J Atheroscler Thromb, 2017; 24: 227-239.
doi: 10.5551/jat.RV16005

Review

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

Maryam Zaid[1], Akira Fujiyoshi[2], Aya Kadota[1, 2], Robert D.Abbott[1] and Katsuyuki Miura[1, 2]

Maryam Zaid and Akira Fujiyoshi contributed equally to this work.

[1]Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Shiga, Japan
[2]Department of Public Health, Shiga University of Medical Science, Shiga, Japan

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

(1) Brief Overview of Atherosclerosis

Atherosclerosis, a chronic condition of the arterial wall, is a leading cause of death worldwide[1)] and is characterized by the accumulation of lipids in arteries, leading to plaque formation and eventually to coronary heart disease (CHD) or stroke[2)]. 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 mellitus[3)]. 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 life[4)] and its prevalence and extent increases with age[5)]. 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 examined[5)]. 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

Address for correspondence: Akira Fujiyoshi, Department of Public Health, Shiga University of Medical Science, Seta Tuskinowa-cho, Otsu, Shiga, Japan, 520-2192
E-mail: afujiy@belle.shiga-med.ac.jp
Received: August 29, 2016
Accepted for publication: October 19, 2016

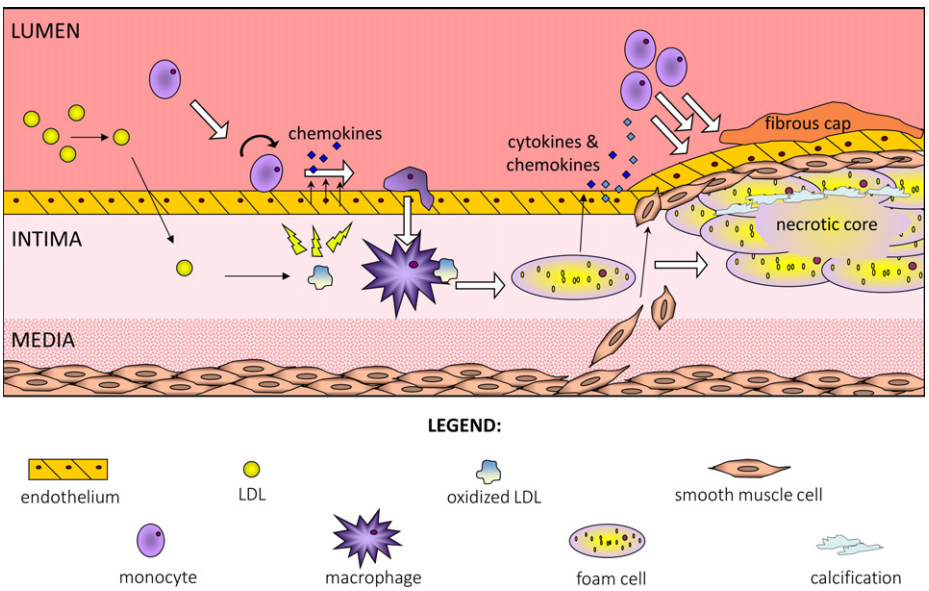


Fig. 1. A schematic of the theoretical LDL-initiated formation of atherosclerotic plaques in the arterial wall

A high concentration of circulating LDL causes damage to the arterial wall and allows for entry and oxidization of LDL in the intimal layer. This leads to the secretion of chemokines and expression of leukocyte adhesion markers by endothelial cells. Monocytes are recruited to the site of injury. Once inside the intima, monocytes differentiate into macrophages and engulf the oxidized LDL. Continual uptake of oxidized LDL (due to prolonged high levels of circulating LDL) causes macrophages to become lipid-laden foam cells. Foam cells remain in the intima, secrete pro-inflammatory cytokines and chemokines, thus recruiting more monocytes. Dying foam cells lead to the formation of the necrotic core, which may become calcified. Smooth muscle cells migrate to the lipid pool of foam cells in an attempt to stabilize the plaque, however, local macrophages secrete enzymes that degrade the fibrous cap, causing the plaque to be vulnerable to rupture. Once ruptured, thrombosis ensues and may lead to myocardial infarction or stroke.

