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Original Article

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Assessing the Validity of the Criteria for the Extreme Risk Category of Atherosclerotic Cardiovascular Disease: A Nationwide Population-Based Study

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ABSTRACT

Objective: To validate the criteria for the extreme risk category for atherosclerotic cardiovascular disease (ASCVD).
Methods: An observational cohort study of 35,464 individuals with established ASCVD was performed using the National Health Information Database. Incident myocardial infarction (MI), ischemic stroke, and death in patients with established ASCVD was investigated to validate the criteria for the extreme risk category of ASCVD defined as the presence of diabetes mellitus (DM), chronic kidney disease (CKD), and history of premature ASCVD.
Results: Among 35,464 patients, 77.97% of them were classified into the extreme risk group of ASCVD. A total of 28.10%, 39.61%, and 32.12% had DM, CKD, and a history of premature ASCVD, respectively. During a mean follow-up of 8.39 years, MI, ischemic stroke, and all-cause death were found in 3.87%, 8.51%, and 23.98% of participants, respectively. In multivariate analysis, patients with DM had higher risk for MI (hazard ratio [HR], 1.62; 95% confidence interval [CI], 1.45–1.81), ischemic stroke (HR, 1.39; 95% CI, 1.29–1.50), and all-cause death (HR, 1.52; 95% CI, 1.45–1.59) than those without DM. Patients with CKD had 1.56 times higher risk for MI, 1.12 times higher risk for ischemic stroke, and 1.34 times higher risk for death than those without CKD. However, the risk for MI, ischemic stroke, and all-cause death was not different between patients with and without a history of premature ASCVD.
Conclusion: DM and CKD, but not a history of premature ASCVD, could be considered as reasonable criteria of an extreme risk for ASCVD.

Keywords: Atherosclerosis; Cardiovascular diseases; Risk assessment; Validation study

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death throughout the world despite recent improvements in overall rates of lipid disorders.[1-5] Increasing life expectancy and various metabolic diseases might have contributed to the

and Atherosclerosis.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization: Kim KS, Hong S, Han K, Park CY; Formal analysis: Han K; Investigation: Kim KS, Hong S, Park CY; Methodology: Kim KS, Hong S, Han K, Park CY; Project administration: Kim KS; Resources: Kim KS; Supervision: Hong S, Han K, Park CY; Validation: Kim KS, Hong S, Han K, Park CY; Writing - original draft: Kim KS; Writing - review & editing: Kim KS, Hong S, Han K, Park CY.

increase in the number of patients with ASCVD.[6-8] Especially, patients with established ASCVD are at high risk of ASCVD reoccurring in the same artery or different arteries.[9,10] Post-myocardial infarction (MI) individuals are at a 5- to 7-fold increased risk for a recurrent MI and post-stroke individuals are at a 9-fold increased risk for a recurrent stroke compared to the general population.[11,12]

Many clinical practice guidelines for dyslipidemia have suggested various risk factors for ASCVD and recommended classifying individuals based on the risk of ASCVD events.[13-15] Very high-risk criteria included established ASCVD, diabetes mellitus (DM), chronic kidney disease (CKD), and heterozygous familial hypercholesterolemia.[13,14] It is obvious that treating patients with a very high risk for ASCVD is particularly important. In addition, the number of individuals with multi-morbidity (e.g., DM plus established ASCVD) has increased as time goes by.[8] In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) proposed a new "extreme risk" category to appropriately manage individuals with multi-morbidity.[16] The Korean Society of Lipid and Atherosclerosis (KSoLA) also mentioned the extreme risk group in the guidelines for the management of dyslipidemia published in 2018.[13] However, few studies have evaluated the patients with an extreme risk for ASCVD. Moreover, no study has assessed the validity of criteria of the extreme risk group so far. Thus, the aim of this study was to validate the criteria for the extreme risk category of ASCVD using a nationwide database.

MATERIALS AND METHODS

1. Study database, participants, and design

This observation cohort study was performed using data from the National Health Information Database (NHID) produced by the National Health Insurance Service with linkage to the National Death Registry and the National Health Screening Program. The NHID contains de-identified sociodemographic details and reimbursement claims with International Classification of Disease, 10th revision (ICD-10) coding. Data for a medical interview and postural examination, blood test, urine test, and additional functions were obtained from the National Health Screening Program. Death information was obtained from the National Death Registry.

