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Predicting the Development of Myocardial Infarction in Middle-Aged Adults with Type 2 Diabetes: A Risk Model Generated from a Nationwide Population-Based Cohort Study in Korea

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Background: Most of the widely used prediction models for cardiovascular disease are known to overestimate the risk of this disease in Asians. We aimed to generate a risk model for predicting myocardial infarction (MI) in middle-aged Korean subjects with type 2 diabetes.

Methods: A total of 1,272,992 subjects with type 2 diabetes aged 40 to 64 who received health examinations from 2009 to 2012 were recruited from the Korean National Health Insurance database. Seventy percent of the subjects (n=891,095) were sampled to develop the risk prediction model, and the remaining 30% (n=381,897) were used for internal validation. A Cox proportional hazards regression model and Cox coefficients were used to derive a risk scoring system. Twelve risk variables were selected, and a risk nomogram was created to estimate the 5-year risk of MI.

Results: During 7.1 years of follow-up, 24,809 cases of MI (1.9%) were observed. Age, sex, smoking status, regular exercise, body mass index, chronic kidney disease, duration of diabetes, number of anti-diabetic medications, fasting blood glucose, systolic blood pressure, total cholesterol, and atrial fibrillation were significant risk factors for the development of MI and were incorporated into the risk model. The concordance index for MI prediction was 0.682 (95% confidence interval [CI], 0.678 to 0.686) in the development cohort and 0.669 (95% CI, 0.663 to 0.675) in the validation cohort.

Conclusion: A novel risk engine was generated for predicting the development of MI among middle-aged Korean adults with type 2 diabetes. This model may provide useful information for identifying high-risk patients and improving quality of care.

Keywords: Myocardial infarction; Risk; Diabetes mellitus, type 2

INTRODUCTION

It is well established that diabetes and related metabolic disturbances increase the risk of cardiovascular diseases (CVDs). Despite the observation that the incidence rate of CVD is decreasing, people with diabetes still have a two to three times greater

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risk of developing ischemic heart disease, myocardial infarction (MI), and cerebrovascular diseases [1,2]. Therefore, efforts to prevent CVD through risk stratification are emphasized in the representative diabetes management guidelines [3-6].

Various risk factors, including anthropometric indices, lifestyle factors, family history, comorbidities, and blood parameters, contribute to the development of CVD [7-11]. The usefulness of more direct assessments, such as coronary computed tomography angiography, has been suggested, although its efficacy as a screening modality is unclear [12,13]. For comprehensive risk assessment, numerous risk engines that mathematically combine multiple predictors have been developed and are being utilized. However, the predictive value of the models remains unclear due to methodological shortcomings, and lack of external validation and a lack of model impact studies [14]. Because the risk of CVD is considerably different according to the background comorbidities and ethnicities, the development and validation of tailored risk models would increase the prediction accuracy for specific populations. Therefore, using a large-scale nationwide population-based database, we aimed to develop a new risk model for predicting MI in middle-aged Korean adults with type 2 diabetes.

METHODS

Data source and study subjects

The Korean National Health Insurance Service (NHIS) is a single, government-managed insurer to which all residents in Korea subscribe. Because it has adopted a fee-for-service system to pay healthcare providers, the NHIS obtains various information representing the entire Korean population. The database contains comprehensive healthcare information, including an eligibility database (e.g., age, sex, income rank, disability, type of eligibility), a medical treatment database (general information on specification, consultation statements, diagnosis statements defined by the International Classification of Disease 10th revision [ICD-10], and prescription statements), a health examination database (results of general health examinations and questionnaires on lifestyle and behavior), and a medical care institution database (types of medical care institutions, location, equipment, and number of physicians). Beneficiaries of the NHIS are encouraged to undergo standardized health examinations at least every two years. Hospitals performing health examinations were certified by the NHIS and received regular quality control. Details on the database are described elsewhere [15,16].

A total of 2,706,620 people with type 2 diabetes who received health examinations between 2009 and 2012 were selected. We excluded subjects aged <40 or ≥65 years (n=849,899) because old age itself is undisputedly the strongest risk factor for MI and because we aimed to develop a risk model in middle-aged adults. Those with missing data for one or more variables (n=572,439) and those with a history of MI before the index year (n=11,290) were also excluded. The final study population consisted of 1,272,992 people. The original database was split into two datasets, the development cohort and the validation cohort. For the development cohort, 70% of the eligible subjects (n=891,095) were sampled to develop the risk prediction models. The remaining 30% (n=381,897) were extracted according to Harrell's bootstrap resampling method for internal validation. This study was approved by the Institutional Review Board of Yeouido St. Mary's Hospital, The Catholic University of Korea (No. SC19ZESE0027). As anonymous and deidentified data were used for analysis, informed consent was waived.

