Applicability and potential clinical effects of 2013 cholesterol guidelines on major cardiovascular events

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Background The applicability to different race/ethnic groups and effects on cardiovascular disease (CVD) outcomes of the 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for cholesterol management remain to be determined. We estimated the proportion of Korean adults who would be affected by the 2013 cholesterol guidelines and to determine the related effects on cardiovascular events.

Methods Using data from the Korean National Health and Nutrition Examination Survey of 2008 to 2012 (n = 18,573), we compared the estimated number of statin candidates under the 2013 ACC/AHA and the Third Adult Treatment Panel (ATP-III) guidelines and extrapolated the results to 19.0 million Koreans between the ages of 40 and 75 years. Using an external cohort (n = 63,329) from the 2003 National Health Examination with 7 years of prospective follow-up, we determined the potential effects of recent recommendations changes on atherosclerotic CVD events (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).

Results Compared with the ATP-III guidelines, the ACC/AHA guidelines would increase the number of statin candidates from 3.5 million (18.6%) to 6.7 million (35.1%). The increase of statin candidates would be larger among older adults (60-75 years; from 29.8% to 74.9%) as compared with younger adults (40-59 years; from 15.6% to 19.8%) and among men (from 25.7% to 45.4%) compared with women (from 14.6% to 26.8%). In the external cohort, compared with adults who were recommended by neither of the 2 guidelines, those who were recommended by both and those who were recommended by ACC/AHA but not ATP-III guidelines had significantly higher risks of atherosclerotic CVD events (hazard ratios [HRs] 3.65 [95% CI, 3.33-4.02] and 3.98 [95% CI 3.64-4.35], respectively). However, adults who were recommended by ATP-III but not ACC/AHA guidelines did not have an increased risk (HR 0.90, 95% CI 0.64-1.28).

Conclusions In the Korean population, the 2013 ACC/AHA cholesterol guidelines would substantially increase the number of adults who are potentially eligible for statin therapy and would recommend statin therapy for more adults at higher cardiovascular risk. However, the clinician-patient discussion of the potential benefits, possible harms, and other factors before the initiation of statin therapy must be considered. (Am Heart J 2015;170:598-605.e7.)

Similar to the findings in Western populations, the association between elevated cholesterol levels and cardiovascular disease (CVD) is well documented in Asian populations.[1,2] Over the past decade, the guidelines of the Third Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program for lipid management had been commonly used worldwide, including in Asian countries.[3-5] The 2013 guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) for the management of cholesterol substantially modified previous recommendations, expanding the number of adults in the United States now considered recommended for statin therapy.[6,7] The ACC/AHA cholesterol guidelines use the pooled cohort equations to estimate 10-year risk to identify adults for statin therapy for primary prevention.[8] These risk equations are derived from observational cohort studies

in the United States, and therefore, it is expected that the equations would overestimate risk in some other populations and underestimate risk in others.

The applicability of 2013 cholesterol guidelines in Asian populations, who account for more than 60% of the world population, and the potential clinical effects of these guidelines on future CVD events remain unclear given considerable differences in the risks of coronary heart disease (CHD) and the rates of cardiovascular events in an Asian population.[9] It is also important to determine whether the new equations are relevant to the Korean population and, if not, whether recalibration or, most appropriately, race- or ethnic-specific equations can correct these limitations. To address these issues, we sought to compare the number of adult persons potentially eligible for statin therapy under the 2013 ACC/AHA guidelines with those eligible under the ATP-III guidelines using data from the Korea National Health and Nutrition Examination Surveys (KNHANES). We then determined how the differences in recommendations under each set of guidelines would affect the future risk of atherosclerotic CVD (ASCVD) events when applied to an external validation cohort from the Korean National Health Examination.

Methods
Study population

To compare the number of adults who would be recommended to receive statin therapy between the 2013 ACC/AHA guidelines and the previous ATP-III guidelines among Korean adults, we used a population-based sample data collected between 2008 and 2012 as part of the KNHANES, a nationally representative survey of the noninstitutionalized Korean adults.[10] Of the 21,268 KNHANES participants between the ages of 40 and 75 years for whom fasting data were available, we excluded 482 participants who had triglyceride levels of more than 400 mg/dL (4.52 mmol/L), 2,191 participants who had missing data on low-density lipoprotein (LDL) cholesterol levels, and another 22 participants who had missing information on KNHANES-supplied sample weights. After these exclusions, 18,573 participants were included in the final analyses. Baseline characteristics of the KNHANES participants included vs those excluded are summarized in online Appendix Supplementary Table I.

Statin therapy eligibility under ATP-III and the 2013 ACC/AHA guidelines was evaluated and details of the eligibility criteria applied using each guideline are described in online Appendix Supplementary Table II. The pooled cohort equations were also validated using the online ACC/AHA tool (http://tools.cardiosource.org/ASCVD-Risk-Estimator/), and same results were generated. Prevalent CVD at baseline was defined as CHD (acute coronary syndromes, myocardial infarction [MI], or coronary revascularization), angina, or stroke. Diabetes was determined by a fasting glucose

≥126 mg/dL or current use of antidiabetic drugs or by physician diagnosis. All study participants provided informed consent, and the study protocol was approved by the institutional review board of the Korea Centers for Disease Control and Prevention. This study was partly funded by the National Evidence-based Healthcare Collaborating Agency, Seoul, Korea (project number NP-14-006).

External validation cohort

To determine the impact of differential recommendations for statin therapy between the ATP-III and the ACC/AHA guidelines and validate each risk function, we evaluated ASCVD event rates among adults enrolled in the 2003 National Health Examination, performed by the Korean National Health Insurance Service (NHIS), between the ages of 40 and 74 years.[11] Of the 70,085 participants, we excluded 6,283 participants who had missing information on components of the prediction models; 79 participants who died before January 1, 2004; 346 participants who had no follow-up after January 1, 2004; and 48 participants who had laboratory examination data outliers. After these exclusions, 63,329 participants were included in the final analyses.

The primary outcome was *ASCVD events*, defined as a composite of cardiovascular death, MI, or stroke. *CHD* events were defined as a composite of cardiovascular death or MI. Data regarding hospital admissions for MI or stroke were ascertained using national claims data from the NHIS. Events were assessed until December 31, 2010, and all outcomes were identified through linkages to administrative databases in the NHIS with a complete event ascertainment.

Statistical analysis

Because subjects for the KNHANES were selected by a stratified, complex, multistage, clustered probability sampling design to represent the entire noninstitutionalized, civilian population in Korea, we used domain analysis including KNHANES-supplied sample weights to extrapolate the results from the KNHANES sample to all Korean adults between the ages of 40 and 75 years. This accounted for oversampling and nonresponse rates. Clinical characteristics were summarized for the KNHANES sample and as extrapolated to the national population.

We examined adults with concordant and discordant sets of recommendations based on the 2 sets of guidelines: neither recommended, recommended by ATP-III but not ACC/AHA guidelines, recommended by ACC/AHA but not ATP-III guidelines ("new candidates"), or both recommended. By this, we estimated the number and proportion of adults in Korea who would be eligible for statin therapy on the basis of the ATP-III and ACC/AHA guidelines. Analyses were further stratified according to prespecified age (younger adults 40-59 years vs older adults 60-75 years) and sex groups. As a sensitivity