Coronary Artery Calcium and Carotid Artery Intima Media Thickness and Plaque: Clinical Use in Need of Clarification

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Atherosclerosis begins in early life and has a long latent period prior to onset of clinical disease. Measures of subclinical atherosclerosis, therefore, may have important implications for research and clinical practice of atherosclerotic cardiovascular disease (ASCVD). In this review, we focus on coronary artery calcium (CAC) and carotid artery intima-media thickness (cIMT) and plaque as many population-based studies have investigated these measures due to their non-invasive features and ease of administration. To date, a vast majority of studies have been conducted in the US and European countries, in which both CAC and cIMT/plaque have been shown to be associated with future risk of ASCVD, independent of conventional risk factors. Furthermore, these measures improve risk prediction when added to a global risk prediction model, such as the Framingham risk score. However, no clinical trial has assessed whether screening with CAC or cIMT/plaque will lead to improved clinical outcomes and healthcare costs. Interestingly, similar levels of CAC or cIMT/plaque among various regions and ethnic groups may in fact be associated with significantly different levels of absolute risk of ASCVD. Therefore, it remains to be determined whether measures of subclinical atherosclerosis improve risk prediction in non-US/European populations. Although CAC and cIMT/plaque are promising surrogates of ASCVD in research, we conclude that their use in clinical practice, especially as screening tools for primary prevention in asymptomatic adults, is premature due to many vagaries that remain to be clarified.

Key words: Subclinical atherosclerosis, Coronary artery calcium, Carotid intima-media thickness, Plaque, Primary prevention

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(1) Brief Overview of Atherosclerosis

Atherosclerosis, a chronic condition of the arterial wall, is a leading cause of death worldwide¹ and is characterized by the accumulation of lipids in arteries, leading to plaque formation and eventually to coronary heart disease (CHD) or stroke⁶. Various lifestyle-related factors that contribute to the development of atherosclerosis have been identified (called “risk factors”). These include elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol, increased local shear forces from elevated blood pressure, chemical toxins from cigarette smoke, insulin resistance, and glycosylated end-product formation in diabetes mellitus⁷. One of the widely-accepted models of plaque formation, LDL-initiated atherogenesis, is depicted in Fig. 1.

Many studies have demonstrated that atherosclerosis begins in early life⁴ and its prevalence and extent increases with age⁸. An autopsy study of 2,876 adolescents and young adults (aged 15–34 years old) in the United States (US) who died of external causes has reported some evidence of atherosclerosis in all individuals examined⁹. Atherosclerosis is therefore considered to have a long latent period prior to developing into a full-blown clinical disease, such as CHD, stroke, or other atherosclerotic cardiovascular disease (ASCVD). Measuring atherosclerosis at its subclinical
phase may have important implications for understanding its progression into clinical disease and for the possibility of early life intervention in clinical and public health practice. Intervention before and during preclinical phases of atherosclerosis may be an effective way of eliminating the vast majority of ASCVDs that occur in middle adulthood and late life.

(2) Subclinical Atherosclerosis

Today, a variety of invasive and non-invasive measures are available in assessing subclinical atherosclerosis. Conventional angiography is an invasive procedure that has been commonly used to assess presence and severity of luminal stenosis caused by atherosclerosis. In more recent years, similar information can be obtained with less invasive techniques. Computed tomography (CT) angiography with intravenous injection of a contrast media or magnetic resonance angiography with or without contrast media are examples of less-invasive procedures. An alternate, yet invasive, technique is intravascular ultrasound used to obtain detailed characteristics of plaque by utilizing a small ultrasound transducer which is placed at the tip of an intravascular catheter.

In this review paper, however, we primarily focus on two well-known measures of subclinical atherosclerosis: (1) coronary artery calcium (CAC) assessed by CT (Fig. 2), and (2) carotid artery intima-media thickness and plaque (cIMT/plaque) measured by ultrasonography (Fig. 3). These two measures have been utilized among studies of community-based asymptomatic populations due to their non-invasive nature and ease of administration. We have reviewed the available literature on these two measures and have largely focused on the utility of such measures in primary prevention of ASCVD.

