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

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There is some disparity in the morbidity and mortality rates of cardiovascular disease (CVD) according to race, ethnicity, and geographic regions. Although prediction algorithms that evaluate risk of cardiovascular events have been established using traditional risk factors, they have also demonstrated a number of differences along with race and ethnicity. Of various risk assessment modalities, coronary artery calcium (CAC) score is a sensitive marker of calcific atherosclerosis and correlates well with atherosclerotic plaque burden. Although CAC score is now utilized as a useful tool for early detection of coronary artery disease, prior studies have suggested some variability in the presence and severity of coronary calcification according to race, ethnicity, and/or geographic regions. Among Asian populations, it would appear necessary to reappraise the utility of CAC score and whether it remains superior over and above established clinical risk prediction algorithms. To this end, the Korea initiatives on coronary artery calcification (KOICA) registry has been designed to identify the effectiveness of CAC score for primary prevention of CVD in asymptomatic Korean adults. This review discusses the important role of CAC score for prognostication, while also describing the design and rationale of the KOICA registry.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among industrialized nations. CVD is responsible for 31% of global mortality, accounting for approximately 17.5 million deaths from CVD in 2012 alone. Of these deaths, an estimated 7.4 million were attributable to coronary artery disease (CAD) and approximately 6.7 million due to stroke.[1] Notably, prior epidemiologic evidence indicates that these morbidity and mortality rates attributable to CVD tend to vary depending on race, ethnicity, or geographic regions, even within a particular country.[2-6] In an effort to prevent adverse cardiovascular events, accurate assessment of absolute CVD risk is para-

mount. Though to date, several studies have documented some discrepancies based on ethnicity or geographic region when utilizing risk prediction algorithms for the assessment of adverse cardiovascular risk.[7-13]

Foremost, coronary artery calcium (CAC) score is considered a robust method for early detection of CAD, and the use of CAC score is primarily recommended for risk stratification in national guidelines.[14] Yet, it has emerged that there exists some ethnic disparity in the features of coronary calcification.[15-18] Further still, most studies thus far related to CAC score are based on populations derived from Western societies. Given that CAC score has been reported to provide additional prognostic value beyond conventional risk prediction tools, it seems prudent that the predictive value of CAC score, particularly among Asian populations, is necessary. In relation, the Korea initiatives on coronary artery calcification (KOICA) registry is a novel study designed to assess the effectiveness of CAC score for primary prevention of CVD in a large cohort of asymptomatic Korean adults. In the following review, we describe the design and rationale of the KOICA registry, and how it might lend further insight towards the clinical utility of CAC score for prognostication in non-Western populations.

ETHNIC AND RACIAL DISPARITY IN THE PRESENCE OF CVD

CVD reflects a cluster of disorders in the heart and blood vessels including CAD and stroke. Although CVD manifests clinically as various diseases, CAD and stroke account for approximately 75% of all CVD-related deaths.[19] Globally, CVD accounts for the highest number of deaths related to any cause, thus contributing extensively to the economic burden associated with health costs. Notably, over three quarters of CVD deaths typically occur in low-to-middle income countries, with the rate beginning to increase further in most Asian countries.[1]

In light of the epidemiologic disparities in CVD,[3-6] previous studies have demonstrated differing CVD mortality rates based on race, ethnicity, and geographic region.[4)20-23] While the results have been largely heterogeneous in most studies, CAD mortality in Black individuals is somewhat higher compared with other races. Moreover, Asian populations tend to present with lower mortality as compared with other racial groups (Fig. 1). In a large international study of individuals representing seven pre-defined ethnic/racial groups, Meadows et al.[3] demonstrated the important ethnic-specific differences in cardiovascular risk factors as well as variations in cardiovascular mortality. Specifically, among all Asian groups that included East Asians, South Asians, and other Asians, the cardiovascular death rates were significantly lower compared with other groups (overall, 2.1% vs. 4.5%, $p < 0.001$). Data from World Health Organization describing age-adjusted mortality rates of CAD and stroke have also demonstrated different results between Western countries and some selected Asian countries in 2002.[4]