A total of 4,234,341 individuals participated in the National Health Screening Program in 2009. They were also included in the NHID. We excluded individuals aged 90 years or older (n=1,848), who had low-density lipoprotein (LDL)-cholesterol of 400 mg/dL or greater (n=14,379), who had missing data (n=171,737), and those who had no ASCVD history (n=4,010,913) (**Fig. 1**). Finally, a total of 35,464 individuals with established ASCVD history were enrolled in 2009 and followed up until 2018. We investigated incident CVD (MI or ischemic stroke) and death in patients with established ASCVD history to validate the criteria for the extreme risk group of ASCVD.[16] Among the criteria for the extreme risk, progressive ASCVD including unstable angina in patients after achieving LDL-cholesterol <70 mg/dL and heterozygous familial hypercholesterolemia could not be evaluated because of limited information in our database. Therefore, patients were considered to belong to the extreme risk group if they met one of the following criteria: the presence of DM, CKD, and history of premature ASCVD (<55 years for males and <65 years for females). In this study, we validated the aforementioned 3 criteria for the extreme risk group. The requirement for the informed consent was waived because we did not access personal identifying information. Approval for

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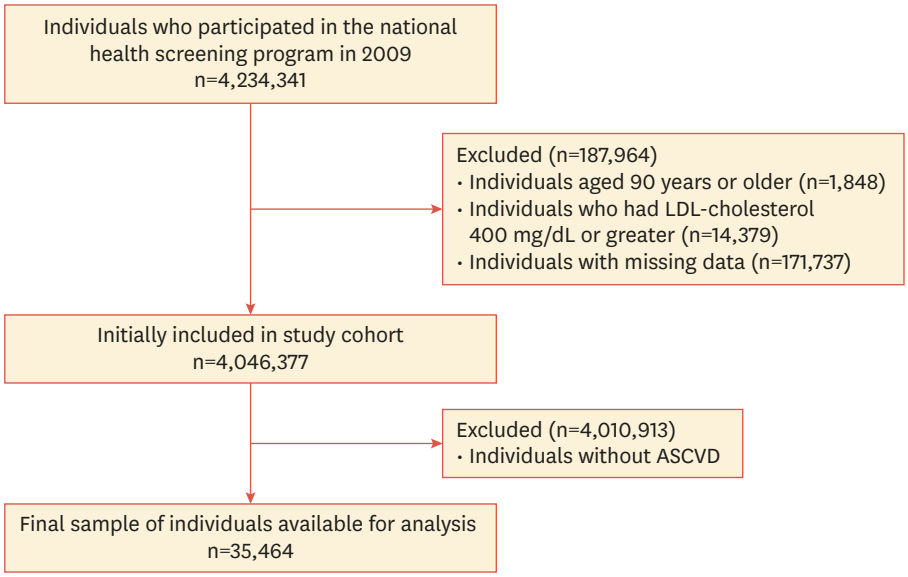

Fig. 1. Flow chart showing the selection of the study population.
ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

the present study protocol (2019-09-002) was obtained from the Institutional Review Board of Kangbuk Samsung Hospital.

2. Measurements

Body weight and height were measured for all subjects while wearing light clothing without shoes. Blood pressure (both systolic and diastolic values) was measured by a trained clinician while subjects were seated. Venous blood samples were drawn after an overnight fast for at least 8 hours to measure glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, and LDL-cholesterol levels. Estimated glomerular filtration rate (eGFR) was calculated using the equation from the Modification of Diet in Renal Disease study: $eGFR=175\times serum\ creatinine^{-1.154}\times age^{-0.203}\times 0.742$ (for women).

Information about smoking status, alcohol consumption, and regular exercise was obtained using a standardized self-assessment questionnaire. Heavy alcohol consumption was defined as drinking more than 30 g/day. Regular exercise was defined as more than 30 minutes of moderate physical activity performed at least 5 times per week or more than 20 minutes of strenuous physical activity performed at least 3 times per week.

3. Definitions

We defined established ASCVD, DM, CKD, and premature ASCVD at baseline (2009). Individuals with established ASCVD were identified as those with a history of MI, ischemic stroke, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). In this study, MI was defined as ICD-10 code I21 or I22 during hospitalization. Ischemic stroke was defined as ICD-10 code I63 or I64 during hospitalization with claims for brain magnetic resonance imaging (MRI) or computed tomography (CT). PCI was defined as ICD-10 code M6551, M6552, M6553, M6554, M6561, M6562, M6563, M6564, M6565, M6566, M6567, M6571, or M6572. CABG was defined as ICD-10 code O1642, OA642, O1640, O1641, O1647, O1648, O1649, OA640, OA641, OA647, OA648, or OA649.