(3) Basic Description of CAC and cIMT/Plaque

a) CAC

In the 1960s, calcification in the coronary arteries, identified by fluoroscopy, was found to positively correlate with prevalence of clinically significant coro-
A) CT images of coronary arteries:

B) Calculation of CAC score (Agatston Method):

Definition of calcified lesion:
1) $≥130$ Hounsfield Unit (HU) density
2) $≥1$ mm² Area of lesion

Weights assigned to lesion density:

| Lesion density | Weight | Lesion Score |
|----------------|--------|--------------|
| 130 to <200 HU | 1      | -            |
| 200 to <300 HU | 2      | Weight $\times$ Area of lesion (mm²) |
| 300 to <400 HU | 3      | -            |
| $≥400$ HU      | 4      | -            |

Total CAC Score: Sum of all lesion scores for all coronary CT slices (3mm)

Fig. 2. A) CT images of four different individuals with varying degrees of coronary artery calcium (CAC) and B) calculation of CAC score (Agatston method)

On CT image, calcification is expressed as a white lesion ($≥ 130$ Hounsfield Unit (HU)). Calcification in the left anterior descending artery is depicted by arrows. Ao = aorta, LA = left atrium.

Fig. 3. Visualization of the carotid artery

A) A simplified diagram of the carotid artery. The layers of the arterial wall are depicted, with the distance from the intima to the media-adventitia interface being intima-media thickness (IMT). IMT measurements of common carotid artery (CCA), bifurcation, and internal carotid artery (ICA) are often included in cIMT. B) An ultrasound image of the CCA, with the distance between arrow heads corresponding to IMT. C) A plaque found in the bifurcation of the carotid artery.
nary atherosclerotic lesions\(^6\). Decades later, quantification of CAC by CT emerged as a promising measure of subclinical atherosclerosis, and Agatston's method\(^7\) has become the most frequently employed quantitative protocol for CAC\(^8\). In this review, therefore, we define CAC scoring exclusively as Agatston's score. This score is obtained as a weighted sum of the area of calcification (\(\geq 1\) mm\(^2\)) with its density, measured in Hounsfield Units, having different weights for different densities (a denser calcification has higher Hounsfield Units and thus has as a greater weight)\(^7\) (Fig. 2). Histopathological studies on human coronary arteries have shown that the CAC assessed with electron-beam computed tomography (EBCT) was highly positively correlated with coronary plaque area\(^9, 10\). The area of calcium deposition, however, was much smaller than that of histological plaque\(^9\), and was poorly related to luminal narrowing and severity\(^10\). Regardless, a significant strong relationship was found between calcified area and plaque area within heart and within artery\(^10\). Thus, the amount of calcium is considered to be an “excellent method” for measuring overall magnitude of atherosclerotic plaque burden but not for identifying localized stenotic lesions\(^10\).

The exact mechanism of calcium deposition in atherosclerotic plaque remains to be elucidated. However, many researchers consider it an active process involving arterial osteoblasts and osteoclasts\(^11, 12\). Not surprisingly, CAC score was correlated with conventional coronary risk factors in a similar fashion to CHD in multiethnic groups in the US\(^13\), western, and Asian populations\(^14, 15\). In a study of Caucasian men in the US and Japanese men in Japan, a higher CAC score was more prevalent in men having more conventional risk factors (smoking, hypertension, dyslipidemia, overweight, and diabetes mellitus) in a broad age range, regardless of ethnicity or country (Fig. 4)\(^16\).

**Fig. 4.** Prevalence of CAC scores of 0-9, 10-99, 100-399, \(\geq 400\) according to number of risk factors in Japanese men in Japan (2006-2008) and Caucasian men in the US (2000-2002), aged 45 to 74 years. (Modified from Am J Epidemiol. 2014; 180 (6): 590-598.)

Crude prevalence of each CAC category was shown according to age group (45-54 y, 55-64 y, and 65-74 y) and number of 5 conventional risk factors assessed. Number of participants was given in parenthesis under each bar. Five risk factors: (A) Current smoking; (B) Overweight defined as body mass index \(\geq 25\) kg/m\(^2\); (C) Diabetes mellitus defined as fasting glucose \(\geq 126\) mg/dL or medication; (D) Hypertension defined as systolic/diastolic blood pressure \(\geq 140/90\) mmHg or medication; (E) Dyslipidemia defined as LDL-c \(\geq 160\) mg/dL or HDL-c < 40 mg/dL or medication.
b) cIMT/Plaque