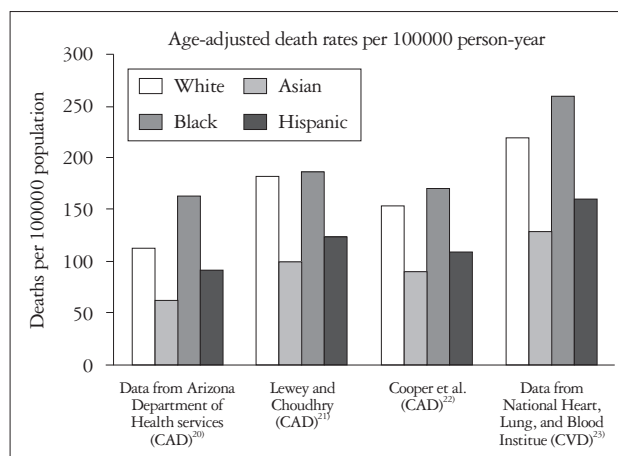Considering the rapid rise in Asian populations, now com-

Fig. 1. Age-adjusted death rates of CAD and CVD according to race/ethnicity. CAD: coronary artery disease, CVD: cardiovascular disease.

prising 60% of the world's current population,[24] CVD prevention in this ethnic subgroup is of significant health concern. In South Korea, stroke mortality rate has continuously declined since the 2000s, whereas CAD mortality rate has paradoxically increased since the 1980s.[25] In the World Health Organization multinational monitoring of trends and determinants in cardiovascular disease project, CVD incidence among numerous countries was examined, using standardized diagnostic criteria.[5)6] The age-adjusted incidence rates of acute myocardial infarction and stroke were compared among the different countries. Notably, Japan and China did not appear to have a higher incidence of stroke when compared with Western nations. However, the latter East Asian countries had a much lower incidence of acute myocardial infarction compared with those Western populations. Subsequently, East Asian countries may appear to have a lower incidence of CAD-related events as compared with Western countries.

The heterogeneity in morbidity and mortality linked to CVD may be due to some ethnic dissimilarities in the prevalence of coronary artery atherosclerosis and related risk factors,[26] alongside possible variability in the utilization of preventive therapies or availability of health care services.[27] Despite this, some variation in CVD may result from diverse mechanisms of plaque formation, erosion, rupture, or occlusive thrombosis, all of which may lead to acute coronary events.[28] Thus, any racial or ethnic differences in CVD can potentially be studied for identification of persons with subclinical atherosclerosis and correlated risk.[29] Recently a remarkable decline in the risk of CAD mortality in developed Western countries may likely reflect a reduction in the prevalence of cardiovascular risk factors, along with improved medical management.[30] On the other hand, as a result of industrialization and substantial economic development throughout Asia, the prevalence of obesity and type 2 diabetes mellitus (DM) has markedly risen in Asian nations, primarily due to altered diet and adopting a sedentary lifestyle.[31] Despite a relatively low mean cholesterol level in most Asian

countries as compared with Western countries, the increasing metabolic risk factors, such as glucose intolerance, hypercholesterolemia and insufficient control of hypertension, may well have contributed towards the trend in CAD incidence in Asian populations.

RACIAL AND ETHNIC VARIATION IN RISK PREDICTION ALGORITHMS

A significant number of patients with nonfatal myocardial infarction or sudden cardiac death often do not demonstrate a history of any prior symptoms or cardiovascular diagnosis.[32] Hence, treatments focused on patients who already experienced symptoms may have some inherent limitations when attempting to improve outcomes of morbidity and mortality related to CAD. This emphasizes the importance of early screening and improved treatment strategies for occult CAD in asymptomatic individuals.[32] Moreover, CAD is a multifactorial disease that is influenced by numerous risk factors as well as socioeconomic status. Therefore, it seems more clinically beneficial to estimate the risk of CAD by simultaneously considering numerous factors associated with CAD rather than focusing on single factors alone. The Framingham heart study initially developed a risk algorithm to predict the development of CAD, and included major risk factors such as age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, DM status, and electric left ventricular hypertrophy.[33] Since, the Framingham risk score (FRS) has continuously been developed[34] and widely adopted for the prediction of the absolute risk of future cardiovascular events worldwide.[35]