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Individuals with hypertension were defined as patients with blood pressure ≥140/90 mmHg or patients who had at least one claim per year for an antihypertensive medication prescription under ICD-10 codes I10–I15. DM was defined as fasting plasma glucose (FPG) levels ≥126 mg/dL or patients who were prescribed anti-diabetic drugs under ICD-10 codes (E11–E14). CKD was defined as eGFR <60 mL/min/1.73 m^2. A history of premature ASCVD was defined as when events occurred before age 55 years in males and 65 years in females.

In this study, extreme risk was considered for individuals with established ASCVD who met one of the following criteria: the presence of DM, CKD, or history of premature ASCVD (<55 years for males and <65 years for females).

4. Study outcomes and follow-up

End points of this study were incident CVD (MI or ischemic stroke) or death in patients with established ASCVD history. Incident MI was defined as ICD-10 code I21 or I22 during hospitalization for more than 3 days with claims for PCI or CABG. Incident ischemic stroke was defined as ICD-10 code I63 or I64 during hospitalization for more than 3 days with claims for brain MRI or CT. Patients without incident CVD during their follow-up periods were considered to have completed the study at the date of their death or at the end of follow-up. If CVD events occurred before death, it was included as incident MI or stroke cases. The study population was followed from baseline to the date of incident CVD events or death, or until December 31, 2018.

5. Statistical analysis

Data for continuous variables are presented as mean±standard deviation or median (interquartile range) values. Data for categorical factors are reported as number (%) values. The significance of differences in measurements between groups was assessed using the independent sample *t*-test and χ^2 test. Incidence rates are presented as the number of events occurrences per 1,000 person-years. Hazard ratios (HRs) and 95% confidence interval (CI) values for all-cause death, MI, and stroke were calculated using a Cox proportional hazards model for the presence of DM, CKD, or premature ASCVD. A multivariable-adjusted proportional hazards model was adjusted for age, sex, body mass index (BMI), hypertension, smoking, drinking, regular exercise, eGFR, TG lowering agent use, and statin use. All data analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and a *p*-value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients with established ASCVD are shown in **Table 1**. Their mean age was 63.40 years and the mean BMI was 24.30 kg/m^2. Among 35,464 patients with established ASCVD, 77.97% of patients were classified into the extreme risk group for ASCVD. Patients with extreme risk were younger, less likely to be male, more likely to have lower baseline BMI, blood pressure (systolic and diastolic), and eGFR, less likely to be smoker, less likely to perform regular exercise, less likely to have hypertension, and more likely to use TG lowering agent than those without an extreme risk for ASCVD, while they had higher FPG, total cholesterol, and TG levels. There were no significant differences in statin use, HDL-cholesterol, or LDL-cholesterol between patients with and without an extreme risk for ASCVD.

In patients with established ASCVD, 28.10% had DM, 39.61% had CKD, and 32.12% had a history of premature ASCVD (**Table 2**). Patients with DM were older, more likely to be male,

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Table 1. Baseline characteristics of individuals with established atherosclerotic cardiovascular disease according to the presence of extreme risk

