Original Article

Application of New Guidelines for the Primary Prevention of Atherosclerotic Cardiovascular Disease in a Korean Population

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***Aim*: We investigated the proportion of people who would qualify for statin treatment with an atherosclerotic cardiovascular disease (ASCVD) 10-year risk of ≥7.5% and who exhibit an LDL cholesterol (LDL-C) of 70 to 189 mg/dL according to the new ACC/AHA guidelines for the treatment of increased cardiovascular risk.**

***Methods*: The study population (8,742 subjects) included individuals who underwent health examinations at Kangbuk Samsung Hospital in South Korea in 2010. We also evaluated the data obtained from the 2008-2010 Korea National Health and Nutrition Examination Survey (KNHANES) of 16,892 adults.**

***Results*: Approximately 90% of men ≥60 years of age and women ≥70 years of age had an ASCVD 10-year risk of ≥7.5% and LDL-C level of ≥70 mg/dL. The proportions of subjects with a Framingham 10-year risk of ≥10%, coronary artery calcium score of >20 and >100 and fatty liver each increased in association with an increasing ASCVD 10-year risk quartile in both sexes. Furthermore, age was significantly associated with the ASCVD 10-year risk in both sexes (all *p*-value <0.001). The KNHANES data also showed that over 85.0% of men ≥60 years of age and 95.0% of women ≥70 years of age had an ASCVD 10-year risk of ≥7.5% and an LDL-C level of ≥70 mg/dL.**

***Conclusions*: Adopting the new ASCVD prevention guidelines would result in the treatment of almost all Korean men and women (≥60 years and ≥70 years of age, respectively) without evidence of cardiovascular disease. Therefore, Asian-specific guidelines are needed to avoid unnecessary over treatment in an aging global population.**

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Key words: Guidelines, Coronary artery calcium, Statin, Risk factor

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is one of the most important global causes of morbidity and mortality. Within the last decade, many guidelines have been produced that emphasize the role of statin treatment in high-risk individuals to reduce cardiovascular risks by decreasing the low-density lipoprotein cholesterol (LDL-C) concentrations. In 2001, the National Cholesterol Education Program Expert Panel for the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults released their third report (NCEP-ATP III)[1)] and within three years, these guidelines were updated[2)]. The Screening for Heart Attack Prevention and Education (SHAPE) task force

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report was published in 2006[3], and further guidelines followed in November 2013, with the ACC/AHA guidelines for the treatment of blood cholesterol to reduce ASCVD[4]. This new set of guidelines identifies four major groups in whom ASCVD risk reduction with statin treatment may produce benefits: 1) subjects with clinical evidence of ASCVD, including coronary heart disease, stroke and peripheral arterial disease, 2) subjects with primary causes of an LDL-C level of >190 mg/dL, 3) subjects with diabetes, an age of 40 to 75 years and an LDL-C concentration of 70 to 189 mg/dL but without evidence of ASCVD and 4) subjects with no clinical evidence of ASCVD or diabetes who exhibit an LDL-C level of 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%[4]. The advice for people in the first three groups is similar to that published previously; however, advocating treatment for the fourth group is new and potentially very controversial, with major implications for public health. Furthermore, the development of these new guidelines was based predominantly on randomized placebo controlled trials in Western populations[4], and the applicability of the trial data to Asian populations remains unclear. Since there are considerable public health implications for widespread statin use in the fourth group, which includes individuals without evidence of disease, we evaluated the proportion of people who would qualify for statin treatment according to these guidelines in a population-based cohort of Korean subjects.

Methods

The study population consisted of individuals who underwent comprehensive health examinations in 2010 at Kangbuk Samsung Hospital, College of Medicine, Sungkyunkwan University in South Korea. The population included 8,742 participants 40~75 years of age who received a coronary artery calcium (CAC) score following coronary CT scanning. The study protocol was approved by the institutional review board at Kangbuk Samsung Hospital. Informed consent requirement was waived because personal identifying information was not accessed. Our study population is not a fully representative randomized sample of the Korean population. Therefore, in order to evaluate whether the results of our study are representative of the results for a randomized sample of the Korean population, we compared our findings with the data obtained from the Korea National Health and Nutrition Examination Survey (KNHANES).

BMI was calculated as weight in kilograms divided by height in meters squared. Blood samples were collected after an overnight fast. The measurement techniques included an enzymatic colorimetric assay for the serum total cholesterol (TC) and triglyceride (TG) levels and direct measurement using a homogenous enzymatic colorimetric assay for the LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, which were analyzed using Roche Diagnostics reagent kits on an automated chemistry analyzer (Modular DPP; Roche Diagnostics, Tokyo, Japan). The high-sensitivity C-reactive protein (hs-CRP) level was analyzed according to particle-enhanced immunonephelometry with the BNII System (Dade Behring, Marburg, Germany) using a lower limit of detection of 0.175 mg/L.