A potential drawback of the FRS is its development in a predominantly Caucasian middle-class study sample; hence, generalization of this algorithm to other diverse ethnic populations may be somewhat limited. Considering most individuals tend to have multiple sub-threshold risks, determining their true personal cardiovascular risk is often more difficult. In light of this, the FRS may not be suitable or practical for identifying diverse high cardiovascular risk populations.[7]

Several studies have assessed the validity and utility of the FRS. Based on results of a multiple ethnic groups investigation, for white men and women as well as for black men and women, FRS performed reasonably well for prediction of cardiovascular risk within 5 years of follow-up.[8] On the other hand, FRS largely overestimated the risk among Native American women, Hispanic men, and Japanese Americans. A number of investigators also indicated that overestimation of cardiovascular risk was reported when FRS was directly applied to other populations in Asia[7]8] including Korea,[13] as well as across Europe, in countries such as Germany,[9] Spain,[10] France,[11] and Italy.[12] Liu et al.[7] assessed the predictive performance of the FRS in a large Chinese population. In that study, FRS overestimated the 10-year absolute CAD risk in both Chinese men and women with larger predicted differences compared with actual observed rates. For instance, among men in the 10th risk decile, the predicted rate of CAD mortality was 20% compared with an observed rate of 3%. In another study consisting of French men, the overall FRS estimated that the number of CAD events was twice as high when compared with the actual observed number of CAD events.[11]

The results of previous studies displaying discrepancies between observed and predicted risk of CAD have significant implications for the primary prevention of CAD, as the overestimation of absolute risk could lead to inappropriate or inadequate treatments and excessive expenditures in individuals who have actually lower CAD risk than anticipated. Against this background, prior studies have undertaken large efforts to recalibrate the original FRS, in an effort to improve predictive ability.[7]8)12] In a large cohort study comprising multiple ethnic groups residing in the US, the FRS fit well in other populations following recalibration, even after considering the difference in prevalent risk factors and underlying rates of developing CAD.[8] Foremost, while the original FRS model appeared to overestimate actual observed CAD events, the recalibrated FRS model was in close agreement with the new model in this study. In addition, numerous efforts have been made to establish a novel risk prediction tool that is suitable for estimating cardiovascular risk, depending on specific race or ethnicity.[9]13) For example, in Korea, Jee et al.[13] developed a new CAD prediction tool and demonstrated that the model provided accurate and reliable prediction of cardiovascular risk specifically among Korean individuals.

PREDICTIVE VALUE OF CAC SCORE

To date, there have been numerous risk prediction models, serum biomarkers, and imaging modalities for the purpose of screening CVD in asymptomatic individuals. Among them, CAC score is a specific surrogate marker of calcific atherosclerosis in the coronary arteries and is frequently used to quantify coronary atherosclerotic plaque burden.[36] The CAC score determined by cardiac computed tomography (CT) has been well established as a robust imaging modality for early detection of CAD, enabling direct visualization of coronary atherosclerosis, particularly in asymptomatic individuals as compared to other cardiac risk factor-based paradigms.[37]

A robust relationship has been found between CAC score and atherosclerotic burden as well as future cardiovascular events in asymptomatic populations. Indeed, increasing CAC score has been consistently associated with increased cardiovascular risk.[38] In addition, others have found that the CAC score provides incremental benefit over and above conventional risk factors. Although the FRS has often proven to be a useful risk algorithm, this prediction tool may misclassify a number of truly high-risk individuals who are likely to benefit from preventive treatment.[39] To this end, previous studies have indicated that the CAC score provides incremental benefit in addition to the FRS and additional advantage towards risk strat-

ification when assessing cardiovascular risk. Greenland et al.[40] reported that CAC score assessment combined with FRS in asymptomatic persons provides prognostic information superior to either method alone. In the Multi-Ethnic Study of Atherosclerosis (MESA), Yeboah et al.[41] compared the predictive utility of several novel risk markers for incident CVD and documented superior discrimination and reclassification based on the CAC score. Albeit, while CAC score is considered to improve risk classification as advocated by recent guidelines,[14] the results from prior studies are largely derived from predominantly Caucasian populations, with findings according to other racial or ethnic groups still lacking.[29]

