Reassessment of Inclusion Criteria in the 2013 the American College of Cardiology and the American Heart Association Cholesterol Guidelines for Cardiovascular Disease Prevention

Jong Weon Lee[a]*
Hunsun Lim[b]*
Jong Hun Kim[c]
Hyoung Seop Kim[a]

[a]Department of Physical Medicine
 and Rehabilitation,
 National Health Insurance Service
 Ilsan Hospital, Goyang, Korea
[b]Research and Analysis Team,
 National Health Insurance Service
 Ilsan Hospital, Goyang, Korea
[c]Department of Neurology,
 National Health Insurance Service
 Ilsan Hospital, Goyang, Korea

Correspondence
Jong Hun Kim, MD, PhD
Department of Neurology,
National Health Insurance Service
Ilsan Hospital,
100 Ilsan-ro, Ilsandong-gu,
Goyang 10444, Korea
Tel +82-31-900-0213
Fax +82-31-900-0343
E-mail jh7521@naver.com

Hyoung Seop Kim, MD
Department of Physical Medicine
and Rehabilitation,
National Health Insurance Service
Ilsan Hospital,
100 Ilsan-ro, Ilsandong-gu,
Goyang 10444, Korea
Tel +82-31-900-0137
Fax +82-31-900-0343
E-mail rehappydoc@gmail.com

*These authors contributed equally to
this work.

Background and Purpose The American College of Cardiology and the American Heart Association (ACC-AHA) have released new guidelines and expanded indications for statin treatment. We aimed to reveal the clinical efficacy of each indication in the guidelines using a large-scale national cohort.

Methods We used National Health Screening Cohort data to determine the proportions of participants for whom statin therapy would be recommended using the different guidelines. We assessed the cumulative incidence rates of major adverse cardiovascular events (MACE) using the Cox proportional-hazards model.

Results Under the 2013 ACC-AHA guidelines, 111,600 participants were additionally eligible to receive statins, compared with 50,023 participants according to the Third Adult Treatment Panel (ATP-III). Most of the additional statin-eligible participants in the ACC-AHA guidelines were indicated by their 10-year cardiovascular disease risk. The increase in statin-eligible participants in the ACC-AHA guidelines mainly involved elderly patients aged 60−75 years. Among participants not requiring statin, participants who were eligible for a statin under the ACC-AHA guidelines had a significantly higher hazard ratio of MACE when compared with those eligible under the ATP-III guidelines. Among the not-recommended groups, patients with diabetes and low-density lipoprotein <70 mg/dL constituted the group with the highest risk of MACE.

Conclusions The 2013 ACC-AHA guidelines increase the number of statin-eligible participants, especially among the elderly. These guidelines provide a stronger recommendation for statins to high-risk groups, but it remains necessary to consider the characteristics of the population in the risk equation. In addition, the aggressive use of statin in diabetes patients and further studies of older subjects are needed.

Key Words cardiovascular disease, myocardial infarction, stroke, statins.

INTRODUCTION

In 2013 and 2018, the American College of Cardiology and the American Heart Association (ACC-AHA) released new guidelines for the management of cholesterol, to replace the Third Adult Treatment Panel (ATP-III) guidelines of the National Cholesterol Education Program.[1-4] Without changing the number of statin-recommended subjects from the 2013 guidelines, the 2018 guidelines added intermediate- and high-risk groups.[3] The previous ATP-III guidelines were primarily target-based, with treatment decisions based largely on observed levels of low-density lipoprotein (LDL)-cholesterol.[1] In contrast, the proposed ACC-AHA guidelines are based on the evidence that the administration of statins should be determined by the risk threshold of atherosclerotic cardiovascular dis-

ease (ASCVD).[5]

There have been some concerns that the ACC-AHA guidelines substantially increase the number of subjects who are potentially eligible for statin therapy.[6-8] The largest increase in statin-eligible subjects was due to the indication of a 10-year predicted cardiovascular disease (CVD) risk of ≥7.5%, for the purpose of primary prevention.[7] The Pooled-Cohort Risk Assessment Equations were developed to predict the ASCVD risk in non-Hispanic, Caucasian, and African-American populations.[5,9] Therefore, the working group responsible for developing the ACC-AHA guidelines called for further research that included analyses of the short- and long-term risks in diverse racial groups.[2] Several studies have applied the ACC-AHA pooled-cohort equations in different populations.[6,10]

The aim of the present study was to verify the efficacy of and differences in statin-recommended groups between the 2013 ACC-AHA guidelines and the ATP-III guidelines. In addition, we sought to determine how well the guidelines predict the occurrence of major adverse cardiovascular events (MACE) using the National Health Insurance Service National Health Screening Cohort (NHIS-HEALS).[11]

METHODS

Study population

According to health examination legislation in Korea, it is obligatory for all employees to undergo a nationwide health screening examination annually and for the unemployed to be screened biannually. Among the 5.15 million screened examinees who were aged 40−79 years as of December 2002, 10% were randomly sampled as part of the NHIS-HEALS data set (*n*=514,866) and followed until 2013 to observe changes in their health conditions, economic status, usage of health-care facilities, and other factors. These cohort data are provided without any personal identification in order to support their utilization in academic research, and they can be accessed through the homepage of the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/). The usage of a statin or other drugs was collected from prescription data. Since LDL-cholesterol was first recorded in 2009, we excluded 176,534 participants who did not have LDL-cholesterol measurements. We evaluated the eligibility of the remaining 338,332 participants for statin treatment using both the ACC-AHA and ATP-III guidelines.