Definitions and follow-up

Type 2 diabetes was diagnosed in the presence of at least one claim per year with ICD-10 codes E11–14 and the prescription of antidiabetic medication, or fasting glucose level ≥126 mg/dL. Subjects with the disease code of insulin-dependent diabetes (E10) or gestational diabetes (O24.4 and O24.9) were not included in this study. MI was defined when ICD-10 codes I21 or I22 were newly recorded during hospitalization. The study population was followed-up by the date of MI, or until 31 December 2017, whichever came first. The mean follow-up period was 7.1±1.2 years.

Predictor variables

We identified potential risk factors for MI in people with type 2 diabetes based on the literature and selected variables that were most likely to have good predictive ability and available from the NHIS database [2,7-11,17]. Age was divided into three groups (40 to 49, 50 to 59, and 60 to 64 years). Smoking status was identified by a self-reported questionnaire and divided into two groups (current smoker vs. non- or ex-smoker) because the risk of MI was similar between non-smoker and ex-smoker. Individuals performing more than 30 minutes of moderate physical activity at least five times per week or more than 20 minutes of strenuous physical activity at least three times per week were regarded as performing regular exercise. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Individuals were categorized into three BMI groups according to the World Health Organization criteri-

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on for Asians: <18.5 kg/m^2 (underweight), 18.5 to 22.9 kg/m^2 (normal weight), and ≥23.0 kg/m^2 (overweight or obese). The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease formula: 175×serum Cr (mg/dL)$^{-1.154}$×age (yr)$^{-0.203}$×0.742 (if female). Chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2. Because hemoglobin A1c (HbA1c) levels were not available in the NHIS database, we used the duration of diabetes and the number of anti-diabetic medications to account for the severity of diabetes. The duration of diabetes was categorized as <5 and ≥5 years using the date of the first claim for diabetes and the index date. The number of anti-diabetic medications was categorized as 0–1 and ≥2 or the use of insulin. Fasting blood glucose (FBG) levels were categorized into five groups: <100, 100 to 140, 140 to 160, 160 to 180, and ≥180 mg/dL. Systolic blood pressure (SBP) was categorized into five groups: <130, 130 to 140, 140 to 150, 150 to 160, and ≥160 mm Hg. Total cholesterol (TC) levels were categorized into four groups: <160, 160 to 200, 200 to 240, and ≥240 mg/dL. Diagnosis of atrial fibrillation (AF) was based on the recording of ICD-10 codes I48.

Statistical analysis

Baseline characteristics are presented as numbers and frequencies as percentages, and the chi-square test was used to identify differences in categorical variables. Incidence rates are expressed as events per 1,000 person-years. Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) values for MI according to the risk group. Variable selection to build the risk prediction model was conducted using the multivariate model. We assigned risk scores based on the HR for each risk factor in the final Cox proportional hazards regression model. Each of the 12 variables, including age, sex, smoking status, regular exercise, BMI, CKD, duration of diabetes, number of anti-diabetic medications, FBG, SBP, TC, and AF, was applied with scores of 0–100. The risk prediction model for MI was translated into a risk score nomogram, and each variable was made to correspond to a specific point by drawing a line straight up the score axis. C-statistics were used to assess discriminative power. Predicted and observed 5-year risks of MI in the development and validation cohorts were compared by ranking participants into decile groups of total risk score. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A P<0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of the study population

The mean ages of the study subjects without or with incident MI were 53.5±6.8 and 55.4±6.4 years, respectively. During follow-up, 24,809 cases of MI (1.9%) developed. In both the development and validation cohorts, subjects with incident MI were older, more likely to be male and current smokers, engage in less regular exercise, have a longer duration of diabetes, and take more anti-diabetic medications or insulin compared with subjects without MI. They were also likely to have higher levels of SBP, and TC, and higher prevalence of CKD and AF. Underweight people were more frequent in the group with incident MI (Table 1).