Questionnaires were used to ascertain information regarding alcohol consumption (glass/day), smoking (never, ex, current) and the frequency of moderate activity per week. Moderate activity was defined as more than 30 minutes of activity per day that induced slight breathlessness.

CT scanning was performed with a 64-slice MDCT scanner (Lightspeed VCT XTe-64 slice; GE Healthcare, Milwaukee, WI) using the following standard scanning protocol: 32×0.625-mm section collimation, 400-msec rotation time, 120-kV tube voltage and a tube current of 31 mAS (310 mA*0.1 sec) under electrocardiographic-gated dose modulation. Quantitative CAC scores were calculated according to the method described by Agatston *et al.*[5].

Abdominal ultrasonography (Logic Q700 MR; GE, Milwaukee, WI, USA) using a 3.5-MHz probe was performed in all subjects by experienced clinical radiologists, and fatty liver was diagnosed based on standard criteria, including hepatorenal echo contrast, liver brightness and vascular blurring. Mild fatty infiltration was classified as a minimal increase in the echogenicity of the liver compared with that of the renal cortex, in which the diaphragm and intrahepatic vessels appeared normal. Moderate to severe fatty infiltration was classified based on a moderate increase in echogenicity of the liver and slightly impaired appearance of the diaphragm and intrahepatic vessels or a marked increase in liver echogenicity with poor penetration of the deep parenchyma and impaired visualization of the intrahepatic vessels and diaphragm[6].

The KNHANES is a cross-sectional, nationwide, population-based survey that has been conducted periodically since 1998 to assess the health and nutritional status of the South Korean population. KNHANES V data (available at https://knhanes.cdc.go.kr) were collected between 2008 and 2010. We analyzed the findings for 16,892 subjects over 20 years of age with available 10-hour fasting data. There were 7,060 men

and 9,832 women (58.2% of the total subjects), including 5,377 subjects over 60 years of age (31.8% of the total subjects).

Statistical Analysis

The statistical analysis of the data was performed using the SPSS version 15.0 software program (SPSS, Point Richmond, CA, USA). Continuous variables are expressed as the mean ± SD for normally distributed variables and the median (interquartile range) for other variables. The ASCVD risk was stratified into quartiles. Categorical variables are expressed as percentages and were compared between groups using the χ^2 test. The association between age and the 10-year ASCVD risk was evaluated according to a Pearson's correlation analysis.

Results

Among the 8,742 individuals (7,197 men), 81.4%, 16.0%, 2.1% and 0.4% were in the 40-49 years, 50-59 years, 60-69 years and 70-75 years age groups, respectively. For men, 82.1%, 15.9%, 1.7% and 0.3% were in the 40-49 years, 50-59 years, 60-69 years age and 70-75 years age groups, respectively.

Table 1 presents the proportion of subjects with an ASCVD 10-year risk of ≥7.5% and/or LDL-C level of ≥70 mg/dL stratified by age group and sex. The proportion of subjects with an ASCVD 10-year risk of ≥7.5% significantly increased with age in both men and women ($p<0.001$ in both sexes), irrespective of diabetes mellitus (DM). In addition, the proportion of subjects with an LDL-C level of ≥70 mg/dL was associated with age in women ($p=0.017$ in total subjects, $p=0.024$ in subjects without DM), with a non-significant trend in men ($p=0.092$ in total subjects, $p=0.250$ in subjects without DM). Furthermore, the proportion of subjects with both an ASCVD 10-year risk of ≥7.5% and LDL-C level of ≥70 mg/dL (who would therefore qualify for statin treatment according to the new guidelines) increased in association with age for both men and women ($p<0.001$ for both sexes), irrespective of DM. Approximately 90% of men ≥60 years of age and women ≥70 years of age had an estimated ASCVD 10-year risk of ≥7.5% and an LDL-C level of ≥70 mg/dL (**Table 1**).

An estimated Framingham 10-year risk of cardiovascular disease (CVD) of ≥10% was significantly associated with an ASCVD 10-year risk of ≥7.5% among both men and women ($p<0.001$ in both sexes). A total of 89.6% of men and 18.8% of women with an ASCVD 10-year risk of ≥7.5% had a Framingham 10-year CVD risk of ≥10.0% (**Supplementary Table 1**). Among the subjects with an ASCVD 10-year risk of ≥7.5%, men had lower HDL-C levels, higher TC levels, systolic blood pressure (SBP) values and frequency of DM and a significantly higher rate of smoking than women (**Supplementary Table 2**).

