Coronary Artery Calcification in the Asian Population: An Overview of the Results from the Korea Initiatives on Coronary Artery Calcification Registry

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Coronary artery calcium score (CACS), determined using computed tomography, is a robust marker of calcific atherosclerosis and is associated with atherosclerotic plaque burden. Although CACS is a well-established tool for early coronary artery disease (CAD) detection, prior studies have revealed some differences in the prevalence and severity of CAC according to ethnicity or race, which underscores the need to re-appraise the clinical utility of CACS in the Asian population. Korea Initiatives on Coronary Artery Calcification (KOICA) was designed to identify the effectiveness of CACS for primary prevention of CAD in asymptomatic Korean adults. This registry comprises 86,165 adults who underwent CAC scanning at one of five centers in Korea between 2002 and 2014. Based on its multisite approach and large sample size, KOICA has and will continue to provide answers to important questions regarding the effect of CACS on CAD. This article discusses the rationale of CACS use in the Asian population and describes key findings from KOICA.

Key words Coronary artery disease · Calcium · Atherosclerosis.

INTRODUCTION

Cardiovascular disease (CVD) is a global concern and is considered a major cause of global morbidity and mortality. Approximately 17.5 million people died from CVD in 2012, which represents one-third of all global deaths [1]. CVD is associated with several diseases; coronary artery disease (CAD) and cere-

brovascular disease, such as stroke, account for over two-thirds of all mortalities related to CVD [2,3]. Of these deaths, around 7.4 million people died because of CAD. Prior epidemiologic evidence indicates that the prevalence and severity of CAD vary according to ethnicity and race [3-9]. Noticeably, at least three-quarters of the world's CAD-related mortalities occur in low- and middle-income countries [1]. Commonly, the prevalence and severity of CAD are influenced by traditional risk factors (RFs), which contribute to CAD development and progression. In the context of CAD prevention, various risk prediction al-

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gorithms have been developed and utilized, underscoring the significance of precise assessment of CAD risk. However, prior studies have reported discrepancies in ethnicity or race when using risk prediction tools. Over half of the world's population presently lives in Asian countries; thus, identification and control of underlying traditional RFs related to CAD are essential health issues for primary and secondary prevention of CAD in the Asian population.

Notably, coronary artery calcium score (CACS) is a well-established independent surrogate for predicting cardiovascular risk and is currently used in atherosclerotic burden assessment and risk stratification [10]. Despite this, the prevalence and predictive value of CACS tend to vary, depending on ethnicity and/or race [11-13]. To date, most of the studies related to CACS are based on Western populations. Hence, whether changing trends in the presence and severity of coronary artery calcium (CAC) are responsible for the ethnic and/or race differences in CAD risk remains to be definitely elucidated, especially in Asian populations. The Korea Initiatives on Coronary Artery Calcification (KOICA) registry aimed to assess the effectiveness of CACS for primary prevention of CAD in a large cohort of asymptomatic Korean adults. To date, several investigations utilizing this registry have revealed the usefulness of CACS. In this review, we aimed to describe the rationale regarding the clinical utility of CACS for prognostication principally in non-Western populations and to summarize some of the current main findings from the KOICA registry.

RATIONALE BEHIND THE KOICA REGISTRY

Precise prediction of cardiovascular risk in asymptomatic individuals is of great importance in the primary prevention of CAD [14]. Given that CAD is a multifactorial disease influenced by numerous cardiovascular RFs as well as socioeconomic status, several risk estimation algorithms, developed from existing conventional RFs, have been utilized to predict CAD risk, which include the Framingham 10-year risk score (FRS) and the recently introduced pooled cohort equation for atherosclerotic cardiovascular disease risk assessment. The FRS has been adapted for the prediction of cardiovascular event risk worldwide [15,16]. Although FRS is being used as a valuable tool for cardiovascular risk assessment, general extrapolation of this algorithm to various ethnicities or races may misclassify CAD risk in as much as the FRS was predominantly established based on a Caucasian population [17,18]. To this end, several previous studies have examined multiple ethnic or racial groups in an effort to test the utility or validity of the FRS. Several investigators have demonstrated the overestimation of cardiovascular risk when FRS was directly applied to other ethnicities, such as in Asia including South Korea and sev-