Risk variables for incident MI

The age- and sex-adjusted HRs (model 1) and all 12 variable-adjusted HRs (model 2) for incident MI are presented in Table 2. The results were obtained using the development cohort. The HRs (95% CI) in the groups aged 50 to 59 and 60 to 64 years were 1.50 (95% CI, 1.44 to 1.56) and 1.98 (95% CI, 1.89 to 2.07), respectively. Females had a significantly lower risk of MI than males. Current smoking and the presence of CKD or AF were associated with a more than 60% increased risk of MI, whereas engaging in regular exercise had a protective effect against MI. Subjects with normal weight and overweight or obesity had a 25% lower risk of MI compared to underweight people. Subjects with a diabetes duration of more than 5 years and who were taking more than two anti-diabetic medications or insulin had an approximately 30% higher risk of MI. There was a J-shaped association between FBG and the risk of MI. Subjects with FBG levels of <100 or ≥160 mg/dL were at higher risk compared with people with FBG levels between 100 and 140 mg/dL. The associations between FBG and the risk of MI were consistent in subjects with or without use of anti-diabetic medications (P for interaction=0.17). There was a graded association between SBP or TC levels and the risk of MI.

Development of the MI risk engine

A risk nomogram based on the risk prediction model was created to estimate the 5-year risk of MI (Fig. 1). The total risk score, which is the sum of the scores for 12 variables, ranged from 0 to 654 (Table 3). Among the variables, old age, current smoking, presence of CKD or AF, and high levels of SBP or TC were the main contributors increasing the risk of MI. For example, a 61-year-old (100 points) man (41 points) with type 2 diabetes

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Table 1. Baseline Characteristics of the Study Participants According to Incident MI in the Development and Validation Cohorts

Characteristic	Development cohort (n=891,095)			Validation cohort (n=381,897)		
	MI (–)	MI (+)	P value	MI (–)	MI (+)	P value
Number	873,635	17,460		374,548	7,349	
Age, yr			<0.0001			<0.0001
40–49	248,957 (28.5)	3,292 (18.9)		106,452 (28.4)	1,359 (18.5)	
50–59	407,974 (46.7)	8,179 (46.8)		175,093 (46.8)	3,519 (47.9)	
60–64	216,704 (24.8)	5,989 (34.3)		93,003 (24.8)	2,471 (33.6)	
Sex			<0.0001			<0.0001
Male	558,919 (64.0)	12,300 (70.5)		239,500 (63.9)	5,324 (72.5)	
Female	314,716 (36.0)	5,160 (29.5)		135,048 (36.1)	2,025 (27.5)	
Smoking status			<0.0001			<0.0001
Current	251,445 (28.8)	6,811 (39.0)		107,852 (28.8)	2,866 (39.0)	
Regular exercise			<0.0001			<0.0001
Yes	462,446 (52.9)	8,236 (47.2)		197,412 (52.7)	3,505 (47.7)	
BMI, kg/m^2			<0.0001			0.0008
<18.5	9,559 (1.1)	272 (1.6)		4,174 (1.1)	116 (1.6)	
18.5–23	204,207 (23.4)	4,235 (24.3)		87,438 (23.3)	1,689 (23.0)	
≥23	659,869 (75.5)	12,953 (74.2)		282,936 (75.5)	5,544 (75.4)	
Chronic kidney disease			<0.0001			<0.0001
Yes	57,407 (6.6)	2,171 (12.4)		24,636 (6.6)	895 (12.2)	
Duration of diabetes, yr			<0.0001			<0.0001
≥5	261,606 (29.9)	7,332 (42.0)		112,894 (30.1)	3,123 (42.5)	
No. of anti-diabetic medication			<0.0001			<0.0001
≥2 or insulin	401,728 (46.0)	10,127 (58.0)		172,378 (46.0)	4,274 (58.2)	
FBG, mg/dL			<0.0001			<0.0001
<100	70,407 (8.1)	1,701 (9.7)		30,108 (8.0)	765 (10.4)	
100–140	415,280 (47.5)	7,074 (40.5)		178,335 (47.6)	3,004 (40.9)	
140–160	164,414 (18.8)	2,990 (17.1)		70,556 (18.8)	1,220 (16.6)	
160–180	79,768 (9.1)	1,722 (9.9)		34,087 (9.1)	706 (9.6)	
≥180	143,766 (16.5)	3,973 (22.8)		61,462 (16.4)	1,654 (22.5)	
SBP, mm Hg			<0.0001			<0.0001
<130	437,693 (50.1)	7,942 (45.5)		188,024 (50.2)	3,340 (45.5)	
130–140	259,144 (29.7)	5,229 (30.0)		110,947 (29.6)	2,184 (29.7)	
140–150	90,379 (10.4)	2,064 (11.8)		38,401 (10.3)	857 (11.7)	
150–160	51,886 (5.9)	1,241 (7.1)		22,365 (6.0)	547 (7.4)	
≥160	34,533 (4.0)	984 (5.6)		14,811 (4.0)	421 (5.7)	
Total cholesterol, mg/dL			<.0001			<0.0001
<160	156,649 (17.9)	2,866 (16.4)		67,804 (18.1)	1,210 (16.5)	
160–200	323,364 (37.0)	5,900 (33.8)		138,613 (37.0)	2,507 (34.1)	
200–240	263,924 (30.2)	5,425 (31.1)		112,479 (30.0)	2,203 (30.0)	
≥240	129,698 (14.9)	3,269 (18.7)		55,652 (14.9)	1,429 (19.4)	
Atrial fibrillation			<0.0001			<0.0001
Yes	5,263 (0.6)	196 (1.1)		2,359 (0.6)	100 (1.4)	