Table 2 presents the proportion of subjects with an ASCVD 10-year risk equal to or above 7.5% and an LDL-C level equal to or above 70 mg/dL according to age group in the 2008-2010 KNHANES data. These results were very similar to our findings. For example, the proportion of subjects with an ASCVD 10-year risk of ≥7.5% significantly increased in association with age in both men and women ($p<0.001$ in both sexes). Moreover, the proportion of subjects with both an ASCVD 10-year risk of ≥7.5% and LDL-C level of ≥70 mg/dL (who would therefore qualify for statin treatment according to the new guidelines) increased with age in both men and women ($p<0.001$ for both sexes). These results also showed that over 85.0% of men ≥60 years of age and over 95.0% of women ≥70 years of age had an ASCVD 10-year risk of ≥7.5% and LDL-C level of ≥70 mg/dL (**Table 2**).

Table 3 presents the characteristics of the subjects according to the ASCVD risk quartiles for men and women. The individuals in the highest ASCVD risk quartile were older and smoked more frequently. Furthermore, these subjects had higher BMI, waist circumference and SBP and diastolic blood pressure (DBP) values and more unfavorable cardiometabolic and lipid profiles. Metabolic syndrome, hypertension and diabetes were also more prevalent among the subjects in the highest ASCVD risk quartile for both men and women (**Table 3**).

The prevalence of fatty liver also increased with an increasing ASCVD 10-year risk quartile, with an increasing linear trend in both men and women (p value for the trend <0.001 in men; and p value for the trend <0.001 in women) (**Fig. 1**). In addition, the proportion of subjects with a 10-year Framingham risk score of ≥10% increased in association with the ASCVD 10-year risk quartile in both men and women (**Fig. 1**), and the number of subjects with an increased coronary artery calcium score of >20 and >100 increased with an increasing ASCVD 10-year risk quartile in both sexes (p-values for men and women all <0.001) (**Fig. 1**).

Finally, age was found to be significantly correlated with the ASCVD 10-year risk in both men and women ($r=0.579$, $p<0.001$ in men without DM, $r=0.764$, $p<0.001$ in women without DM) (**Fig. 2**).

Table 1. Proportion of subjects with an atherosclerotic cardiovascular disease (ASCVD) 10-year risk of ≥7.5% and/or LDL cholesterol level of ≥70 mg/dL according to age group in the total and non-diabetic men and women

(a) Men					
Total subjects					
Age (years) (number)	40-49 (5909)	50-59 (1147)	60-69 (119)	70-75 (22)	*p*-value
Diabetes mellitus	360 (6.1)	124 (10.8)	21 (17.6)	3 (13.6)	<0.001
ASCVD ≥7.5%, n (%)	426 (7.2)	285 (4.8)	110 (92.4)	22 (100.0)	<0.001
LDL-C ≥70mg/dL, n (%)	5782 (97.9)	1126 (98.2)	115 (96.6)	20 (90.9)	0.092
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	415 (7.0)	279 (24.3)	107 (89.9)	20 (90.9)	<0.001
Excluding subjects with diabetes mellitus					
Age (years) (number)	40-49 (5549)	50-59 (1023)	60-69 (98)	70-75 (19)	*p*-value
ASCVD ≥7.5%, n (%)	298 (5.4)	188 (18.4)	89 (90.8)	19 (100.0)	<0.001
LDL-C ≥70mg/dL, n (%)	5445 (98.1)	1011 (98.8)	97 (99.0)	18 (94.7)	0.250
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	294 (5.3)	187 (18.3)	89 (90.8)	18 (94.7)	<0.001
(b) Women					
Total subjects					
Age (years) (number)	40-49 (1210)	50-59 (255)	60-69 (67)	70-75 (13)	*p*-value
Diabetes mellitus	40 (3.3)	16 (6.3)	5 (7.5)	2 (15.4)	0.011
ASCVD ≥7.5%, n (%)	0 (0.0)	2 (0.8)	18 (26.9)	12 (92.3)	<0.001
LDL-C ≥70mg/dL, n (%)	1160 (95.9)	253 (99.2)	67 (100.0)	13 (100.0)	0.017
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	0 (0.0)	2 (0.8)	18 (26.9)	12 (92.3)	<0.001
Excluding subjects with diabetes mellitus					
Age (years) (number)	40-49 (1170)	50-59 (239)	60-69 (62)	70-75 (11)	*p*-value
ASCVD ≥7.5%, n (%)	0 (0.0)	0 (0.0)	15 (24.2)	10 (90.9)	<0.001
LDL-C ≥70mg/dL, n (%)	1121 (95.8)	237 (99.2)	62 (100.0)	11 (100.0)	0.024
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	0 (0.0)	0 (0.0)	15 (24.2)	10 (90.9)	<0.001

ASCVD: atherosclerotic cardiovascular disease, n: number, LDL-C: low-density lipoprotein cholesterol.

Discussion

Our data showed that approximately 90% of Korean men and women (≥60 and ≥70 years of age, respectively) without ASCVD would require take statin treatment according to the new ASCVD guidelines. Interestingly, NAFLD is now accepted to be an independent cardiovascular risk factor[7], and our results clearly showed that the proportion of subjects with fatty liver increased across the ASCVD 10-year risk quartiles in both men and women (all *p*-values <0.001).

