Atherosclerotic cardiovascular disease prediction model and prescribing rates of Statins: the Korean Heart Study

Keum Ji Jung

The Graduate School

Yonsei University

Department of Public Health

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Keum Ji Jung

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This certifies that the dissertation of Keum Ji Jung is approved.

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Thesis Supervisor: Sun Ha Jee

_____

Yangsoo Jang: Thesis Committee Member #1

_____

Chungmo Nam: Thesis Committee Member #2

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Byung-Ho Nam: Thesis Committee Member #3

_____

Hye Young Kang: Thesis Committee Member #4

The Graduate School

Yonsei University

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ABSTRACT

Atherosclerotic cardiovascular disease prediction model and prescribing rates of Statins: the Korean Heart Study

Jung, Keum Ji
Dept. of Public Health
The Graduate School
Yonsei University

Background and Aims: The aims of the study were to evaluate the performance of the American College of Cardiology/American Heart Association (ACC/AHA) 2013 Pooled Cohort Equations in the Korean Heart Study (KHS) population, to develop a Korean Risk Prediction Model (KRPM) for atherosclerotic cardiovascular disease (ASCVD) events, and to evaluate the relation between 10-year ASCVD risk score from two different ASCVD prediction equations and actual statin prescriptions in the last 10 years (2004-2013) in Korean general population.

Methods: The KHS cohort included 200,010 Korean adults aged 40–79 years who were free from ASCVD at baseline. Discrimination and calibration of the ACC/AHA 2013 Pooled Cohort Equations in predicting 10-year ASCVD risk in the KHS cohort were evaluated. Recalibration of the ACC/AHA Equations was done using

coefficients from the pooled cohorts' Cox model but mean values of risk factors and ASCVD incidence rates from the KHS cohort. The KRPM was derived using coefficients, mean risk factor values, and mean incidences from the KHS cohort. Per equations, we also calculated the prescribing rates of statins using cumulative incidence.

Results: In the discriminatory analysis, the ACC/AHA Equations for either White or African-American (AA) moderately distinguished cases from non-cases in the KHS cohort, and were similar to the KRPM: For men, the area under the receiver operating characteristic curve (AUROCs) were 0.727 (White model), 0.725 (AA model), and 0.741 (Korean model); for women, the AUROCs were 0.738, 0.739, and 0.745, respectively. Absolute 10-year ASCVD risk for men in the KHS cohort was overestimated by 56.5% in the White model and 74.1% in the AA model, while the risk for women was underestimated by 27.9% in the White model and overestimated by 29.1% in the AA model. Recalibration of the ACC/AHA Equations did not affect discriminatory ability but improved calibration substantially, especially in men in the White model. Of the three ASCVD risk prediction models, the KRPM showed the best calibration, with the lowest Hosmer-Lemeshow X^2 for both men and women when used in a validation subsample. During the follow-up period, an overall prescribing rate of statins in women was 33.5% greater than that of men, 26.3%.

Conclusions: The ACC/AHA Equations should not be directly applied for ASCVD risk prediction in a Korean population. The KRPM showed best predictive ability for ASCVD risk. Therefore, utilization of the prediction risk score in deciding on preventive statin therapy is suggested for Korean population.

keywords: Prediction**,** Statin, Atherosclerotic cardiovascular disease, Cohort study

I. INTRODUCTION

In 2013, the Risk Assessment Work Group (Work Group) appointed by the National Heart, Lung, and Blood Institute released the risk assessment tool for initial atherosclerotic cardiovascular disease (ASCVD) events, defined as the occurrence of coronary death or fatal stroke or the first occurrence of nonfatal myocardial infarction (MI) or stroke (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. 2002; Grundy et al. 2004; Goff et al. 2014). To estimate the 10-year risk of developing a first ASCVD event, American College of Cardiology/American Heart Association (ACC/AHA) Equations were developed using data from large epidemiological studies (n = 24,626) conducted in the US (Atherosclerosis Risk in Communities, Cardiovascular Health Study, Coronary Artery Risk Development in Young Adults, and the Framingham and Framingham Offspring studies) (Goff et al. 2014). These Pooled Cohort Equations provide sex- and race-specific estimates of the 10-year risk of ASCVD for African-American and White men and women 40 to 79 years of age (Goff et al. 2014). However, the Work Group has recognized that data are limited for follow-up of Hispanic and Asian-American cohorts and specifically called for further research that includes "analyses of short- and long-term risk in diverse groups...." (Goff et al. 2014). Subsequently, several cohort (Kavousi et al. 2014; Muntner et al. 2014; DeFilippis et al. 2015) and cross-sectional (Blaha et al. 2014; Ford et al; 2014; Kandula et al. 2014; Lee 2014, Oh et al. 2014) studies have applied the ACC/AHA 2013 Pooled Cohort Equations in different populations, with varying results. The direct application of this American assessment tool in other non-US populations is

questionable, particularly in Asian populations such as Korea, where there are possible differences in genetics as well as ASCVD risk factors and event rates (Jee et al. 2014; Kim et al. 2014). However, experience from the Framingham risk prediction algorithms for coronary heart disease (CHD) showed that the Framingham functions, when recalibrated, had improved predictive ability for several different ethnic groups in the US (D'Agostino et al. 2001; Liu et al. 2004) and China (Liu et al. 2004).

In Korea, the Korean Heart Study (KHS) for cardiovascular disease has conducted a 10-year follow-up and successfully developed a CHD risk prediction model which used the Framingham risk prediction algorithms as starting point (Jee et al. 2014). The Korean experience provides the opportunity to examine the performance of the original and recalibrated ACC/AHA 2013 Pooled Cohort Equations as a 10-year ASCVD risk assessment tool.

Also, according to the ACC/AHA 2013 guidelines, statin therapy is recommended if the subject's 10-year ASCVD risk exceeds 7.5% (Stone et al. 2014; Goff et al. 2014; Kavousi et al. 2014; Muntner et al, 2014), and roughly two-thirds of the US adults may be eligible for statins (Kavousi et al. 2014). However, studies assessing its applicability in an Asian population-wide setting or association between statins and 10-year ASCVD risk score are scarce. Furthermore, as Asian population including Korean lacks a representative ASCVD risk tool, in-depth analysis of the last 10-year statin prescriptions and evaluation of ASCVD risk models are necessary. The results of this study may be used as a baseline data to guide implementation of policy measuring the adequacy of therapy for dyslipidemia and ASCVD high risk groups among the general population.

II. OBJECTIVES

The objectives of this study were to evaluate the performance of the ACC/AHA 2013 Pooled Cohort Equations in the KHS population, to develop a Korean Risk Prediction Model (KRPM) for ASCVD, and to evaluate the relation between 10-year ASCVD risk score from two different ASCVD prediction equations and actual statin prescriptions in the last 10 years (2004-2013) in Korean general population.

III. MATERIALS AND METHODS

A. Study population

Study members are participants in routine health assessments at health promotion centers across South Korea. The centers are used by members of the public following referral by themselves, their family physician, their employer, or upon recommendation by a family member or friend. Of 80 health promotion centers in South Korea, around half routinely store their records electronically; of these, 18 agreed to provide data (Jee et al. 2014). Participating centers were generally geographically representative of the country with the exception of the South West where there was no participating centers. The South Korean population is assigned a personal identification number at birth. This number facilitated linkage with hospital admission records and death registers. All Koreans are members of the National Health Insurance Service (NHIS), formerly, the Korean Medical Insurance Corporation and National Health Insurance Corporation. To ensure anonymity, all linkages were carried out by NHIS staff. The record linkage resulted in 430,920 study members (164,138 women) aged 30–74 years at health assessment at baseline between 1996 and 2004. According to the Bioethics and Safety Act (no. 7159) from the Ministry of Health and Welfare in January, 2005, a retrospective study was performed using the data collected from participants who underwent medical examinations before December 2004 (participants without written consent).

First, in a study to develop a KPRM, all enrollees of the health centers aged 75-79 years (N=1,670) were included while those aged 30-39 (N=123,868) were excluded, thus corresponding to the age range of the ACC/AHA 2013 Pooled Cohort Equations

which was 40-79 years (Goff et al. 2014). The baseline period of this study was 1996 to 2001 for the development of a 10-year ASCVD risk prediction model. Therefore, all participants had a minimum of 10 or more potential years of follow-up by the end of December 2012 **(Figure 1)**. Among the participants with at least 10 years follow-up, individuals who were receiving lipid-lowering medication at baseline (n = 8,809), those with stroke or cardiovascular disease (n =10,066), or those with missing values of essential variables (n =4,234) such as blood pressure, total serum cholesterol, high density cholesterol, fasting serum glucose, smoking status, or body mass index were excluded. The study ultimately included 192,605 individuals (114,622 men and 77,983 women).

Second, in a comparing the two models, all enrollees of the health centers aged 75-79 years (N=1,670) were included while those aged 30-39 (N=123,868) were excluded, thus corresponding to the age range of the ACC/AHA 2013 Pooled Cohort Equations which was 40-79 years (Goff et al. 2014). Among the 308,722 participants, individuals who were receiving lipid-lowering medication at baseline (n = 19,364) were excluded. Then, 289,358 participants had a minimum of 9 or more potential years of follow-up by the end of December 2013. For analyses on examining the ASCVD event, CVD mortality, and prescribing rates of statins, exclusions were made using the criteria from each equation **(Figure 2)**.

The Institutional Review Board of Human Research of Yonsei University approved the study (IRB approval number 4-2007-0065). Data for this study were collected from routine health examinations and therefore no written content was necessary.

