Shimane J. Med. Sci., Vol.34 pp.1-5, 2017

Coronary Artery Calcification for Prevention of Atherosclerotic Cardiovascular Disease

Takashi HISAMATSU

Department of Environmental Medicine and Public Health, Shimane University Faculty of Medicine, Izumo, 693-8501, Japan

（Received May 22, 2017; Accepted June 12, 2017）

Atherosclerotic cardiovascular disease（ASCVD）, including coronary heart disease, remains a major cause of death and disability among developed countries. Coronary artery calcification（CAC）, which is detected by computed tomography scanning, is a well-known measure of subclinical atherosclerosis. CAC is considered to have important implications for understanding the long-term accumulated burden of cardiovascular risk factors and for the possibility of reclassification at the preclinical phase for preventing ASCVD. This review focuses on CAC and its usability in primary prevention of ASCVD. Numerous epidemiological studies, mainly in Western countries, have indicated that, among asymptomatic individuals, the CAC score is associated with future ASCVD. Additionally, the CAC score provides improved predictive values for estimating the risk of ASCVD beyond traditional cardiovascular risk factors. However, a lack of evidence for this score in other populations warrants further investigations. Clinical trials are also necessary to demonstrate the usefulness and safety of CAC screening for primary prevention of ASCVD.

Key words: atherosclerotic cardiovascular disease, coronary artery calcification, primary prevention, epidemiology

Corresponding author: Takashi Hisamatsu, MD, Ph.D
Department of Environmental Medicine and Public Health, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan
Tel: +81-853-20-2164
Fax: +81-853-20-2160
E-mail: hisataka@med.shimane-u.ac.jp

Atherosclerotic cardiovascular disease（ASCVD）, including coronary heart disease（CHD）, is a major cause of death and disability among developed countries [1]. The mortality for ASCVD has gradually decreased over the last decades among developed countries, although it still causes approximately one-third of all deaths in people of middle and older age [2-4]. Additionally, more than half of the deaths from CHD occur outside the hospital and approximately 50% of these are sudden [5]. A total of 50% of men and 64% of women who die suddenly of CHD have no previous symptoms of this disease [5]. In Japan, the incidence of CHD, including acute myocardial infarction（MI）, has recently shown an increasing trend [6]. Therefore, primary prevention and risk stratification of ASCVD, including CHD, among asymptomatic adults is of great importance for clinical practice and public health.

Screening asymptomatic individuals using atherosclerosis at its subclinical phase for preventing ASCVD is currently the subject of intensive research [7]. Atherosclerosis begins in early life and accumulates silently until clinical symptoms appear late in the clinical disease. Histopathological studies have shown that the extent of atherosclerosis is associated with traditional risk factors for cardiovascular disease [8, 9]. Therefore, measuring subclinical atherosclerosis may have important implications for understanding the accumulated burden of cardiovascular risk factors during the long-term latent period prior to clinical diseases. Additionally, measuring subclinical atherosclerosis may be important for intervention, such as reclassification, at the preclinical phase for preventing ASCVD that occurs in later life.

Currently, various noninvasive measures are available for assessment of subclinical atherosclerosis. This review focuses on coronary artery calcification

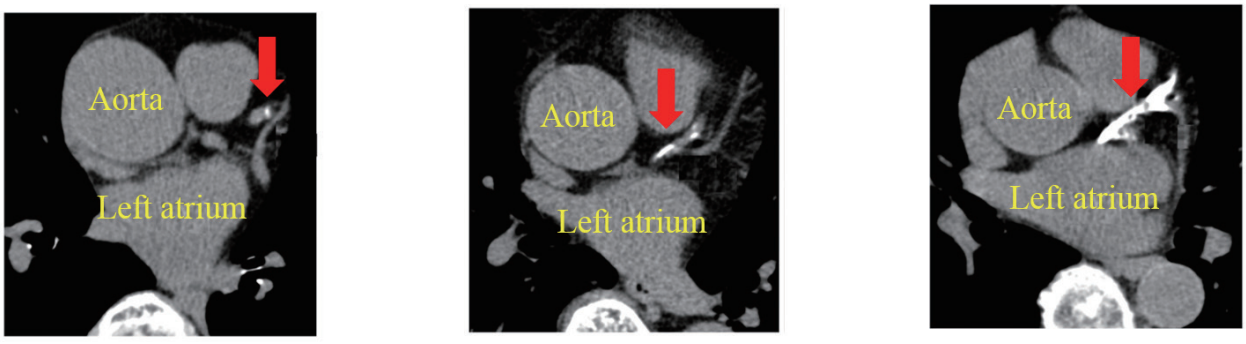
(CAC) which is a well-known measure of subclinical atherosclerosis, as quantified by computed tomography (CT). This review also addresses the usability of CAC based on population-based studies for primary prevention of ASCVD, including CHD.

