EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2016;31:402-409
http://dx.doi.org/10.3803/EnM.2016.31.3.402
pISSN 2093-596X · eISSN 2093-5978

Eligibility for Statin Treatment in Korean Subjects with Reduced Renal Function: An Observational Study

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Background: The purpose of this study was to investigate the relationship between statin eligibility and the degree of renal dysfunction using the Adult Treatment Panel (ATP) III and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines in Korean adults.

Methods: Renal function was assessed in 18,746 participants of the Kangbuk Samsung Health Study from January 2011 to December 2012. Subjects were divided into three groups according to estimated glomerular filtration rate (eGFR): stage 1, eGFR ≥90 mL/min/1.73 m^2; stage 2, eGFR 60 to 89 mL/min/1.73 m^2; and stages 3 to 5, eGFR <60 mL/min/1.73 m^2. Statin eligibility in these groups was determined using the ATP III and ACC/AHA guidelines, and the risk for 10-year atherosclerotic cardiovascular disease (ASCVD) was calculated using the Framingham Risk Score (FRS) and Pooled Cohort Equation (PCE).

Results: There were 3,546 (18.9%) and 4,048 (21.5%) statin-eligible subjects according to ATP III and ACC/AHA guidelines, respectively. The proportion of statin-eligible subjects increased as renal function deteriorated. Statin eligibility by the ACC/AHA guidelines showed better agreement with the Kidney Disease Improving Global Outcomes (KDIGO) recommendations compared to the ATP III guidelines in subjects with stage 3 to 5 chronic kidney disease (CKD) (κ value, 0.689 vs. 0.531). When the 10-year ASCVD risk was assessed using the FRS and PCE, the mean risk calculated by both equations significantly increased as renal function declined.

Conclusion: The proportion of statin-eligible subjects significantly increased according to worsening renal function in this Korean cohort. ACC/AHA guideline showed better agreement for statin eligibility with that recommended by KDIGO guideline compared to ATP III in subjects with CKD.

Keywords: Renal insufficiency, chronic; Cholesterol guidelines; Statin

INTRODUCTION

Many studies have shown that statin treatment reduces atherosclerotic cardiovascular disease (ASCVD) risk and mortality in pre-dialysis chronic kidney disease (CKD) patients [1-3]. A recent randomized clinical trial indicated that low density lipopro-

Received: 1 March 2016, **Revised**: 26 June 2016, **Accepted:** 30 June 2016
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tein cholesterol (LDL-C) reduction with a statin and ezetimibe safely reduced cardiovascular disease (CVD) in a wide range of CKD stages, confirming the results of previous studies [4]. Given that statins prevent ASCVD in CKD patients, the 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for lipid management recommended that all adults 50 years of age or older with CKD and not on dialysis be prescribed a statin [5].

In 2001, the Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) issued its third set of guidelines (NCEP ATP III) for the identification and management of dyslipidemia, which was further updated in 2004 [6,7]. According to most recent NCEP ATP III guidelines, CKD is not considered a coronary heart disease (CHD) risk equivalent, despite the fact that prior studies showed this reclassification would increase the proportion of statin-eligible CKD individuals [8,9]. In 2011, the European Society of Cardiology/European Atherosclerosis Society guidelines for dyslipidemia management acknowledged CKD as a coronary artery disease (CAD) risk equivalent, and patients with moderate to severe CKD were classified as "very high" risk [10].

In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force released a new report on dyslipidemia treatment and identified four patient groups who would benefit from statin treatment, irrespective of their LDL-C level [11]. However, moderate or severe CKD were not specifically mentioned in these recommendations. A recent study using data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study analyzed the calibration and discriminative power of the new cholesterol treatment recommendations in the CKD population [12]. They reported a high concordance between the ACC/AHA and the KDIGO guidelines in their recommendations for statin therapy. However, these results have not been confirmed in an Asian population.