Main outcome measures

The main outcomes were MACE, including CVD mortality, fatal or nonfatal myocardial infarction (MI), and stroke. The information about previous CVD included the MI history,

coronary or other arterial revascularization, stroke or focal transient ischemic attack, and heart failure. Complete descriptions of diagnostic criteria are provided in Supplementary Fig. 1 (in the online-only Data Supplement).

Statistical analysis

We started the analysis by examining the proportion of the study population for whom statin therapy was recommended according to the two guidelines. We then assessed sex, age, body mass index (BMI), and other baseline characteristics for significant differences. Furthermore, risk-factor profiles such as previous CVD and total cholesterol were compared between the two guidelines.

For the current-statin-user group, the statin-recommended group, and the not-recommended group in the two guidelines, the cumulative incidence rates of MACE were plotted on Kaplan-Meier survival curves. For MACE in the two guidelines, hazard ratios (HRs) in the univariate or multivariate Cox regression analyses were estimated for the current-statin-user group and the statin-recommended group with reference to the not-recommended group. The covariates adjusted in the multivariate Cox model were sex, age, economic status, total cholesterol, hypertension, systolic blood pressure, diabetes, BMI, previous CVD, smoking status, alcohol status, high-density lipoprotein cholesterol, and LDL-cholesterol. The HRs of MACE were also estimated for concordant and discordant recommended groups with reference to the concordant not-recommended group in the two guidelines. Lastly, MACE were further stratified into CVD mortality, fatal or nonfatal MI, and stroke. The incidence and HR of each component were analyzed for both guidelines.

This study used the NHIS-2016-2-127 NHIS-HEALS data set provided by the NHIS. All analyses in this study were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA). An alpha level of <0.05 and no overlap of 95% confidence intervals (CIs) were used as the criteria for statistical significance in all tests. The need for patient consent was waived, and all components and procedures of this study were approved by the Institutional Review Board of our hospital (IRB File No.: 2015-05-008).

RESULTS

Study sample

We restricted the analysis to the 338,332 participants with LDL-cholesterol measurements who were aged 40 years to 75 years as of December 2009 in the NHIS-HEALS data set. The baseline characteristics of the study participants are listed in Table 1. The sample included 69,163 participants (20.4%) who were already receiving statin therapy. Based on the ATP-

Table 1. Baseline characteristics of the study participants

	ATP-III guidelines				ACC-AHA guidelines			
	Statin used currently	Recommended	Not recommended	p^*	Statin used currently	Recommended	Not recommended	p^*
All participants	69,163 (20.4)	50,023 (14.8)	219,146 (64.8)		69,163 (20.4)	111,600 (33.0)	157,569 (46.6)	
Sex (male)	31,576 (45.7)	36,066 (72.1)	115,544 (52.7)	<0.01	31,576 (45.7)	81,893 (73.4)	69,717 (44.3)	<0.01
Age, years	59.7±7.7	58.8±8.2	56.4±7.6	<0.01	59.7±7.7	62.0±8.1	53.3±5.1	<0.01
BMI, kg/m²	24.8±3.0	24.5±2.9	23.7±2.8	<0.01	24.8±3.0	24.1±2.9	23.7±2.8	<0.01
Economic status, decile				<0.01				<0.01
0 (medical aid)	104 (0.2)	45 (0.1)	170 (0.1)		104 (0.2)	135 (0.1)	80 (0.1)	
1–3	13,967 (20.2)	9,981 (20.0)	44,214 (20.2)		13,967 (20.2)	23,937 (21.5)	30,258 (19.2)	
4–6	15,560 (22.5)	11,350 (22.7)	50,793 (23.2)		15,560 (22.5)	26,271 (23.5)	35,872 (22.8)	
7–9	25,862 (37.4)	18,731 (37.4)	80,881 (36.9)		25,862 (37.4)	40,681 (36.5)	58,931 (37.4)	
10 (highest)	13,670 (19.8)	9,916 (19.8)	43,088 (19.7)		13,670 (19.8)	20,576 (18.4)	32,428 (20.6)	
Hypertension	48,137 (69.6)	28,416 (56.8)	72,177 (32.9)	<0.01	48,137 (69.6)	60,173 (53.9)	40,420 (25.7)	<0.01
Diabetes	27,046 (39.1)	16,865 (33.7)	24,892 (11.4)	<0.01	27,046 (39.1)	33,814 (30.3)	7,943 (5.0)	<0.01
Total cholesterol, mg/dL	207.8±49.1	223.6±34.2	192.6±30.9	<0.01	207.8±49.1	201.6±36.6	196.1±31.5	<0.01
HDL, mg/dL	55.7±32.5	52.0±29.8	56.0±30.3	<0.01	55.7±32.5	51.7±24.9	57.7±33.3	<0.01
LDL, mg/dL	122.1±47.8	145.8±45.0	111.5±29.0	<0.01	122.1±47.8	121.5±41.5	115.4±29.7	<0.01
Systolic BP, mm Hg	127.4±15.2	128.7±15.9	123.4±14.7	<0.01	127.4±15.2	129.4±15.2	120.9±14.0	<0.01
Previous CVD†	14,321 (20.7)	12,064 (24.1)	5,236 (2.4)	<0.01	14,321 (20.7)	17,300 (15.5)	0 (0.0)	<0.01
Smoking status				<0.01				<0.01
Nonsmoker	47,443 (68.6)	22,865 (45.7)	146,689 (66.9)		47,443 (68.6)	55,596 (49.8)	113,958 (72.3)	
Ex-smoker	12,342 (17.8)	8,452 (16.9)	41,282 (18.8)		12,342 (17.8)	21,884 (19.6)	27,850 (17.7)	
Current smoker	9,378 (13.6)	18,706 (37.4)	31,175 (14.2)		9,378 (13.6)	34,120 (30.6)	15,761 (10.0)	
Alcohol, drinks/week	1.77±1.45	2.13±1.66	1.95±1.58	<0.01	1.77±1.45	2.23±1.82	1.82±1.39	<0.01