eral countries in Europe [17-22]. In a study based on a Korean population, the investigators reported that FRS overestimated CAD risk and CAD incidence was low [18]. Direct application of FRS to different ethnicities may cause unnecessary or inadequate treatment and further socioeconomic burden. Consequently, various efforts have established a novel risk prediction algorithm or a recalibrated model of FRS that could accurately estimate CAD risk in relation to a specific ethnicity or race. As such, Jee et al. [18] developed a CAD risk prediction model and demonstrated the feasibility of the model, showing accurate and reliable prediction of CAD risk among Korean adults.

Of the various risk prediction algorithms used to screen CAD in asymptomatic individuals, CACS is a well-established robust surrogate marker of atherosclerotic progression in coronary arteries [10,23,24]. The extent of calcified plaques has been well correlated with overall plaque burden [25,26]. A recent guideline for cardiovascular risk assessment recommended that CAC screening should be considered for primary risk assessment in asymptomatic individuals [14]. Coronary calcifications determined by cardiac computed tomography (CT) are usually expressed as the Agatston score [27]. In various previous studies, CACS has been shown to be an accurate and reliable predictor for the detection of subclinical CAD and to have further prognostic benefit over conventional RFs [24,28,29]. For instance, Greenland et al. [24] documented that a high CACS can modify the predicted risk obtained from FRS, especially among intermediate-risk category patients. In the Multi-Ethnic Study of Atherosclerosis (MESA) study investigating the prevalence, correlates, and progression of subclinical CAD in subjects without known CAD, Polonsky et al. revealed that the addition of CACS to the standard Framingham RFs resulted in significant improvements in risk prediction, with net reclassification improvement of 0.25 (95% CI: 0.16–0.34; $p < 0.001$) [29]. More recently, a MESA sub-study with a median follow-up of 7.6 years also reported that CACS showed an incremental benefit over the FRS (FRS alone was used as a reference), demonstrating that CACS had the highest improvement in both area under the receiver operating characteristic curve (AUC) and net reclassification improvement (NRI) when added to the FRS compared with other risk markers [28].

Several previous studies have suggested that CACS differs among ethnic and racial groups [11,12,30-32]. Bild et al. [12] observed ethnic differences in the presence and quantity of coronary calcification in a MESA sub-study; the calcification prevalence in Hispanics and Blacks was substantially lower compared to that in Whites, and there was a slightly lower calcification prevalence in Chinese than in Whites. In another MESA sub-study with 6,110 subjects, the investigators found differences in CACS according to race, age, and gender [32]. In women, for example, Whites had the highest percentiles, Hispanics in gen-

eral had the lowest, while Chinese women in the oldest age group had the lowest values. In men, Whites had the highest percentiles, followed by Hispanics. Budoff et al. [11] demonstrated a significant difference in the presence and severity of coronary calcification according to ethnicity, independent of traditional RFs. They reported that Asians and African-Americans had lower prevalence and severity of calcification than Hispanics and non-Hispanic Whites. More recently, in a MESA sub-study comprising four different groups, Detrano et al. [10] examined the predictive value of CACS for adverse outcomes in a multi-ethnic population in the USA, including Whites, Blacks, Hispanics, and Chinese. In each group, the CAD risk associated with doubling of CACS significantly increased by 15 to 35% for a major coronary event and by 18 to 39% for any coronary event, except in Chinese populations. No interaction between the risk associated with heightened CACS and ethnicity was found in that study. Moreover, Nasir et al. [33] showed the differential prognostic value of the extent and severity of CAC in ethnic minority subsets and reported that African-Americans who had higher CACS tended to have higher mortality than non-Hispanic Whites. To date, plausible theories on differences in CACS based on ethnicity/race remain unclear. There are several factors possibly associated with ethnic differences, such as environment, behavior, or genetic predisposition, which warrants further investigation.