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.

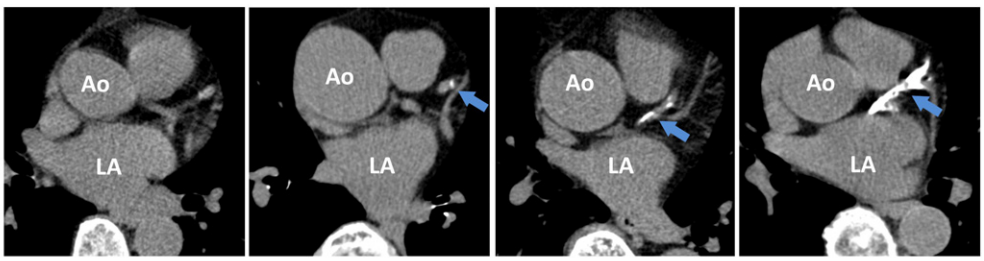
In this review paper, however, we primarily focus on two well-known measures of subclinical atherosclerosis: (1) coronary artery calcium (CAC) assessed by CT (**Fig. 2**), and (2) carotid artery intima-media thickness and plaque (cIMT/plaque) measured by ultrasonography (**Fig. 3**). These two measures 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) ≥1mm^2 Area of lesion

Weights assigned to lesion density:

Lesion density	Weight	Lesion Score
130 to <200 HU	1	= Weight × Area of lesion (mm^2)
200 to <300 HU	2	
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.

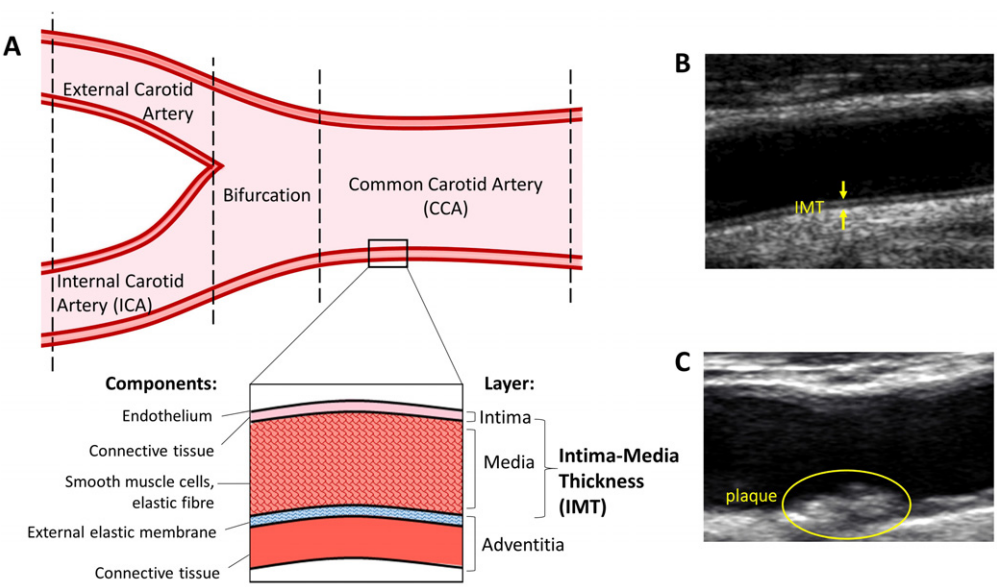


Fig. 3. Visualization of the carotid artery

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.