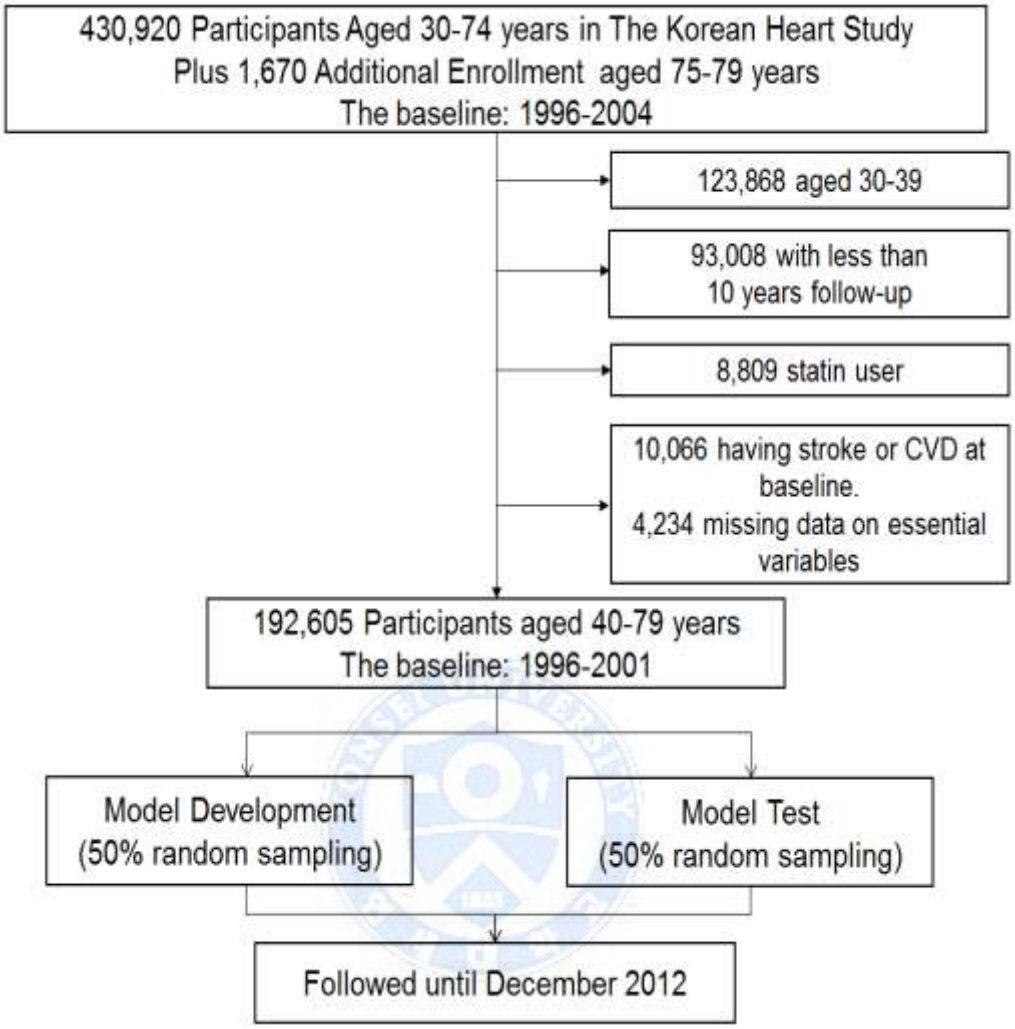

Figure 1. Flow chart describing study population, KHS

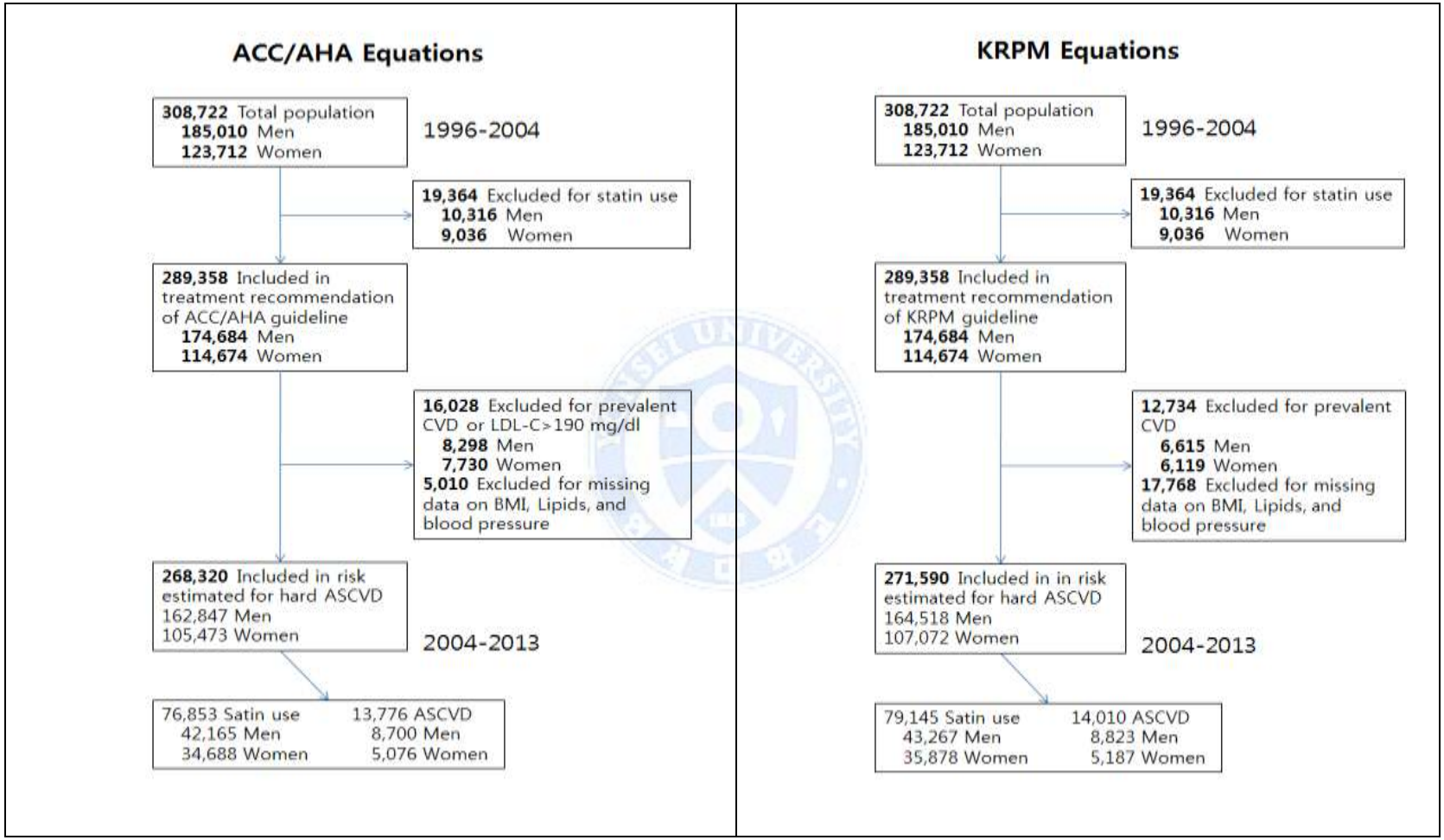

Figure 2. Inclusion and exclusion criteria for the KHS for assessment of different ASCVD risk prediction equations

B. Data collection

Participants were interviewed using a structured questionnaire to collect information on personal history of cigarette smoking (current, former, never) and physician diagnosis of significant chronic diseases (diabetes, hypertension, stroke, myocardial infarction, angina). A registered nurse or medical technician measured blood pressure using a standard mercury/automatic sphygmomanometer. A 12-hour fasting blood sample was taken and a clinical chemistry assay of fasting glucose, lipid profiles, and other biomarkers were measured with a COBAS INTEGRA 800 and a 7600 Analyzer (Hitachi, Tokyo, Japan). In all risk assessments, diabetes was defined as fasting serum glucose >126 mg/dL or diabetic treatment history; hypertension was systolic blood pressure ≥140 mmHg or use of hypertension medication; and former smoker was classified as non-smoker.

C. Outcome variables

First "hard" ASCVD events, comprising the occurrence of death from CHD or fatal stroke or the first occurrence of nonfatal myocardial infarction or stroke, were recorded (Goff et al. 2014). The events among the study cohort were identified from insurance claims reported to the National Health Insurance System (NHIS). Since the NHIS is a national organization, follow-up was expected to be 100% complete. We ascertained nonfatal MI or stroke events, defined according to the International Classification of Diseases 10th (ICD-10) Revision, from health insurance claims data from the NHIS. Cases of fatal ASCVD, including deaths from CHD (ICD-10, I20-I25),

and deaths from stroke (ICD-10, I63), were ascertained from the cause of death listed on death certificates.

A validation study has been conducted by the Korean Society of Cardiology through the formation of the Event Validation Committee (July 2008 to May 2009). For participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, and 73% of the cases of myocardial infarction were validated (Kimm et al. 2012). The updated validation study was improved to 93% of MI events between 2008 and 2011 (Kim 2013). Another study reported that 83% of stroke diagnoses were validated among a sample of 626 stroke patients (Park et al. 2000).

Actual prescription of statins was followed-up by the end of December 2013. Statins use was defined by investigating prescription frequency of the following drugs: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. We evaluated proportion of individuals for whom statins subscribed as cumulative incidence and prescribing rate per 100 person-years.

D. Statistical analysis

i. Evaluation of the ACC/AHA 2013 Pooled Cohort Equations for 10-year ASCVD risk prediction

The predictive ability of the ACC/AHA 2013 Pooled Cohort Equations for the KHS population was evaluated based on discrimination and calibration of the models for both White and African-American men and women. Discrimination is the capability to

categorize those with and without disease based on predictive values. Calibration is the measure of how accurately the predicted risk matched the observed risk. For all analyses, follow-up was censored at 10 years.

a) **Discrimination**: The discriminatory power of the ACC/AHA model in predicting ASCVD end points among the KHS participants was assessed by using the area under the receiver operating characteristic curve (AUROC) or c statistic (Pencina et al. 2004).

b) **Calibration**: A calibration analysis, which measured how closely the predicted risk fit the actual risk, was conducted by dividing participants, within each sex, into deciles of predicted risk. The observed and predicted 10-year ASCVD risks in each decile were compared using the Hosmer–Lemeshow test. Calibration was also determined graphically by plotting the observed and predicted ASCVD events, grouped according to deciles of predicted probabilities (Nam 2000).

ii. Recalibration of the ACC/AHA Pooled Cohort Equations to the KHS population

The ACC/AHA 2013 Pooled Cohort Equations were recalibrated for the KHS population following the method proposed by D'Agostino et al (2001) (D'Agostino et al.2001). In the recalibrated ACC/AHA Equations, the coefficients were taken from the ACC/AHA Equations' Cox model, but the risk factors in the ACC/AHA Equations were replaced by the mean values of the risk factors from KHS cohort, while the ACC/AHA average incidence rate $S_0(t)$ was replaced by the KHS cohort's own average incidence rate.

iii. Development of the KPRM for ASCVD

For the KRPM, coefficients in the KHS Cox proportional hazard models, mean values of the risk factors, and mean incidences in the KHS cohort were used. Risk scores for this ASCVD Risk Prediction Model were developed by Cox proportional hazard models derived in men and women after testing for the assumptions underlying its use. We stratified the cohort data into 2 groups: a 50% random sampling (development data set) for model development and the remaining 50% (test data set) for internal validation (**Figure 1**). The predictive ability of the KRPM for the KHS population was assessed based on discrimination and calibration of the models in the test dataset.