Furthermore, various studies have examined the prognostic value of CACS in Asian populations [34-37]. In a study of an asymptomatic general Korean population comprising 5,182 patients with CACS determined by contrast-enhanced coronary CT angiography, Park et al. [34] revealed that FRS and CACS were both independent parameters for adverse cardiovascular outcome prediction ($p < 0.001$ for both FRS and CACS). However, when the degree of coronary stenosis was added to the model, CACS was not significantly associated with adverse outcomes ($p = 0.391$). In another study examining the difference between risk stratifications by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) guidelines and CACS among 7,988 Korean adults, CAD risk was possibly underestimated in approximately 10–20% of asymptomatic Korean individuals classified as low to moderate risk according to the NCEP-ATP III guidelines [37]. The study proposed that image-based risk assessment, such as CACS, should be considered for a more precise risk stratification among Koreans at low to moderate risk. Further studies among Asian adults, particularly Koreans, are warranted to reassess the efficacy and predictive significance of CACS.

OVERVIEW OF THE KOICA REGISTRY

The rationale and design of the KOICA registry have been

previously described [38]. Briefly, the KOICA registry is a dynamic single-ethnicity multicenter observational registry designed to investigate the effectiveness and prognostic value of CACS for the primary prevention of CAD in asymptomatic Korean adults. The study population includes self-referred individuals who completed self-reported medical questionnaires to obtain personal clinical data and medical history for the purpose of a health check-up at a healthcare center. A total of 86,165 individuals were enrolled in the current study between December 2002 and July 2014 from five centers in South Korea. Baseline demographic data, including significant underlying disease or RFs, such as hypertension, CAD, hyperlipidemia, diabetes mellitus, and chronic kidney disease, and family history of underlying diseases, were collected during the initial visit to the healthcare centers using self-reported medical questionnaires. Other information, including smoking, alcohol, and exercise as well as laboratory test results, were obtained. All individuals in this registry underwent CACS measurement using a more than 16-slice multi-detector CT scanner; each center had a specific scanner type. Moreover, other cardiovascular screening tests for risk assessment included arterial stiffness assessment and exercise treadmill test. However, not all demographic parameters or tests were performed in all individuals, which possibly led to some heterogeneity in the analytical sample sizes.

RECENT INVESTIGATIONS UTILIZING DATA FROM THE KOICA REGISTRY

To reexamine the efficacy and predictive value of CACS, which has been shown to be superior to extant traditional risk prediction algorithms, further investigations among Asian subjects, especially Koreans, are warranted. Several epidemiological and clinical questions regarding CACS among the Korean population exist. Hence, this study reviews several significant findings based on the KOICA registry. A current list of published studies is provided in Table 1.

Incremental value of CACS beyond FRS on all-cause mortality (ACM)

Existing literature on CACS is typically based on Western populations; accordingly, little is known about the added prognostic benefit of CACS beyond traditional coronary RFs in relation to different ethnicities, especially among Asians. Using the KOICA registry, Han et al. [39] evaluated the distribution of CACS and its incremental value over FRS in 34,386 asymptomatic Korean adults. The FRS was obtained using traditional risk stratification and categorized as follows: <10% (low), 10–15% (low-intermediate), 15–20% (high-intermediate), and >20% (high). The CACS was computed in log (CACS+1) and categorized as follows: 0, 1–100, 101–400, and >400. In a me-