Therefore, using data from a large cohort of Korean adults undergoing health screening, we analyzed statin eligibility according to each set of guidelines in subgroups based on renal function. We also identified the distribution of the 10-year ASCVD and CHD risk in these groups via the Pooled Cohort Equation (PCE) and the Framingham Risk Score (FRS), respectively [13,14].

METHODS

Study population

The study population comprised 18,746 participants who participated in the Kangbuk Samsung Health Study (KSHS) between January 2011 and December 2012 at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. This medical health program promotes employee health through regular checkups with the goal of enhancing early detection of existing diseases. This study was a sub-analysis of a previously published study that analyzed the association between coronary artery calcification (CAC) and statin eligibility in Korean adults [15].

The design, protocol, and consent procedure for this study were reviewed and approved by the Institutional Review Board of Kangbuk Samsung Hospital in accordance with the Helsinki Declaration of 1975.

Anthropometric and laboratory measurements

The height and weight were measured twice and averaged. The body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). Blood pressure was measured using a standardized sphygmomanometer after 5 minutes of rest.

All of the subjects were examined after an overnight fast. The hexokinase method was used to test fasting glucose concentrations (Hitachi Modular D2400, Roche, Tokyo, Japan), and the total cholesterol and triglyceride concentrations were measured by enzymatic calorimetry. The selective inhibition method was used to measure the high density lipoprotein cholesterol, and a homogeneous enzymatic calorimetric test was used to quantify LDL-C.

The presence of diabetes mellitus was determined via a self-administered questionnaire and the diagnostic criteria of the American Diabetes Association [16]. Briefly, the presence of diabetes was defined as having a fasting blood glucose level of ≥ 126 mg/dL, glycated hemoglobin ≥6.5% or as taking an anti-hyperglycemic agent. The use of anti-hypertensive medications and smoking status were determined by self-report. A history of myocardial infarction or ischemic stroke was also assessed using the same questionnaire.

Assessment of renal function

The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation: [(140–age)×weight in kg×0.85 if female]/(serum creatinine×72) [17]. Subjects were divided into three groups according to the CKD staging system based on eGFR grade: stage 1, eGFR ≥90 mL/min/1.73 m^2; stage 2, eGFR 60 to 89 mL/min/1.73 m^2; and stages 3 to 5, eGFR <60 mL/min/1.73 m^2 [18].

Assessment of statin eligibility

The eligibility for statin use was first determined using the updated 2004 ATP III criteria [6,7]. Statin eligibility was then reassessed using the 2013 ACC/AHA Blood Cholesterol guidelines [11].

Next, the KDIGO guidelines were used to evaluate for statin eligibility in subjects with CKD, and the concordance of all of the guidelines was further analyzed in subjects with an eGFR <60 mL/min/1.73 m^2 [5]. FRS and PCE were used to calculate the 10-year CHD and ASCVD risks, respectively [13,14].

Statistical analyses

All data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The comparison of the mean values and prevalence of variables in each statin-eligible population was analyzed using the Student *t* test. Statin eligibility among the three groups divided by renal function was compared using the chi-square test. The cardiovascular risk variables (FRS, PCE) in these groups were evaluated by one-way analysis of variance and *post hoc* analyses using Tukey method. We analyzed the κ value in order to estimate the concordance rates between the statin-eligibility guidelines. Statistical significance was defined as a *P* value less than 0.05.

RESULTS

Study population

The baseline patient characteristics are presented in Table 1. Among the 18,746 KSHS participants, the mean age was 46 years (range, 40 to 75), 80.1% were men and 19.9% were women, and the mean BMI was 24.4 kg/m^2. In total, 979 subjects (5.2%) in this population were already taking statins and were included in the statin-eligible cohort. The mean eGFR was 89 mL/min/1.73 m^2 (range, 5 to 216), and the proportion of patients in each of the three groups were as follows: 8,559 patients in stage 1 (45.7%); 9,916 in stage 2 (52.9%); and 271 in stages 3 to 5 (1.4%). The average 10-year CHD and ASCVD risks were significantly greater for men than for women (Table 1).