The thickness of the two innermost layers of the arterial wall, intima and media, is referred to as cIMT (Fig. 3). The measurement of cIMT was initially used as a surrogate marker for CHD, as higher cIMT levels were found to be associated with increased risk of future coronary events\textsuperscript{17}. This was confirmed in later studies\textsuperscript{18, 19}. The relationship of cIMT with CHD can be explained in part by the shared common risk factors of carotid and coronary atherosclerosis\textsuperscript{17}. Moreover, based on autopsy results, cIMT measurement has been shown to be a reliable indicator of generalized atherosclerosis\textsuperscript{20}. The overall thickening of the intima-media layers is considered to represent development of vascular wall hypertrophy, intimal hyperplasia, and atherosclerotic plaque burden\textsuperscript{21}, which may have been caused by the effect of multiple risk factors, such as blood pressure and total cholesterol, on the carotid arterial wall over time\textsuperscript{21}.

Carotid plaque is often defined either subjectively, as a localized thickening of arterial layer\textsuperscript{22} or in terms of cIMT, eg. cIMT > 1 mm\textsuperscript{23} or cIMT > 1.5 mm\textsuperscript{24}. Like cIMT, carotid plaque is measured from ultrasound images (Fig. 3C), depicts the level of atherosclerotic burden in the carotid arteries, and is a predictor of ASCVD events\textsuperscript{22, 25}. Thus, due to the evident overlap of cIMT and plaque, we make no general distinction between these two measures in this review, although some differences are discussed in a later paragraph.

Examination of cIMT/plaque by high-resolution B-mode ultrasonography is non-invasive, inexpensive, repeatable, and provides quantitative measures of structural changes in the arterial wall\textsuperscript{17, 26}. Because of these advantages, measurement of cIMT/plaque has been proposed in clinical routine for early screening of asymptomatic individuals\textsuperscript{19} to further reduce CHD events in the general population\textsuperscript{20}.

(4) Utility of CAC and cIMT/Plaque

The uses of CAC and cIMT/plaque will be assessed under different categories: as predictors of ASCVD for primary prevention, as predictors of ASCVD in high-risk populations, and as quantitative measures of atherosclerotic burden or a surrogate for clinical event.

a) As Predictors of ASCVD for Primary Prevention

For the primary prevention of ASCVD in asymptomatic adults, clinical guidelines are typically based on traditional risk factors, such as age, sex, blood lipid levels, blood pressure, diabetes mellitus, and smoking. These risk factors are incorporated into a prediction model, which estimates an individual’s absolute risk of developing ASCVD. The Framingham risk score in the US\textsuperscript{27}, SCORE in Europe\textsuperscript{28}, and NIPPON DATA80 Risk Assessment Chart and Suita Score in Japan\textsuperscript{29, 30} are all examples of such prediction models. The estimated risk obtained from these models helps both patients and health care providers to make a decision regarding the degree of aggressive management required of a patient’s risk factors, such as administering a specific dose-range of statin therapy. Measures of subclinical atherosclerosis have been suggested as novel ways to identify individuals who will benefit from aggressive management of risk factors. In order for a measure to be useful in clinical management, however, it needs to satisfy the following three phases of evidence: [Phase A] a measure is shown to predict ASCVD events independent of conventional risk factors (independent association); [Phase B] a measure is shown to improve prediction of ASCVD events when added to an existing prediction model (improved prediction); [Phase C] a measure-guided management strategy is shown to lower ASCVD events (improved outcome). Moreover, the overall benefit of such screening, including reduced ASCVD events and future health costs, should reasonably outweigh potential disadvantages, such as the cost of implementation and other consequences related to false positives, false negatives, and incidental findings\textsuperscript{31}.

Studies in US and Europe

In population studies of asymptomatic individuals conducted in US and other western countries, CAC and cIMT/plaque have been shown to be associated with not only CHD, but also stroke and/or other ASCVD\textsuperscript{19, 32-34}. These associations were maintained even after accounting for traditional risk factors\textsuperscript{35, 36} (Phase A: independent association). Additionally, both CAC and cIMT/plaque have been shown to improve risk prediction of cardiovascular events in people with intermediate risk and properly reclassifying them into higher or lower risk groups\textsuperscript{35, 36} (Phase B: improved prediction). Nevertheless, CAC appeared to be one of the most promising predictors for CHD in US/western populations in refining risk prediction among individuals at intermediate risk based in part on head-to-head comparative studies on CAC, cIMT, and other novel markers\textsuperscript{37, 38}. Both American and European clinical guidelines, targeted for the general population, recommend CAC, but not cIMT/plaque, as an adjunctive tool in management of modifiable risk factors of an individual at moderate/intermediate risk for CHD/ASCVD\textsuperscript{39, 40}. However, in the 2013 ACC/AHA Prevention Guidelines, the task force acknowledges that their recommendation of CAC is only an
expert opinion as none of these measures (CAC/cIMT/plaque or other promising markers identified) had been properly assessed in randomized controlled trials, having clinical events as outcomes\textsuperscript{31, 39} (i.e., not meeting Phase C: improved outcome).