Data are mean±standard-deviation or n (%) values.
*p value using ANOVA for continuous data or the χ^2 test for discrete data, †Myocardial infarction, stroke, or CVD.
ACC-AHA: the American College of Cardiology and the American Heart Association, ATP-III: the Third Adult Treatment Panel, BMI: body mass index, BP: blood pressure, CVD: cardiovascular disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

III guidelines, 50,023 participants (14.8%) would be additionally eligible for statin therapy, compared with 111,600 participants (33.0%) according to the ACC-AHA guidelines. The age in the statin-recommended group was higher in the ACC-AHA guidelines (62.0±8.1 years vs. 58.8±8.2 years, mean±standard deviation). On the other hand, the ATP-III guidelines showed a higher percentage of patients with hypertension (56.8% vs. 53.9%), diabetes (33.7% vs. 30.3%), and current smokers (37.4% vs. 30.6%), as well as higher total cholesterol (223.6±34.2 mg/dL vs. 201.6±36.6 mg/dL) and LDL- cholesterol (145.8±45.0 mg/dL vs. 121.5±41.5 mg/dL).

Supplementary Fig. 1 (in the online-only Data Supplement) depicts the clinical criteria for recommending statin therapy in the two guidelines. The ACC-AHA guidelines expanded the statin recommendation by including all patients with previous CVD history, regardless of the LDL-cholesterol threshold of 100 mg/dL. This criterion resulted in the inclusion of 5,162 participants who had clinical CVD and LDL-cholesterol levels lower than 100 mg/dL. Moreover, the ACC-AHA guidelines lowered the LDL-cholesterol criterion in

diabetes patients to 70 mg/dL, thus increasing the number of participants included for statin recommendation from 11,210 to 15,274.

In order to further analyze the number of statin-recommended subjects by age, we divided them into two groups: older than 59 years and younger than 60 years (Supplementary Fig. 2 in the online-only Data Supplement). The proportion of statin recommendations increased by 7.0% for those aged 40 years to 59 years, and the increase was much greater among those aged 60 years to 75 years, at 38.0% (46,518 subjects).

Table 2 presents the number of participants for whom statin recommendations were discordant between the two guidelines. Only 4,229 participants (1.5%) were reclassified "downward" (statins recommended only by the ATP-III guidelines), whereas 65,806 (24.4%) were reclassified "upward" (statins recommended only by the ACC-AHA guidelines).

Cumulative incidence of MACE during follow-up

The mean follow-up duration was 4.6 years. Fig. 1 depicts the Kaplan-Meier survival curves showing the cumulative

Table 2. Descriptive statistics according to concordant and discordant recommendations for statin therapy

	Concordant recommendations		Discordant recommendations	
	Neither recommend statin therapy	Both recommend statin therapy	Recommended by ATP–III guidelines but not ACC–AHA guidelines	Recommended by ACC–AHA guidelines but not ATP–III guidelines
All participants	153,340	45,794	4,229	65,806
Sex, male	66,624 (43.5)	32,973 (72.0)	3,093 (73.1)	48,920 (74.3)
Age, years	53.3±5.1	59.4±8.2	52.6±5.3	63.8±7.4
BMI, kg/m²	23.6±2.8	24.5±2.9	24.3±2.7	23.9±2.9
Economic status, decile				
0 (medical aid)	78 (0.1)	43 (0.1)	2 (0.1)	92 (0.1)
1–3	29,614 (19.3)	9,337 (20.4)	644 (15.2)	14,600 (22.2)
4–6	34,971 (22.8)	10,449 (22.8)	901 (21.3)	15,822 (24.0)
7–9	57,180 (37.3)	16,980 (37.1)	1,751 (41.4)	23,701 (36.0)
10 (highest)	31,497 (20.5)	8,985 (19.6)	931 (22.0)	11,591 (17.6)
Hypertension	38,040 (24.8)	26,036 (56.9)	2,380 (56.3)	34,137 (51.9)
Diabetes	7,872 (5.1)	16,794 (36.7)	71 (1.7)	17,020 (25.9)
Total cholesterol, mg/dL	195.1±31.0	222.5±34.9	235.2±22.8	187.0±30.0
HDL, mg/dL	57.7±33.1	51.5±28.6	57.8±40.7	51.8±21.9
LDL, mg/dL	114.2±29.2	144.9±46.6	155.5±17.0	105.1±27.4
Systolic BP	120.8±13.9	129.2±15.8	123.2±16.1	129.5±14.8
Previous CVD*	0 (0.0)	12,064 (26.3)	0 (0.0)	5,236 (8.0)
Smoking status				
Nonsmoker	112,365 (73.3)	21,272 (46.5)	1,593 (37.7)	34,324 (52.2)
Ex-smoker	27,288 (17.8)	7,890 (17.2)	562 (13.3)	13,994 (21.3)
Current smoker	13,687 (8.9)	16,632 (36.3)	2,074 (49.0)	17,488 (26.6)
Alcohol, drinks/week	1.8±1.4	2.1±1.7	2.2±1.5	2.3±1.9

Data are mean±standard-deviation or *n* (%) values.
*Myocardial infarction, stroke, or CVD.
ACC–AHA: the American College of Cardiology and the American Heart Association, ATP–III: the Third Adult Treatment Panel, BMI: body mass index, BP: blood pressure, CVD: cardiovascular disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

incidence of MACE. Current statin users showed the highest incidence of MACE in both guidelines (Supplementary Fig. 3 in the online-only Data Supplement). Moreover, the cumulative incidence of MACE in the not-recommended group was higher under the ATP-III guidelines than under the ACC-AHA guidelines.