Table 1. Summary of the KOICA studies already published

No.	Study	Year	No. of patients	Title	Conclusion
1.	Han et al. [39]	2015	34,386	Incremental benefit of coronary artery calcium score above traditional risk factors for all-cause mortality in asymptomatic Korean adults	CACS improved discrimination and reclassification beyond FRS for the prediction of ACM.
2.	Lee et al. [38]	2015	-	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	This article provided the rationale and design of the KOICA registry and discussed the significant role of CACS for prognostication in Asian population.
3.	Choi et al. [59]	2016	25,972	Combined effects of exercise capacity and coronary atherosclerotic burden on all-cause mortality in asymptomatic Koreans	High CACS in subjects with higher aerobic fitness had smaller effect on ACM than in those with lower aerobic fitness. Thus, good exercise capacity may lessen the adverse effect of high coronary atherosclerotic burden.
4.	Han et al. [51]	2016	26,018	Association between elevated resting heart rate and subclinical atherosclerosis in asymptomatic Korean adults undergoing coronary artery calcium scoring	Elevated resting heart rate was independently associated with an increased atherosclerotic burden appraised by CACS.
5.	Han et al. [40]	2016	5,427	Prevalence and distribution of coronary artery calcification in asymptomatic United States and Korean adults -cross-sectional propensity-matched analysis	As compared to US population, Korean adults have a lower prevalence and severity of atherosclerotic burden measured by CACS, however the difference in CACS by ethnicity may attenuate as increased older age.
6.	Lee et al. [45]	2016	48,215	Warranty period of zero coronary artery calcium score for predicting all-cause mortality according to cardiac risk burden in asymptomatic Korean adults	Zero CACS presented improved survival based on a warranty period on ACM, when no other risk factors were observed. But, the usefulness of zero CACS and its warranty period requires further validation in the presence of multiple risk factor factors.

KOICA: Korea Initiatives on Coronary Artery Calcification, CACS: coronary artery calcium score, FRS: Framingham 10-year risk score, ACM: all-cause mortality, US: United States

dian follow-up duration of 4.9 years [interquartile range (IQR), 3.0–7.1], a total of 303 (0.9%) individuals had all-cause mortality (ACM) as the primary endpoint. ACM incidence was significantly different among CACS categories. Notably, CACS >400 showed a total annualized ACM incidence of 0.6% in the low FRS group (<10%), while the high FRS group (FRS >20%) with zero CACS had a 0.2% ACM incidence (Fig. 1). Following adjustment, the log-transformed CACS independently increased the hazard for ACM by 1.1 (95% CI: 1.05–1.17), and CACS 101–400 and >400 had a 1.51- and 2.34-fold (95% CI: 1.04–2.19 and 1.54–3.54, respectively) increase in ACM risk, respectively, compared with zero CACS. Moreover, adding CACS to FRS significantly improved the prognostic value for ACM (AUC difference=0.04, 95% CI: 0.01–0.06, $p=0.002$; likelihood ratio, $\chi^2=75.42$, $p<0.001$; continuous NRI=0.40, 95% CI: 0.29–0.51). These findings were not significantly different from those in 16,879 individuals with a follow-up duration ≥ 5

years. Given that FRS may misclassify risk when applied to different ethnicities as well as overestimate coronary risk in Asian populations [17,18], the findings of this investigation indicate that CAC screening, when added to extant traditional risk algorithm, effectively improves adverse outcome prediction in a larger multicenter registry of asymptomatic Korean adults. Further still, several efforts have been made to apply a new risk prediction algorithm, which is appropriate for the prediction of cardiovascular risk depending on ethnicity. As such, Jee et al. [18] developed a new CAD prediction algorithm and displayed more accurate and reliable prediction of cardiovascular risk among Korean individuals compared to the FRS.

Comparison of CACS in asymptomatic US and Korean adults

In a cross-sectional study using the KOICA registry, Han et al. [40] investigated ethnic differences related to subclinical coro-

Fig. 1. Annual mortality rate according to CACS and FRS. FRS: Framingham 10-year risk score, CACS: coronary artery calcium score. Adapted from Han et al. *Circ J* 2015;79:2445-2451, with permission of The Japanese Circulation Society [39].