To ensure comparability with the ACC/AHA 2013 Pooled Cohort Equations, age, blood pressure, total and HDL-cholesterol levels, diabetes, and smoking status were considered for inclusion in the Korean ASCVD risk score. In terms of blood pressure, cases were classified into treated and untreated. Contemporary guidelines (Goff et al. 2014) were used to define diabetes as self-reported or fasting glucose ≥126 mg/dL.

iv. Sensitivity analysis

Discrimination and calibration analyses of the KRPM were repeated by excluding subjects with diabetes or low density lipoprotein levels >190mg/dl.

v. Actual statin prescriptions in the last 10 years (2004-2013)

Both cumulative incidence and prescribing rates of statins per 100 person-years were calculated. Using Kaplan-Meier method, cumulative incidence of statins was expressed as proportions of individuals who subscribed statins in overall, before, and after the 1st ASCVD event during follow-up.

All analyses were conducted using SAS version 9.1.2 (SAS Institute Inc., Cary, NC, USA).

IV. RESULTS

A. General characteristics of study population

Overall, mean ages of KHS participants were similar among men (50.13 years; SD 7.94) and women (51.81 years; SD 8.12). Mean systolic blood pressure values were also similar between the sexes. However, smoking was highly prevalent in men (49.40%) but uncommon in women (4.49%) **(Table 1)**.

Table 1. General characteristics of study to develop a KPRM participants aged 40–79 Years from the KHS (1996–2004), N=200,010

	Men (N=119,715)	Women (N=80,295)
	Mean (SD)	**Mean (SD)**
Age, year	50.13 (7.94)	51.81 (8.12)
Body Mass Index, kg/m^2	23.84 (2.69)	23.72 (3.03)
Total cholesterol, mg/dL	196.84 (34.79)	201.22 (37.44)
HDL-cholesterol, mg/dL	47.98 (10.88)	54.23 (12.83)
LDL-cholesterol, mg/dL	120.14 (32.54)	123.59 (34.04)
Systolic blood pressure, mmHg	124.79 (17.61)	124.49 (20.30)
Insurance premium, Korean won*	145,449 (158,873)	131,308 (142,791)
	%	%
Statin use	4.25	2.88
Smoking status		
Ex smokers	26.46	4.10
Current smokers	49.40	4.49
Diabetes[†] (Yes)	10.49	7.43
Regular exercise (Yes)	53.15	39.35

* A measure of socioeconomic status was the health insurance premium per year, in South Korean 'Won' (1,129 Won = 1.00 US Dollar).

[†] Diabetes was defined as fasting serum glucose ≥126 mg/dL or a history of treatment for diabetes.

KRPM, Korean Risk Prediction Model; KHS, Korean Heart Study; SD, standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein;

B. ASCVD incidence

During the mean 12.8 years of follow-up, 12,327 ASCVD events (including 2,175 nonfatal MI, 478 fatal CHD, 10,049 nonfatal stroke, and 749 fatal stroke) occurred among the study participants **(Table 2).** The ASCVD incidences per 100,000 person-years were 765.7 for men and 721.5 for women. Among the total stroke events, ischemic stroke accounted for 58.5% among men and 52.2% among women.

Compared with the regression coefficients from the KHS for similar variables, the published regression coefficients for the ACC/AHA Equations differed in values but had the same directions **(Table 3 and 4)**.

Table 2. Person-years of follow-up and ASCVD events in men and women aged 40–79 years from the KHS (1997–2012), N=192,605§

	Men (n=114,622)			Women (n=77,983)		
	Person-Years of Follow-up	Events	Incidence per 100,000 PY*	Person-Years of Follow-up	Events	Incidence per 100,000 PY*
Total ASCVD	1,441,296	7,669	765.7	1,046,510	4,658	721.5
Nonfatal myocardial infarction	1,469,872	1,718	144.4	1,027,594	457	74.0
Fatal coronary heart disease	1,479,886	357	38.7	1,030,249	121	35.5
Nonfatal stroke	1,450,495	5,874	598.9	1,008,014	4,175	627.7
Ischemic stroke	1,459,375	3,585	372.8	1,017,659	2,256	380.7
Hemorrhagic stroke	1,471,817	1,258	120.1	1,025,569	876	116.4
Fatal stroke	1,479,886	480	68.0	1,030,249	269	61.2
Ischemic stroke	1,479,886	133	24.4	1,030,249	64	20.3
Hemorrhagic stroke	1,479,886	209	24.6	1,030,249	126	20.8

§ Excluded for statin use at baseline

* Incidences were standardized to the age distribution in the 2005 Korean population

ASCVD, atherosclerotic cardiovascular disease; KHS, Korean Heart Study

Table 3. Equation parameters of the KHS model and the ACC/AHA 2013 Pooled Cohort Equations for estimation of 10-year risk for ASCVD events in men Aged 40–79 Years

	KHS Model		ACC/AHA (W)	KHS Model		ACC/AHA (AA)
	Mean	Coefficient (SE)	Coefficient	Mean	Coefficient (SE)	Coefficient
Ln Age	3.902	10.212 (2.333)	12.344	3.902	3.970 (0.076)	2.469
Ln Total cholesterol	5.263	7.916 (1.639)	11.853	5.263	0.692 (0.066)	0.302
Ln Age * Ln Total cholesterol	20.538	-1.806 (0.409)	-2.664	-	-	-
Ln HDL-cholesterol	3.847	-4.346 (1.283)	-7.990	3.847	-0.590 (0.051)	-0.307
Ln Age * Ln HDL-cholesterol	15.014	0.936 (0.319)	1.769	-	-	-
Ln Treated SBP	0.262	2.037 (0.082)	1.797	0.262	2.041 (0.080)	1.916
Ln Untreated SBP	4.555	2.011 (0.081)	1.764	4.555	2.013 (0.081)	1.809
Current smoker	0.496	2.519 (0.590)	7.837	0.496	0.449 (0.024)	0.549
Ln Age * Current smoker	1.923	-0.517 (0.147)	-1.795	-	-	-
Diabetes[†]	0.101	0.409 (0.030)	0.658	0.101	0.412 (0.030)	0.645
Baseline Survival		0.96394	0.9144		0.96346	0.8954

KHS, Korean Heart Study; ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; Ln, natural log; HDL, high-density lipoprotein; SBP, systolic blood pressure; SE, standard error; W, white; AA, African–American

[†] Diabetes was defined as fasting serum glucose ≥126 mg/dL or history of treatment for diabetes

Table 4. Equation parameters of the KHS model and the ACC/AHA 2013 Pooled Cohort Equations for estimation of 10-year risk for ASCVD events in women aged 40–79 years

	KHS Model		ACC/AHA (W)	KHS Model		ACC/AHA (AA)
	Mean	Coefficient (SE)	Coefficient	Mean	Coefficient (SE)	Coefficient
Ln Age	3.935	-16.121 (4.905)	-29.799	3.935	11.000 (3.654)	17.114
Ln Age square	15.507	2.518 (0.561)	4.884	-	-	-
Ln Total cholesterol	5.284	1.812 (2.242)	13.540	5.284	0.272 (0.084)	0.940
Ln Age * Ln Total cholesterol	20.801	-0.368 (0.554)	-3.114	-	-	-
Ln HDL-cholesterol	3.965	-2.325 (1.692)	-13.578	3.965	-1.269 (1.732)	-18.920
Ln Age * Ln HDL-cholesterol	15.600	0.455 (0.418)	3.149	15.600	0.199 (0.428)	4.475
Ln Treated SBP	0.329	1.698 (0.096)	2.019	0.329	8.078 (2.547)	29.291
Ln Age * Ln Treated SBP	-	-	-	1.326	-1.577 (0.629)	-6.432
Ln Untreated SBP	4.483	1.643 (0.098)	1.957	4.483	8.179 (2.610)	27.820
Ln Age * Ln Untreated SBP	-	-	-	17.616	-1.616 (0.644)	-6.087
Current smoker	0.045	1.446 (1.446)	7.574	0.045	0.444 (0.063)	0.691
Ln Age * Current smoker	0.177	-0.253 (0.358)	-1.665	-	-	-
Diabetes[†]	0.072	0.427 (0.042)	0.661	0.072	0.426 (0.042)	0.874
Baseline Survival		0.96928	0.9665		0.97001	0.9533

KHS, Korean Heart Study; ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; Ln, natural log; HDL, high-density lipoprotein; SBP, systolic blood pressure; SE, standard error; W, white; AA, African–American

[†] Diabetes was defined as fasting serum glucose ≥126 mg/dL or history of treatment for diabetes

C. ACC/AHA 2013 Pooled Cohort Equations

In the discriminatory analysis, the ACC/AHA Equations for either White or African-American (AA) men moderately distinguished cases from non-cases in the KHS cohort. For men, the AUROCs were 0.727 (95% Confidence Interval (CI), 0.721–0.734) using the White model and 0.725 (95% CI, 0.718–0.731) using the AA model. For women, the AUROCs were 0.738 (95% CI, 0.729–0.746) using the White model and 0.739 (95% CI, 0.731–0.747) using the AA model **(Figure 3)**.

However, in calibration, the ACC/AHA Equations statistically overestimated the event rates observed in the KHS cohort. For men, the Hosmer–Lemeshow X^2 was 1,364.26 for the White model ($P < 0.001$) and 2,059.60 for the AA model ($P < 0.001$). For women, the Hosmer–Lemeshow X^2 was 683.12 for the White model ($P < 0.001$) and 604.83 for the AA model ($P < 0.001$; **Figure 3**). Absolute 10-year ASCVD risk for men in the KHS cohort was overestimated by 56.5% in the White model and 74.1% in the AA model, while the risk for women was underestimated by 27.9% in the White model and overestimated by 29.1% in the AA model. For men, larger differences were observed in higher deciles of predicted risk, particularly in the AA model. For example, in the 10^{th} decile in men, the predicted rate was about 23% while the actual rate was only about 16%.