Characteristics	All	Extreme risk (–)	Extreme risk (+)	*p*
Number	35,464 (100.00)	7,812 (22.03)	27,652 (77.97)	
Age (yr)	63.40±11.58	65.74±6.42	62.74±12.59	<0.001
20–29	212 (0.60)	0 (0.00)	212 (0.77)	
30–39	802 (2.26)	0 (0.00)	802 (2.90)	
40–49	3,343 (9.43)	0 (0.00)	3,343 (12.09)	
50–59	7,622 (21.49)	1,527 (19.55)	6,095 (22.04)	
60–69	11,044 (31.14)	3,904 (49.97)	7,140 (25.82)	
70–79	10,203 (28.77)	2,221 (28.43)	7,982 (28.87)	
80–89	2,238 (6.31)	160 (2.05)	2,078 (7.51)	
Male	21,275 (59.99)	5,980 (76.55)	15,295 (55.31)	<0.001
BMI (kg/m^2)	24.30±3.28	24.92±2.93	24.12±3.35	<0.001
Smoking	6,270 (17.68)	1,497 (19,16)	4,773 (17.26)	<0.001
Drinking				<0.001
Non	25,627 (72.26)	5,287 (67.68)	20,340 (73.56)	
Moderate	8,187 (23.09)	2,073 (26.54)	6,114 (22.11)	
Heavy	1,650 (4.65)	452 (5.79)	1,198 (4.33)	
Regular exercise	6,948 (19.59)	1,727 (22.11)	5,221 (18.88)	<0.001
Hypertension	25,968 (73.22)	5,822 (74.53)	20,340 (73.56)	<0.001
Statin use	15,471 (43.62)	3,402 (43.55)	12,069 (43.65)	0.878
TG lowering agent use	1,025 (2.89)	158 (2.02)	867 (3.14)	<0.001
Systolic blood pressure (mmHg)	127.81±16.46	128.67±15.65	127.57±16.67	<0.001
Diastolic blood pressure (mmHg)	78.10±10.51	78.78±9.98	77.90±10.65	<0.001
eGFR (mL/min/1.73 m^2)	68.00±27.34	76.24±20.77	65.67±28.50	<0.001
FPG (mg/dL)	107.53±35.86	95.69±11.98	110.88±39.46	<0.001
Total cholesterol (mg/dL)	185.00±41.36	183.03±38.79	185.55±42.05	<0.001
TG (mg/dL)	123 (88–176)	120 (87–168)	124 (88–178)	<0.001
HDL-cholesterol (mg/dL)	52.67±34.28	52.84±35.31	52.62±33.98	0.609
LDL-cholesterol (mg/dL)	105.04±37.39	104.62±35.68	105.16±37.86	0.262

BMI, body mass index; TG, triglycerides; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

more likely to have higher BMI and hypertension, and more likely to use statin than those without DM, but they were more likely to have lower LDL-cholesterol levels. Patients with CKD were older, less likely to be male, more likely to have lower BMI and hypertension, and less likely to use statin than those without CKD, but they were more likely to have high LDL-cholesterol levels. Patients with a history of premature ASCVD were less likely to be male, more likely to have higher BMI, less likely to have hypertension, less likely to use statin, and more likely to have high LDL-cholesterol levels than those without a history of premature ASCVD.

During a mean follow-up of 8.39 years, MI, ischemic stroke, and all-cause death were found in 1,374 (3.87%), 3,018 (8.51%), and 8,504 (23.98%) participants, respectively (**Table 3**). Incidence rate of MI was 7.29/1,000 person-year in patients with DM and 3.76/1,000 person-year in patients without DM (**Fig. 2A**). Incidence rate of MI was 5.98/1,000 person-year in patients with CKD, higher than that (3.98/1,000 person-year) in patients without CKD. However, the incidence rate was 3.35/1,000 person-year in patients with a history of premature ASCVD, lower than that (5.44/1,000 person-year) in patients without a history of premature ASCVD. Incidence rate of ischemic stroke and death showed similar trend as MI. The incidence rate of ischemic stroke was higher in patients with DM (14.30/1,000 person-year) or CKD (15.32/1,000 person-year) than in those without DM (9.20/1,000 person-year) or CKD (7.92/1,000 person-year), but lower in patients with a history of premature ASCVD (4.76/1,000 person-year) than in those without a history of premature ASCVD (13.79/1,000 person-year) (**Fig. 2B**). Incidence rate of all-cause death in patients with or without DM was 38.37/1,000 person-year or 24.97/1,000 person-year, respectively. It was 52.15/1,000 person-

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Table 2. Baseline characteristics of individuals with established ASCVD according to the presence of each extreme risk criteria