nary atherosclerosis measured with CACS. The investigators sought to compare the prevalence and distribution of CACS among asymptomatic US and Korean adults. A propensity score-matching approach was implemented based on traditional coronary RFs, such as age, gender, hypertension, diabetes, dyslipidemia, and current smoking status, which resulted in two cohorts of 5,427 matched pairs. The age group was further categorized (i.e., 45–54, 55–64, and 65–74 years), and subjects were classified according to the severity of CACS based on the following: 1) score of 0, 1–100, 101–400, or >400 and 2) >0, the presence of any CAC; >100 (moderate CACS) or >400 (severe CACS). Overall, the prevalence and severity of CAC differed according to ethnicity, i.e., higher in US than in Korean adults, regardless of gender difference. Furthermore, compared with Korean adults, US adults had a higher CACS percentile, with similar tendency across age groups regardless of gender. In a logistic regression analysis showing the ethnic difference and likelihood of CACS, the odds for any, moderate, or severe CACS in Korean adults were inferior to those in US adults, which was most obvious in Korean women than Korean men. In comparison with US adults, the odds of a severe CACS in 65- to 74-year-old Korean adults were 0.66 (95% CI: 0.48–0.91), 0.78 (95% CI: 0.52–1.19), and 0.50 (95% CI: 0.29–0.86) for overall, men, and women, respectively. Notably, CACS differences between US and Korean adults were attenuated with increasing age (Fig. 2). However, an accurate mechanism to explain this finding remains to be elucidated. A few prior studies have documented how several coronary RFs might influence the differences in atherosclerosis development and progression [12,41]. Yet, the effect on coronary atherosclerosis varies according to ethnicity, race, and geographic region, thereby emphasizing that further

Fig. 2. Coronary artery calcium score and its associated population, according to age percentiles in US vs. Korean adults. US: United States.

investigation is warranted.

The differences in the prevalence and severity of CACS among different East Asian populations remain to be elucidated. KOICA investigators are now exploring the epidemiologic trends related to the prevalence and severity of CACS, along with possible changes according to geographic area and study time period (i.e., recent time versus past time), among separate East Asian cohorts, such as Chinese and Koreans, applying a propensity score approach according to traditional RFs. The results from these ongoing studies will soon be available.

Warranty period of zero CACS for predicting ACM according to cardiac risk burden

Previous studies have reported that the absence of CAC is possibly associated with a lower CAD risk in asymptomatic and selected symptomatic individuals and, therefore, can be considered a protective marker for obstructive CAD [42,43]. A few studies have examined the significance of zero CACS and its warranty period, showing its protective effect, in a Western population [44]. To this end, Lee et al. [45] examined the beneficial effect of zero CACS for predicting ACM risk and identified the warranty period of zero CACS, especially according to pre-specified RFs and RF burden. A total of 48,215 individuals were included in the analysis, and the RFs were as follows: hypertension, diabetes, current smoking, high low-density lipoprotein cho-

lesterol (≥ 130 mg/dL), and low high-density lipoprotein cholesterol (< 40 mg/dL). The RF burden was summed in the composite score as the presence of 0, 1–2, or ≥ 3 RFs. The warranty period was defined as the duration in years in which a subject remained within a cumulative mortality rate $< 1\%$. During a median follow-up of 4.4 years (IQR, 2.7–6.6 years), 415 (0.9%) individuals died. Following adjustment for the pre-specified RFs, the overall hazard ratio of non-zero CACS for ACM was 2.20 (95% CI: 1.70–2.86, $p < 0.001$). The presence of any CAC was significantly associated with higher ACM risk in each individual RF group, with the exception of current smoking (hazard ratio, 1.16, 95% CI: 1.00–2.60, $p = 0.05$). Irrespective of RF burden, the ACM incidence per 1,000 person-years was consistently lower in individuals with zero CACS than in those with non-zero CACS. Overall, the warranty period of zero CACS was 9 years, whereas that of the non-zero group was 5 years, which did not differ across individual RFs. Furthermore, although individuals with zero CACS seemed to have a lower ACM incidence per 1,000 person-years than those with non-zero CACS, the difference in warranty period between zero CACS and non-zero CAC decreased with increased RF burden (Fig. 3). In an asymptomatic Korean population, this finding underscores the finding

that the zero CACS is associated with improved outcome based on the warranty period in the absence of other RFs. However, the efficacy and warranty period of zero CACS necessitate further validation in individuals with multiple RFs.