**Studies in Asia**

There are considerably fewer studies on CAC and cIMT/plaque in Asian populations, including Japan, in comparison to western ones. For a population-based sample in Asia, we were unable to find studies that examined whether CAC score predicts future ASCVD in a graded fashion. One study on cIMT/plaque, however, has found that cIMT/plaque was independently associated with an increased risk of stroke in a general population of elderly Japanese men\textsuperscript{41}. Japanese are characteristically known for having lower risk of CHD than western populations\textsuperscript{42}; thus, studies on CHD in Japan are limited due to the large sample size needed for an adequate number of cases for analysis.

However, the ongoing westernization of lifestyle in Japan may translate into a trend of increased CHD\textsuperscript{43, 44}. This was foreshadowed in migrant studies of ethnic Japanese populations in the 1970’s, where migration to the US (synonymously, a change to a western lifestyle) was linked to an increased risk of CHD\textsuperscript{55} and was likely due to a change in environmental factors, such as increased intake of animal fat, saturated fatty acid, and simple sugars\textsuperscript{46}, and less strenuous physical activity\textsuperscript{45}. Thus, subclinical atherosclerosis assessment may be important in the prevention of CHD in Japan.

To date, no study in East Asia has reported that the inclusion of CAC or cIMT/plaque in a risk prediction model improves coronary risk prediction in an asymptomatic general population (Phase B). Thus, no clinical guidelines for primary prevention in Japan have been recommended for or against the use of CAC or cIMT/plaque.

**b) Studies in Asia in High Risk Populations (as Predictors)**

**CAC**

Hospital-based studies in Japan\textsuperscript{47} and Korea\textsuperscript{48} have shown a graded or positive association of CAC with ASCVD events. The participants of these studies were at higher risk of CHD than the general population. A longitudinal study on 5,182 asymptomatic patients in Korea, for example, showed an association of CAC with ASCVD events (cardiac death, acute coronary syndrome, and stroke) during median follow-up of 48 months\textsuperscript{49}. The association was independent of Framingham risk score and high sensitive C-reactive protein. Another hospital-based longitudinal study in Japan has shown that among patients with suspected CHD, baseline CAC had a graded relation with all coronary events, including cardiac death, non-fatal myocardial infarction and late coronary revascularization (\textgreater{} 3 months after baseline CT) during a mean follow-up of 4 years\textsuperscript{50}. Annual rate for the composite endpoints were 0.3\%, 1.0\%, 2.5\% and 4.0\% in the patients with a CAC score of 0, 1–99, 100–399, and 400 or greater, respectively. The corresponding adjusted hazard ratios [95\% confidence interval] were 1.0 (reference), 3.08 [0.89, 14.1], 7.07 [2.13, 32.1], and 9.29 [2.68, 43.4], respectively after multi-variable adjustment\textsuperscript{51}. Such findings suggest that CAC may help a clinician to identify patients at higher risk\textsuperscript{50} who may require more aggressive diagnostic procedures and treatments, such as coronary angiography and subsequent angioplasty.

**cIMT/Plaque**

In a high-risk Japanese population, cIMT has been confirmed to be an independent predictor of overall cardiovascular events, including myocardial infarction, ischemic or hemorrhagic stroke, unstable angina, or therapeutic/surgical intervention for coronary or peripheral artery diseases. High-risk individuals in the highest cIMT tertile (> 1.18 mm) had a relative risk [95\% confidence interval] of 3.6 [1.4, 9.0] for overall cardiovascular events (stated above) compared to individuals in the lowest cIMT tertile (< 0.90 mm). Similarly, in diabetic Japanese patients, baseline cIMT was positively associated with incident nonfatal CHD, including angina pectoris or nonfatal myocardial infarction, independent of traditional vascular risk factors\textsuperscript{52}. Furthermore, cIMT in combination with Framingham Risk Score has been shown to improve prediction of cardiovascular events in Japanese diabetic patients\textsuperscript{54}. Thus, similar to the findings in western studies, cIMT/plaque are associated with traditional vascular risk factors and events in Japanese studies.