RACIAL AND ETHNIC DIFFERENCES IN CORONARY ARTERY CALCIFICATION

Few recent studies have found some differences in the prevalence and severity of CAC score according to race and ethnicity.[15-18] In a sample of 1461 asymptomatic high-risk adults, Tang et al.[17] demonstrated significant ethnic differences in the prevalence of coronary calcium. In that study, African Americans were found to have a significantly lower prevalence of coronary calcium as compared with Asian Americans or Caucasians. Budoff et al.[16] reported that African Americans and Asians had a lower prevalence and severity of calcification compared with non-Hispanic Whites and Hispanics. These disparities persisted after adjusting for standard cardiac risk factors. In the MESA Study, there was a similar result of a substantially lower prevalence of coronary calcification among Hispanics and blacks versus whites and a slightly lower prevalence in Chinese versus whites.[15] Also, in that study, even after controlling for

risk factors, the prevalence of CAC score was lower in ethnic minorities. More recently, in a cross-sectional study comparing CAC score between US Caucasian men and Japanese men,[42] the investigators found that Caucasian men aged between 45–74 years had a higher burden of coronary artery atherosclerosis compared with Japanese men of the same age. In addition, this trend appeared to become more prominent with advancing age, even after adjusting for traditional risk factors.

Despite recent advances offering insight into the ethnic and racial disparities in CAC scores, the precise factors that actually modify CAC score on the background of race or ethnicity are not well defined. Several possible mechanisms have been considered. Notably, ethnic minorities tend to present with a higher number of conventional risk factors, comorbidities, and a lower access to health care treatment.[29] Further still, other factors including behavioral, environmental, biochemical, and genetic predispositions, may modify the CAC score according to ethnicity or race. Though, clearly, additional studies are needed to test this notion.

REAPPRAISING THE VALUE OF CAC SCORE IN ASIAN POPULATIONS

Prior studies have investigated the differences in the prevalence and severity of CAC score according to race and ethnicity. However most of the extant CAC score literature has predominantly highlighted its relationship with adverse outcomes among Caucasian populations. Several previous studies have reported CAC score incremental to conventional risk factors in Korean adults.[43-48] Table 1 summarizes the results of available studies that examined the prognostic value of CAC score among

Table 1. The studies investigating value of CAC score in Asian population

Authors	Settings	Population (n)	Follow-up duration (yr)	Main findings
Park et al.[43]	Retrospective cohort	Korea (5182)	4.0	CAC score predicted adverse cardiac outcome alone, when assessed with other parameters, degree of stenosis performed better as a prognostic tool than CAC score
Kim et al.[44]	Cross-sectional	Korea (7988)		FRS underestimated cardiovascular risk in around 10% and by CAC score, 9.4% was reclassified to the discordantly higher risk group. CAC score should be considered for more accurate risk stratification in subjects at low to moderate risk
Sung et al.[45]	Cross-sectional	Korea (1653)		Risk stratifications by CAC score and 10-year FRS showed a large discrepancy in around 9% of participants. CAC score is more useful predictor in adults older than 50 years and/or in metabolic syndrome patients
Itani et al.[46]	Prospective cohort	Japan (6120)	4.0	CAC was detected in 10 of 14 patients (71.4%) who died of cardiac disease, and in 31 of 64 patients (48.4%) who died of other diseases ($p = 0.084$). The relative risk of CAC for cardiac death was 2.66 (95% CI: 0.76–9.37)
Fujimoto et al.[47]	Retrospective cohort	Japan (2238)	1.8	High CAC score and non-culprit high-risk plaque on CCTA performed before revascularization are significant predictors of cardiac events after revascularization, with greatly discriminatory power
Yamamoto et al.[48]	Retrospective cohort	Japan (317)	6.0	HR for cardiac death in patients with a CAC score > 1000 was 2.98 (95% CI: 1.15–9.40) compared with those with a CAC score 0 to 100. CAC score has a predictive value for CAD and long-term mortality from cardiac disease