In the statin-recommended groups, participants with 'previous CVD with LDL ≥100 mg/dL' and 'previous CVD' showed the highest incidence of MACE in the ATP-III and ACC-AHA guidelines, respectively (Fig. 1A and B). Participants with previous CVD and LDL <100 mg/dL were not eligible for statin therapy according to the ATP-III guidelines, but they were eligible under the ACC-AHA guidelines. This group showed the highest cumulative incidence of MACE in the not-recommended group (Fig. 1C).

HR of MACE under the two guidelines
The incidence of MACE was 2.1% in the entire study population and 3.6% in the current-statin-user group (Table 3).

The indication of a 10-year CVD risk of ≥7.5% increased the statin recommendation most substantially, by 74,826 subjects. However, the cumulative incidence of MACE in this group was lower than that in other studies based on the US population.

Based on the ATP-III guidelines, the incidence rates of MACE in the statin-recommended and not-recommended groups were 3.2% and 1.4%, respectively. The univariate HR between these two groups was 2.38 (95% CI=2.24−2.53). In contrast, the incidence rates of MACE in the statin-recommended and not-recommended groups according to the ACC-AHA guidelines were 3.2% and 0.7%, respectively. The univariate HR of 4.83 (95% CI=4.51−5.17) was higher, and the 95% CI did not overlap with that for the ATP-III guidelines. In the multivariate analysis, participants who were eligible for a statin under the ACC-AHA guidelines had a significantly higher HR for the incidence of MACE when compared with those eligible under the ATP-III guidelines: 1.28 (95% CI=1.18−1.39) vs. 1.06 (95% CI=0.99−1.14), respectively.
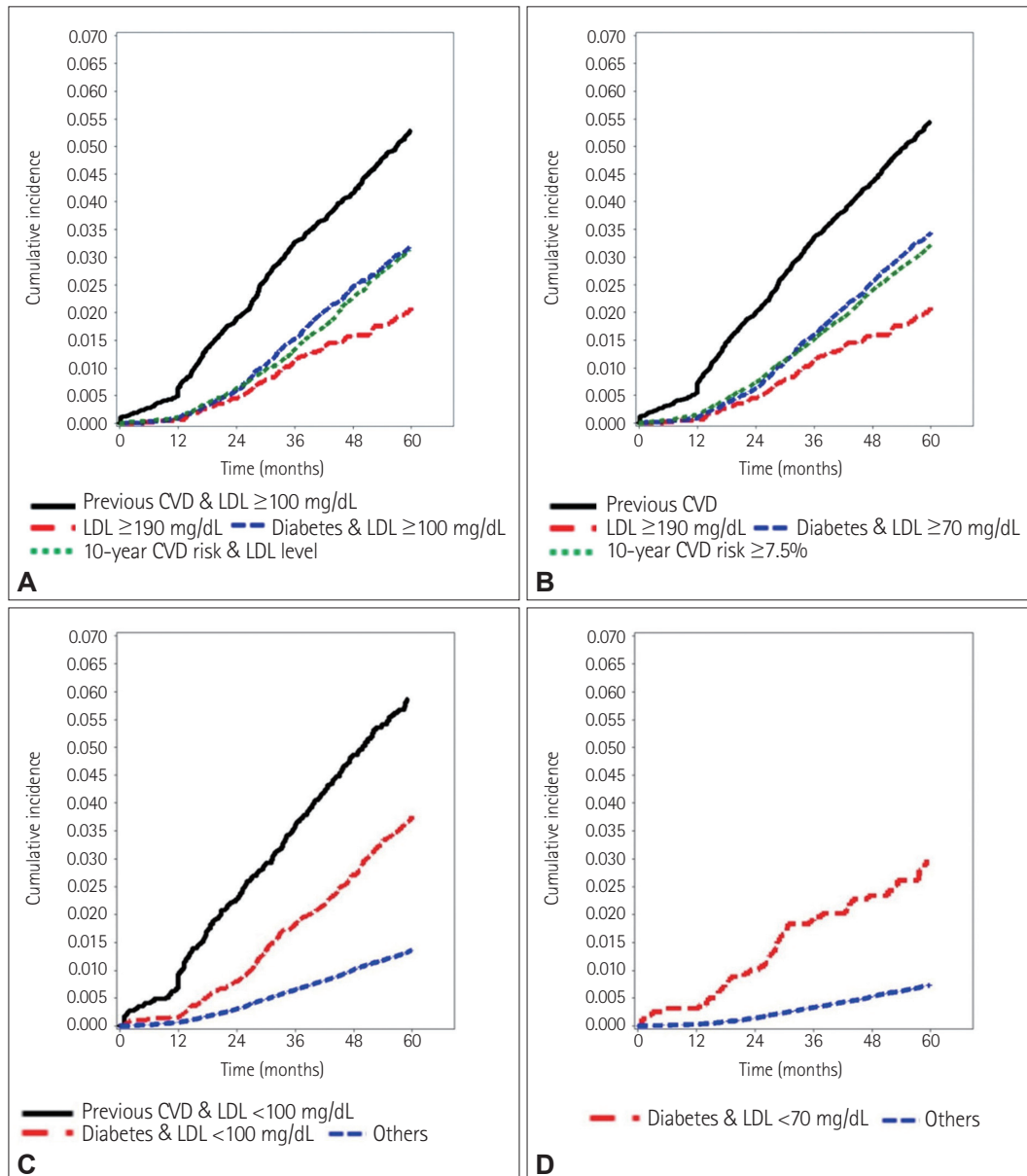
Fig. 1. Kaplan-Meier survival curves for the cumulative incidence of MACE under the two guidelines: the Third Adult Treatment Panel (A and C) the American College of Cardiology and American Heart Association (B and D). The cumulative incidence rates of MACE are shown during the mean follow-up of 4.6 years. MACE include CVD mortality, fatal or nonfatal myocardial infarction, and stroke. Panels A and B are statin-recommended groups, and panels C and D are not-recommended groups. CVD: cardiovascular disease, LDL: low-density lipoprotein, MACE: major adverse cardio-vascular events.