Measurement of CAC

For decades, quantification of CAC by CT has continued to improve and become a standardized measure of subclinical atherosclerosis. The first practically applicable quantitative CAC protocol was introduced by Agatston *et al.* in 1990 [10]. In this method, CAC is defined as any structure that has a density of 130 Hounsfield units or greater and an area of 1 mm^2 or greater (Fig. 1) [10]. Agatston's score requires a relatively complex measurement technique. Therefore, in an effort to simplify measurement of coronary calcium and increase its reproducibility, the volume score was first introduced by Callister *et al.* [11]. This score is simply calculated based on the segmented calcified plaque area and the number of slices containing each of those plaques. However, the Agatston method has still remained the standard method in CAC scoring. Therefore, in this review, CAC scoring is exclusively defined as Agatston's score. Histopathological studies in humans have shown that CAC identified by CT was strongly and positively correlated with coronary plaques measured by autopsy. However, the area of calcium was one fifth or smaller than the plaque area [12], and was poorly related to the severity of luminal stenosis [13]. In addition, non-calcified or partially calcified plaques with a large necrotic core and expansive remodeling more frequently lead to myocardial infarctions [14]. Because of the strong association between the calcium area and plaque area in the coronary artery, the amount of CAC is considered to represent an overall magnitude of atherosclerotic burden [13].

Prevalence of CAC as shown by International Studies

International comparison with well-standardized methods can be used to investigate the difference in distribution of diseases and risk factors responsible for the difference. Therefore, this can increase understanding of genetic and environmental origins of disease, which could result in prevention of disease [15]. The Electron-Beam Tomography, Risk Factor Assessment Among Japanese and US Men in the Post-World War II Birth Cohort (ERA JUMP) study investigated asymptomatic Japanese in Japan, Caucasians, and Japanese Americans in the USA aged in their 40s [16-18]. This study showed that Japanese in Japan had significantly lower levels of coronary atherosclerosis, which was detected by CAC, than did Caucasian or Japanese Americans in the USA. However, Japanese Americans in the USA had similar to or higher levels of coronary atherosclerosis compared with Caucasians in the USA. The prevalence of a CAC score of 10 or higher in Japanese in Japan, Caucasians, and Japanese Americans was 9.3%, 26.1%, and 31.4%, respectively [16-18]. These findings suggest that various lifestyles, such as diet, but not genetic factors, would contribute to the difference in coronary atherosclerosis between



Mild Moderate Severe

Fig. 1
CT images in participants with various amounts of coronary artery calcification (CAC). Arrows indicate mild, moderate, and severe calcifications in left anterior descending artery.

Japan and the USA [15]. Another international comparison was made between two epidemiological studies, the Multiethnic Study of Atherosclerosis (MESA) in the USA and the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), of Caucasian and Japanese men aged 45 to 74 years [19]. This comparison showed that Caucasian men in the USA had a higher burden of coronary atherosclerosis, which was detected by CAC, than did Japanese men. However, the ethnic difference was smaller in younger age groups (e.g., adjusted odds ratios for Caucasian men having a CAC score of ≥100 were 2.05, 2.43, and 3.86 among those aged 45-54, 55-64, and 65-74 years, respectively) [19].

Similar to CHD, the CAC score was also related to traditional cardiovascular risk factors in Western, as well as Asian, populations [20, 21]. In the MESA and SESSA comparison, regardless of country and ethnicity, higher CAC scores were more common in men who had worse traditional cardiovascular risk factors profiles, such as hypertension, dyslipidemia, diabetes, smoking, and obesity [19].