Values are expressed as number (%).
MI, myocardial infarction; BMI, body mass index; FBG, fasting blood glucose; SBP, systolic blood pressure.

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Table 2. Hazard Ratios (95% Confidence Intervals) for Incident Myocardial Infarction According to Risk Categories

Variable	Number	No. of events	Incidence rate, /1,000 person-yr	Model 1	Model 2
Age, yr					
40–49	252,249	3,292	1.86	1 (reference)	1 (reference)
50–59	416,153	8,179	2.75	1.52 (1.46–1.59)	1.50 (1.44–1.56)
60–64	222,693	5,989	3.71	2.11 (2.02–2.20)	1.98 (1.89–2.07)
Sex					
Male	571,219	12,300	3.03	1 (reference)	1 (reference)
Female	319,876	5,160	2.24	0.68 (0.66–0.70)	0.76 (0.73–0.78)
Smoking status					
Non/Ex	632,839	10,649	2.35	1 (reference)	1 (reference)
Current	258,256	6,811	3.75	1.69 (1.63–1.75)	1.65 (1.59–1.71)
Regular exercise					
No	420,413	9,224	3.08	1 (reference)	1 (reference)
Yes	470,682	8,236	2.45	0.78 (0.76–0.81)	0.82 (0.80–0.84)
BMI, kg/m^2					
<18.5	9,831	272	3.94	1 (reference)	1 (reference)
18.5–23	208,442	4,235	2.84	0.72 (0.64–0.81)	0.75 (0.67–0.85)
≥23	672,822	12,953	2.70	0.69 (0.61–0.78)	0.75 (0.66–0.84)
Chronic kidney disease					
No	831,517	15,289	2.58	1 (reference)	1 (reference)
Yes	59,578	2,171	5.02	1.77 (1.69–1.85)	1.68 (1.61–1.76)
Duration of diabetes, yr					
<5	622,157	10,128	2.30	1 (reference)	1 (reference)
≥5	268,938	7,332	3.75	1.49 (1.45–1.54)	1.31 (1.26–1.36)
No. of anti-diabetic medication					
0, 1	479,240	7,333	2.19	1 (reference)	1 (reference)
≥2 or insulin	411,855	10,127	3.37	1.46 (1.42–1.51)	1.30 (1.26–1.35)
FBG, mg/dL					
<100	72,108	1,701	3.24	1.30 (1.23–1.37)	1.19 (1.13–1.25)
100–140	422,354	7,074	2.36	1 (reference)	1 (reference)
140–160	167,404	2,990	2.51	1.08 (1.03–1.12)	1.03 (0.98–1.07)
160–180	81,490	1,722	2.94	1.26 (1.20–1.33)	1.12 (1.06–1.18)
≥180	147,739	3,973	3.75	1.66 (1.60–1.73)	1.34 (1.29–1.40)
SBP, mm Hg					
<130	445,635	7,942	2.50	1 (reference)	1 (reference)
130–139	264,373	5,229	2.77	1.06 (1.03–1.10)	1.08 (1.04–1.12)
140–149	92,443	2,064	3.13	1.17 (1.12–1.23)	1.19 (1.13–1.25)
150–159	53,127	1,241	3.27	1.21 (1.14–1.29)	1.21 (1.14–1.29)
≥160	35,517	984	3.87	1.44 (1.35–1.54)	1.39 (1.30–1.49)
Total cholesterol, mg/dL					
<160	159,515	2,866	2.51	1 (reference)	1 (reference)
160–200	329,264	5,900	2.50	1.04 (0.99–1.08)	1.09 (1.04–1.14)
200–240	269,349	5,425	2.83	1.22 (1.17–1.28)	1.31 (1.25–1.38)
≥240	132,967	3,269	3.48	1.58 (1.50–1.66)	1.68 (1.59–1.77)
Atrial fibrillation					
No	885,636	17,264	2.73	1 (reference)	1 (reference)
Yes	5,459	196	5.06	1.60 (1.39–1.84)	1.64 (1.42–1.89)

Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, smoking, regular exercise, body mass index, chronic kidney disease, duration of diabetes, numbers of anti-diabetic medication, fasting blood glucose, systolic blood pressure, total cholesterol, and atrial fibrillation.
BMI, body mass index; FBG, fasting blood glucose; SBP, systolic blood pressure.

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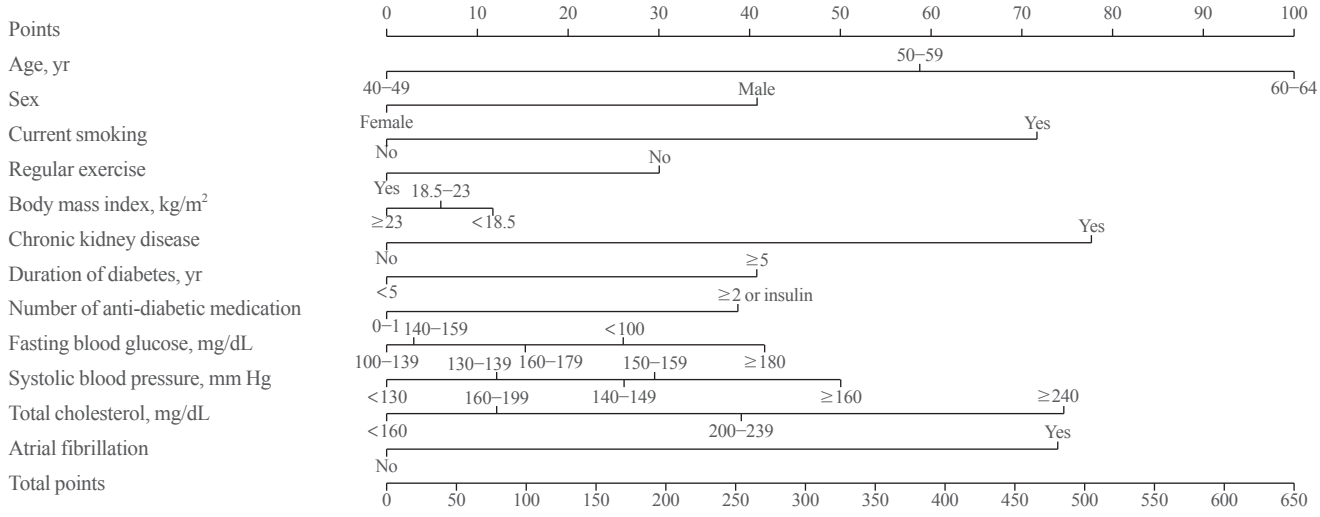

Fig. 1. A nomogram for the prediction of the 5-year probability of myocardial infarction. Each of the 12 variables was applied with scores from 0 to 100. Each variable corresponds to a specific point by drawing a line straight up to the score axis. The total score, which is the sum of the scores for each of the 12 variables at the bottom of the nomogram, ranges from 0 to 654.

who is a current smoker (72 points), did not engage in regular exercise (30 points), had a BMI of 24.8 kg/m^2 (0 points), had diabetes for 8 years (41 points), was on insulin treatment (39 points), had an FBG level of 145 mg/dL (3 points), had an SBP of 142 mm Hg (26 points), had a TC of 228 mg/dL (39 points), and did not have CKD (0 points) or AF (0 points) had a total risk score of 391. This score corresponds to a 3.8% 5-year incidence probability of MI (Fig. 2). If this man quits smoking and performs regular exercise, the total risk score will become 289, and the 5-year incidence probability of MI will be decreased to 1.9%. When the total risk score is 540 points, the 5-year incidence probability of MI is estimated to be >10%. The concordance index for MI prediction was 0.682 (95% CI, 0.678 to 0.686) in the development cohort. An interactive web-based platform (http://md.koobian.com/mi) that automatically calculates the risk of MI is available for easier clinical application.