Characteristics	DM		p	CKD		p	Premature ASCVD		p
	(−)	(+)		(−)	(+)		(−)	(+)	
Number	25,498 (71.90)	9,966 (28.10)		21,415 (60.39)	14,049 (39.61)		24,074 (67.88)	11,390 (32.12)	
Age (yr)	62.70±12.17	65.19±9.70	<0.001	58.24±10.70	71.26±7.87	<0.001	69.38±7.32	50.75±8.30	<0.001
20–29	206 (0.81)	6 (0.06)		210 (0.98)	2 (0.01)		0 (0)	212 (1.86)	
30–39	744 (2.92)	58 (0.58)		789 (3.68)	13 (0.09)		0 (0)	802 (7.04)	
40–49	2,774 (10.88)	569 (5.71)		3,230 (15.08)	113 (0.80)		0 (0)	3,343 (29.35)	
50–59	5,619 (22.04)	2,003 (20.10)		6,673 (31.16)	949 (6.75)		2,616 (10.87)	5,006 (43.95)	
60–69	7,438 (29.17)	3,606 (36.18)		7,133 (33.31)	3,911 (27.84)		9,017 (37.46)	2,027 (17.80)	
70–79	7,042 (27.62)	3,161 (31.72)		3,173 (14.82)	7,030 (50.04)		10,203 (42.38)	0 (0)	
80–89	1,675 (6.57)	563 (5.65)		207 (0.97)	2,031 (14.46)		2,238 (9.30)	0 (0)	
Male	15,150 (59.42)	6,125 (61.46)	<0.001	14,426 (67.36)	6,849 (48.75)	<0.001	15,438 (64.13)	5,837 (51.25)	<0.001
BMI (kg/m^2)	24.11±3.23	24.79±3.34	<0.001	25.09±3.1	23.09±3.16	<0.001	24.04±3.21	24.84±3.36	<0.001
Smoking	4,481 (17.57)	1,789 (17.95)	0.403	4,505 (21.04)	1,765 (12.56)	<0.001	3,911 (16.25)	2,359 (20.71)	<0.001
Drinking			<0.001			<0.001			<0.001
Non	18,130 (71.10)	7,497 (75.23)		13,955 (65.16)	11,672 (83.08)		18,240 (75.77)	7,387 (64.86)	
Moderate	6,209 (24.35)	1,978 (19.85)		6,187 (28.89)	2,000 (14.24)		4,795 (19.92)	3,392 (29.78)	
Heavy	1,159 (4.55)	491 (4.93)		1,273 (5.94)	377 (2.68)		1,039 (4.32)	611 (5.36)	
Regular exercise	4,911 (19.26)	2,037 (20.44)	0.012	4,828 (22.54)	2,120 (15.09)	<0.001	4,483 (18.62)	2,465 (21.64)	<0.001
Hypertension	17,561 (68.87)	8,407 (84.36)	<0.001	14,731 (68.79)	11,237 (79.98)	<0.001	19,121 (79.43)	6,847 (60.11)	<0.001
Statin use	10,005 (39.24)	5,466 (54.85)	<0.001	9,474 (44.24)	5,997 (42.69)	0.004	10,780 (44.78)	4,691 (41.19)	<0.001
TG lowering agent use	541 (2.12)	484 (4.86)	<0.001	611 (2.85)	414 (2.95)	0.607	659 (2.74)	366 (3.21)	0.013
Systolic blood pressure (mmHg)	127.1±16.25	129.64±16.84	<0.001	126.91±15.71	129.19±17.44	<0.001	129.33±16.70	124.59±15.44	<0.001
Diastolic blood pressure (mmHg)	78.12±10.31	78.03±11.03	0.477	78.30±10.32	77.78±10.80	<0.001	78.21±10.59	77.85±10.35	0.003
eGFR (mL/min/1.73 m^2)	68.90±26.38	65.68±29.55	<0.001	82.91±24.59	45.27±10.49	<0.001	60.09±24.19	84.71±26.07	<0.001
FPG (mg/dL)	95.06±12.05	139.44±52.80	<0.001	106.84±33.20	108.59±39.54	<0.001	108.56±36.28	105.36±34.85	<0.001
Total cholesterol (mg/dL)	187.01±40.32	179.83±43.51	<0.001	184.21±40.68	186.20±42.36	<0.001	183.06±41.04	189.10±41.75	<0.001
TG (mg/dL)	119 (85–168)	135 (96–195)	<0.001	124 (88–179)	122 (88–172)	0.033	124 (87–181)	123 (89–173)	0.315
HDL-cholesterol (mg/dL)	53.61±34.46	50.24±33.69	<0.001	52.68±34.46	52.65±33.99	0.950	52.33±35.89	53.37±30.59	0.008
LDL-cholesterol (mg/dL)	107.39±36.70	99.02±38.44	<0.001	104.00±37.05	106.63±37.85	<0.001	104.00±36.97	107.25±38.18	<0.001