Our investigation of specific indications for a statin recommendation revealed that previous CVD was the most notable indication with the highest incidence: 4.8% in the ATP-III guidelines and 5.0% in the ACC-AHA guidelines. In the not-recommended groups for the ATP-III guidelines, those with previous CVD and LDL <100 mg/dL also showed the highest incidence, of 5.5%. Moreover, those with diabetes and LDL <100 mg/dL showed an incidence of MACE of 3.4%. These two groups would be included in the statin-recommended group according to the 2013 ACC-AHA guide-

lines, with the only exclusion being the presence of diabetes and LDL <70 mg/dL. Compared with not-recommended groups, the HR of MACE in the presence of diabetes and LDL ≥100 mg/dL in the ATP-III guidelines was not statistically significant (HR=1.04, 95% CI=0.92−1.17), while the HR of MACE in the presence of diabetes and LDL ≥70 mg/dL in the ACC-AHA guidelines was statistically significant (HR=1.31, 95% CI=1.15−1.48).

Applying the ATP-III guidelines resulted in 22,549 participants being recommend to receive statins due to their 10-

Table 3. Incidence of MACE under the two guidelines

Treatment category	All participants (*n*=338,332)	MACE (*n*=7,145)	Univariate	Multivariate*
ATP-III guidelines				
Statin used currently	69,163 (20.4)	2,507 (3.6)	2.68 (2.54–2.83)	1.30 (1.23–1.39)
Previous CVD	14,321 (4.2)	992 (6.9)	5.26 (4.90–5.65)	1.09 (0.95–1.24)
Primary prevention	54,842 (16.2)	1,515 (2.8)	2.03 (1.91–2.16)	1.36 (1.27–1.46)
Recommended	50,023 (14.8)	1,620 (3.2)	2.38 (2.24–2.53)	1.06 (0.99–1.14)
Previous CVD & LDL 100 mg/dL	12,064 (3.6)	580 (4.8)	3.59 (3.29–3.93)	0.92 (0.80–1.07)
LDL 90 mg/dL	4,200 (1.2)	79 (1.9)	1.38 (1.10–1.73)	1.13 (0.89–1.44)
Diabetes & LDL 100 mg/dL	11,210 (3.3)	326 (2.9)	2.13 (1.90–2.39)	1.04 (0.92–1.17)
10-year CVD risk & LDL level	22,549 (6.7)	635 (2.8)	2.05 (1.88–2.23)	1.10 (1.00–1.21)
Not recommended	219,146 (64.8)	3,018 (1.4)	1.00	1.00
Previous CVD & LDL <100 mg/dL	5,162 (1.5)	282 (5.5)	1.00	1.00
Diabetes & LDL <100 mg/dL	5,646 (1.7)	191 (3.4)	1.00	1.00
Others	208,338 (61.6)	2,545 (1.2)	1.00	1.00
ACC-AHA guidelines				
Statin used currently	69,163 (20.4)	2,507 (3.6)	5.50 (5.12–5.91)	1.55 (1.42–1.70)
Previous CVD	14,321 (4.2)	992 (6.9)	10.80 (9.90–11.77)	3.07 (2.77–3.39)
Primary prevention	54,842 (16.2)	1,515 (2.8)	4.17 (3.85–4.51)	1.58 (1.44–1.73)
Recommended	111,600 (33.0)	3,575 (3.2)	4.83 (4.51–5.17)	1.28 (1.18–1.39)
Previous CVD	17,300 (5.1)	863 (5.0)	7.65 (7.00–8.37)	2.66 (2.41–2.94)
LDL 90 mg/dL	4,200 (1.2)	79 (1.9)	2.83 (2.25–3.56)	1.31 (1.03–1.67)
Diabetes & LDL 70 mg/dL	15,274 (4.5)	473 (3.1)	4.66 (4.18–5.19)	1.31 (1.15–1.48)
10-year CVD risk 7.5%	74,826 (22.1)	2,160 (2.9)	4.34 (4.03–4.67)	1.25 (1.15–1.37)
Not recommended	157,569 (46.6)	1,063 (0.7)	1.00	1.00
Diabetes & LDL <70	1,582 (0.5)	44 (2.8)	1.00	1.00
Others	155,987 (46.1)	1,019 (0.7)	1.00	1.00

Data are *n* (%) or hazard ratio (95% confidence interval) values.
*Multivariate Cox model adjusted for sex, age, economic status, total cholesterol, hypertension, systolic blood pressure, diabetes, body mass index, previous CVD disease, smoking status, drinking status, high-density lipoprotein, and LDL. Each subcategory is compared with the non-recommended group under each set of guidelines.
ACC-AHA: the American College of Cardiology and the American Heart Association, ATP-III: the Third Adult Treatment Panel, CVD: cardiovascular disease, LDL: low-density lipoprotein, MACE: major adverse cardiovascular events.

year CVD risk and LDL-cholesterol level, and the incidence of MACE in this group was 2.8%. The HR of MACE was not statistically significant (HR=1.10, 95% CI=1.00−1.21) in the comparison with the not-recommended groups. In contrast, applying the ACC-AHA guidelines resulted in 74,826 participants being recommended to receive statins due to their 10-year CVD risk, as calculated by the pooled equation. The incidence of MACE was 2.9% and the HR of MACE was statistically significant at 1.25 (95% CI=1.15−1.37) in the comparison with the not-recommended groups.

