptomatic patients at risk for suspected CAD [4].

Screening for coronary artery calcification (CAC) has emerged as a relatively inexpensive noninvasive imaging modality that is widely accessible to asymptomatic adults at risk of CAD. CAC scoring is considered a robust method for early detection of coronary heart disease (CHD), particularly in asymptomatic patients when compared with other risk-factor-based paradigms, such as The Framingham 10-year risk score (FRS) and the European Society of Cardiology Score [5]. Moreover, epidemiological evidence have documented that CAC scoring represents an independent prognostic indicator of adverse cardiovascular events over and above numerous conventional risk factors [6,7].

The following review summarizes the role of CT screening for detection of CAC, by outlining the methods used in the acquisition of CAC, along with its role as an important predictor of adverse events, while also discussing the implications and future directions of CT for determining CAC in the clinical setting.

2. Image acquisition of CAC

In the field of atherosclerotic imaging, among others, electron beam computed tomography (EBCT) has been used in quantification of CAC; however, multidetector computed tomography (MDCT) has emerged as the more commonly used imaging modality employed for the

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quantification of the amount of plaque present in the coronary arteries [8]. Indeed, progressive advancements in these imaging tools have allowed researchers and clinicians to expand our understanding of the risk of CAD and its consequences. Some of the major advantages of using EBCT include a lower radiation dose along with less motion artifacts, while notable benefits of using MDCT include a reduction in noise, along with a higher spatial resolution [9], and large volume data acquisition [10].

Typically, CAC is scanned prospectively using an electrocardiogram (ECG)-triggered mode with 2.5–3.0-mm axial slice thickness. EBCT utilizes a sophisticated approach that enables rapid acquisition of 100-ms scanning times in a prospective mode using 3-mm slice thickness that permits reliable measurement of calcium deposits in the coronary arteries [11,12]. Some of the most commonly used 64-slice CT scanners use a rotation gantry speed of up to 330 ms [10]. More contemporary MDCT scanners are capable of acquiring up to 128–320 slices of the heart, producing a higher temporal resolution. The relative abilities of EBCT and MDCT have been discussed elegantly in a recent review by Nasir and coworkers [11].

Using conventional CT scanners, CAC is defined as a hyperattenuating lesion above a threshold of 130 HU, with an area of at least three adjacent pixels [8]. Several methods have been used to quantify calcium scores based on CT imaging. The Agatston score is the most universal metric used for CAC scoring [8]. Although several CAC cut points have been proposed, the following reference categories have generally been employed when evaluating the relationship between calcium and risk of CAC: 0 (none), 1–99 (mild), 100–400 (moderate), and >400 (severe) [13]. Interreader and intrareader variabilities of CAC scoring are low, and approximate 3% and <1%, respectively. Interscan variability is roughly 15% [8]. In light of certain limitations of Agatston CAC scoring (e.g., inconsistent interscanner comparability), other scoring approaches have been proposed and include the calcium volume score and calcium mass score. Prior studies have demonstrated that these methods are comparable with the Agatston approach, especially in terms of reproducibility [14].

Importantly, the radiation dose administered for CAC testing is low, with an effective median radiation dose of 2.3 mSv, which is equivalent to 1.5 screening mammograms performed [15]. Although the radiation exposure on the background of a traditional CT appears low, every effort should be made to attempt to lower the margin in radiation dose even further without mitigating the ability to assess the burden of CAC in the coronary arteries.

3. Role of CAC in adverse cardiovascular risk

Prior studies have reported on the robustness of cardiac CT for identifying arterial calcification, indicating a high sensitivity for detecting significant coronary obstructive disease [11]. In one study, Rumberger and colleagues revealed an intimate relation between CAC measured by EBCT with direct histologic plaque areas in autopsied hearts [16]. However, in that investigation, not all plaques were found to be calcified. There can exist individual differences in the coronary arteries with a poor correlation between the degree of plaque calcification and extent of luminal stenosis using invasive coronary angiography [17,18]. Despite this, CAC estimates using cardiac CT correlate well with total atherosclerotic burden [17].