Association between elevated resting heart rate and CACS

Previous studies have found that elevated resting heart rate (RHR) is associated with coronary atherosclerosis and cardiovascular outcomes [46–48]. Although the mechanisms of this finding remain unclear, recent evidence indicates that elevated RHR and the inflammatory process interact at several levels of the cardiovascular continuum, which may allow for the development and progression of atherosclerotic plaques, thus increasing the likelihood of future adverse cardiovascular outcomes [49,50]. Han et al. [51] assessed the cross-sectional relationship between a high RHR and subclinical atherosclerosis, as measured by CACS, among asymptomatic Korean adults. RHR was stratified as follows: < 60 , 60–79, 70–79, and ≥ 80 beats/min, and RHR differences were examined based on the following CACS categories: 0, 1–100, 101–400, and > 400 . In this study, RHR (10 beats/min) was a robust predictor of increasing CACS

Fig. 3. Warranty period of CACS=0 vs. CACS>0 according to risk factor burden (A. 0 risk factor, B. 1 to 2 risk factors, and C. ≥ 3 risk factors). CACS: coronary artery calcium score. Adapted from Lee et al. *Circ J* 2016;80:2356–2361, with permission of The Japanese Circulation Society [45].

(beta coefficients: 0.03, standard errors: 0.01, $p < 0.001$) after adjusting for age, sex, and other traditional RFs. In a multivariable logistic regression analysis, each 10 beats/min increase in RHR was significantly associated with greater odds of having CACS >100 (odds ratio: 1.13, 95% CI: 1.08–1.18) or >400 (odds ratio: 1.22, 95% CI: 1.13–1.31). Moreover, for individuals with $\text{RHR} \geq 80$ beats/min, the presence of CACS >100 or >400 increased the odds for ACM by 1.42 (95% CI: 1.19–1.69) and 1.86 (95% CI: 1.42–2.47), respectively, compared to those who had an $\text{RHR} < 60$ beats/min (Fig. 4). Notably, this result did not differ in a sensitivity analysis of individuals without history of CAD. Nonetheless, given that RHR can be influenced by several stimuli, such as physical, psychological, or environmental conditions [52], cautious interpretation of the findings is needed.

Furthermore, since this study had a cross-sectional feature, the significance of the synergistic relationship between elevated RHR and CACS to predict adverse outcomes may need to be further investigated. Both elevated RHR and the presence of CAC are indicative of subclinical atherosclerosis and are perhaps responsible for heightening an inflammatory activity. As previously described, KOICA investigators recently documented that elevated RHR, particularly >80 beats/min, was independently associated with increased CACS. However, evidence of a concomitant relationship between RHR and CACS for forecasting adverse cardiovascular outcomes remains to be further investigated. Hence, the investigators are now actively working on building a database and cleaning up the information on ACM as a primary outcome in the KOICA registry, which would enable future studies to identify a synergistic relationship, if any, between high RHR and CACS for the prediction of ACM.

Fig. 4. Odds ratios with 95% CI for the likelihood of CACS >0 , >100 , or >400 according to RHR group. CACS: coronary artery calcium score, CI: confidence interval, RHR: resting heart rate.