ASCVD is one of the most important global causes of morbidity and mortality, and the most significant treatable risk factor is LDL-C. Until recently, many Western guidelines have focused on LDL-C reduction and the use of statins for the treatment and prevention of CVD[1-3]. Although there is new concern that statins increase the risk of incident diabetes[8], it is widely accepted that in high-risk patients, the benefits clearly outweigh the risks[9, 10]. The new guidelines rec-

Table 2. Proportion of subjects with an atherosclerotic cardiovascular disease (ASCVD) 10-year risk of ≥7.5% and LDL cholesterol level of ≥70 mg/dL according to age group in the 16,892 subjects over 20 years of age with available 10-hour fasting data in the 2008-2010 Korea National Health and Nutrition Examination Survey (KNHANES)

(a) Men								
Age (years) (number)	20-29 (601)	30-39 (1397)	40-49 (1460)	50-59 (1290)	60-69 (1302)	70-79 (858)	80-89 (152)	*p*-value
ASCVD ≥7.5%, n (%)	0 (0.0)	29 (2.1)	207 (14.2)	707 (54.8)	1228 (94.3)	858 (100.0)	152 (100.0)	<0.001
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	0 (0.0)	29 (2.1)	200 (13.7)	663 (51.4)	1107 (85.0)	779 (90.8)	138 (90.8)	<0.001
(b) Women								
Age (years) (number)	20-29 (795)	30-39 (2133)	40-49 (2004)	50-59 (1835)	60-69 (1677)	70-79 (1151)	80-89 (237)	*p*-value
ASCVD ≥7.5%, n (%)	10 (1.3)	1 (0.0)	6 (0.3)	88 (4.8)	892 (53.2)	1137 (98.8)	237 (100.0)	<0.001
ASCVD ≥7.5% and LDL-C ≥70mg/dL, n (%)	10 (1.3)	1 (0.0)	6 (0.3)	87 (4.7)	854 (50.9)	1097 (95.3)	232 (97.9)	<0.001

ASCVD: atherosclerotic cardiovascular disease, n: number, LDL-C: low-density lipoprotein cholesterol.

ommend statin treatment for individuals without evidence of clinical ASCVD or diabetes who exhibit an LDL-C level of 70-189 mg/dL and an estimated 10-year ASCVD risk of >7.5%[4]. The new guidelines recommend the use of the 10-year ASCVD risk threshold in both white and black men and women, and it is uncertain whether such a threshold should be applied to Asian populations[4].

In the current study, an ASCVD 10-year risk of ≥7.5% was found to be significantly correlated with a Framingham 10-year risk score of ≥10%, and this relationship was more pronounced in men than women. This sex difference is due to the poorer cardiometabolic status of men compared to women. The new ASCVD risk calculator uses several risk factors, including sex, age, race, smoking status, TC, HDL-C, SBP and treatment for high blood pressure or diabetes[4]. The Framingham 10-year risk score, applied in the NCEP-ATP III study, uses similar risk factors (age, sex, TC and HDL-C concentrations, smoking status, SBP, history of diabetes and use of antihypertensive medications)[1, 11]. These risk factors are widely accepted to be the major risk factors for CVD. However, the Framingham risk score is also intended to be used to predict death due to myocardial infarction and coronary heart disease, whereas ASCVD risk prediction incorporates the risk of coronary heart disease, stroke and peripheral artery disease[1, 3].

The present study showed that approximately 90% of men ≥60 years of age and women ≥70 years of age in our study population and approximately 85% of men ≥60 years of age and 95% of women ≥70 years of age in the KNHANES population would be eligible for statin treatment[4]. There may be a case for the high frequency of use of statin treatment in these groups. ASCVD events occur after age 70, resulting in the greatest potential for highest absolute risk reduction in this age group[4] and CVD is usually more hazardous in older patients[12]. However, that said, the willingness to take statin medications is highly sensitive to the occurrence of statin-associated side effects, such as mild fatigue, muscle aches and pain or fuzzy thinking in older persons[13].

To date, there are few data from community-based studies showing the effects of statin treatment in older subjects without CVD[14]. One study of 25,378 older women suggested that the duration and potency of statin therapy are not associated with the onset of frailty[15]. Furthermore, another cohort study of subjects 65 years of age or older reported that the incidence of colorectal, lung and breast cancer in people treated with statins (n=24,439) is very similar to the rates for these diseases observed in the general population[16].

Statin treatment causes several adverse side effects, including myalgia, creatinine kinase elevation, transaminase elevation and, very rarely, rhabdomyolysis. A meta-analysis of 35 trials involving 74,102 subjects concluded that statin therapy is associated with only a small excess risk of transaminase elevation and not an increased risk of myalgia, creatine kinase elevation, rhabdomyolysis or withdrawal of therapy compared with a placebo[17]. Furthermore, several studies have recommended strategies to enhance the safety of statins in elderly patients[14, 18, 19].