DM, diabetes mellitus; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; TG, triglycerides; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. HRs and 95% CIs for MI, ischemic stroke, and all-cause death

Variables	MI		Ischemic stroke		All-cause death	
	No. of events	HR (95% CI)	No. of events	HR (95% CI)	No. of events	HR (95% CI)
DM*						
(−)	804	1 (ref.)	1,927	1 (ref.)	5,420	1 (ref.)
(+)	570	1.62 (1.45–1.81)	1,091	1.39 (1.29–1.50)	3,084	1.52 (1.45–1.59)
CKD†						
(−)	742	1 (ref.)	1,454	1 (ref.)	2,890	1 (ref.)
(+)	632	1.56 (1.36–1.78)	1,564	1.12 (1.02–1.22)	5,614	1.34 (1.27–1.41)
A history of premature ASCVD‡						
(−)	1,031	1 (ref.)	2,533	1 (ref.)	7,849	1 (ref.)
(+)	343	1.03 (0.85–1.24)	485	0.88 (0.77–1.02)	655	1.02 (0.93–1.13)

ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.
*Adjusted for age, sex, body mass index, hypertension, smoking, drinking, regular exercise, estimated glomerular filtration rate, triglyceride lowering agent use, and statin use; †Adjusted for age, sex, body mass index, DM, hypertension, smoking, drinking, regular exercise, triglyceride lowering agent use, and statin use; ‡Adjusted for age, sex, body mass index, DM, hypertension, smoking, drinking, regular exercise, estimated glomerular filtration rate, triglyceride lowering agent use, and statin use.

year or 15.23/1,000 person-year in patients with or without CKD, respectively. In patients with or without a history of premature ASCVD, Incidence rate of all-cause death was 6.29/1,000 person-year or 40.61/1,000 person-year, respectively (**Fig. 2C**).

Multivariate-adjusted HR of patients with DM was 1.62 (95% CI, 1.45–1.81) for MI, 1.39 (1.29–1.50) for ischemic stroke, and 1.52 (1.45–1.59) for all-cause death compared to those without DM after adjusting for age, sex, BMI, hypertension, smoking, drinking, regular

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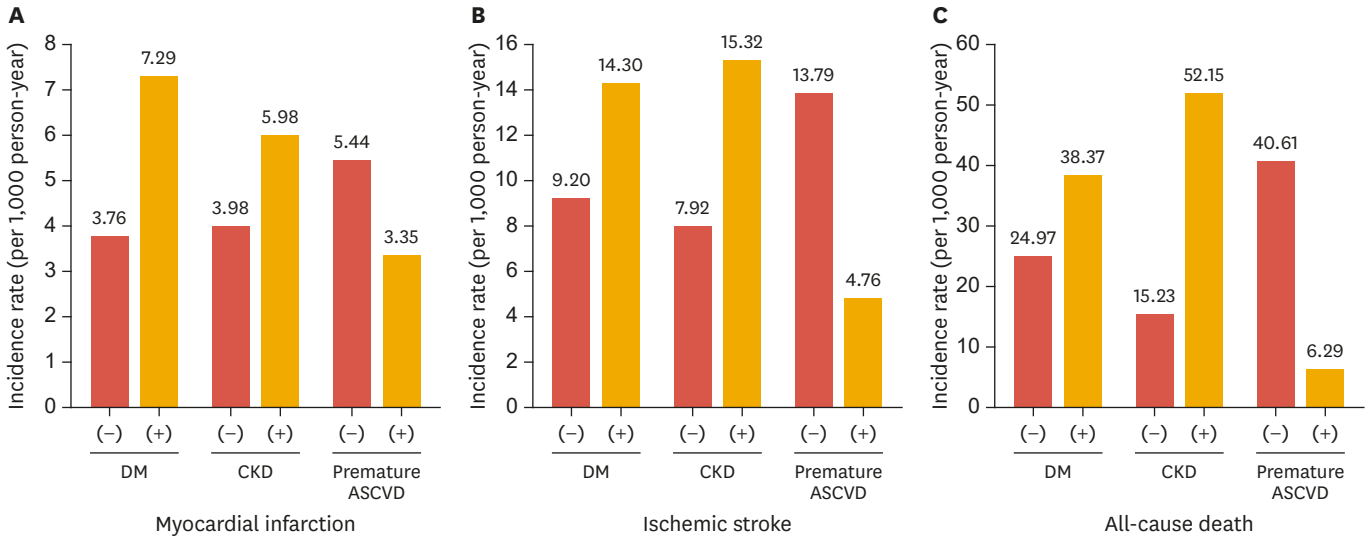