Combined effects of exercise capacity and CACS on ACM

Prior investigations have documented that good physical fitness or exercise capacity is well correlated with favorable cardiovascular prognosis [53–56]. Furthermore, several prior studies have reported that cardiorespiratory fitness measured by treadmill test is inversely associated with CAC prevalence [57,58]. Nevertheless, whether there is a significant interaction between exercise capacity and CACS influencing adverse outcomes remains unclear. Choi et al. [59] assessed the combined effect of exercise capacity and CACS on ACM prediction in 25,972 asymptomatic Korean individuals. Exercise capacity with metabolic equivalent (MET) was graded as METs <10 (lower exercise capacity) or ≥ 10 (higher exercise capacity). The CACS was divided into five categories using the Agatston score: 0, 1–9, 10–99, 100–399, and ≥ 400 . The Kaplan-Meier survival curve revealed that increasing CACS predicted higher mortality in asymptomatic Korean individuals. Further, Fig. 5 shows the Kaplan-Meier survival curves of the two CACS categories, in which significant survival differences between individuals with CACS <400 and those with ≥ 400 exist not only in those with higher exercise capacity (≥ 10 METs, log-rank $p = 0.0051$), but also in those with lower exercise capacity (<10 METs, log-rank $p < 0.0001$). Notably, the prognostic effect of high CACS varied, depending on the exercise capacity. In a multivariate Cox proportional analysis with interaction term, CACS ≤ 400 increased the hazard for ACM by 3.328 in individuals with lower exercise capacity; those with higher exercise capacity had a hazard ratio of 1.108 (p value for interaction = 0.024). In this large cohort of asymptomatic Korean adults, the effect of CACS on ACM was attenuated by good exercise capacity. The effect of CACS ≥ 400 on ACM prediction in individuals with higher exercise capacity was reduced. Good aerobic fitness may reduce the adverse effect of high coronary atherosclerotic burden.

CURRENT ONGOING STUDIES FROM THE KOICA REGISTRY

Assessment of CACS for statin treatment strategy according to ACC/AHA guidelines

The burden of cardiovascular outcomes tends to vary depending on ethnicity or race, and prior reports have shown that Asians usually have a low cardiovascular risk [17,18]. Thus, evaluating the efficacy of statin treatment based on the recently updated 2013 ACC/AHA guidelines may be essential [14], especially among the Asian population. KOICA investigators are assessing the influence of CACS on ACM risk stratification of statin candidates in an asymptomatic Korean population. Subjects will be categorized by statin eligibility as follows: statin recommended, considered, and not recommended based on

Fig. 5. Kaplan-Meier survival curves according to CACS in individuals with lower (METs <10) and higher (METs ≥10) exercise capacity. CACS: coronary artery calcium score, MET: metabolic equivalent. Adapted from Choi et al. *Atherosclerosis* 2016;251:396-403, with permission of Elsevier Inc [59].

the ACC/AHA guidelines. The results will be helpful in identifying whether CACS evaluation is valuable for guiding treatment decision-making, including initiating statin therapy, in primary prevention practice.

Serial CAC scanning for ACM prediction

Prior studies have documented that coronary calcification progression is associated with unfavorable cardiovascular prognosis [60-62]. Serial CACS evaluation has the potential not only to monitor coronary atherosclerosis progression, but also to evaluate or monitor the effectiveness of medical therapies for minimizing adverse cardiovascular risk. Germane to this, KOICA investigators are currently building a database of serial CAC scanning results, expecting that future study utilizing serial CACS data will identify the predictive effect of CAC progression and the association with traditional cardiovascular RFs in predicting CAC progression among Korean individuals. Accordingly, for reliable measurement of CACS, it should be noted that repeat CAC scanning can provide lower inter-scanning variability. In light of this, prior studies have demonstrated excellent inter-scanning reproducibility for Agatston, mass, and volume score [63].

LIMITATIONS

The KOICA registry has several limitations. The current registry was based on a retrospective observational cohort, which limits our inference of a causal relationship and is prone to re-

sidual confounding. The study sample of this registry was self-referred for routine health check-up program and, thus, may not be fully representative of the overall Korean population, thereby inducing possible selection bias. Moreover, the sample was composed of a single-ethnicity cohort of Korean adults who were predominantly male. Therefore, caution should be used in extrapolating the findings to other more heterogeneous Asian populations as well as to women. Furthermore, despite the large sample size, ACM incidence is relatively small because this registry originated from a health check-up database, which possibly restricted the data to the event rate of ACM that occurred during the follow-up period.

CONCLUSION

To date, the KOICA study has elicited various prognostic findings related to CAD risk identification through coronary atherosclerosis determined by coronary calcification. Based on its multisite approach among asymptomatic Korean adults, the results derived from the KOICA study are valuable and warrant several further prognostic investigations related to CAD.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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