According to the ATP-III guidelines, 208,338 (61.6%) participants were not recommended to receive statins due to other reasons, and the incidence of MACE was 1.2%. Based on the ACC-AHA guidelines this number dropped to 155,987 (46.1%), and the incidence of MACE also decreased, to 0.7%.

Additionally, each component of MACE was evaluated separately; the HRs are presented in Table 4 and Supplementary Tables 1−4 (in the online-only Data Supplement). Stroke

showed a statistically significant HR of 1.24 (95% CI=1.13−1.36) for the statin-recommended group in comparison with the not-recommended group according to the ACC-AHA guidelines only (Table 4).

HR of MACE according to concordant and discordant recommendations for statin therapy

Under both guidelines, 45,794 participants were recommended to receive statins, while 153,340 were not recommended under either of the guidelines (Table 2). The numbers of participants recommended to receive statins solely based on the ATP-III and ACC-AHA guidelines were 4,229 and 65,806, respectively. In comparing discordant recommendations, the group recommended only by the ACC-AHA guidelines were older (63.8±7.4 years vs. 52.6±5.3 years) and a higher incidence rates of diabetes [*n*=17,020 (25.9%) vs. *n*=71 (1.7%)] and previous CVD history [*n*=5,236 (8.0%) vs. *n*=0 (0%)]. On the other hand, participants recommended particularly by

Table 4. Incidence of stroke under the two guidelines

Treatment category	All participants (n=338,332)	Stroke (n=5,803)	Univariate	Multivariate
ATP-III guidelines				
Statin used currently	69,163 (20.4)	1,943 (2.8)	2.43 (2.29–2.57)	1.14 (1.06–1.22)
Previous CVD	14,321 (4.2)	801 (5.6)	4.95 (4.57–5.36)	0.98 (0.85–1.13)
Primary prevention	54,842 (16.2)	1,142 (2.1)	1.79 (1.67–1.92)	1.19 (1.10–1.28)
Recommended	50,023 (14.8)	1,282 (2.6)	2.20 (2.05–2.35)	1.02 (0.95–1.11)
Previous CVD & LDL 100 mg/dL	12,064 (3.6)	513 (4.3)	3.75 (3.41–4.12)	0.95 (0.81–1.11)
LDL 190 mg/dL	4,200 (1.2)	48 (1.1)	1.00 (0.75–1.33)	0.89 (0.66–1.21)
Diabetes & LDL 100 mg/dL	11,210 (3.3)	258 (2.3)	1.99 (1.75–2.26)	1.00 (0.87–1.15)
10-year CVD risk & LDL level	22,549 (6.7)	463 (2.1)	1.72 (1.56–1.90)	1.04 (0.93–1.16)
Not recommended	219,146 (64.8)	2,578 (1.2)	1.00	1.00
Previous CVD & LDL <100 mg/dL	5,162 (1.5)	248 (4.8)	1.00	1.00
Diabetes & LDL <100 mg/dL	5,646 (1.7)	160 (2.8)	1.00	1.00
Others	208,338 (61.6)	2,170 (1.0)	1.00	1.00
ACC-AHA guidelines				
Statin used currently	69,163 (20.4)	1,943 (2.8)	5.01 (4.63–5.43)	1.34 (1.22–1.48)
Previous CVD	14,321 (4.2)	801 (5.6)	10.24 (9.31–11.26)	2.74 (2.45–3.06)
Primary prevention	54,842 (16.2)	1,142 (2.1)	3.69 (3.39–4.03)	1.58 (1.44–1.73)
Recommended	111,600 (33.0)	2,957 (2.7)	4.72 (4.38–5.08)	1.24 (1.13–1.36)
Previous CVD	17,300 (5.1)	762 (4.4)	8.00 (7.27–8.82)	2.69 (2.41–3.00)
LDL 190 mg/dL	4,200 (1.2)	48 (1.1)	2.07 (1.55–2.77)	1.04 (0.77–1.40)
Diabetes & LDL 70 mg/dL	15,274 (4.5)	381 (2.5)	4.44 (3.93–5.00)	1.27 (1.10–1.45)
10-year CVD risk 7.5%	74,826 (22.1)	1,766 (2.4)	4.18 (3.86–4.53)	1.22 (1.11–1.34)
Not recommended	157,569 (46.6)	903 (0.6)	1.00	1.00
Diabetes & LDL <70 mg/dL	1,582 (0.5)	37 (2.3)	1.00	1.00
Others	155,987 (46.1)	866 (0.6)	1.00	1.00

Data are n (%) or hazard ratio (95% confidence interval) values.
ACC-AHA: the American College of Cardiology and the American Heart Association, ATP-III: the Third Adult Treatment Panel, CVD: cardiovascular disease, LDL: low-density lipoprotein.

the ATP-III guidelines had higher total cholesterol (235.2± 22.8 mg/dL vs. 187.0±30.0 mg/dL) and LDL-cholesterol (155.5±17.0 mg/dL vs. 105.1±27.4 mg/dL) levels.