CAC: coronary artery calcium, FRS: Framingham risk score, CCTA: coronary computed tomography angiography, CAD: coronary artery disease, HR: hazard ratio, CI: confidence interval

study populations across Asia. Park et al.[43] revealed that CAC score was an important predictor of poor cardiovascular outcomes when evaluated alongside traditional biomarkers and risk factors; however, when the extent of coronary stenosis was added to the model, CAC score did not improve prognostic power. Another study comprising 7988 Korean participants at intermediate cardiovascular risk evaluated the differences among risk stratifications along with the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guide-

line and CAC score.[44] In that study, the NCEP-ATP III guidelines underestimated cardiovascular risk in approximately 10% of enrolled individuals, whereas 9.4% were correctly reclassified to the higher risk group by including CAC score, thus emphasizing that CAC score should be considered for more accurate risk classification. Nevertheless, while the effectiveness of CAC score has been universally verified in numerous populations, its utilization is often overlooked in clinical practice in Korea. Given these circumstances, further studies among Asian

Table 2. Examination components of the KOICA registry

Examination components	Description
Demographics	
Sex, age, height, weight, BMI, weight circumflex, SBP, DBP, HR	Measured and collected at the time of each visit to the healthcare centers
Past disease history	
HTN, CAD, hyperlipidemia, DM, CKD, and stroke	Based on self-reported medical questionnaires about past history or current medication
Family disease history	
HTN, CAD, DM, and stroke	Based on self-reported medical questionnaires
Smoking status	Based on self-reported medical questionnaires
Alcohol use	Based on self-reported medical questionnaires
Lifestyle	
Exercise status, time and frequency	Based on self-reported medical questionnaires
Socioeconomics	
Education and income	Based on self-reported medical questionnaires
Laboratory tests	
CBC	
WBC, Hb, hematocrit, platelet	Obtained at the time of each visit to the healthcare centers
Serum chemistry	
HbA1c, glucose, BUN, creatinine, lipid profile (TC, TG, HDL, LDL), total protein, albumin, liver function test (total bilirubin, GGT, AST, ALT), thyroid function test T3, free T4, TSH), electrolytes (Na, K, Cl, tCO_2, Ca, P), uric acid, high-sensitivity CRP	Obtained at the time of each visit to the healthcare centers
Urine analysis	
Urine pH, protein, glucose	Obtained at the time of each visit to the healthcare centers
Cardiovascular screening tests	
CAC scanning	
Agatston score, calcium volume and mass	Acquired by using a greater than 16-slices multi-detector CT scanner. Each center used specific CT scanner types (the Philips Brilliance 256 iCT, Philips Brilliance 40 channel multi-detector CT, Siemens 16-slice Sensation, and GE 64-slices Lightspeed)
Arterial stiffness assessment	baPWV was evaluated in two sites. CAVI was measured at one site using a VaSera VS-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan)
Exercise treadmill test	Performed using Bruce protocol (Quinton Q4500, Cardiac Science Corp., Bothell, WA, USA and Case8000, GE Healthcare, Wauwatosa, WI, USA). Exercise capacity was recorded as METs