Table 1. General Characteristics of the Participants

Characteristic	Total (*n*=18,746)	Male (*n*=15,015)	Female (*n*=3,731)
Age, yr	46.0±5.9	45.6±5.5	47.5±7.2
Body mass index, kg/m^2	24.4±3.0	24.8±2.8	23.0±3.1
Fasting glucose, mg/dL	100.8±18.1	101.9±18.5	96.4±15.5
SBP, mm Hg	114.0±12.6	115.3±12.2	109.0±13.2
DBP, mm Hg	74.7±10.1	76.0±9.9	69.5±9.4
Total cholesterol, mg/dL	205.0±33.4	205.8±33.4	201.5±33.4
Triglyceride, mg/dL	141.3±86.8	151.0±90.3	102.4±56.7
HDL-C, mg/dL	53.5±13.1	51.1±12.2	60.9±14.0
LDL-C, mg/dL	131.6±30.9	133.0±30.7	126.0±31.1
Glycated hemoglobin, %	5.8±0.6	5.8±0.6	5.8±0.6
Diabetes	1,528 (8.2)	1,309 (8.7)	219 (5.9)
Hypertension	2,431 (13.0)	2,091 (13.9)	340 (9.1)
Hyperlipidemic therapy	979 (5.2)	777 (5.2)	202 (5.4)
10-Year CHD risk according to FRS, %	5.6±3.7	6.3±3.6	2.6±2.6
10-Year cardiovascular risk according to PCE, %	1.3±0.7	1.3±0.7	1.1±0.4
eGFR, mL/min/1.73 m^2	89.1±17.4	89.3±17.4	88.6±17.2
≥90	8,559 (45.7)	6,863 (45.7)	1,696 (45.5)
60≤&<90	9,916 (52.9)	7,969 (53.1)	1,947 (52.2)
<60	271 (1.4)	183 (1.2)	88 (2.4)

Values are expressed as mean±SD or number (%).
SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CHD, coronary heart disease; FRS, Framingham Risk Score; PCE, Pooled Cohort Equation; eGFR, estimated glomerular filtration rate.

Proportion of statin-eligible subjects according to ATP III and ACC/AHA guidelines

ATP III and ACC/AHA guidelines were applied to the study populations, and the characteristics of the statin-eligible subjects are provided in Table 2, respectively.

A total of 3,546 subjects (18.9%) and 4,048 (21.5%) were eligible for statins based on the ATP III and ACC/AHA guidelines, respectively (Table 2). Among the statin-eligible subjects according to the ATP III guideline, the mean eGFR was 88 mL/min/1.73 m^2; when the subjects were divided into three groups by renal function, most were in stage 2. Similar results were observed in statin-eligible subjects according to the ACC/AHA guideline (Table 2).

Statin-eligible subjects according to renal function

We analyzed the number and proportions of statin-eligible subjects within each CKD stage (Fig. 1). The number of statin-eligible subjects according to the ATP III and ACC/AHA guidelines significantly increased as renal function deteriorated: 17.5%, 19.7%, and 35.1% in stages 1, 2, and 3 to 5, respectively. However, the proportion of statin-eligible subjects identified by the ACC/AHA guidelines was higher than that according to the ATP III guidelines across all stages of renal function (Fig. 1).

In contrast to the KDIGO guidelines, the ACC/AHA guidelines did not specify the contribution of CKD to the ASCVD risk, and CKD was not considered in the indications for statin therapy [14]. Colantonio et al. [12] performed the REGARDS study to investigate the concordance rate of the KDIGO and ACC/AHA cholesterol treatment guidelines and found a high concurrence between these guidelines for the initiation of statin therapy. To estimate the KDIGO concordance rate with ACC/AHA and ATP III guidelines in the Korean population, we utilized κ values between each set of guidelines in CKD subjects with an eGFR <60 mL/min/1.73 m^2. When the agreements for