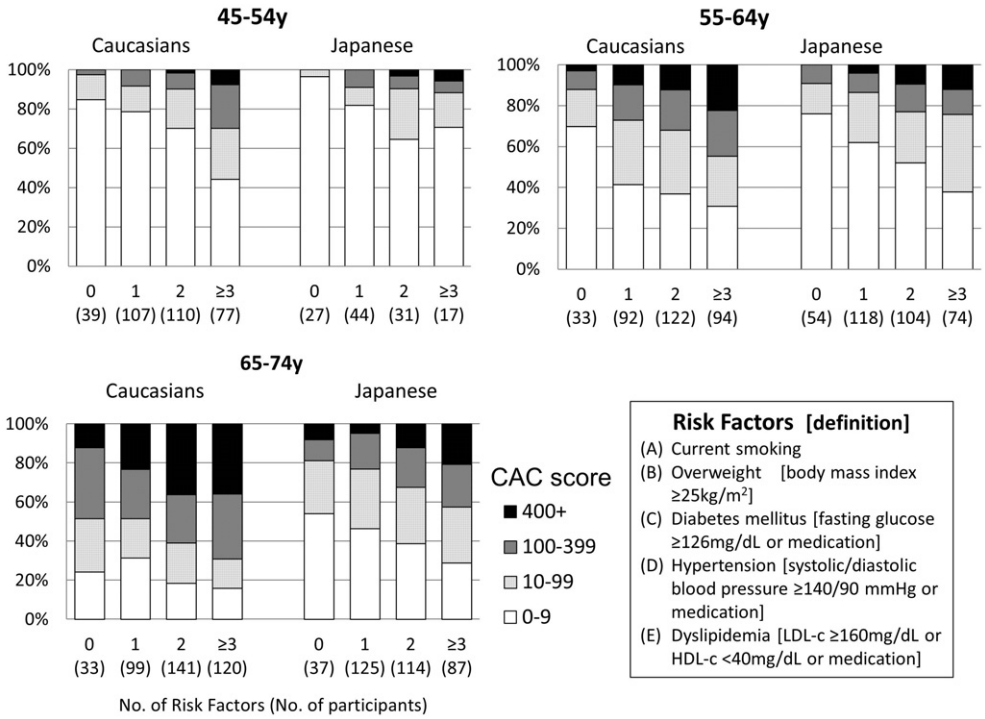


Fig. 4. Prevalence of CAC scores of 0-9, 10-99, 100-399, ≥ 400 according to number of risk factors in Japanese men in Japan (2006-2008) and Caucasian men in the US (2000-2002), aged 45 to 74 years. (Modified from Am J Epidemiol. 2014; 180 (6): 590-598.)

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 ≥ 25 kg/m^2; (C) Diabetes mellitus defined as fasting glucose ≥ 126 mg/dL or medication; (D) Hypertension defined as systolic/diastolic blood pressure ≥ 140/90 mmHg or medication; (E) Dyslipidemia defined as LDL-c ≥ 160 mg/dL or HDL-c < 40 mg/dL or medication.

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 (≥ 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]. This is in contrast to a passive process of calcification occurring in arterial medial layers (known as "Mönckeberg's sclerosis") that is associated with advanced tissue degeneration[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].

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[17]. This was confirmed in later studies[18, 19]. The relationship of cIMT with CHD can be explained in part by the shared common risk factors of carotid and coronary atherosclerosis[17]. Moreover, based on autopsy results, cIMT measurement has been shown to be a reliable indicator of generalized atherosclerosis[20]. The overall thickening of the intima-media layers is considered to represent development of vascular wall hypertrophy, intimal hyperplasia, and atherosclerotic plaque burden[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[21].

Carotid plaque is often defined either subjectively, as a localized thickening of arterial layer[22] or in terms of cIMT, eg. cIMT >1 mm[23] or cIMT >1.5 mm[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[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[17, 26]. Because of these advantages, measurement of cIMT/plaque has been proposed in clinical routine for early screening of asymptomatic individuals[19] to further reduce CHD events in the general population[21].

(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[27], SCORE in Europe[28], and NIPPON DATA80 Risk Assessment Chart and Suita Score in Japan[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[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[19, 32-34]. These associations were maintained even after accounting for traditional risk factors[33, 34] (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[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[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[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[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[41]. Japanese are characteristically known for having lower risk of CHD than western populations[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[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[45] and was likely due to a change in environmental factors, such as increased intake of animal fat, saturated fatty acid, and simple sugars[46], and less strenuous physical activity[43]. 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[47] and Korea[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[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 (>3 months after baseline CT) during a mean follow-up of 4 years[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[51]. Such findings suggest that CAC may help a clinician to identify patients at higher risk[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)[52]. 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[53]. Furthermore, cIMT in combination with Framingham Risk Score has been shown to improve prediction of cardiovascular events in Japanese diabetic patients[54]. Thus, similar to the findings in western studies, cIMT/plaque are associated with traditional vascular risk factors and events in Japanese studies.