Fig. 2. Incidence rates of MI (A), ischemic stroke (B), and all-cause death (C) according to the presence of DM, CKD, and premature ASCVD.
MI, myocardial infarction; DM, diabetes mellitus; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease.

exercise, eGFR, TG lowering agent use, and statin use (**Table 3**). After adjusting for age, sex, BMI, DM, hypertension, smoking, drinking, regular exercise, TG lowering agent use, and statin use, patients with CKD had 1.56 (1.36–1.78) times higher risk for MI, 1.12 (1.02–1.22) times higher risk for ischemic stroke, and 1.34 (1.27–1.41) times higher risk for all-cause death than those without CKD. However, the risk for MI, ischemic stroke, or all-cause death was not significant different between patients with and without a premature ASCVD history.

DISCUSSION

The extreme risk category for ASCVD was introduced by AACE/ACE and KSoLA dyslipidemia guideline.[13,16] Many clinicians believe that we should carefully manage patients at extreme risk. However, no study has assessed the validity of criteria for the extreme risk group. In the present study, of 35,464 patients with established ASCVD who belonged to a very high-risk group, 77.97% of patients were found to belong to the extreme risk group of ASCVD. Specifically, in patients with established ASCVD, 28.10% had DM, 39.61% had CKD, and 32.12% had a history of premature ASCVD. The risk of MI, ischemic stroke, and death was higher in patients with DM or CKD than in those without DM or CKD, although it was not significantly different between patients with and without a history of premature ASCVD.

It is natural that patients with established ASCVD are at a high risk of recurrent ASCVD if they have other risk factors considered as CVD risk equivalent.[13,16] The extreme risk category was defined with this background, but few studies have investigated patients with an extreme risk. One study showed that 55% of 1,629 patients with stable coronary artery disease (CAD) were at an extreme risk for ASCVD.[17] More specifically, among patients with stable CAD, 32% had DM, 33% had premature CAD, and 9.2% had heterozygous familial hypercholesterolemia. We investigated 35,464 patients with established ASCVD and found that 77.97% of them were at an extreme risk defined as DM, CKD, and premature ASCVD. More patients belonged to the extreme risk category than aforementioned study, but the finding that about one-third of patients had DM or premature ASCVD was similar. The difference in the prevalence rate of the

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extreme risk might be because heterozygous familial hypercholesterolemia (9.2%) was included to define the extreme risk group in the aforementioned study while CKD (39.61%) was included in the present study. Interestingly, in this study, patients with extreme risk were less likely to be smoker and to have hypertension, which is one of the important risk factors for ASCVD. This was because patients with CKD and premature ASCVD history were less likely to be smoker and patients with premature ASCVD history were less likely to have hypertension. However, patients with extreme risk showed an elevated risk for recurrent ASCVD despite of less frequent hypertension and smoking. Although it is difficult to generalize results of this study, we should keep in mind that more than half of patients with established ASCVD were at a very high risk of having multi-morbidity and at an extreme risk for ASCVD.

Many studies have shown that patients with DM plus prior ASCVD have 50% to 100% higher risk for recurrent or initial ASCVD than patients with a single morbidity such as DM without prior ASCVD or prior ASCVD without DM.[18-20] In the study of Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), which was conducted for those aged ≥40 years and prior established clinical ASCVD (MI, ischemic stroke, or peripheral artery disease), patients with DM in the placebo group experienced a 12.2% (508 events in 5,516 patients) of 3-year Kaplan-Meier rate at the key secondary composite (cardiovascular death, MI, or stroke) endpoint.[21] A study conducted with more than 3.5 million participants showed that patients with DM and CAD were associated with peripheral artery disease (odds ratio [OR], 2.75; 95% CI, 2.66–2.85) and carotid artery stenosis (OR, 2.57; 95% CI, 2.49–2.66).[22] In a very large epidemiologic study including nearly 700,000 participants, patients with dual morbidities such as DM and MI or DM and stroke had 2 times higher mortality rate (32.0–32.8 per 1,000 person-years) and HRs (3.5–3.8) compared with single morbidities.[20] Furthermore, patients with dual or triple morbidities were associated with 13–20 years-of-life-lost in women and 16–23 years-of-life-lost in men while patients with single morbidities were associated with 7–8 years-of-life-lost in women and 8–10 years-of-life-lost in men.[20] In this study, although patients with DM were more likely to use statin and more likely to have lower LDL-cholesterol levels, ASCVD patients with DM showed a high risk for MI, ischemic stroke, and all-cause death than ASCVD patients without DM. It seems to be natural that DM is suitable as a criterion for defining the extreme risk category of patients with established ASCVD.