Generally, women show later onset and a lower

Table 3. Characteristics of the subjects according to the 10-year atherosclerotic cardiovascular disease risk quartile in men and women

(a) Men					
10 year ASCVD risk % (n)	~1.5414 (1799)	1.5414~2.7072 (1799)	2.7072~4.8540 (1800)	4.8540~ (1799)	*p*-value
Age (years)	42.4 ± 2.11	44.7 ± 3.10	46.3 ± 4.05	48.9 ± 6.50	< 0.001
Glucose (mg/dL)	94.1 ± 8.99	96.1 ± 10.9	98.4 ± 16.1	105.1 ± 26.7	< 0.001
Triglyceride (mg/dL)	107.2 ± 50.1	146.8 ± 82.0	156.8 ± 92.7	195.4 ± 132.3	< 0.001
HDL-C (mg/dL)	56.9 ± 12.6	51.3 ± 11.0	49.5 ± 10.3	46.3 ± 9.88	< 0.001
LDL-C (mg/dL)	116.2 ± 27.4	131.5 ± 30.6	134.6 ± 31.5	140.1 ± 32.0	< 0.001
hs-CRP (mg/L)	1.17 ± 3.02	1.32 ± 4.16	1.19 ± 2.46	1.55 ± 3.53	0.002
BMI (kg/m^2)	23.9 ± 2.72	24.9 ± 2.69	25.1 ± 2.75	25.5 ± 2.84	< 0.001
Waist (cm)	83.9 ± 6.92	86.4 ± 6.96	87.0 ± 6.84	88.4 ± 7.02	< 0.001
SBP (mmHg)	114.7 ± 10.7	118.6 ± 11.0	119.2 ± 12.0	122.7 ± 12.6	< 0.001
DBP (mmHg)	73.9 ± 8.02	76.3 ± 8.23	76.6 ± 8.76	78.8 ± 9.31	< 0.001
HOMA-IR	1.16 ± 0.72	1.42 ± 0.92	1.46 ± 1.02	1.76 ± 1.45	< 0.001
Alcohol (u/day)	1.80 ± 2.94	2.00 ± 2.75	2.36 ± 3.30	2.69 ± 3.59	< 0.001
LDL-C ≥ 70mg/dL, n (%)	1732/1799 (96.3)	1763/1799 (98.0)	1778/1800 (98.8)	1770/1799 (98.4)	< 0.001
Exercise, n (%)	309/1798 (17.2)	355/1796 (19.8)	324/1800 (18.0)	310/1799 (17.2)	0.151
Smoking, n (%)					< 0.001
No	890/1799 (49.5)	740/1799 (41.1)	465/1800 (25.8)	224/1799 (12.5)	
Current	30/1799 (1.7)	185/1799 (10.3)	692/1800 (38.4)	1275/1799 (70.9)	
Ex	879/1799 (48.9)	874/1799 (48.6)	643/1800 (35.7)	300/1799 (16.7)	
MS, n (%)	125/1798 (7.0)	346/1799 (19.2)	446/1797 (24.8)	736/1797 (41.0)	< 0.001
HTN, n (%)	184/1799 (10.2)	349/1799 (19.4)	431/1800 (23.9)	649/1799 (36.1)	< 0.001
HTN medication, n (%)	59/1799 (3.3)	144/1799 (8.0)	190/1800 (10.6)	319/1799 (17.7)	< 0.001
DM, n (%)	14/1799 (0.8)	50/1799 (2.8)	103/1800 (5.7)	341/1799 (19.0)	< 0.001
(b) Women					
10 year ASCVD risk % (n)	~0.3584 (386)	0.3584~0.6084 (386)	0.6084~1.1326 (387)	1.1326~ (386)	*p*-value
Age (years)	42.3 ± 2.11	44.3 ± 2.75	46.1 ± 3.45	53.1 ± 7.73	< 0.001
Glucose (mg/dL)	89.1 ± 7.66	91.7 ± 8.27	93.1 ± 11.7	100.0 ± 21.9	< 0.001
Triglyceride (mg/dL)	68.4 ± 24.5	88.0 ± 35.6	112.6 ± 58.5	138.7 ± 90.2	< 0.001
HDL-C (mg/dL)	69.3 ± 12.3	61.9 ± 12.7	57.0 ± 11.9	53.5 ± 14.0	< 0.001
LDL-C (mg/dL)	96.6 ± 20.8	114.6 ± 24.9	132.3 ± 28.3	142.0 ± 33.6	< 0.001
hs-CRP (mg/L)	0.86 ± 2.55	0.95 ± 3.54	0.93 ± 1.58	1.35 ± 2.30	0.043
BMI (kg/m^2)	21.4 ± 2.46	22.6 ± 3.01	23.6 ± 3.18	24.5 ± 3.56	< 0.001
Waist (cm)	75.3 ± 6.86	78.6 ± 7.68	80.9 ± 7.98	83.7 ± 9.08	< 0.001
SBP (mmHg)	103.5 ± 10.2	108.5 ± 11.2	114.4 ± 11.1	121.6 ± 13.2	< 0.001
DBP (mmHg)	65.2 ± 7.71	68.4 ± 8.21	71.4 ± 8.26	76.1 ± 9.26	< 0.001
HOMA-IR	0.93 ± 0.51	1.14 ± 0.74	1.35 ± 1.06	1.70 ± 1.52	< 0.001
Alcohol (u/day)	0.29 ± 0.72	0.26 ± 0.68	0.25 ± 0.85	0.26 ± 0.85	0.935
LDL-C ≥ 70mg/dL, n (%)	347/386 (89.9)	376/386 (97.4)	385/387 (99.5)	385/386 (99.7)	< 0.001
Exercise, n (%)	98/385 (25.5)	97/382 (25.4)	116/387 (30.0)	102/384 (26.6)	0.434
Smoking, n (%)					< 0.001
No	374/386 (96.9)	375/386 (97.2)	376/387 (97.2)	364/386 (94.3)	
Current	0/386 (0.0)	3/386 (0.8)	2/387 (0.5)	17/386 (4.4)	
Ex	12/386 (3.1)	8/386 (2.1)	9/387 (2.3)	5/386 (1.3)	
MS, n (%)	2/385 (0.5)	19/384 (4.9)	66/387 (17.1)	163/386 (42.2)	< 0.001
HTN, n (%)	9/386 (2.3)	23/386 (6.0)	44/387 (11.4)	152/386 (39.4)	< 0.001
HTN medication, n (%)	3/386 (0.8)	9/386 (2.3)	24/386 (6.2)	94/386 (24.4)	< 0.001
DM, n (%)	0/386 (0.0)	3/386 (0.8)	12/387 (3.1)	48/386 (12.4)	< 0.001