Prior studies have indicated some drawbacks when using conventional risk factors (i.e., such as those encompassing FRS) for classifying individuals, especially those belonging to an intermediate-risk group. This has led some researchers to consider more novel risk markers for the purpose of screening for CVD. For instance, the CAC score, along with carotid intima–media thickness, C-reactive protein (CRP), ankle–brachial index (ABI), brachial flow-mediated dilation, as well as other imaging parameters, is beginning to emerge as a more informative parameter for risk prediction. Moreover, several studies have assessed the usefulness of these novel risk markers for improving cardiovascular risk assessment. In the Multi-Ethnic Study of Atherosclerosis (MESA) consisting of 6814 participants, 1330 individuals were classified as being at intermediate risk, defined as having an FRS between 5% and 20% [19]. In that study, CAC, ABI, CRP, and family history of early CAD were all independently associated with incident CHD. Importantly, CAC provided superior discrimination and risk reclassification compared with the other markers. In the Heinz Nixdorf Recall Study, Möhlenkamp and colleagues demonstrated a strong relationship of CAC, FRS, and CRP with CAD in 3966 patients without known CAD or acute inflammation [20]. Notably, however, the improvement in risk prediction and discrimination was predominantly driven by CAC. In a recent study from the Rotterdam cohort, Kavousi et al. assessed the predictive ability of CAC along with 11 other novel biomarkers and imaging methods [21]. The findings from that study highlighted that the NRI on the background of CAC was 19.3%, whereas the Net reclassification improvement (NRI) relative to the other markers ranged from 0.4% to 7.6%. The improvement in discrimination (defined as the change in *C*-statistic) for CAC was 0.05, while for the other markers, the *C*-statistic ranged between 0.00 and 0.02. Notably, most of the extant literature has proposed that CAC scoring reflects a robust, independent, and incremental predictor of future adverse cardiovascular events over and above other available risk markers.

CAC is a well-established surrogate of cardiovascular risk and has shown to provide incremental benefit over traditional risk tools. In a meta-analysis comprising six CAC studies, a higher CAC score was associated with a higher event rate and higher relative risk ratio [22]. In the latter analysis, the adjusted relative risks according to CAC categories 11–100, 101–400, 401–1000, and >1000 were 1.9, 4.3, 7.2, and 10.8, respectively. Additionally, CAC displays a meaningful improvement in the prediction of CVD beyond traditional risk algorithms, such as FRS [23,24]. In MESA, the CAC score provided improved prediction beyond that conveyed by traditional risk factors, a finding that extended to different racial and ethnic groups [25].

Given that the addition of CAC to traditional risk factors led to a significant improvement in the classification of risk [21,26,27], further stratification by use of the CAC score may help guide treatment decision making in clinical practice. Foremost, in a substudy of participants enrolled in MESA who presented with similar inclusion criteria as reported in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial [28], nearly half had a zero CAC score, and these individuals had a very low event rate [29]. In the same study, one quarter of patients were identified as having a CAC score greater than 100, and most CHD events (74%) had occurred in this subset of individuals. Moreover, the number needed to treat with statin medication in order to prevent one CHD outcome over the course of a 5-year study period was favorable at 24 [29]. Similarly, of those eligible to receive aspirin treatment for the primary prevention of CVD in a substudy from MESA, patients with CAC ≥ 100 had favorable risk/benefit estimation on the background of aspirin use, while subjects with a zero CAC were more likely to experience harm from using aspirin [30]. These observations underline the importance of CAC and how it may be used to stratify subgroups of patients who are expected to derive the most and least optimal benefits from receiving medical treatment. Forthcoming randomized controlled trials are needed to examine whether treatments guided by a patient's CAC status may lead to improved health and well-being [31].

4. Clinical implications

4.1. Zero CAC score

Understanding the broad spectrum of CAC scoring for the identification of patients at risk of developing CAD while advocating clinically relevant cutoff points and their use in forthcoming studies is of important concern. Several studies have documented the utility of a zero CAC score for the purpose of risk stratification in clinical practice. In a meta-analysis of CAC screening comprising a study sample of 71,595 asymptomatic patients, the pooled risk of experiencing a cardiovascular event in the absence of CAC relative to the presence of any CAC was 0.15 (95% confidence interval, 0.10–0.21; $P<.001$) [32]. Notably, the presence of minimal CAC (i.e., CAC score 1–10) has been shown to