Table 2. Baseline Characteristics of Statin-Eligible Participants

Characteristic	Statin-eligible by ATP-III guidelines			Statin-eligible by ACC/AHA guidelines		
	Total (*n*=3,546)	Male (*n*=3,038)	Female (*n*=508)	Total (*n*=4,048)	Male (*n*=3,461)	Female (*n*=587)
Age, yr	48.4±7.1	47.7±6.4	53.0±8.8	49.6±8.0	48.9±7.5	54.0±9.7
Body mass index, kg/m^2	25.5±3.0	25.6±2.9	24.6±3.5	25.4±3.1	25.5±2.9	24.4±3.5
Fasting glucose, mg/dL	113.3±31.2	113.8±31.2	110.0±31.1	114.5±31.6	115.2±31.7	110.2±30.7
SBP, mm Hg	117.9±13.7	118.4±13.4	114.9±15.0	118.0±13.2	118.5±12.9	115.2±14.9
DBP, mm Hg	77.8±10.8	78.6±10.7	72.4±9.5	77.3±10.1	78.1±10.0	72.2±9.5
Total cholesterol, mg/dL	225.4±40.6	225.9±39.9	222.2±45.0	216.8±43.4	216.9±43.0	216.0±45.8
Triglyceride, mg/dL	172.0±94.5	178.5±97.1	133.4±64.3	179.3±115.6	187.4±120.1	131.6±67.0
HDL-C, mg/dL	49.8±11.7	48.8±11.1	55.9±13.1	49.8±12.3	48.6±11.7	56.5±13.4
LDL-C, mg/dL	151.4±38.2	152.0±37.0	147.7±44.1	141.6±41.0	141.6±40.4	141.2±44.6
Glycated hemoglobin, %	6.2±1.0	6.2±1.0	6.4±1.1	6.3±1.0	6.2±1.0	6.4±1.1
Diabetes	1,242 (35.0)	1,061 (34.9)	181 (35.6)	1,528 (37.7)	1,309 (37.8)	219 (37.3)
Hypertension	881 (24.8)	777 (25.6)	104 (20.5)	895 (22.1)	778 (22.5)	117 (19.9)
Hyperlipidemic therapy	979 (27.6)	777 (25.6)	202 (39.8)	979 (24.2)	777 (22.5)	202 (34.4)
10-Year CHD risk according to FRS, %	9.5±5.2	10.1±5.1	5.6±4.2	9.1±5.2	9.8±5.1	5.4±3.9
10-Year cardiovascular risk according to PCE, %	1.9±1.0	1.9±1.0	1.3±0.7	1.9±1.0	2.0±1.0	1.4±0.8
eGFR, mL/min/1.73 m^2	88.3±19.1	88.9±18.9	84.7±20.1	88.1±19.5	88.7±19.2	84.6±20.5
≥90	1,498 (42.2)	1,328 (43.7)	170 (33.5)	1,684 (41.6)	1,484 (42.9)	200 (34.1)
60≤&<90	1,953 (55.1)	1,648 (54.2)	305 (60.0)	2,234 (55.2)	1,891 (54.6)	343 (58.4)
<60	95 (2.7)	62 (2.0)	33 (6.5)	130 (3.2)	86 (2.5)	44 (7.5)

Values are expressed as mean±SD or number (%).
ATP, Adult Treatment Panel; ACC/AHA, American College of Cardiology/American Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CHD, coronary heart disease; FRS, Framingham Risk Score; PCE, Pooled Cohort Equation; eGFR, estimated glomerular filtration rate.