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, HTN: hypertension, CAD: coronary artery disease, DM: diabetes mellitus, CKD: chronic kidney disease, CBC: complete blood count, WBC: white blood cell, Hb: hemoglobin, BUN: blood urea nitrogen, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, GGT: gamma-glutamyl transpeptidase, AST: aspartate aminotransferase, ALT: alanine transaminase, TSH: thyroid stimulating hormone, CAC: coronary artery calcium, Na: sodium, K: potassium, Cl: chloride, tCO_2: total carbon dioxide, Ca: calcium, P: phosphorus, CRP: C-reactive protein, baPWV: brachial-ankle pulse wave velocity, CAVI: cardio-ankle vascular index, METs: metabolic equivalen, KOICA: Korea initiatives on coronary artery calcification, HbA1c: glycated hemoglobin

individuals, especially Koreans, are warranted in order to reappraise the efficacy and predictive significance of the CAC score, which has been proven to be superior to other traditional risk prediction algorithms. Hence, the KOICA registry was designed to evaluate the usefulness and prognostic importance of CAC score for predicting all-cause mortality (ACM) in a large cohort of asymptomatic Korean adults.

KOICA Registry

Study design

The KOICA registry is a retrospective, single ethnicity multicenter observational study designed to investigate the effectiveness and prognostic value of CAC score for primary prevention of CVD in asymptomatic Korean adults. Overall, there were 3 sites involved in the KOICA registry. The study population includes self-referred individuals who underwent self-reported medical questionnaires to obtain personal clinical data and medical history with the purpose of a health check-up at a healthcare center in South Korea. A total of 48903 subjects were initially enrolled in the study between December 2002 and July 2014. The appropriate institutional review board committees at each study site approved the study protocol, and all study participants provided written informed consent.

Study measures

Table 2 summarizes the examination components of the KOICA registry. All data were obtained using a health check database at the healthcare center of each site in South Korea. Baseline demographic parameters were measured at the time of each visit to the health care centers and collected by self-reported medical questionnaires. Each underlying disease including hypertension, CAD, hyperlipidemia, and DM was defined according to participants' self-reported medical history. Laboratory tests were obtained from a complete blood count, serum chemistry, and urinalysis that included numerous biochemical parameters. Other cardiovascular screening tests for risk assessment included arterial stiffness assessment and exercise treadmill test. Though, it bears mentioning that not all demographic parameters or tests were performed in all patients, which will likely lead to some heterogeneity in forthcoming analytic sample sizes.

CAC screening procedures

CAC score was acquired using a greater than 16 slice multidetector CT scanner. Specific CT scanner types used within each center included the Philips Brilliance 256 iCT (Philips Healthcare, Cleveland, OH, USA), Philips Brilliance 40 channel MDCT (Philips Healthcare, Cleveland, OH, USA), Siemens 16-slice Sensation (Siemens, Forchheim, Germany), and GE 64-slice Lightspeed (GE Healthcare, Milwaukee, WI, USA). All three centers performed standard prospective or retrospective methods.

Study endpoint

The mean follow-up duration was 4.8 years (interquartile range: 2.7–6.7 years). The primary endpoint in the KOICA registry is ACM, which was confirmed by querying the Ministry of Security and Public Administration records up until December 2014 for 2 centers, and up until September 2014 for the remaining center, allowing for 100% ascertainment of mortality status. Over the course of the study period, a total of 415 (0.9%) events were recorded in the KOICA registry. According to the Personal Information Protection Act, only data regarding all-cause and not cause-specific mortality were available for analysis