The concordantly recommended group had a significant HR of 1.29 (95% CI=1.17−1.42) in the comparison with the concordantly not-recommended group (Table 5). The HR of 1.09 (95% CI=0.80−1.47) was not statistically significant for the group recommended under the ATP-III guidelines but not by the ACC-AHA guidelines. The group recommended exclusively by the ACC-AHA guidelines showed a statistically significant HR of 1.28 (95% CI=1.17−1.40).

DISCUSSION

This study investigated whether applying statin therapy to more people at risk of future CVD would reduce the incidence of MACE. We detected the number of statin-recommended subjects under each indication criterion and the occurrence of MACE under the ACC-AHA and ATP-III guidelines. Our study included a large number of subjects and followed up the incidence of MACE with a low dropout rate, which was possible because all Koreans are obligatorily enrolled in the national insurance service.

The ACC-AHA guidelines have the shortcoming of too many patients being included in the statin-recommendation group. The greatest increase was observed in the group with a 10-year CVD risk of ≥7.5%, although the incidence of MACE was still lower than in other studies of the US population (Table 3 and Supplementary Fig. 3 in the online-only Data Supplement).[7,8,12] The risk equation for ACC-AHA has a problem of overestimation,[13] which seems to be greater in the Asian population. Therefore, the optimal method of applying prediction equations varies between different populations.

The increase in statin recommendations was much more pronounced among older subjects (Supplementary Fig. 2 in the online-only Data Supplement).[8] Strictly controlling the blood pressure, diabetes, and hyperlipidemia from the age of 40 years can reduce the risk of vascular dementia, but even if CVD risk factors are controlled from the age of 60 years,

Table 5. MACE according to concordant and discordant recommendations under the two guidelines

Treatment category (ATP–III guidelines/ACC–AHA guidelines)	All participants	MACE	Univariate	Multivariate
Total	338,332 (100.0)	7,145 (2.1)		
Recommended/recommended	45,794 (13.5)	1,575 (3.4)	5.27 (4.87–5.70)	1.29 (1.17–1.42)
Recommended/not recommended	4,229 (1.3)	45 (1.1)	1.60 (1.18–2.15)	1.09 (0.80–1.47)
Not recommended/recommended	65,806 (19.5)	2,000 (3.0)	4.65 (4.31–5.02)	1.28 (1.17–1.40)
Not recommended/not recommended	153,340 (45.3)	1,018 (0.7)	1.00	1.00
Previous CVD & LDL				
Recommended/recommended				
Previous CVD & LDL ≥100 mg/dL	12,064 (3.6)	580 (4.8)	7.49 (6.76–8.29)	2.60 (2.32–2.91)
Recommended/not recommended	0 (0.0)	0 (0.0)	–	–
Not recommended/recommended				
Previous CVD & LDL <100 mg/dL	5,162 (1.5)	282 (5.5)	8.52 (7.47–9.72)	2.84 (2.47–3.27)
Not recommended/not recommended				
Diabetes & LDL <70 mg/dL or others/others	153,340 (45.3)	1,018 (0.7)	1.00	1.00
Diabetes & LDL				
Recommended/recommended				
Diabetes & LDL ≥100 mg/dL	11,210 (3.3)	326 (2.9)	4.45 (3.93–5.04)	1.23 (1.07–1.42)
Recommended / not recommended	0 (0.0)	0 (0.0)	–	–
Not recommended/recommended				
Diabetes & LDL ≥70 & <100 mg/dL	4,064 (1.2)	147 (3.6)	5.52 (4.64–6.56)	1.53 (1.27–1.84)
Not recommended/not recommended				
Diabetes & LDL <70 mg/dL or others/others	153,340 (45.3)	1,018 (0.7)	1.00	1.00
10-year CVD risk & LDL level/10-year CVD risk 7.5%				
Recommended/recommended				
10-year CVD risk & LDL level/10-year CVD risk ≥7.5%	18,320 (5.4)	590 (3.2)	4.90 (4.42–5.42)	1.31 (1.17–1.48)
Recommended/not recommended				
10-year CVD risk & LDL/others	4,229 (1.3)	45 (1.1)	1.60 (1.19–2.15)	1.09 (0.81–1.47)
Not recommended/recommended				
Others/10-year CVD risk ≥7.5%	56,506 (16.7)	1,570 (2.8)	4.25 (3.93–4.60)	1.24 (1.13–1.36)
Not recommended/not recommended				
Diabetes & LDL <70 mg/dL or others/others	153,340 (45.3)	1,018 (0.7)	1.00	1.00

Data are n (%) or hazard ratio (95% confidence interval) values.
ACC-AHA: the American College of Cardiology and the American Heart Association, ATP-III: the Third Adult Treatment Panel, CVD: cardiovascular disease, LDL: low-density lipoprotein, MACE: major adverse cardiovascular events.

the dementia prevention effect is insignificant.[14-18] The usefulness of using statins to prevent CVD in older subjects is also controversial.[19] Therefore, the prediction equations or criteria for statin-eligible subjects need to vary according to race and age.

In comparison with the ATP-III guidelines, the ACC-AHA guidelines have successfully recommended statins for patients at a high risk of MACE. The cumulative incidence of MACE in the not-recommended group was higher under the ATP-III guidelines than under the ACC-AHA guidelines (Fig. 1), which is due to the exclusion of more subjects to whom statins should be recommended. The ATP-III guidelines restrict statins to people with previous CVD or diabetes using the LDL ≥100 mg/dL criterion, which results in more-

vulnerable patients remaining in the not-recommended group and thus increases the incidence of MACE.