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[55] or Japanese-American men in Honolulu[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[57]. The authors have concluded that use of CAC score as a surrogate for CHD can be validly applied in epidemiological studies[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[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[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[61], as described by the Japan Atherosclerosis Society guidelines, 2012[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)[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[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[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[67].

cIMT/Plaque

Whether actual changes in cIMT translate to alterations in ASCVD risk is under debate[68-70]. Several individual studies have found that cIMT progression was significantly delayed with effective cardiovascular drug therapies, such as statins[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[69, 73]. Thus, the 2013 American College of Cardiology/American Heart Association Task Force[39] as well as the 2016 European guidelines on cardiovascular disease prevention[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[37], they are likely to be different measures of the atherosclerotic phenotype. CAC looks directly at an area of CHD occurrence, the coronary arteries, rather than a surrogate location, as in cIMT. The use of cIMT measurement assumes that injuries in the carotid wall are representative of 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[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[75]. 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 MDCT)[76].

Given the methodological and standardization issues with cIMT measurement, carotid plaque alone has been advocated as a more accurate predictor of ASCVD[25], demonstrating improvement in risk prediction beyond the Framingham Risk Score[22].

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[8].

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 carotid arteries. Because ultrasound equipment is safe, cost effective, and feasible, many researchers worldwide have utilized cIMT/plaque in their studies[36]. Unfortunately, this has led to poor standardized methodology and an inconsistent definition of cIMT[70]. Although many have strongly recommended[19, 24] and some have attempted[77], 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)[36, 61]. (2) Only mean IMT of CCA[77]. (3) Mean of all maximal values in the carotid tree[18]. (4) Single highest value of all IMT values in the carotid tree[75].

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[78], rather than atherosclerotic plaques, which are more often found in ICA and bifurcation[70, 79]. In support of this, CCA IMT is more directly associated with prevalent stroke, whereas the bifurcation IMT is associated with prevalent CHD[80]. Moreover, cIMT measurements have improved diagnostic accuracy when they involve measurements of the bifurcation or ICA in addition to the CCA[25]. Because CCA measurements are generally more stable and reproducible than those of ICA or bifurcation[21], they have been more commonly used in cIMT measurements[79]. 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[19]. Altogether, this has led to the inability to generate universal or regional population reference or cut-off values for cIMT[81] 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[21]. The final occurrence of clinical ASCVD endpoints may be more closely linked to plaque rather than generalized carotid wall thickening[70].

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[82]. 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[83]. 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 test, such as mammography for breast cancer (0.7 mSv) or CT-scan for lung cancer (1–2 mSv)[84]. 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[85]. 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)[86]. There is a possibility that similar CAC score among various regions is associated with significantly different absolute risk of ASCVD[87] 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[88], 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[81]. Abnormal values of cIMT also depend on the methodology used for IMT measurements[21]. 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[70]. 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)[23] is lower than those in European[24] or American guidelines[22] (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[31]. 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.

References

1) Barquera S, Pedroza-Tobias A, Medina C, Hernandez-Barrera L, Bibbins-Domingo K, Lozano R, Moran AE: Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. Arch Med Res, 2015; 46: 328-338
2) Hansson GK, Libby P: The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol, 2006; 6: 508-519
3) Toth PP: Subclinical atherosclerosis: what it is, what it means and what we can do about it. Int J Clin Pract, 2008; 62: 1246-1254
4) McNamara JJ, Molot MA, Stremple JF, Cutting RT: Coronary artery disease in combat casualties in Vietnam.