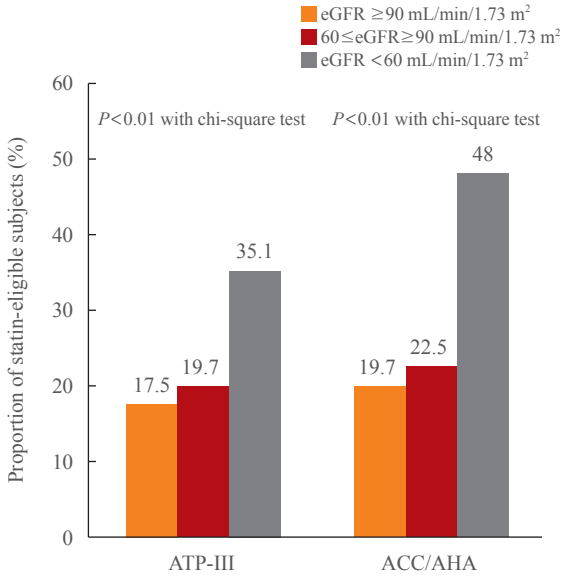

Fig. 1. Proportion of statin-eligible subjects according to Adult Treatment Panel (ATP)-III and American College of Cardiology/American Heart Association (ACC/AHA) guidelines and renal function. eGFR, estimated glomerular filtration rate.

the statin eligibility between the guidelines and KDIGO in subjects with eGFR <60 mL/min/1.73 m^2 were analyzed, statin-eligible subjects according to the ACC/AHA guideline showed higher κ value compared with those recommended by ATP III guideline (Table 3).

Table 3. Concordance of Guideline Recommendations for Statin Therapy[a]

	κ value
KDIGO-ATP III	0.531[b]
KDIGO-ACC/AHA	0.689[b]

KDIGO, Kidney Disease Improving Global Outcomes; ATP, Adult Treatment Panel; ACC/AHA, American College of Cardiology/American Heart Association.
[a]Only in subjects with estimated glomerular filtration rate <60 mL/min/1.73 m^2; [b]P<0.05.

Table 4. Comparison of the 10-Year Atherosclerotic Cardiovascular Disease Risk Analyzed by Two Different Risk Calculators

	Renal function, mL/min/1.73 m^2			P value[a]
	eGFR ≥90	60≤eGFR<90	eGFR <60	
FRS	5.4±3.6	5.7±3.8	7.8±5.7	<0.001
PCE	1.3±0.6	1.3±0.7	1.9±1.2	<0.001

Values are expressed as mean±SD.
eGFR, estimated glomerular filtration rate; FRS, Framingham Risk Score; PCE, Pooled Cohort Equation.
[a]Analyzed by one-way analysis of variance test.

Comparison of the 10-year ASCVD risk calculations obtained using two different calculators according to renal function

We compared the FRS and PCE results in the three aforementioned CKD groups (Table 4). The 10-year ASCVD risk calculated using both methods significantly increased as renal function deteriorated from stage 1 to 3–5 (Table 4). However, the mean risk values calculated using the PCE were lower compared to those calculated via the FRS, although statistical analyses were not performed.

DISCUSSION

In a large population study of Korean adults participating in the KSHS health-screening program, subjects with impaired renal function showed a higher proportion of statin eligibility according to both the ATP III and ACC/AHA cholesterol management guidelines. Furthermore, upon comparing these recommendations to those obtained using the KDIGO guidelines, the ACC/AHA guidelines showed a higher degree of agreement with the KDIGO recommendations than the ATP III guidelines. In addition, subjects with decreased renal function showed an increased 10-year risk for ASCVD.

In the CKD population, multiple pathophysiological mechanisms contribute to the high prevalence of CVD. The presence of left ventricular hypertrophy (LVH), particularly in elderly patients, predicts increased cardiovascular morbidity and mortality due to major CAD events and stroke [19-21]. One important factor linking CKD to increased left ventricular mass is increased arterial stiffness, which manifests as a higher incidence of systolic hypertension and elevated pulse pressure [22]. CKD itself, in addition to the contribution of calcification, may worsen arterial stiffening [23], leading to a vicious cycle. In non-hypertensive patients, the LVH and CKD association is due to a chronic, low-grade inflammatory state created by mediators such as cytokines and oxidative stress [24].