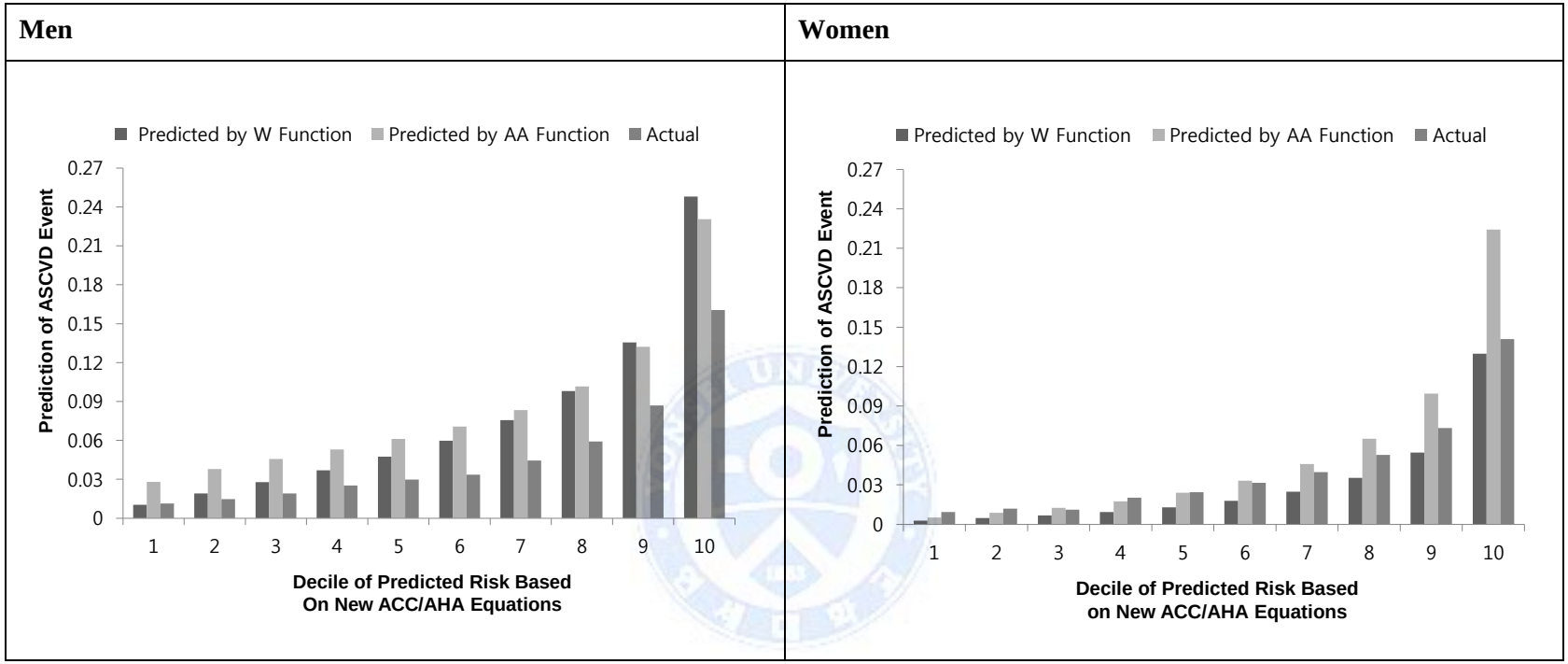

Figure 3. Ten-year probability of predicted and actual ASCVD events in men and women from the KHS using the ACC/AHA 2013 Pooled Cohort Equations for White (W) and African-American (AA)

ASCVD, atherosclerotic cardiovascular disease; KHS, Korean Heart Study; ACC/AHA, American College of Cardiology/American Heart Association

W, "White equation" of new ACC/AHA equations; AA, "African–American equation" of new ACC/AHA equations.

W: Calibration for χ^2: 1,364.26, $P < 0.0001$; AA: Calibration for χ^2: 2,059.60, $P < 0.0001$ for men

W: Calibration for χ^2: 683.12 $P < 0.0001$; AA: Calibration for χ^2: 604.83, $P < 0.0001$ for women.

D. Recalibrated ACC/AHA 2013 Pooled Cohort Equations

Recalibration did not affect the discriminatory ability of the ACC/AHA Equations but improved calibration substantially, especially in men in the White model. The X^2 was 110.25 for men ($P < 0.001$) and 439.50 for women ($P < 0.001$) **(Figure 4)**. The largest difference between the actual and predicted rates after recalibration was 1.7% (in the 10^{th} decile in men) compared with the difference of 8.75% for the direct ACC/AHA Equations. The recalibrated ACC/AHA 2013 pooled cohort equations are given in Appendix A.

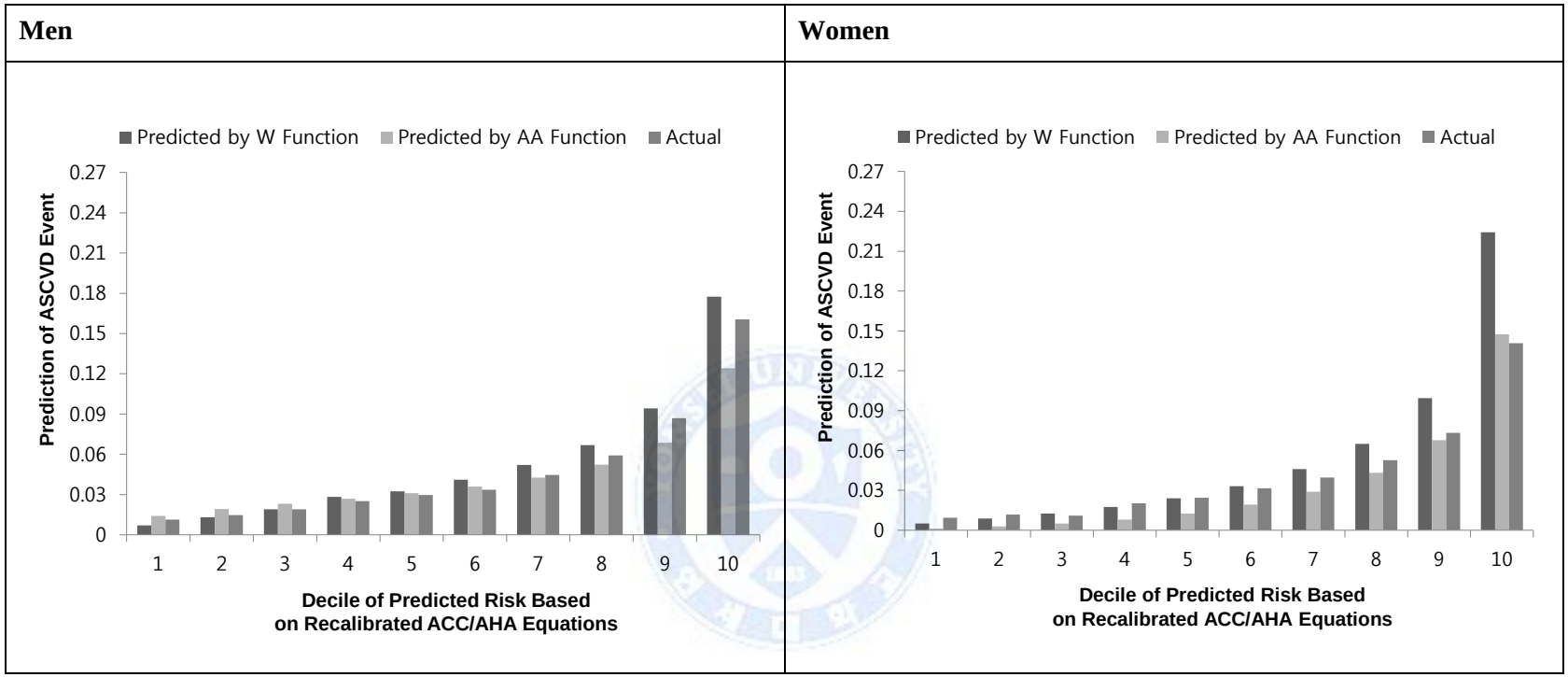

Figure 4. Ten-year probability of predicted and actual ASCVD events in men and women from the KHS using the recalibrated ACC/AHA 2013 Pooled Cohort Equations for White (W) and African-American (AA)

ASCVD, atherosclerotic cardiovascular disease; ACC/AHA, American College of Cardiology/American Heart Association; KHS, Korean Heart Study

W, "White equation" of new ACC/AHA equations; AA, "African–American equation" of new ACC/AHA equations.

W: Calibration for χ^2: 110.25, $P < 0.0001$; AA: Calibration for χ^2: 221.49, $P < 0.0001$ for men

W: Calibration for χ^2: 439.50, $P < 0.0001$; AA: Calibration for χ^2: 694.77, $P < 0.0001$ for women

E. KRPM for ASCVD

In the discriminatory analysis, the AUROCs for men and women were 0.734 (95% CI, 0.727–0.740) and 0.741 (95% CI, 0.733–0.750) **(Table 5)**, respectively, showing good ability to distinguish cases from non-cases. Regarding calibration, the Hosmer–Lemeshow X^2 was 25.90 for men ($P = 0.002$) and 14.69 for women ($P = 0.100$), showing that the actual ASCVD rates in the KHS cohort were similar to the event rates predicted by the KRPM **(Figure 5)**. The KRPM algorithm is given in Appendix B.