c**c) As Measures of Atherosclerotic Burden or a Surrogate for Clinical Event**

**CAC**

CAC is also used as a quantitative measure of overall atherosclerotic burden and as a surrogate for ASCVD in epidemiological studies. For example, a sample of Japanese men aged 40–49 years was shown to have less subclinical atherosclerosis (i.e., CAC) as compared to that of white men in Pittsburgh\textsuperscript{55} or Japanese-American men in Honolulu\textsuperscript{56} within the same age group, even after accounting for differences in traditional risk factors. The authors have suggested
further studies to identify factors that protect against atherosclerosis in Japanese men. Another example is a population-based study in China that has reported a 2.5 to 3 times higher CAC score in the northern city of Beijing as compared to those in southern cities, which is consistent with higher incident CHD in northern compared to southern areas in China\textsuperscript{57}. The authors have concluded that use of CAC score as a surrogate for CHD can be validly applied in epidemiological studies\textsuperscript{57}. Based on a cross-sectional design comparing CAC (as a surrogate) and estimated risk by a prediction model, Korean researchers have also reported that CAC score provides additional information beyond conventional prediction models\textsuperscript{14, 58}).

**cIMT/Plaque**

Similar to CAC, investigators have been using cIMT/plaque as a surrogate for ASCVD and as a measure of atherosclerotic burden. For example, cIMT/plaque have been recently shown to be associated with serum concentrations of HDL-particle and LDL-particle, independent of traditional lipid profiles and risk factors\textsuperscript{59, 60}). The authors have suggested that the association of cIMT/plaque with lipid particles may reflect unknown but important roles of these particles related to atherosclerotic plaque formation beyond traditional lipid profiles (e.g., HDL-cholesterol, LDL-cholesterol).

Also, a population-based study of men has shown that cIMT/plaque was concordant with 10-year estimated risk strata of CHD mortality\textsuperscript{61}, as described by the Japan Atherosclerosis Society guidelines, 2012\textsuperscript{62}).

Thus, the use of CAC or cIMT/plaque can provide researchers important insight into discerning the pathogenesis of atherosclerosis, understanding ecological differences in ASCVD risk, and possibly forecasting clinical events.

(5) Other Topics

a) Progression

**CAC**

A longitudinal study from the multi-ethnic study of atherosclerosis (MESA) in the US (median follow-up of 7.6 years) has reported that progression of CAC alone predicts increased risk of myocardial infarction and fatal CHD, collectively defined as “hard CHD.” Among persons with CAC score $= 0$ at baseline, a 5-unit annual change in CAC was associated with an adjusted hazard ratio of 1.5 (95%CI 1.1 to 2.1) for hard CHD. Among those with CAC score $> 0$ at baseline, the hazard ratio (per 100 unit annual change) was 1.3 (1.1 to 1.5)\textsuperscript{63}.

It remains uncertain whether CAC can regress significantly as a consequence of improved risk factors. Some evidence, however, suggests otherwise, i.e., the denser the calcium deposition in plaques, the less ASCVD risk\textsuperscript{64}). For example, randomized trials of statin therapy have reported a tendency for the statin group to have higher CAC score than placebo group after intervention\textsuperscript{65, 66}). Nevertheless, it may be reasonable to assume that CAC is cumulative, and may only progress, but rarely regress. If this is the case, CAC may be a stronger predictor of ASCVD than any combination of risk factors measured at a single time point since traditional risk factors, such as blood pressure, lipid concentrations and smoking status, may fluctuate or vary over time. This concept is supported by a study from the Honolulu Heart Program, in which a graded relationship of CAC with risk of death in the very old was reported. Among all of the cardiovascular risk factors examined, CAC was the only measure having a significant relationship with death\textsuperscript{67}.