There are many studies showing the positive effects of statins on cardiovascular events in patients with CKD. According to an analysis by Strippoli et al. [3], statin use was associated with a considerable reduction in the risk of non-fatal cardiovascular events in subjects with CKD. Barylski et al. [1] demonstrated that statin treatment was associated with a 45% decrease in car-

diovascular events and a 34% stroke reduction among predialysis CKD patients. In an analysis by Navaneethan et al. [25] including 25,017 predialysis CKD patients, statins reduced cardiovascular events by 20%. A drop in the incidence cardiovascular events was observed in CKD patients receiving pravastatin in a *post hoc* analysis of the Cholesterol and Recurrent Events trial (hazard ratio, 0.72; 95% confidence interval, 0.55 to 0.95) [26]. In the Study of Heart and Renal Protection trial, the combination of 20 mg simvastatin and 10 mg ezetimibe decreased CVD events in CKD patients, again suggesting the protective effects of LDL-C reduction on CVD events [4]. However, contrary to previous guidelines, the 2013 ACC/AHA guidelines did not include CKD patients as an at-risk group [10,11].

In this study, we quantified the number of statin-eligible subjects according to two different cholesterol management guidelines in a large Korean cohort and compared them according to the degree of renal dysfunction. Weiner et al. [27] reported that the Framingham CHD risk prediction equation, which was used in the creation of the ATP III guidelines, was not well calibrated for predicting CHD events among individuals with CKD and was, therefore, unsuitable for guiding therapy. Muntner et al. [28] reported that the 2013 PCE for estimating ASCVD risk was well calibrated with moderately good discrimination among individuals with CKD. Of the study population, the vast majority of individuals 50 to 79 years of age with predialysis CKD were either taking a statin or recommended for statin therapy based on the ACC/AHA guidelines [28]. We found that both guidelines identified a higher proportion of statin-eligible subjects in the group with decreased eGFR than in individuals with normal renal function. In addition, we utilized κ values to estimate the degree of concordance of the KDIGO and ATP III with the KDIGO guidelines in select CKD subjects (eGFR <60 mL/min/1.73 m^2) within the Korean population. The κ value between the KDIGO and ACC/AHA guidelines was significantly higher compared to the value between the KDIGO and ATP III guidelines. This suggests that the ACC/AHA guidelines are an adequate and more appropriate screening tool for statin therapy than the ATP III guidelines in moderate and severe CKD populations.

Our study had several limitations. First, despite our large representative population, the study was cross-sectional in nature; therefore, it could not be used to determine a cause-and-effect relationship. Second, we had no data on the presence of proteinuria, which is included in the definition of CKD; thus, we may have underestimated the CKD population. Third, the number of individuals with an eGFR lower than 60 mL/min/1.73 m^2 was relatively small because the KSHS conducted examinations on healthy Korean adults. Fourth, we used the eGFR instead of directly measuring the glomerular filtration rate (GFR) to define CKD. Stevens et al. [29] reported that the eGFR was inaccurate in subjects with previously undiagnosed CKD. However, the eGFR facilitates the detection and evaluation of CKD; thus, many organizations recommend the use of a calculated GFR in epidemiologic studies [29]. Another weak point of our GFR estimation was that we used the Cockcroft-Gault equation instead of the CKD-Epidemiology Collaboration or Modification of Diet in Renal Disease equations. The reason for using this equation was in part due to its ease of use in comparison to other formulas. In addition, the other equations do not consider weight in their calculations; therefore, they could be inaccurate in obese or underweight people. Lastly, as this study was a sub-analysis of a previously published study that reported an association between statin eligibility and CAC in Koreans, selection bias could exist in study population and thus, in the study results. Despite these limitations, this study was novel in relating statin eligibility with renal function in the comparison of two guidelines in Korean adults.

In conclusion, the proportion of statin-eligible subjects was greater when using the ACC/AHA guidelines over the ATP III guidelines. When we divided the subjects into three groups according to degree of renal dysfunction, the proportion of statin-eligible subjects increased significantly with decreasing renal function. Moreover, among the ACC/AHA statin-eligible patients, the intergroup differences in the calculated ASCVD risk were larger and more prominent than those in the ATP III statin-eligible subjects.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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