Table 5. Equation parameters of the KRPM in men and women aged 40–79 Years from the KHS (1997–2012)

	Men			Women		
	KRPM	ACC/AHA (White)	ACC/AHA (AA)	KRPM	ACC/AHA (White)	ACC/AHA (AA)
	Coefficient (SE)			Coefficient (SE)		
Ln Age	9.36 (4.41)	10.21 (2.33)	3.97 (0.08)	-9.52 (4.73)	-16.12 (4.91)	11.00 (3.65)
Ln Age square	2.42 (0.42)	-	-	3.42 (0.58)	2.52 (0.56)	-
Ln Total cholesterol	6.41 (1.60)	7.92 (1.64)	0.69 (0.07)	0.32 (0.08)	1.81 (2.24)	0.27 (0.08)
Ln Age * Ln Total cholesterol	-1.43 (0.40)	-1.81 (0.41)		-	-0.37 (0.55)	-
Ln HDL-cholesterol	-3.84 (1.26)	-4.35 (1.28)	-0.59 (0.05)	-0.48 (0.06)	-2.32 (1.69)	-1.27 (1.73)
Ln Age * Ln HDL-cholesterol	0.81 (0.31)	0.94 (0.32)	-	-	0.46 (0.42)	0.20 (0.43)
Ln Treated SBP	18.59 (2.00)	2.04 (0.08)	2.04 (0.08)	13.40 (2.58)	1.70 (0.10)	8.08 (2.55)
Ln Age * Ln Treated SBP	-4.12 (0.50)	-	-	-2.89 (0.64)	-	-1.58 (0.63)
Ln Untreated SBP	18.54 (2.00)	2.01 (0.08)	2.01 (0.08)	13.29 (2.63)	1.64 (0.10)	8.18 (2.61)
Ln Age * Ln Untreated SBP	-4.11 (0.50)	-	-	-2.88 (0.65)	-	-1.62 (0.64)
Current smoker	2.46 (0.60)	2.52 (0.59)	0.45 (0.02)	0.42 (0.06)	1.45 (1.45)	0.44 (0.06)
Ln Age * Current smoker	-0.50 (0.15)	-0.52 (0.15)	-	-	-0.25 (0.36)	-
Diabetes[†]	0.41 (0.03)	0.41 (0.03)	0.41 (0.03)	0.42 (0.04)	0.43 (0.04)	0.43 (0.04)
Baseline Survival	0.96427	0.96394	0.96346	0.96963	0.96928	0.97001
AUC	0.734(0.727-0.740)	0.732(0.725-0.739)	0.731(0.725-0.738)	0.741(0.733-0.750)	0.741(0.733-0.749)	0.741(0.733-0.749)

KRPM, Korean Risk Prediction Model; KHS, Korean Heart Study; Ln, natural log; HDL, High-density lipoprotein; SBP, systolic blood pressure; SE, standard error; AUC, Area Under the receiver operation characteristic Curve

[†] Diabetes was defined as fasting serum glucose >126 mg/dL or diabetic treatment history

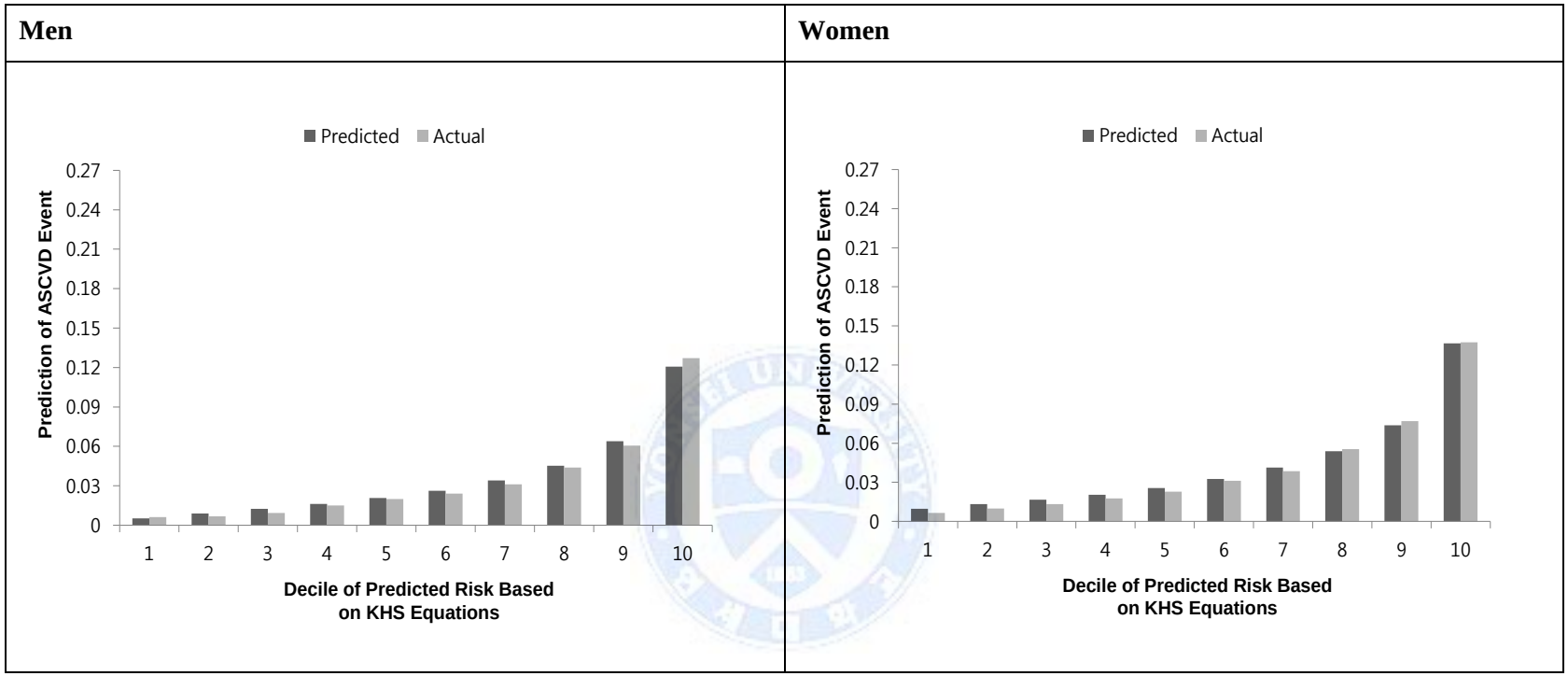

Figure 5. Ten-year probability of predicted and actual ASCVD events in men and women from the KHS using the KRPM

ASCVD, atherosclerotic cardiovascular disease; KHS, Korean Heart Study; KRPM, Korean Risk Prediction Model;

Calibration for χ^2: 25.90, P = 0.002 for men; 14.69, P = 0.100 for women

F. Sensitivity Analysis

In the sensitivity analyses, the AUROCs for the subset of men and women without diabetes & LDL>70 mg/dL or LDL>190 mg/dL were not significantly different from the whole study population **(Table 6)**.

Table 6. Equation parameters of the KRPM in men and women aged 40–79 years from the KHS (1997–2012) excluding subjects with LDL >190 mg/dL, or diabetes & LDL >70mg/dL

	Men			Women		
	KRPM	ACC/AHA (White)	ACC/AHA (AA)	KRPM	ACC/AHA (White)	ACC/AHA (AA)
	Coefficient (SE)			Coefficient (SE)		
Ln Age	8.32 (4.63)	10.38 (2.48)	4.00 (0.08)	-11.53 (4.93)	-18.20 (5.15)	12.15 (3.83)
Ln Age square	2.55 (0.44)	-	-	3.83 (0.61)	2.81 (0.58)	-
Ln Total cholesterol	6.66 (1.72)	8.25 (1.75)	0.63 (0.07)	0.35 (0.09)	1.65 (2.41)	0.30 (0.09)
Ln Age * Ln Total cholesterol	-1.51 (0.43)	-1.91 (0.44)	-	-	-0.32 (0.60)	-
Ln HDL-cholesterol	-4.16 (1.32)	-4.73 (1.35)	-0.60 (0.05)	-0.50 (0.07)	-1.90 (1.75)	-0.73 (1.80)
Ln Age * Ln HDL-cholesterol	0.89 (0.33)	1.03 (0.34)	-	-	0.34 (0.43)	0.06 (0.45)
Ln Treated SBP	18.29 (2.10)	2.03 (0.08)	2.04 (0.08)	14.47 (2.69)	1.69 (0.10)	8.53 (2.67)
Ln Age * Ln Treated SBP	-4.05 (0.52)	-	-	-3.16 (0.66)	-	-1.69 (0.66)
Ln Untreated SBP	18.36 (2.14)	2.00(0.09)	2.01 (0.09)	14.35 (2.74)	1.63 (0.10)	8.64 (2.73)
Ln Age * Ln Untreated SBP	-4.07 (0.53)	-	-	-3.14 (0.68)	-	-1.73 (0.68)
Current smoker	2.29 (0.63)	2.39 (0.62)	0.45 (0.02)	0.36 (0.07)	1.70 (1.53)	0.39 (0.07)
Ln Age * Current smoker	-0.49 (0.16)	-0.49 (0.16)	-	-	-0.33 (0.38)	-
Diabetes[†]	0.47 (0.04)	0.47 (0.04)	0.47 (0.04)	0.39 (0.06)	0.39 (0.06)	0.40 (0.06)
Baseline Survival	0.96595	0.96567	0.96521	0.97111	0.97072	0.97149
AUC	0.730(0.723-0.738)	0.729(0.722-0.736)	0.729(0.721-0.736)	0.740(0.731-0.748)	0.739(0.730-0.748)	0.739(0.730-0.748)

KRPM, Korean Risk Prediction Model; KHS, Korean Heart Study; Ln, natural log; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; SBP, systolic blood pressure; SE, standard error; AUC, Area Under the receiver operation characteristic Curve

[†] Diabetes was defined as fasting serum glucose >126 mg/dL or diabetic treatment history

G. Actual statin prescriptions in the last 10 years (2004-2013)

Baseline characteristics of the participants are presented in **Table 7**. Overall, mean ages of the Korean Heart Study participants were similar among men (50.2 years) and women (52.0 years). Mean systolic blood pressure values were also similar between the sexes. However, smoking was highly prevalent in men (48.2%) but uncommon in women (4.2%).

During the mean follow-up of 10.5 years, 14,010 ASCVD events (2,175 nonfatal MI, 528 fatal CHD, 11,649 nonfatal stroke, and 827 fatal stroke) occurred among the study participants **(Figure 2).** The ASCVD incidence per 100,000 person-years was 464 for men and 410 for women. For total stroke events, ischemic stroke accounted for 58.5% of men and 52.2% of women.