JAMA, 1971; 216: 1185-1187
5) Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP, 3rd, Herderick EE, Cornhill JF: Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA, 1999; 281: 727-735
6) Eggen DA, Strong JP, McGill HC, Jr.: Coronary calcification. Relationship to clinically significant coronary lesions and race, sex, and topographic distribution. Circulation, 1965; 32: 948-955
7) Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol, 1990; 15: 827-832
8) Alluri K, Joshi PH, Henry TS, Blumenthal RS, Nasir K, Blaha MJ: Scoring of coronary artery calcium scans: history, assumptions, current limitations, and future directions. Atherosclerosis, 2015; 239: 109-117
9) Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS: Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation, 1995; 92: 2157-2162
10) Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS: Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. Journal of the American College of Cardiology, 1998; 31: 126-133
11) Doherty TM, Asotra K, Fitzpatrick LA, Qiao JH, Wilkin DJ, Detrano RC, Dunstan CR, Shah PK, Rajavashisth TB: Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proc Natl Acad Sci U S A, 2003; 100: 11201-11206
12) Towler DA: Vascular calcification: A perspective on an imminent disease epidemic. IBMS BoneKEy, 2008; 5: 41-58
13) Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF: Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation, 2005; 111: 1313-1320
14) Sung J, Lim SJ, Choe Y, Choi YH, Lee MK, Lee SH, Hong KP, Park JE: Comparison of the coronary calcium score with the estimated coronary risk. Coron Artery Dis, 2008; 19: 475-479
15) Park HE, Kim MK, Choi SY, Lee W, Shin CS, Cho SH, Oh BH: The prevalence and distribution of coronary artery calcium in asymptomatic Korean population. Int J Cardiovasc Imaging, 2012; 28: 1227-1235
16) Fujiyoshi A, Miura K, Ohkubo T, Kadowaki T, Kadowaki S, Zaid M, Hisamatsu T, Sekikawa A, Budoff MJ, Liu K, Ueshima H for the SESSA and MESA Research Groups: Cross-sectional comparison of coronary artery calcium scores between Caucasian men in the United States and Japanese men in Japan: the multi-ethnic study of atherosclerosis and the Shiga epidemiological study of subclinical atherosclerosis. Am J Epidemiol, 2014; 180: 590-598
17) Salonen JT, Salonen R: Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb, 1991; 11: 1245-1249
18) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE: Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation, 1997; 96: 1432-1437
19) Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M: Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation, 2007; 115: 459-467
20) Iwakiri T, Yano Y, Sato Y, Hatakeyama K, Marutsuka K, Fujimoto S, Kitamura K, Kario K, Asada Y: Usefulness of carotid intima-media thickness measurement as an indicator of generalized atherosclerosis: findings from autopsy analysis. Atherosclerosis, 2012; 225: 359-362
21) Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J: Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens, 2002; 20: 159-169
22) Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, O'Leary DH: The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. J Am Heart Assoc, 2013; 2: e000087
23) Katakami N, Kaneto H, Shimomura I: Carotid ultrasonography: A potent tool for better clinical practice in diagnosis of atherosclerosis in diabetic patients. J Diabetes Investig, 2014; 5: 3-13
24) Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Jaff M, Kownator S, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS, Zannad F, Zureik M: Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis, 2007; 23: 75-80
25) Inaba Y, Chen JA, Bergmann SR: Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis, 2012; 220: 128-133
26) Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation, 1986; 74: 1399-1406
27) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. Circulation, 1998; 97: 1837-1847
28) Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM and group Sp: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J, 2003; 24: 987-1003
29) NIPPON DATA80 Research Group: Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J, 2006; 70: 1249-1255

30) Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y: Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study. J Atheroscler Thromb, 2014; 21: 784-798
31) Polonsky TS, Greenland P: CVD screening in low-risk, asymptomatic adults: clinical trials needed. Nat Rev Cardiol, 2012; 9: 599-604
32) Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol, 1997; 146: 483-494
33) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr.: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med, 1999; 340: 14-22
34) Gibson AO, Blaha MJ, Arnan MK, Sacco RL, Szklo M, Herrington DM, Yeboah J: Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. JACC Cardiovasc Imaging, 2014; 7: 1108-1115
35) Baldassarre D, Amato M, Pustina L, Castelnuovo S, Sanvito S, Gerosa L, Veglia F, Keidar S, Tremoli E, Sirtori CR: Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events. Atherosclerosis, 2007; 191: 403-408
36) Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM: Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol, 2010; 55: 1600-1607
37) Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, Budoff MJ, Liu K, Shea S, Szklo M, Tracy RP, Watson KE, Burke GL: Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med, 2008; 168: 1333-1339
38) Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC: Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med, 2012; 156: 438-444
39) Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G: 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129: S49-73
40) Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, European Association for Cardiovascular P, Rehabilitation and Guidelines ESC-CfP: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J, 2012; 33: 1635-1701
41) Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, Shimamoto T: Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke, 2004; 35: 2788-2794
42) Ueshima H: Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb, 2007; 14: 278-286
43) Watanabe H, Yamane K, Egusa G, Kohno N: Influence of westernization of lifestyle on the progression of IMT in Japanese. J Atheroscler Thromb, 2004; 11: 330-334
44) Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Abbott RD, Ueshima H: Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI Registry, 1990-2001. Am J Epidemiol, 2008; 167: 1358-1364
45) Robertson TL, Kato H, Rhoads GG, Kagan A, Marmot M, Syme SL, Gordon T, Worth RM, Belsky JL, Dock DS, Miyanishi M, Kawamoto S: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. Am J Cardiol, 1977; 39: 239-243
46) Egusa G, Murakami F, Ito C, Matsumoto Y, Kado S, Okamura M, Mori H, Yamane K, Hara H, Yamakido M: Westernized food habits and concentrations of serum lipids in the Japanese. Atherosclerosis, 1993; 100: 249-255
47) Fujimoto S, Kondo T, Kumamaru KK, Shinozaki T, Takamura K, Kawaguchi Y, Matsumori R, Hiki M, Miyauchi K, Daida H, Rybicki FJ: Prognostic Value of Coronary Computed Tomography (CT) Angiography and Coronary Artery Calcium Score Performed Before Revascularization. J Am Heart Assoc, 2015; 4: e002264
48) Lee JH, B OH, Han D, Park HE, Choi SY, Sung J, Chang HJ: Reassessing the Usefulness of Coronary Artery Calcium Score among Varying Racial and Ethnic Groups by Geographic Locations: Relevance of the Korea Initiatives on Coronary Artery Calcification Registry. J Cardiovasc Ultrasound, 2015; 23: 195-203
49) Park HE, Chun EJ, Choi SI, Lee SP, Yoon CH, Kim HK, Youn TJ, Kim YJ, Choi DJ, Sohn DW, Cho GY: Clinical and imaging parameters to predict cardiovascular out-