Statistical methods and study objectives

Continuous variables are reported as mean ± standard deviation, and categorical variables are reported using counts with proportions. For continuous parameters, Student's t-test or Wilcoxon rank-sum test will be employed as appropriate for two-group comparisons, or one way ANOVA or Kruskal-Wallis test for more than two-group comparisons, as appropriate. Comparison of categorical variables will be performed using Pearson's chi-square test. The primary objective of the KOICA registry is to determine the effectiveness of CAC score for predicting adverse outcomes in asymptomatic Korean adults, with ACM as the study endpoint. Cumulative ACM event rates over time according to CAC score categories will be estimated using the Kaplan Meier survival curve and compared using the log rank test. Multivariable Cox proportional hazards regression models will be used to calculate the hazard ratios with 95% confidence intervals (95% CIs) for risk of ACM according to CAC score categories. The added prognostic value of CAC score over and above established risk factors (e.g., the FRS) will be evaluated using the likelihood ratio χ^2 test, the C-statistic, as well as the continuous net reclassification improvement index. In secondary analyses, we intend to examine: 1) the usefulness of atherosclerotic burden as determined by CAC score for predicting ACM according to pre-specified subgroups; 2) the CAC score as a valid and robust cardiovascular tool among Koreans. Additional to the above mentioned statistical procedures, we will also study the diagnostic performance of CAC score by determining sensitivity, specificity, as well as negative and positive predictive values in an effort to establish the CAC score as a useful screening tool among asymptomatic Korean adults; and 3) we will analyze the disparity, if any, in the severity and outcome of CAC according to ethnic and socioeconomic background via the international cooperation institutions database. Using a binary logistic regression approach reporting odds ratios with 95% CI, we will employ a propensity matching method that will permit matching of patients from both ethnic cohorts according to available demographic characteristics, with the exception of the outcome CAC score.

DISCUSSION

The KOICA registry will provide essential information for determining the effectiveness of CAC score for primary prevention of CVD along with its role in determining clinical CVD in a large cohort of asymptomatic Korean adults. The KOICA registry will enable investigators to identify the characteristics, severity and determinants of CAC score for the purpose of determining Asian-specific cut-off values for screening high-risk Korean adults. The analysis of the relationship between CAC score and traditional risk factors will also be performed. Based on prior findings primarily derived from Western populations, we anticipate that CAC score may provide incremental benefit over and above other risk assessment models for predicting adverse outcomes. To examine the potential disparity according to race or ethnicity, cross-sectional comparison studies will be considered between the KOICA registry and other external study databases comprising different ethnicities in order to evaluate the prevalence and distribution of CAC score and/or events. Further, the long-term protective effects of a zero CAC score can be assessed given the latter beneficial effects are yet to be determined in a Korean population. Also, the KOICA registry will have the capability to evaluate possible interactions between CAC score and other cardiac risk factors that are available in this study.

Though we anticipate the KOICA registry will provide important and additional information to the extant CAC literature, our registry has some inherent limitations that should be emphasized. The present study is retrospective and observational in nature and only recorded a single measure of the CAC score, which will make it a challenge to interpret a long-term causal relationship. Although the KOICA registry incorporates a substantial number of predictors and covariates, as is the case with most observational studies, we cannot discount the possibility of residual confounding due to unmeasured parameters. Our study participants were self-referred at routine health check-up programs, which may have inferred selection bias (i.e., healthy volunteers, or higher socio-economic status). Thus rendering our study sample not fully representative of the overall Korean population. Our study sample is predominantly male; hence caution should be taken when extrapolating our findings to women. Further still, despite the large sample size, the incidence of ACM is relatively small, as this registry was derived from a health check-up database, which limits the event rate that occurred during the follow-up period. In addition, the current study includes only self-reported information regarding certain participants' demographics (i.e., medication use), which, in some cases, may potentially lead to a diminished risk prediction. Last, there is no information regarding cause-specific mortality in this registry. Though, prior reports have revealed that the assessment in the accuracy of death certificates has been mostly problematic, typically with an overestimation of cardiac death.[49] To this end, the use of ACM as the primary endpoint provides an unbiased endpoint in the absence of cause-specific mortality.[50]

CONCLUSION

Reevaluating the prognostic utility of CAC score, which has been proven to be superior to other traditional risk prediction algorithms, is urgently needed, especially among non-Western populations. In light of this, the KOICA registry will provide some information regarding the effectiveness and prognostic value of CAC score for primary prevention of CAD, and may also help identify optimal criteria with regards to screening for cardiovascular risk among asymptomatic Asian (i.e., Korean) adults. Foremost, the anticipated findings from the KOICA registry may prove useful for eliminating unnecessary medical costs by providing appropriate individualized treatment strategies. In time, it is expected that the KOICA registry will lend substantially towards understanding the important role CAC score might have for prognostication in asymptomatic Korean adults and how these finding may reflect differently when compared with other racial or ethnic groups.

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