Table 7. General characteristics of the comparing the two models study participants aged 40 to 79 from the KHS (1996-2004), N=308,722

	Men (N=185,010)	Women (N=123,712)
	Mean (SD)	**Mean (SD)**
Age, years	50.20 (8.10)	51.98 (8.25)
Body mass index, kg/m^2	23.98 (2.73)	23.76 (3.05)
Systolic blood pressure, mmHg	124.55 (17.53)	123.68 (20.29)
Diastolic blood pressure, mmHg	79.07 (11.78)	75.96 (12.31)
Total cholesterol, mg/dL	196.93 (34.92)	200.54 (37.39)
HDL-cholesterol, mg/dL	48.16 (10.98)	54.54 (12.78)
LDL-cholesterol, mg/dL	120.09 (32.89)	123.66 (34.32)
Insurance premium, Korean won*	144,354 (155,187)	125,207 (138,318)
	%	%
Current smoking	48.18	4.23
Diabetes † (Yes)	10.79	7.51
Prevalent ASCVD	4.29	5.80
Antihypertensive treatment (Yes)	6.97	8.22
Statin treatment at baseline (Yes)	5.60	7.31

* A measure of socioeconomic status was the health insurance premium per year, in South Korean 'Won' (1,129 Won = 1.00 US Dollar)
KHS, Korean Heart Study; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation

Figure 6 and **7** shows cumulative incidence of statin use among three groups: no ASCVD event, before ASCVD event, and after ASCVD event during follow-up. For the two equations, statin prescriptions showed a proportional increase with 10-year ASCVD risk category among all groups in men and women (P for trend <0.0001).

Prescribing rates of statins in healthy men and women were 21.9% and 29.9%. Using ACC/AHA equations, 61.6% and 51.2% of men and women had no statin therapy for primary prevention even at risk score of ≥7.5%. Using KRPM equations, 62.3% and 51.8% of men and women had no statin therapy for primary prevention even at risk score of ≥7.5%.

The overall ASCVD risk score using KRPM equations showed moderate association with prescribing rates.

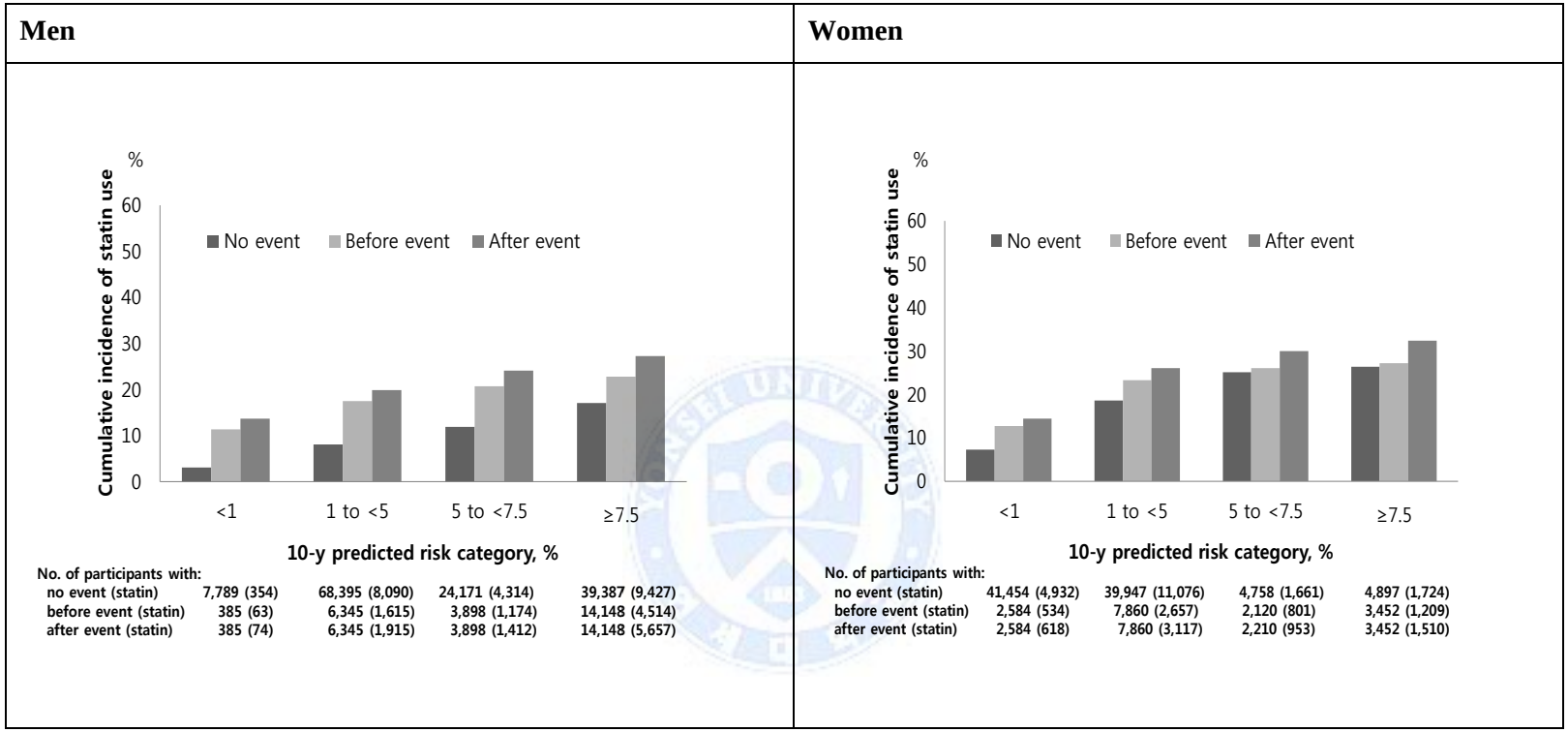

Figure 6. Prescribing rate of statins in relation to ASCVD events by risk score the ACC/AHA 2013 Pooled Cohort Equations among the KHS participants, 2004-2013

ASCVD, atherosclerotic cardiovascular disease; ACC/AHA, American College of Cardiology/American Heart Association; KHS, Korean Heart Study

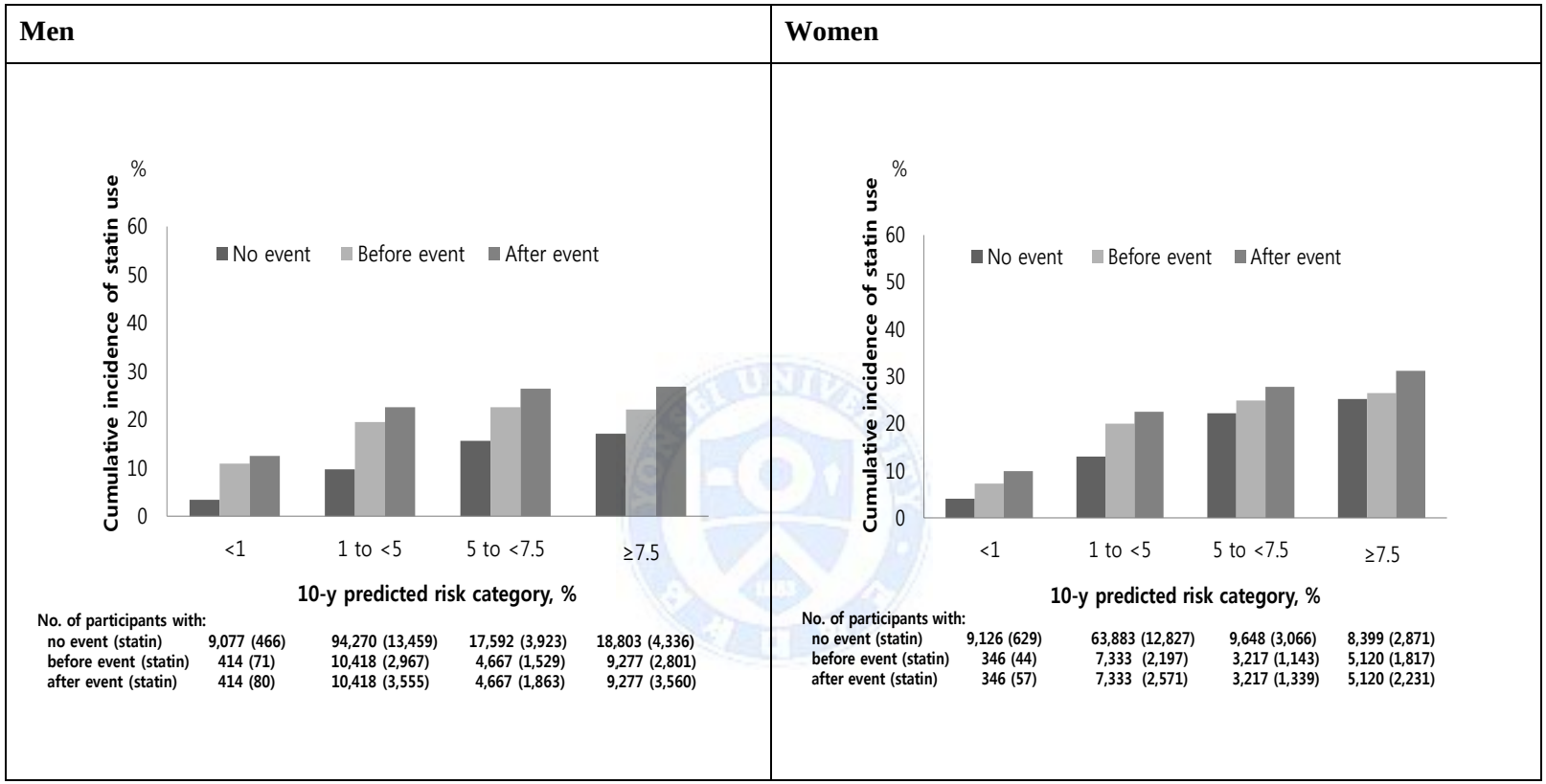

Figure 7. Prescribing rate of statins in relation to ASCVD events by risk score KRPM among the KHS participants, 2004-2013

ASCVD, atherosclerotic cardiovascular disease; KRPM, Korean Risk Prediction Model; KHS, Korean Heart Study

V. DISCUSSION

The Work Group of the ACC/AHA 2013 Risk Assessment Guideline, in their published guideline (Goff et al. 2014), recognized the knowledge gaps in ASCVD risk assessment and recommended further research to assess ASCVD risk in diverse groups. In the present analysis, we tested the performance of the ACC/AHA 2013 Pooled Cohort Equations in a large Korean population over 200,000 participants, both directly and after recalibration was compared them with the performance of functions derived from the Korean cohort itself to determine the absolute 10-year risk of ASCVD. We used both the ACC/AHA White and African-American Equations separately to assess their predictive value.