come in asymptomatic subjects. Int J Cardiovasc Imaging, 2013; 29: 1595-1602
50) Yamamoto H, Kitagawa T, Kihara Y: Clinical implications of the coronary artery calcium score in Japanese patients. J Atheroscler Thromb, 2014; 21: 1101-1108
51) Kunita E, Yamamoto H, Kitagawa T, Ohashi N, Oka T, Utsunomiya H, Urabe Y, Tsushima H, Awai K, Budoff MJ, Kihara Y: Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography. Atherosclerosis, 2014; 233: 447-453
52) Kitagawa K, Hougaku H, Yamagami H, Hashimoto H, Itoh T, Shimizu Y, Takahashi D, Murata S, Seike Y, Kondo K, Hoshi T, Furukado S, Abe Y, Yagita Y, Sakaguchi M, Tagaya M, Etani H, Fukunaga R, Nagai Y, Matsumoto M, Hori M and Group OS: Carotid intima-media thickness and risk of cardiovascular events in high-risk patients. Results of the Osaka Follow-Up Study for Carotid Atherosclerosis 2 (OSACA2 Study). Cerebrovasc Dis, 2007; 24: 35-42
53) Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M: Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. Diabetes Care, 2000; 23: 1310-1315
54) Yoshida M, Mita T, Yamamoto R, Shimizu T, Ikeda F, Ohmura C, Kanazawa A, Hirose T, Kawamori R, Watada H: Combination of the Framingham risk score and carotid intima-media thickness improves the prediction of cardiovascular events in patients with type 2 diabetes. Diabetes Care, 2012; 35: 178-180
55) Sekikawa A, Ueshima H, Kadowaki T, El-Saed A, Okamura T, Takamiya T, Kashiwagi A, Edmundowicz D, Murata K, Sutton-Tyrrell K, Maegawa H, Evans RW, Kita Y, Kuller LH: Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. Am J Epidemiol, 2007; 165: 617-624
56) Abbott RD, Ueshima H, Rodriguez BL, Kadowaki T, Masaki KH, Willcox BJ, Sekikawa A, Kuller LH, Edmundowicz D, Shin C, Kashiwagi A, Nakamura Y, El-Saed A, Okamura T, White R, Curb JD: Coronary artery calcification in Japanese men in Japan and Hawaii. Am J Epidemiol, 2007; 166: 1280-1287
57) Huang J, Wu YF, Liu XQ, Ding D, Zhao LC, Lu B, Li X, Wong ND, Dustin LD, Azen SP, Detrano RC: Subclinical atherosclerosis in northern and southern China: the Chinese paradox. J Geriatr Cardiol, 2011; 8: 72-77
58) Kim BJ, Kim BS, Kang JH: Conventional versus image-based cardiovascular risk assessment in Korean adults. Coron Artery Dis, 2014; 25: 118-124
59) Zaid M, Fujiyoshi A, Miura K, Abbott RD, Okamura T, Takashima N, Torii S, Saito Y, Hisamatsu T, Miyagawa N, Ohkubo T, Kadota A, Sekikawa A, Maegawa H, Nakamura Y, Mitsunami K, Ueshima H and group SR: High-density lipoprotein particle concentration and subclinical atherosclerosis of the carotid arteries in Japanese men. Atherosclerosis, 2015; 239: 444-450
60) Zaid M, Miura K, Fujiyoshi A, Abbott RD, Hisamatsu T, Kadota A, Arima H, Kadowaki S, Torii S, Miyagawa N, Suzuki S, Takashima N, Ohkubo T, Sekikawa A, Maegawa H, Horie M, Nakamura Y, Okamura T, Ueshima H: Associations of serum LDL particle concentration with carotid intima-media thickness and coronary artery calcification. Journal of Clinical Lipidology, 2016; 10: 1195-1202
61) Kadota A, Miura K, Okamura T, Fujiyoshi A, Ohkubo T, Kadowaki T, Takashima N, Hisamatsu T, Nakamura Y, Kasagi F, Maegawa H, Kashiwagi A, Ueshima H, Group SR and Group NDR: Carotid intima-media thickness and plaque in apparently healthy Japanese individuals with an estimated 10-year absolute risk of CAD death according to the Japan Atherosclerosis Society (JAS) guidelines 2012: the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). J Atheroscler Thromb, 2013; 20: 755-766
62) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K and Japan Atherosclerosis S: Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb, 2013; 20: 517-523
63) Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, Shea S, Szklo M, Post W, Lima J, Bertoni A, Wong ND: Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol, 2013; 61: 1231-1239
64) Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA: Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA, 2014; 311: 271-278
65) Houslay ES, Cowell SJ, Prescott RJ, Reid J, Burton J, Northridge DB, Boon NA, Newby DE, Scottish Aortic S and Lipid Lowering Therapy IoRtI: Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. Heart, 2006; 92: 1207-1212
66) Terry JG, Carr JJ, Kouba EO, Davis DH, Menon L, Bender K, Chandler ET, Morgan T, Crouse JR, 3rd: Effect of simvastatin (80 mg) on coronary and abdominal aortic arterial calcium (from the coronary artery calcification treatment with zocor [CATZ] study). Am J Cardiol, 2007; 99: 1714-1717
67) Abbott RD, Ueshima H, Masaki KH, Willcox BJ, Rodriguez BL, Ikeda A, Yano K, White LR, Curb JD: Coronary artery calcification and total mortality in elderly men. J Am Geriatr Soc, 2007; 55: 1948-1954
68) Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK: Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. Am Heart J, 2010; 160: 701-714
69) Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Volzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, Kiechl S, Rundek T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG and Group P-IS: Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet, 2012; 379: 2053-2062