**cIMT/Plaque**

Whether actual changes in cIMT translate to alterations in ASCVD risk is under debate\textsuperscript{68-70}). Several individual studies have found that cIMT progression was significantly delayed with effective cardiovascular drug therapies, such as statins\textsuperscript{71, 72}). However, meta-analyses assessing randomized controlled trials and observational studies on cIMT progression in general and high risk populations have found that regression or slowed progression of cIMT do not translate to reductions in cardiovascular events\textsuperscript{69, 73}). Thus, the 2013 American College of Cardiology/American Heart Association Task Force\textsuperscript{39) as well as the 2016 European guidelines on cardiovascular disease prevention\textsuperscript{74) do not recommend the routine measurement of cIMT for ASCVD risk assessment in clinical practice.

b) Comparison between CAC and cIMT/Plaque

Despite the ability of both cIMT/plaque and CAC to independently predict ASCVD events, with CAC being a better predictor\textsuperscript{57}, they are likely to be different measures of the atherosclerotic phenotype. CAC looks directly at an area of CHD occurrence, the entire arterial bed in the body, especially the coronaries. Also, calcified plaques may be indicative of older or advanced plaques and thus longer time of atherosclerotic burden on the heart, which would undoubtedly coincide with increased CHD risk. Although cIMT can also directly visualize macroscopic processes of atherosclerosis in carotid arterial walls\textsuperscript{68}), the defini-
tion of cIMT may completely alter this ability. Measurements on different segments or walls of the artery, in conjunction with the use of different software, lead to very different variables, all of which have been referred to as cIMT. This lack of standardization of cIMT may have contributed to its weaker association to ASCVD in comparison to CAC and will be discussed in a later section. The consistent predictive ability of CAC can be attributed in part to its standardized methodology (Agatston score) with reasonable reproducibility regardless of CT type (EBCT vs standard CT). Given the methodological and standardization issues with cIMT measurement, carotid plaque alone has been advocated as a more accurate predictor of ASCVD, demonstrating improvement in risk prediction beyond the Framingham Risk Score.

c) Areas of Uncertainty and Unresolved Issues

Calcium Density

As described earlier, recent data suggest that increased calcium density in coronary plaque may be protective for CHD events, the opposite assumption made in Agatston’s scoring method. Dense calcium deposition without a large lipid core may increase the stability of atherosclerotic plaques. However, this phenomenon may be age-dependent and must be further explored in future studies.

Standardization of cIMT

The lack of standardization in protocol presents a major problem for cIMT as a screening tool of subclinical atherosclerosis. The common method of cIMT measurement is B-mode ultrasound of both left and right common carotid arteries. Because ultrasound equipment is safe, cost effective, and feasible, many researchers worldwide have utilized cIMT/plaque in their studies. Unfortunately, this has led to poor standardized methodology and an inconsistent definition of cIMT. Although many have strongly recommended and some have attempted, presently, there is no consensus on the appropriate methodology for measuring and calculating cIMT. Some of the widely used definitions of cIMT include the following measurements of the left and right carotid arteries: (1) Mean of IMT of entire carotid tree, including common carotid artery (CCA), bifurcation and internal carotid artery (ICA). (2) Only mean IMT of CCA. (3) Mean of all maximal values in the carotid tree. (4) Single highest value of all IMT values in the carotid tree.

Different definitions of cIMT and, consequently, measurement of different segments of the carotid tree may represent different phenotypes. The CCA IMT is more related to hypertension, blood pressure, and vascular hypertrophy, rather than atherosclerotic plaques, which are more often found in ICA and bifurcation. In support of this, CCA IMT is more directly associated with prevalent stroke, whereas the bifurcation IMT is associated with prevalent CHD. Moreover, cIMT measurements have improved diagnostic accuracy when they involve measurements of the bifurcation or ICA in addition to the CCA. Because CCA measurements are generally more stable and reproducible than those of ICA or bifurcation, they have been more commonly used in cIMT measurements. Also, carotid tree segments, as assessed in different clinical studies, do not always correspond to the same length or location on the carotid tree. In fact, some do not even overlap. Altogether, this has led to the inability to generate universal or regional population reference or cut-off values for cIMT in prediction of CHD risk.

Further contributing to the vague definition of cIMT, mean and maximum values have been reported. Mean measurements of cIMT in any or all segments represent a generalized wall thickening, incorporating both hypertension-related stress and plaques, while maximum measurements are an index of focal plaque. The final occurrence of clinical ASCVD endpoints may be more closely linked to plaque rather than generalized carotid wall thickening.

Standardization of protocol is needed in order to properly assess whether cIMT should be implemented in clinical practice for subclinical atherosclerosis screening.