The present study provides evidence that the ACC/AHA Equations are not directly applicable in the Korean population and should be used with caution in populations whereas the risk estimator developed by the authors may provide a valuable tool for predicting 10-year ASCVD risk in the Korean population. Despite good discrimination, the 2013 ACC/AHA Equations largely overestimated absolute ASCVD risk among Korean men in particular, resulting in predicted ASCVD events that were twice as high as the observed ASCVD events in our study population since the incidence rate of ASCVD among Korean is low. Patterns of environmental exposures as well as genetic background also vary between the Korean population and the US population of the ACC/AHA model. For example, prevalence of obesity is significantly lower among Korean adults than US adults. These differing rates of ASCVD incidence and associated risk factors may be the reason the ACC/AHA Pooled Cohort Equations do not calibrate

well in our study population. On the other hand, the KRPM developed for this study may be a valuable tool for predicting 10-year ASCVD risk in the Korean population.

Also, in this cohort of healthy men and women, without previous prescription of statins and history of ASCVD, CVD, chronic kidney disease, or diabetes, we found that 19.7% of men and 24.4% of women had newly prescribed stains over 10 year follow-up period. However, we found that 75.3% of men and 72.8% of women with ASCVD had no prescription of stains prior to ASCVD event during the follow-up. Of two equations, ACC/AHA and KRPM equations, 10-year ASCVD risk using KRPM equations showed good predictability with actual ASCVD event in Korean population. However, 10-year ASCVD risk score using ACC/AHA equations showed slightly stronger associations with actual prescribing rates of statins in Korean population than those using KRPM equations.

Various studies that had evaluated the ACC/AHA 2013 Pooled Cohort Equations in different populations found overestimation of risk. In a commentary by Ridker and Cook, the study authors used the ACC/AHA Equations and compared their estimates with observed event rates in three large primary prevention cohorts—the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative Observational Study—and found that the ACC/AHA risk assessment tool overestimated ASCVD risk by 75–150% (Ridker et al. 2013; Ridker et al 2014). And they reported that 2013 new ACC/AHA criteria could result in more than 45 million middle-aged Americans without CVD (about 33% of American adults) for statin therapy recommendation (33,090,000 at ≥7.5% 10-year risk: 12,766,000 at >5.0-7.4% 10-year risk) (Ridker et al. 2013; Ridker et al 2014).

There were three validation cohort studies of the ACC/AHA Equations - a cohort of black and White US adults aged 45 to 79 years (Muntner et al. 2014), an European cohort of Dutch individuals 55 years and older (Kavousi et al. 2014), and the Multiethnic Study of Atherosclerosis cohort of US adults aged 50 to 74 (DeFilippis et al. 2015). In a cohort study of Black and White US adults aged 45 to 79 years (Muntner et al. 2014), Muntner et al evaluated the 5-year risk of ASCVD using the ACC/AHA 2013 Pooled Cohort Equations and found poor calibration and overestimation of risk in their primary study cohort. However they reported that the ACC/AHA Equations were well calibrated in a post-hoc cohort consisting of a subgroup of study participants and subjects >65 years identified in the US Centers for Medicare and Medicaid Services which were not adjudicated. The limitations of this study included follow-up limited to 5 years to evaluate a 10-year risk score as well as the use of unadjudicated events.

In a Dutch cohort of White individuals 55 years and older (Kavousi et al. 2014), Kavousi et al compared the performance of the ACC/AHA Equations, the Adult Treatment Panel III (ATP-III) guidelines and the European Society of Cardiology guidelines, and showed an overestimation of ASCVD events by the ACC/AHA guideline, which would result in recommendation of statin treatments for nearly all men and two-thirds of women, proportions exceeding those with the Adult Treatment Panel III (ATP-III) or the European Society of Cardiology guidelines. In this cohort, the ACC/AHA risk prediction model demonstrated modest discrimination and poor calibration (Kavousi et al. 2014), the latter a reflection of risk overestimation. One limitation of this study was the small number of events for certain outcomes.

In the Multiethnic Study of Atherosclerosis (MESA) cohort of US adults aged 50 to 74 (Seo et al. 2014), DeFilippis et al. examined the performance of the ACC/AHA Equations and 4 other risk scores, and found that the ACC/AHA Equations overestimated

risk for ASCVD events by 86% in men and 67% in women. By their respective end points, 3 of those risk scores—Framingham risk score (FRS) for prediction of CHD, FRS for prediction of CVD, and ATP-III—also overestimated risk in men and women of this MESA cohort. The Reynolds Risk Score, however, overestimated risk in men but underestimated risk in women. This result is similar to our observation that the ACC/AHA White equation, when applied to the KHS population, underestimated risk in Korean women. This unexpected finding deserves further investigation as the potential cause is currently not evident.

Although the performance of the ACC/AHA Pooled Cohort Equations developed by the Work Group remains to be further assessed in other longitudinal populations, the present study provides evidence that recalibration of the ACC/AHA Equations resulted in marked improvement in predictive ability in the Korean population. In particular, recalibrated White-specific functions estimated ASCVD risk well in both Korean men and women. If this process is equally successful in other settings, it can be applicable in other populations.

We previously reported lower CHD rates and risk factor levels in the Korean population compared with those in the United States (Jee et al. 2014). The previous Framingham CHD model overestimated the CHD risk by approximately 5 to 6 times in Koreans (Jee et al. 2014). However, the total stroke rates were comparable with those in the United States. In fact, in many developed countries, the incidence of stroke is declining even though the actual number of strokes is increasing because of the increasingly aging population. While the estimated stroke incidence per 100,000 persons is 250 in Korea (Seo et al. 2014) and 390 in Japan (Yatsuya et al. 2013), it is reported to be 140 in the United States (Feigin et al. 2009). The incidence of stroke among Asian countries was higher than that in the US, suggesting that stroke comprises a large

proportion of ASCVD events in the Korean population. Therefore, while a previous study on CHD showed the Framingham model estimated that the CHD incidence was 5 to 6 times higher in Korean men and women (Muntner et al. 2014), the 2013 ACC/AHA functions overestimated the incidence of ASCVD by about 2 times higher in Korean men and women compared to the 2013 ACC/AHA functions.

In the calibration analysis, a systematic overestimation was observed when the original ACC/AHA Equations were applied directly to the Korean cohort, especially in the higher deciles. One potential cause for the observed overestimation is that the cohorts used to derive the ACC/AHA Equations were several decades older than the KHS cohort, and consequently the significance of the risk factors included in the risk scores may have changed over time.

From our findings, the prescribing rates of statins among those with CHD event were approximately 75% and 67.3% among middle-aged Korean men and women. A survey from 10 Korean educational hospital in 2003 reported 58% prescribing rates of lipid lowering drug among CHD patients (Sung et al. 2005). The prescribing rate of lipid lowering drug among CHD patients in 2007 was nearly 90% in Korea. The US 2013 ACC/AHA cholesterol guideline recommends high-intensity statin therapy after acute myocardial infarction (AMI) in individuals up to age 75 years for whom there are no safety concerns (Stone et al. 2014). Brooks et al. provided strong evidence that providers were attempting to individualize statin prescriptions to patients after AMI. In other study, GP prescribed statins to only one-fifth of those in the 10-19% risk band usually in association with knowing major risk factors. And that study confirmed continuing undertreatment of patients at highest CVD risk (≥20%). Policy interventions promoting

higher statin-use rates after ASCVD including AMI may still need to be re-evaluated with cautions.

According to ACC/AHA guidelines, statin therapies are necessary especially for those who have a 10-year ASCVD risk of 7.5% or higher; however, our study showed that only 30~40% of high risk groups (≥7.5%) have received such treatment. If statins are recommended medications for treatment of those at high ASCVD risk, a sufficient therapy prior to the disease incidence is required (Homer et al. 2015).

The present study showed gender differences in prescribing rates of stains, particularly for ASCVD risk score using ACC/AHA equations. Interestingly, there were also a gender differences in ASCVD incidence in the US adults. Based on recent statistics, incidences of ASCVD including stroke and heart diseases per 100,000 in the US adults aged 45 to 64 years were 1,010 to 2,140 in men and 420 to 890 in women (Lloyd-Jones et al. 2010), while corresponding rates in Korean men and women aged 40 to 79 years were 765 and 721, respectively (Jung et al. 2015). Therefore, there were more than double in gender difference for ASCVD incidence in the US population, while no significant difference was shown in Korean. Further studies should evaluate whether gender differences exist between statin therapy and ASCVD incidence rates.

The strengths of this cohort study include a large sample size, wide age range and a nationwide sample. We ascertained the ASCVD events using the NHIS database. Koreans have good access to medical services as almost all citizens are enrolled in national health insurance. When MI, CHD, or stroke is diagnosed, each hospital reports these medical records to the Health Insurance Review & Assessment (HIRA) for reimbursement. Subsequently, the HIRA board evaluates the accuracy of the requested medical records and grants the reimbursement. The final record is then sent and stored at

the Korean NHIS, where they could link the ASCVD records with KHS subjects' identification numbers for research purposes. We have previously conducted validation studies on nonfatal MI (Kimm et al. 2012; Kim 2013) and stroke (Park et al. 2000) outcomes, but a validation study on mortality data has not been conducted.

The limitations of this study include possible measurement errors: clinical data from the health promotion centers were one-time measurements of blood pressure and other medical outcomes. In addition, the KHS data have limitations of using a non-population-based sample for validating a risk estimator. We have compared the demographic characteristics of KHS subjects with subjects of a nationally representative data, the KNHANES (Jee et al, 2014). General ASCVD risk factors, such as blood pressure and cholesterol, did not differ between the two datasets, but educational level of KHS subjects was about two years higher than those in the KNHANES. Therefore, results using KHS subjects should be interpreted with caution.

VI. CONCLUSIONS

The ACC/AHA 2013 Pooled Cohort Equations overestimate the 10-year risk of ASCVD for KHS participants, and should not be directly incorporated into estimates of ASCVD risk in a Korean population. Recalibration of the ACC/AHA Equations corrects the overestimation and, thus, can be a useful approach for the generalization of the ACC/AHA Equations in other populations. We also developed an ASCVD prediction model for Koreans and compared the estimates from the model with the actual ASCVD cases. This KRPM provides an accurate prediction of the 10-year ASCVD risk among Koreans in our study population. However, 10 year ASCVD risk scores using ACC/AHA and KPRM equations showed moderate associations with prescribing rates of statins.