70) Ravani A, Werba JP, Frigerio B, Sansaro D, Amato M, Tremoli E, Baldassarre D: Assessment and relevance of carotid intima-media thickness (C-IMT) in primary and secondary cardiovascular prevention. Curr Pharm Des, 2015; 21: 1164-1171
71) Crouse JR, 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML and Group MS: Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA, 2007; 297: 1344-1353
72) de Groot E, Jukema JW, Montauban van Swijndregt AD, Zwinderman AH, Ackerstaff RG, van der Steen AF, Bom N, Lie KI, Bruschke AV: B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). J Am Coll Cardiol, 1998; 31: 1561-1567
73) Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M: Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol, 2010; 56: 2006-2020
74) Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM and Authors/Task Force M: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J, 2016; 37: 2315-2381
75) Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, Giral P, Kurl S, Rauramaa R, Mannarino E, Grossi E, Paoletti R, Tremoli E and Group IS: Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. J Am Coll Cardiol, 2012; 60: 1489-1499
76) Budoff MJ, McClelland RL, Chung H, Wong ND, Carr JJ, McNitt-Gray M, Blumenthal RS, Detrano RC: Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the Multi-Ethnic Study of Atherosclerosis. AJR Am J Roentgenol, 2009; 192: 613-617
77) Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS and American Society of Echocardiography Carotid Intima-Media Thickness Task F: Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr, 2008; 21: 93-111; quiz 189-190
78) Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC: Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J, 2002; 23: 934-940
79) O'Leary DH, Bots ML: Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J, 2010; 31: 1682-1689
80) Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, Lowe GD: Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. Stroke, 1999; 30: 841-850
81) Liao X, Norata GD, Polak JF, Stehouwer CD, Catapano A, Rundek T, Ezhov M, Sander D, Thompson SG, Lorenz MW, group P-Is, Balakhonova T, Safarova M, Grigore L, Empana JP, Lin HJ, McLachlan S, Bokemark L, Ronkainen K, Schminke U, Lind L, Willeit P, Yanez DN, Steinmetz H, Poppert H, Desvarieux M, Ikram MA, Johnsen SH, Iglseder B, Friera A, Xie W, Plichart M, Su TC, Srinivasan SR, Schmidt C, Tuomainen TP, Volzke H, Nijpels G, Willeit J, Franco OH, Suarez C, Zhao D, Ducimetiere P, Chien KL, Robertson C, Bergstrom G, Kauhanen J, Dorr M, Dekker JM, Kiechl S, Sitzer M, Bickel H, Sacco RL, Hofman A, Mathiesen EB, Gabriel R, Liu J, Berenson G, Kavousi M, Price JF: Normative values for carotid intima media thickness and its progression: Are they transferrable outside of their cohort of origin? Eur J Prev Cardiol, 2016; 23: 1165-1173
82) Lauer MS: Pseudodisease, the next great epidemic in coronary atherosclerosis?: comment on "Impact of coronary computed tomographic angiography results on patient and physician behavior in a low-risk population". Arch Intern Med, 2011; 171: 1268-1269
83) Kim KP, Einstein AJ, Berrington de Gonzalez A: Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med, 2009; 169: 1188-1194
84) Baron KB, Choi AD, Chen MY: Low Radiation Dose Calcium Scoring: Evidence and Techniques. Curr Cardiovasc Imaging Rep, 2016; 9: 12
85) Berrington de Gonzalez A, Darby S: Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet, 2004; 363: 345-351
86) Orakzai SH, Orakzai RH, Nasir K, Santos RD, Edmundowicz D, Budoff MJ, Blumenthal RS: Subclinical coronary atherosclerosis: racial profiling is necessary! Am Heart J, 2006; 152: 819-827
87) Greenland P, Bonow RO: How low-risk is a coronary calcium score of zero? The importance of conditional probability. Circulation, 2008; 117: 1627-1629
88) Sekikawa A, Ueshima H, Sutton-Tyrrell K, Kadowaki T, El-Saed A, Okamura T, Takamiya T, Ueno Y, Evans RW, Nakamura Y, Edmundowicz D, Kashiwagi A, Maegawa H, Kuller LH: Intima-media thickness of the carotid artery and the distribution of lipoprotein subclasses in men aged 40 to 49 years between whites in the United States and the Japanese in Japan for the ERA JUMP study. Metabolism, 2008; 57: 177-182