CAC for Primary Prevention of ASCVD

A large number of epidemiological studies have indicated that the total amount of CAC is an independent predictor of future ASCVD, including CHD, and provides predictive information beyond that provided by standard cardiovascular risk factors [7]. Individuals with intermediate risk and an elevated CAC score (intermediate Framingham risk score [FRS] and CAC score >300) had a 2.8% annual rate of cardiac death or MI (approximately equivalent to a 10-year rate of 28%) that would be considered high risk [22]. The MESA included a population-based sample of white, African-American, Hispanic, and Chinese-American men and women aged 45 to 84 without clinical CVD at baseline [23]. This study showed that the CAC score was a strong predictor of incident CHD (hazard ratios [95% confidence interval], 3.61 [1.96 to 6.65], 7.73 [4.13 to 14.47], and 9.67 [5.20 to 17.98] for individuals with a CAC score of 1 to 100, 101 to 300, and 301 or greater, respectively, vs. those without CAC). The CAC score also provided predictive information beyond traditional cardiovascular risk factors for men and women and all ethnic groups—at least within the intermediate risk level of FRS-for most participants [23]. Pooled data analysis from six studies among 27,622 asymptomatic patients reported that almost 43% of them had no CAC, resulting in a low event rate of only 0.4%/3-5 years. However, compared with those without CAC, participants with a CAC score of 1 to 99, 100 to 399, 400 to 999, and 1000 or greater showed a significant association with a higher relative risk of 1.9 (95% confidence interval, 1.3 to 2.8), 4.3 (3.1 to 6.1), 7.2 (5.2 to 9.9), and 10.8 (4.2 to 27.7), respectively, for CHD death or MI [24]. Additionally, the corresponding pooled rates of 3- to 5-year CHD death or MI were 4.6% for a CAC score of 400 to 999 and 7.1% for a CAC score of 1000 or greater [24]. With even higher CAC scores, the 3- to 5-year event rates substantially increased.

Based on this evidence, higher CAC scores are associated with higher event rates and higher relative risk ratios for future ASCVD, including CHD. CAC can also play an important role in reclassifying individuals from intermediate risk, using a traditional risk prediction model based on the guideline of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) [25], to high risk [7]. However, measurement of CAC is considered not reasonable for individuals at low risk [7]. Such reclassification is critical because most cardiovascular events occur in individuals at intermediate risk. Interventions for reducing risk among individuals at high risk are better established than those for individuals at intermediate risk [7].

Similar to other subclinical atherosclerosis, such as carotid intima-media thickness, investigators have used CAC as a measure of coronary atherosclerosis burden or as a surrogate marker for ASCVD in epidemiological studies. SESSA is a population-based study that measured CAC in a random sample from a general Japanese population [26, 27]. The SESSA showed a strong association with CAC in current and former smokers compared with never smokers, and this harmful association was attenuated with time since smoking cessation in former smokers. These results support evidence for the negative impact of smoking on coronary atherosclerosis and benefit for preventing CHD by cessation of smoking as early as possible [26]. Another investigation by

the SESSA also showed that higher insulin resistance and fasting insulin were associated with the prevalence and progression of CAC independent of metabolic components, particularly in those without diabetes mellitus. These results indicate that insulin resistance can develop coronary atherosclerosis through a pathway independent of metabolic risk factors, and may be useful in assessing the risk of CHD, especially in people without diabetes mellitus [27].

CONCLUSION

The CAC score is associated with future ASCVD and provides improved predictive values for risk estimation of ASCVD, including CHD, beyond traditional cardiovascular risk factors. CAC is currently suggested for screening of ASCVD, including CHD, in apparently healthy individuals at intermediate risk, particularly in Western countries. Based on 2013 ACC/AHA Prevention Guideline [7], If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of CAC score may be considered to inform treatment decision making (Class *IIb*). However, whether the same benefits are present in other populations, such as the Japanese, remains uncertain. The lack of evidence in these populations warrants further investigations. Additionally, further studies (randomized controlled trials) are necessary to demonstrate the usefulness and safety of CAC screening for assessing ASCVD for primary prevention.