Issues of Screening for Subclinical Atherosclerosis

It is premature to advocate for subclinical atherosclerosis screening by CAC or cIMT/plaque in a general population. Before considering such screening, there are several important issues to consider.

In general, one major drawback of routine clinical screening is overdiagnosis, or “pseudo-disease.” This is a term referring to a situation in which early diagnosis is made, but does not lead to a reduction in clinical disease. Besides, positive results from a screening test may lead to an increase in medication, diagnostic procedures, and invasive treatments, all of which will increase healthcare costs and patient distress. Ideally, whether the potential drawbacks outweigh the expected benefits (reduction in cardiovascular events and future health costs) need to be properly assessed in randomized controlled trials.

In addition, specific to CAC, one of the main concerns of patient harm is exposure to ionizing radiation. Estimated radiation doses per one time CAC scan range from 0.8 to 10.5 (median of 2.3) mSv.
according to a study published in 2009. Recent technical advancements, however, allow for significant reduction in the exposure to a one-time dose of as low as 0.2 mSv, which is lower than those of other screening tests, such as mammography for breast cancer (0.7 mSv) or CT-scan for lung cancer (1–2 mSv). Nevertheless, screening for CAC using computed tomography should also consider the concomitant accumulation of exposures to ionizing radiation from other sources including iatrogenic sources. In one report estimating iatrogenic radiation exposure among 15 developed countries, Japan had one of the highest cumulative cancer risk attributed to diagnostic X-ray. As with the importance of knowing about medication usage, it is equally prudent to ask patients or study subjects about recent radiographic procedures that were received prior to CAC screening.

(6) Future Direction

As discussed earlier, we call for further studies to clarify the role of CAC and cIMT/plaque as a screening tool for primary prevention (randomized controlled trials). We also propose standardization of protocol in cIMT/plaque measurement before it can be considered as a consistent measure of subclinical atherosclerosis.

Moreover, the association between the extent of these measures and ethnic/region-specific absolute risk of ASCVD needs to be examined, especially in non-western regions. Orakzai and colleagues have suggested further studies to examine the relationship between CAC and the incidence of CHD in various geographical locations outside the US. This is because they noted discrepancies between prevalence of CHD risk factors (lower in US) and the prevalence of CAC (greater in US). There is a possibility that similar CAC score among various regions is associated with significantly different absolute risk of ASCVD and, thus, a universal cut-off value of CAC score for increased risk may not be possible. Similarly, in Japanese populations, cIMT is generally lower than that of Caucasians in the US, and so, cut-off values of cIMT for risk prediction obtained from western studies may not be appropriate for the Japanese population or other Asian populations. Abnormal values of cIMT also depend on the methodology used for IMT measurements. As cIMT values are strongly affected by age, sex and population, age-, sex- and country-specific IMT cut-offs would be needed prior to clinical implementation of cIMT/plaque screening for improved estimates of individual risk. As is the case, cutoff values for high cIMT or presence of plaque recommended by the Japanese Society of Ultrasonics in Medicine differ from western ones, most notably, the definition of plaque, in terms of cIMT, in the carotid arteries (cIMT ≥ 1.1 mm or > 1 mm) is lower than those in European or American guidelines (cIMT > 1.5 mm).

Without ethnic or region-specific information on the extent of the relationship of CAC or cIMT/plaque with absolute risk of ASCVD, ecological comparisons of those subclinical measures are limited in interpretability. We suggest that future population-based studies, especially among non-western regions, need to document absolute risk of ASCVD in relation to measures of subclinical atherosclerosis in a way that is well-described and comparable to other studies. Adopting commonly-used cutoffs of CAC score (such as 0, 100, 300, or 400) or providing both segment-specific and total results of cIMT/plaque are examples of desired descriptions of future studies. Such studies also need to rigorously document characteristics of a studied sample, such as detailed information on traditional vascular risk factors, for the purpose of comparison with other studies.

(7) Conclusion

Given the worldwide endemic of ASCVD, CAC and cIMT/plaque are promising measures of subclinical atherosclerosis in research. Based on population-based observational studies conducted in western countries, CAC and cIMT/plaque are known to improve prediction of ASCVD when added to traditional risk prediction models. However, there is a great need for further studies to assess the usefulness and safety of these measures as screening tools for the general population. Until vagaries in their clinical usefulness are clarified, their use in clinical and public health practice is premature.

Conflict of Interest (COI)

All authors declare no conflict of interest.

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