ASCVD: atherosclerotic cardiovascular disease, n: number, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment-insulin resistance, CAC: coronary artery calcium, MS: metabolic syndrome, HTN: hypertension, DM: diabetes mellitus, yr: year.

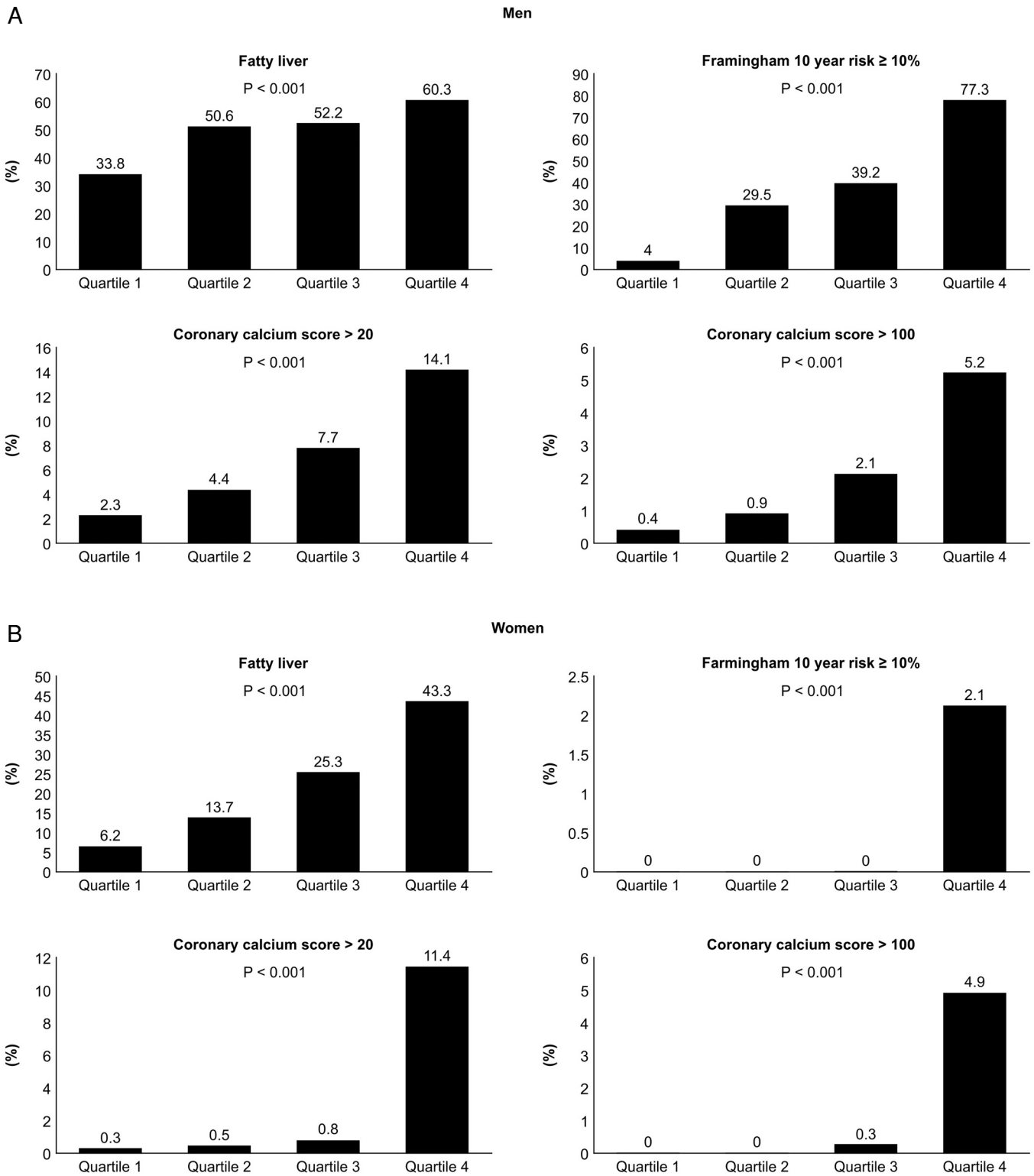

Fig. 1. Prevalence of fatty liver and proportion of subjects with a Framingham 10-year risk of ≥10% and coronary artery calcium score above 20 or 100 according to the atherosclerotic cardiovascular disease (ASCVD) quartile in men and women.

The subjects were stratified according to the atherosclerotic cardiovascular disease 10-year risk (%) quartile: quartile 1 (<1.5414%), quartile 2 (1.5414~2.7072%), quartile 3 (2.7072~4.8540%) and quartile 4 (>4.8540%) in men; quartile 1 (<0.3584%), quartile 2 (0.3584~0.6084%), quartile 3 (0.6084~1.1326%) and quartile 4 (>1.1326%) in women.

prevalence of cardiovascular disease than men[20]. Most previous statin trials have included few women (<25%) and either did not report sex-specific results or reported aggregate events (e.g., major coronary events) and not individual outcomes[21]. However, one review commented that statin therapy, in addition to diet and exercise, in 'moderately hyperlipidemic women' without a previous history of cardiovascular disease provides a significant benefit in preventing coronary heart disease events[21]. Moreover, another Asian study concluded that treatment with a statin (pravastatin) in women with increased cholesterol levels but no history of cardiovascular disease provides a benefit similar to that seen in men, with the benefit being more marked in older women[22]. Finally, in our study, women >70 years of age had a significantly higher estimated absolute ASCVD risk than the women 60-70 years of age. As the absolute risk of CVD is higher in older age groups, these findings support the use of treatment with statins in this age group.

In 2009 and 2012, two Korean studies revealed that the NECP-ATP III guidelines (the most popular Western guidelines for the primary and secondary prevention of cardiovascular disease) were not completely suitable for the Korean population[23, 24]. Additionally, several Japanese studies have reported the clinical significance of statin therapy for the primary and secondary prevention of cardiovascular disease. However, controversial