The ACC-AHA guidelines are more appropriate for diabetes patients. The HR of MACE in diabetics was statistically significant when the LDL-cholesterol threshold was lowered to 70 mg/dL in the ACC-AHA guidelines (HR=1.31, 95% CI=1.15−1.48) (Table 3). The baseline LDL-cholesterol was lower in diabetes patients than in patients without diabetes, while the triglyceride level was higher. Thus, statin treatment may also be required for patients with diabetes and LDL <70 mg/dL. Comparing patients with diabetics between those with mean LDL-cholesterol levels of 80 and 61 mg/dL, the atheroma volume regression was only observed in the latter diabetic patient group, while the nondiabetic patients

showed the same level of regression as the group with a mean LDL-cholesterol of 80 mg/dL.[20] Therefore, our study calls for aggressive statin use in diabetic patients regardless of the LDL-cholesterol level.

The adjusted HR for MACE was higher in the current-statin-user group than in the statin-recommended group under both guidelines (Table 3). The former group includes patient with a history of MI, angina, and CVD. Since patients with a previous medical history have a greater risk of future MACE, the adjusted HR was also higher in this group.

This study was subject to a few limitations. Firstly, the study involved a Korean population, and so the results cannot be generalized to other populations. However, the ACC-AHA guidelines lack a foundation in diverse racial groups due to the pooled-cohort risk assessment equations accounting mostly for non-Hispanic, Caucasian, and African-American populations.[5] Thus, our study utilized a large-scale database from a Korean population and implemented the data using both the ACC-AHA and ATP-III guidelines to confirm their efficacies. Secondly, we could not investigate the new categories of the 2018 ACC-AHA guidelines and nonstatin medications. An intermediate risk category ($\geq$7.5% to <20%) was added to the new guidelines, and a new definition of high risk ($\geq$20%) was established. The new guidelines also recommended nonstatin medications (e.g., ezetimibe) in patients who respond inadequately to statins alone. We did not factor in these new categories and nonstatin medications in this study, and so future studies are warranted to learn more about the efficacy of these additions.

In conclusion, the 2013 ACC-AHA guidelines increase the number of statin-eligible participants, especially among older people. The ACC-AHA guidelines make stronger recommendations for statins to be applied to high-risk groups, but it is necessary to consider the characteristics of the population in the risk equation. Future studies should investigate the aggressive use of statin in diabetes patients and older subjects.

Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.1.86.

Author Contributions
Conceptualization: Jong Weon Lee, Hunsun Lim. Data curation: Jong Weon Lee, Hunsun Lim. Formal analysis: Jong Weon Lee, Hunsun Lim. Methodology: Jong Hun Kim, Hyoung Seop Kim. Supervision: Jong Hun Kim, Hyoung Seop Kim. Validation: Jong Hun Kim, Hyoung Seop Kim. Writing—original draft: Jong Weon Lee. Writing—review&editing: Jong Hun Kim, Kim Hyoung Seop.

ORCID iDs
Jong Weon Lee   https://orcid.org/0000-0003-0361-5986
Hunsun Lim   https://orcid.org/0000-0003-2391-3286
Jong Hun Kim   https://orcid.org/0000-0002-2594-1048
Hyoung Seop Kim   https://orcid.org/0000-0002-5310-4802

REFERENCES

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
2. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935-2959.
3. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;139:e1082-e1143.
4. Pursnani A, Mayrhofer T, Ferencik M, Hoffmann U. The 2013 ACC/AHA cardiovascular prevention guidelines improve alignment of statin therapy with coronary atherosclerosis as detected by coronary computed tomography angiography. *Atherosclerosis* 2014;237:314-318.
5. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;129(25 Suppl 2):S1-S45.
6. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA* 2014;311:1416-1423.
7. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, Williams K, Neely B, Sniderman AD, et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014;370:1422-1431.
8. Ko MJ, Kim YJ, Park CM, Lee SM, Lee WJ, Pencina MJ, et al. Applicability and potential clinical effects of 2013 cholesterol guidelines on major cardiovascular events. *Am Heart J* 2015;170:598-605.e7.
9. Arai H, Sasaki J, Teramoto T. Comment on the new guidelines in USA by the JAS Guidelines Committee. *J Atheroscler Thromb* 2014;21:79-81.
10. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA* 2014;311:1406-1415.
11. Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017;46:799-800.
12. Rhee EJ, Park SE, Oh HG, Park CY, Oh KW, Park SW, et al. Statin eligibility and cardiovascular risk burden assessed by coronary artery calcium score: comparing the two guidelines in a large Korean cohort. *Atherosclerosis* 2015;240:242-249.

13. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;162:266-275.

14. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162:2046-2052.

15. Hauer AJ, Ruigrok YM, Algra A, van Dijk EJ, Koudstaal PJ, Luijckx GJ, et al. Age-specific vascular risk factor profiles according to stroke subtype. *J Am Heart Assoc* 2017;6:e005090.

16. Wolters FJ, Ikram MA. Epidemiology of vascular dementia. *Arterioscler Thromb Vasc Biol* 2019;39:1542-1549.

17. Kimm H, Lee PH, Shin YJ, Park KS, Jo J, Lee Y, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. *Arch Gerontol Geriatr* 2011;52:e117-e122.

18. Pan ML, Hsu CC, Chen YM, Yu HK, Hu GC. Statin use and the risk of dementia in patients with stroke: a Nationwide Population-Based Cohort Study. *J Stroke Cerebrovasc Dis* 2018;27:3001-3007.

19. Kim K, Lee CJ, Shim CY, Kim JS, Kim BK, Park S, et al. Statin and clinical outcomes of primary prevention in individuals aged >75 years: the SCOPE-75 study. *Atherosclerosis* 2019;284:31-36.

20. Stegman B, Puri R, Cho L, Shao M, Ballantyne CM, Barter PJ, et al. High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN. *Diabetes Care* 2014;37:3114-3120.