CKD is also a well-known risk factor for ASCVD and is considered as a coronary heart disease (CHD) risk equivalent.[15,23,24] In a study conducted with 9,270 patients with CKD, the rate of extrapolated 10-year 4-point major adverse cardiovascular events (non-fatal MI, coronary death, non-hemorrhagic stroke, or arterial revascularization procedure) was 51% in patients with CKD and previous vascular disease, higher than that in patients with single morbidities.[25] With a previous ASCVD history, the risk of recurrent ASCVD was also increased when CKD was accompanied by DM, a CHD risk equivalent.[23,24] In the study of Die Deutsche Diabetes Dialyse (4-D), 1,255 patients with type 2 DM who were on hemodialysis for less than 2 years showed 93% of the extrapolated 10-year 3-point major adverse cardiovascular events risk.[26] However, several studies have failed to demonstrate that lipid-lowering therapy could reduce mortality or ASCVD events in dialysis patients.[26-28] There were many factors, but not sufficiently reducing LDL-cholesterol to low enough levels in the extreme risk group might be an important factor. In fact, patients with CKD were less likely to use statin than those without CKD. Thus, they were found to have high LDL-cholesterol levels in this study. Considering the high risk of recurrent ASCVD in patients with previous ASCVD history and CKD, we should manage them carefully.

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Premature ASCVD history was included as a criterion for the extreme risk category.[13,14] However, young age might often create a misperception. Because old age is a leading risk factor of ASCVD, young age may be considered to be protective against ASCVD. The prevalence of metabolic risk factors such as hypertension and DM is often lower in patients with premature ASCVD. Thus, we could assume that nontraditional and nonmetabolic risk factors (e.g., hereditary disorders, inflammatory disorders) might instead be more prevalent in such patients.[29,30] Although old age is a strong risk factor, several studies have noticed that patients with a premature ASCVD history have all-cause and cardiovascular mortality similar to those of older adults.[31,32] In this study, the risk for MI, ischemic stroke, and all-cause death was not significantly different between patients with and without premature ASCVD history, consistent with previous studies. We could not completely investigate patients with premature ASCVD because we had no data prior to 2009. Consequently, patients with premature ASCVD history prior to 2009 or those aged >55 years for males and >65 years for females in 2009 but with an ASCVD history before 2009 might have been excluded. These points could underestimate the effect of premature ASCVD history, so it might be why there was no difference the risk for MI, ischemic stroke, and all-cause death different between patients with and without premature ASCVD history in this study. A cross-sectional study conducted in 1,248,158 patients showed that patients with a premature ASCVD were less likely to use aspirin or statins and to adhere to statin therapy, but it was not for secondary prevention of ASCVD.[33] In the present study, statin use was not different between patients with and without a premature ASCVD history.

This study has some limitations. First, we could not evaluate some categories of the extreme risk group such as progressive ASCVD including unstable angina in patients after achieving as LDL-cholesterol <70 mg/dL and heterozygous familial hypercholesterolemia because of limited information in our database. So, we could not generalize the results of this study to an extreme risk group, but this study suggested that many patients in extreme risk group might have a high risk for recurrent ASCVD. Second, because CKD was defined using eGFR at baseline, we could not reflect the change of CKD status during the follow up period. Third, study end points were incident CVD (MI or ischemic stroke) or death. We could not evaluate peripheral arterial disease, stable angina, or unstable angina known to be important components of ASCVD. Finally, because this study was conducted on Koreans, its results might not be generalizable to other ethnicities. This study, however, was valuable because it validated the criteria for defining an extreme risk category of ASCVD using Korean national-level data.

In conclusion, DM and CKD, but not a history of premature ASCVD, in patients with established ASCVD could be considered as reasonable criteria for defining the extreme risk group of ASCVD. These data suggest the importance of identifying and managing the extreme risk group of patients with ASCVD in Korea.

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