results were obtained with respect to a lower LDL-C level as a better factor in the Japanese population according to Western guidelines[25, 26]. The Japanese guidelines for the diagnosis and prevention of ASCVD were published in 2012[27]. The incidence of coronary artery disease is lower in Japanese individuals than Westerners. Therefore, the Japanese guidelines used different risk calculation methods and include different treatment indications than those applied in Western guidelines. Furthermore, the treatment goals for LDL-C are more generous than previous Western guidelines[27], and current Japanese guidelines comprise more distinct features (presence of numerical goals for lipid control, the use of non-statin drugs and the application of a risk chart based on the NIPPON DATA80) compared to the 2013 ACC/AHA guidelines. Furthermore, the Japanese guidelines are known to be more useful in the Japanese population than the 2013 ACC/AHA guidelines[28]. Therefore, Asian-specific guidelines are needed for Asian populations.

Our study is associated with several limitations. First, our study population included few subjects over 70 years of age (0.4%) and few women (17.7%). However, there are few data for older populations without cardiovascular disease, and most statin trials have evaluated few women[14, 22]. Therefore, we also assessed the 2008-2010 KNHANES data. In this registry, we analyzed data for 16,892 subjects, including 9,832 women (58.2% of the total subjects) and 5,377 subjects over 60 years of age (31.8% of the total subjects). Comparing our study findings to that obtained for the KNHANES population, the results for the two populations were found to be very similar. Taking into account the fact that the KNHANES population constitutes a representative randomized sample of the Korean population, we believe that the results of our study are meaningful. Second, our study population included only Koreans. Several studies have revealed ethnic differences within Asian populations in terms of cardiovascular mortality, with Chinese subjects having the lowest prevalence of coronary heart disease and rate of mortality from ischemic heart disease[29, 30]. Therefore, more studies regarding ethic differences in the prevalence, mortality and prevention of ASCVD in Asian populations are needed.