REFERENCES

1) Roger VL. Epidemiology of myocardial infarction. *Med Clin North Am* 2007;91:537-52;ix.
2) Rosamond W, Flegal K, Furie K, *et al*. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25-146.
3) Lloyd-Jones D, Adams RJ, Brown TM, *et al*. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010;121:948-54.
4) Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014;35:2929.
5) Go AS, Mozaffarian D, Roger VL, *et al*. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129:e28-e292. doi:10.1161/01.cir.0000441139.02102.80.
6) Rumana N, Kita Y, Turin TC, *et al*. Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI Registry, 1990-2001. *Am J Epidemiol* 2008;167:1358-64.
7) Goff DC, Jr., Lloyd-Jones DM, Bennett G, *et al*. 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.
8) Malcom GT, Oalmann MC, Strong JP. Risk factors for atherosclerosis in young subjects: the PDAY Study. Pathobiological Determinants of Atherosclerosis in Youth. *Ann N Y Acad Sci* 1997;817:179-88.
9) Imakita M, Yutani C, Sakurai I, *et al*. The second nationwide study of atherosclerosis in infants, children, and young adults in Japan. Comparison with the first study carried out 13 years ago. *Ann N Y Acad Sci* 2000;902:364-8.
10) 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;15:827-32.
11) Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology* 1998;208:807-14.
12) 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;92:2157-62.
13) Sangiorgi G, Rumberger JA, Severson A, *et al*. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque bur-

den in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998;31:126-33.

14) Eckert J, Schmidt M, Magedanz A, Voigtlander T, Schmermund A. Coronary CT angiography in managing atherosclerosis. *Int J Mol Sci* 2015;16:3740-56.

15) Sekikawa A, Curb JD, Edmundowicz D, *et al*. Coronary artery calcification by computed tomography in epidemiologic research and cardiovascular disease prevention. *J Epidemiol* 2012;22:188-98.

16) Sekikawa A, Ueshima H, Kadowaki T, *et al*. 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;165:617-24.

17) Abbott RD, Ueshima H, Rodriguez BL, *et al*. Coronary artery calcification in Japanese men in Japan and Hawaii. *Am J Epidemiol* 2007;166:1280-7.

18) Sekikawa A, Curb JD, Ueshima H, *et al*. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. *J Am Coll Cardiol* 2008;52:417-24.

19) Fujiyoshi A, Miura K, Ohkubo T, *et al*. Cross-sectional comparison of coronary artery calcium scores between Caucasian men in the United States and Japanese men in Japan: the multiethnic study of atherosclerosis and the Shiga epidemiological study of subclinical atherosclerosis. *Am J Epidemiol* 2014;180:590-8.

20) Bild DE, Detrano R, Peterson D, *et al*. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313-20.

21) Park HE, Kim MK, Choi SY, *et al*. The prevalence and distribution of coronary artery calcium in asymptomatic Korean population. *Int J Cardiovasc Imaging* 2012;28:1227-35.

22) Nasir K, Budoff MJ, Post WS, *et al*. Electron beam CT versus helical CT scans for assessing coronary calcification: current utility and future directions. *Am Heart J* 2003;146:969-77.

23) Detrano R, Guerci AD, Carr JJ, *et al*. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336-45.

24) Greenland P, Bonow RO, Brundage BH, *et al*. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;49:378-402.

25) National Cholesterol Education Program Expert Panel on Detection E and Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

26) Hisamatsu T, Miura K, Arima H, *et al*. Smoking, Smoking Cessation, and Measures of Subclinical Atherosclerosis in Multiple Vascular Beds in Japanese Men. *J Am Heart Assoc* 2016;5(9). pii: e003738. doi:10tu.1161/JAHA.116.003738.

27) Yamazoe M, Hisamatsu T, Miura K, *et al*. Relationship of Insulin Resistance to Prevalence and Progression of Coronary Artery Calcification Beyond Metabolic Syndrome Components: Shiga Epidemiological Study of Subclinical Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2016;36:1703-8.