This risk algorithm should be further tested in another validation cohort before it could be generalized across Korea as an ASCVD risk assessment tool.

We hope that utilization of prediction equations can enhance ASCVD prevention and management through accurate risk stratification. This will subsequently provide a more accurate allocation of preventive therapies and improved control of ASCVD risk factors such as hypertension, hypercholesterolemia, and diabetes.

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APPENDIX

A.1. Recalibrated ACC/AHA 2013 Pooled Cohort Equations Risk Score for ASCVD (White)

Hazard ratios (exponential regression coefficients) are shown in Table 3, 4. From these, a linear equation was constructed to produce the risk score.

For men, the risk score (RACC-WM) is defined using the following steps:

RAC-WM = 12.344 × AGE + 11.853 × TC – 2.664 × AGETC – 7.990 × HDL + 1.769 × AGEHDL + 1.797 × TRSBP + 1.764 × UNSBP + 7.837 × CUSMOK – 1.795 × LAGESMOK + 0.658 × DM

RWMSUM = 12.344 × 3.902 + 11.853 × 5.263 – 2.664 × 20.538 − 7.990 × 3.847 + 1.769 × 15.014 + 1.797 × 0.262 + 1.764 × 4.555 + 7.837 × 0.496 − 1.795 × 1.923 + 0.658 × 0.101

x =RAC-WM − RWMSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, RACC_WM = $(1 – 0.97609^{y})$, where 0.97609 is the baseline survival rate for men.

For women, the risk score (RACC-WW) is defined similarly.

RAC-WW = −29.799 × AGE + 4.884 × AGESQ + 13.540 × TC – 3.114 × AGETC – 13.578 × HDL + 3.149 × AGEHDL + 2.019 × TRSBP + 1.957 × UNSBP + 7.574 × CUSMOK – 1.665 × LAGESMOK + 0.661 × DM

RWWSUM = −29.799 × 3.935 + 4.884 × 15.507 + 13.540 × 5.284 – 3.114 × 20.801 – 13.578 × 3.965 + 3.149 × 15.600 + 2.019 × 0.329 + 1.957 × 4.483 + 7.574 × 0.045 – 1.665 × 0.177 + 0.661 × 0.072

x = RAC-WW − RWWSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, RACC_WW = $(1 - 0.98479^{y})$, where 0. 98479 is the baseline survival rate for women.

Appendix A.2. Recalibrated ACC/AHA 2013 Pooled Cohort Equations Risk Score for ASCVD (African-American)

Hazard ratios (exponential regression coefficients) are shown in Table 3, 4. From these, a linear equation was constructed to produce the risk score.

For men, the risk score (RACC-AM) is defined using the following steps:

RAC-AM = 2.469 × AGE + 0.302 × TC – 0.307 × HDL + 1.916 × TRSBP + 1.809 × UNSBP + 0.549 × CUSMOK + 0.645 × DM

RAMSUM = 2.469 × 3.902 + 0.302 × 5.263 – 0.307 × 3.847 + 1.916 × 0.262 + 1.809 × 4.555 + 0.549 × 0.496 + 0.645 × 0.101

x =RAC-AM − RAMSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, RACC_AM = $(1 - 97609^{y})$, where 97609 is the baseline survival rate for men.

For women, the risk score (RACC-AW) is defined similarly.

RAC-AW = −17.114 × AGE + 0.940 × TC – 18.920 × HDL + 4.475 × AGEHDL + 29.291 × TRSBP – 6.432 × AGETRSBP + 27.820 × UNSBP – 6.087 × AGEUNSBP + 0.691 × CUSMOK + 0.874 × DM

RAWSUM = −17.114 × 3.935 + 0.940× 5.284 – 18.920 × 3.965 + 4.475 × 15.600 + 29.291 × 0.329 – 6.432 × 1.326 + 27.820 × 4.483 – 6.087 × 17.616 + 0.691 × 0.045 + 0.874 × 0.072

x = RAC-AW − RAWSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, RACC_AW = $(1 - 0.98479^{y})$, where 0.98479 is the baseline survival rate for women.

Appendix B. Korean Risk Score for ASCVD

Hazard ratios (exponential regression coefficients) are shown in Table 5. From these, a linear equation was constructed to produce the risk score.

For men, the risk score (KRS-M) is defined using the following steps:

KMSUM = 9.362 × AGE + 2.425 × AGESQ + 6.409 × TC − 1.430 × AGETC −3.843 × HDL + 0.810 × AGEHDL + 18.589 × TRSBP − 4.116 × AGETRSBP + 18.541 × UNSBP − 4.112 × AGEUNSBP + 2.464 × CUSMOK − 0.503 × LAGESMOK + 0.410 × DM

Where AGESQ is the square of age, TC is total cholesterol, HDL is HDL-cholesterol, TRSBP is treated systolic blood pressure, UNSBP is untreated systolic blood pressure, CUSMOK is current smoker and DM is diabetes. All variables except for smoking status and diabetes were used as the log format. When an age interaction is present with lipids or BP, the natural log of age is multiplied by the natural log of the lipid or BP and the result is multiplied by the parameter estimate.

MSUM = 9.362 × 3.902 + 2.425× 15.253 + 6.409× 5.263 − 1.430× 20.538 − 3.843 × 3.847 + 0.810 × 15.014 + 18.589 × 0.262 − 4.116 × 1.049 + 18.541 × 4.555 − 4.112 × 17.754 + 2.464 × 0.496 − 0.503 × 1.923 + 0.410 × 0.101

x =KMSUM − MSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, KRS_M = $(1 - 0.96427^{y})$, where 0.97609 is the baseline survival rate for men.

For women, the risk score (KRS-W) is defined similarly.

KWSUM = −9.519 × AGE + 3.417 × AGESQ + 0.320 × TC – 0.476 × HDL + 13.402 × TRSBP – 2.889 × AGETRSBP + 13.291 × UNSBP – 2.876 × AGEUNSBP + 0.415 × CUSMOK + 0.424 × DM

WSUM = −9.519 × 3.935 + 3.417 × 15.507 + 0.320 × 5.284 − 0.476 × 3.965 + 13.402 × 0.329 − 2.889 × 1.326 + 13.291 × 4.483 − 2.876 × 17.616 + 0.415 × 0.045 + 0.424 × 0.072

x = KWSUM − WSUM

y = exp(x). Finally, the absolute 10-year risk of ASCVD, KRS_W = $(1 - 0.96963^{y})$, where 0.98479 is the baseline survival rate for women.

ABSTRACT IN KOREAN

한국인 심뇌혈관 예측 모형 개발과 스타틴 처방율

연세대학교 대학원 보건학과

정 금 지

배경 및 목적

본 연구의 목적은 미국 심장병 학회/미국 심장협회 (American College of Cardiology/American Heart Association, ACC/AHA)에서 만든 심뇌혈관 질환의 예측모형 (이하 미국 심뇌혈관 질환 예측모형)을 한국인 심장병 연구 (Korean Heart Study, KHS) 대상자에게 적용 하여 평가하고, 한국인 예측 모형 (Korean Risk Prediction Model, KRPM)을 개발하고 예측력을 평가하고자 하였다, 또한 이 두 가지의 심뇌혈관 예측 모형으로부터 한국인 일반 인구를 대상으로 10 년 심뇌혈관 위험 점수를 산출하여 이에 따른 지난 10 년간 (2004-2013)의 스타틴 처방율을 살펴보고자 하였다.

연구 방법

한국인 심장병 연구 대상자 중에서 심뇌혈관 기저질환이 없는 40-79 세의 200,010 명이 대상자로 선정되었다. 한국인 심장병 연구에서 미국 심뇌혈관 질환 예측모형의 구별성 능력과 정확성 능력 검정을 시행하였다. 미국 심뇌혈관 질환 예측모형의 재정확성 분석은 미국 심뇌혈관 질환 예측모형의 회귀계수와 한국인 심장병 연구 코호트에서 산출된 위험 요인들의 평균값과 심뇌혈관 질환의 발생률을 이용하였다. 한국인 예측 모형 개발은 한국인 심장병 연구 코호트에서 산출된 회귀계수, 위험 요인들의

평균값과 심뇌혈관 질환의 발생률을 이용하였다. 또한 각 모형의 누적 발생율을 이용 하여 스타틴 처방율을 계산하였다.

연구 결과

구별성 능력 검정에서는 미국 심뇌혈관 질환 예측모형에서는 백인 모형과 흑인모형 모두에서 질병이 발생한 사람과 그렇지 않은 경우를 구별하는 능력이 중간 정도였으며, 이는 한국인 예측 모형과 유사하였다. 남자의 경우, AUROC 값이 0.727 (백인 모델), 0.725 (흑인 모델), 0.741 (한국인 모델) 이었으며, 여자의 경우 0.738 (백인 모델), 0.739 (흑인 모델), 0.745 (한국인 모델) 였다. 남자의 경우 심뇌혈관질환 10 년 위험도는 백인 모델에서 56.5%, 흑인 모델에서 74.1% 과대 추정되었고, 여자의 경우 백인모델에서 27.9%, 흑인 모델에서 29.1% 과대 추정되었다. 재보정된 미국 심뇌혈관 질환 예측모형에서 구별성 능력 검정은 큰 차이가 없었으나 남자의 백인 모델에서 정확성 검정력이 다소 향상되었다. 세가지 심뇌혈관 예측 모형에서 한국인 예측 모형이 부표본 확인 연구에서 남녀 모두 가장 낮은 Hosmer-Lemshow 카이 제곱 값을 보이면서 가장 좋은 정확성 검정력을 보였다. 추적 관찰 기간 동안 스타틴 처방율은 남자 26.3% 여자 33.5%를 보였다.

결론

한국인 예측 모형이 심뇌혈관 질환의 위험 예측력이 가장 좋았으며, 미국 심뇌혈관 질환 예측모형은 한국인에게 직접 적용할 수 없었다. 그러므로 예방적인 스타틴 치료를 결정하는데 있어 한국인 예측 모형이 도움을 줄 수 있을 것으로 기대된다.

핵심되는 말: 심뇌혈관질환, 예측모형, 스타틴, 코호트 연구