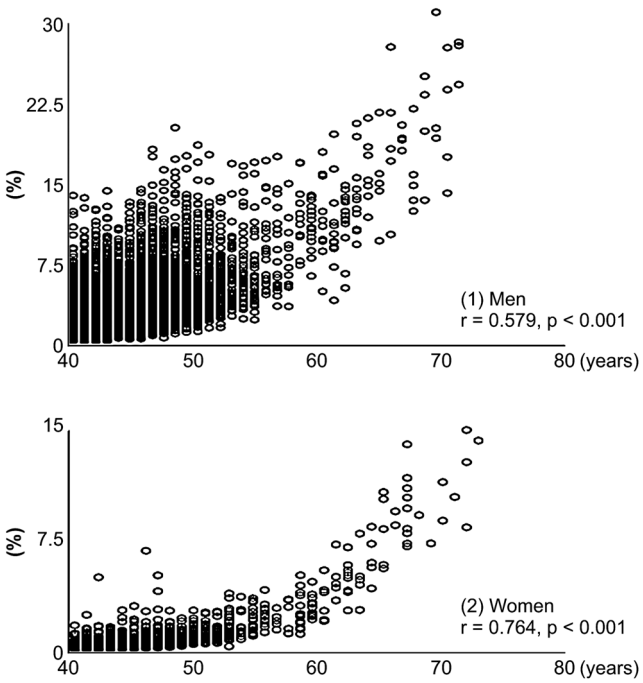

Fig. 2. Correlation between age and the atherosclerotic cardiovascular disease 10-year risk in non-diabetic men and women.

Conclusions

Given the costs, known side effects and public health implications of statin treatment, we conclude that Asian-specific guidelines are needed to avoid unnecessary over treatment in a large number of peo-

ple in an aging population.

Competing Interests

The authors declare that they have no competing interests in association with this study.

Author Contributions

Nan Hee Kim and Ki-Chul Sung conceived of and designed the study, acquired, analyzed and interpreted the data and drafted the manuscript. Min-Suk So, Jeong-Gyu Kang and Dong-sik Cho acquired and interpreted the data. Christopher D. Byrne and Sang Jong Lee critically revised the manuscript for important intellectual content.

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Conflicts of Interest

None.

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Supplementary Table 1.
Association between an estimated Framingham 10-year risk of cardiovascular disease of ≥10% and an ASCVD 10-year risk of ≥7.5% in both men and women

(1) Men (n=7197)			
Framingham 10 year risk	10 year ASCVD risk, n(%)		p-value
	<7.5%	≥7.5%	
<10%	4411 (69.4)	88 (10.4)	<0.001
≥10%	1943 (30.6)	755 (89.6)	
(2) Women (n=1545)			
Framingham 10 year risk	10 year ASCVD risk, n(%)		p-value
	<7.5%	≥7.5%	
<10%	1511 (99.9)	26 (81.3)	<0.001
≥10%	2 (0.1)	6 (18.8)	

ASCVD: atherosclerotic cardiovascular disease, n: number

Supplementary Table 2.
Characteristics of the subjects with an ASCVD 10-year risk of ≥7.5% according to sex

10 year ASCVD risk ≥7.5%, n(%)	Men	Women	p-value
	843/7197 (11.7)	32/1545 (2.1)	
Age (years)	50.9±7.49	68.3±4.28	<0.001
Glucose (mg/dL)	110.5±31.8	102.3±25.1	0.150
Triglyceride (mg/dL)	217.1±159.8	154.2±75.8	0.027
Total cholesterol (mg/dL)	224.7±38.7	220.1±29.1	0.047
HDL-C (mg/dL)	44.8±9.6	55.1±14.9	<0.001
LDL-C (mg/dL)	146.1±35.3	144.8±22.7	0.667
BMI (kg/m^2)	25.6±2.95	23.8±2.86	<0.001
Waist (cm)	88.8±7.26	84.6±8.32	0.001
SBP (mmHg)	134.1±12.6	130.4±12.7	0.005
DBP (mmHg)	79.4±9.40	78.9±9.68	0.772
HOMA-IR	1.95±1.74	1.42±0.91	0.087
Smoking, n(%)			0.049
No	723/843 (85.8)	31/32 (96.9)	
Current or Ex	120/843 (14.2)	1/32 (3.1)	
MS, n(%)	412/843 (49.0)	20/32 (62.5)	0.093
DM, n(%)	249/843 (29.5)	7/32 (21.9)	0.043

ASCVD: atherosclerotic cardiovascular disease, n: number, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment-insulin resistance, MS: metabolic syndrome, DM: diabetes mellitus.