Validation of the MI risk engine

The clinical characteristics of the validation cohort were similar to those of the development cohort, and none of the potential predictors differed significantly between the two groups (Table 1). The concordance index for MI prediction was 0.669 (95% CI, 0.663 to 0.675) in the validation cohort. For the internal validation of the developed risk model, we compared the incidence rate of MI according to the decile groups of the total risk score. The actual incidence rates of MI in the validation cohort were similar to those predicted by the MI risk model (Fig. 3).

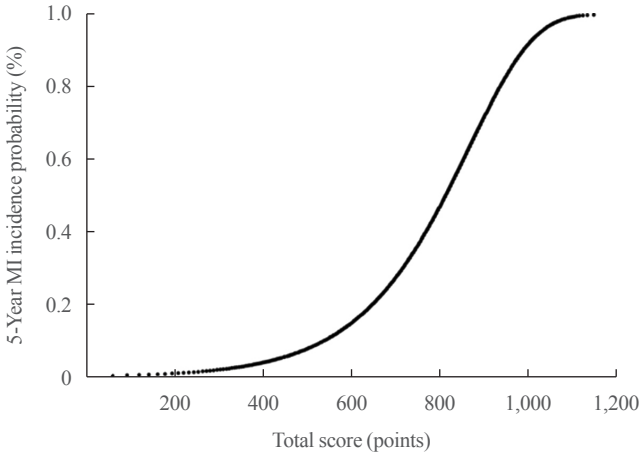

Fig. 2. The 5-year incidence probability of myocardial infarction (MI) according to the total risk score.

DISCUSSION

Using a nationwide population-based cohort database, we generated a novel risk model for predicting the development of MI that can be specifically used in middle-aged Korean adults with type 2 diabetes. Twelve risk variables were identified, and scores for each risk category were determined. All the variables can be easily collected in routine clinical practice, and a web-based calculator was developed for easy application.

Risk stratified interventions based on comprehensive assessment of multiple risk variables are recommended for the prevention of CVD, and there is an abundance of prediction models

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Table 3. Scoring for Each Risk Factor Category

Variable	Value
Age, yr	
40–49	0
50–59	59
60–64	100
Sex	
Male	41
Female	0
Current smoking	
No	0
Yes	72
Regular exercise	
No	30
Yes	0
Body mass index, kg/m^2	
<18.5	12
18.5–23	6
≥23.0	0
Chronic kidney disease	
No	0
Yes	78
Duration of diabetes	
<5	0
≥5	41
No. of anti-diabetic medication	
0–1	0
≥2 or insulin	39
Fasting blood glucose, mg/dL	
<100	26
100–139	0
140–159	3
160–179	15
≥180	42
Systolic blood pressure, mm Hg	
<130	0
130–139	12
140–149	26
150–159	29
≥160	50
Total cholesterol, mg/dL	
<160	0
160–199	12
200–239	39
≥240	75
Atrial fibrillation	
No	0
Yes	74

in the general population [14]. Several well-known models, such as the Framingham risk score [18], Systematic COronary Risk Evaluation (SCORE) [19], and American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equations [20], have been widely used, validated, and implemented in guidelines. However, risk models derived from certain populations may not be applicable to other populations that have different characteristics and incidence rates of the event of interest. For example, when the Framingham risk score was applied to the Chinese population, the risk of coronary heart disease (CHD) was overestimated in all decile risk groups. In the 10th risk decile in men, the predicted CHD death rate was 20%, whereas the actual rate was 3% [21]. The Framingham risk score also overestimated the risk of CHD by 3 to 6-fold in the Korean population [22]. The ACC/AHA equations overestimated the risk of atherosclerotic CVD by more than 50% in Korean men [23]. The U.K. Prospective Diabetes Study (UKPDS) risk engine is another popular risk model for CHD in subjects with type 2 diabetes [24]. However, a recent external validation study in United Kingdom patients with newly diagnosed type 2 diabetes suggested that the risk equation needs to be revised due to significant overestimation of CHD and fatal CHD [25]. In Japanese and Chinese populations, the UKPDS risk engine overestimated the risk of CHD with suboptimal discrimination [26,27]. These observations indicate that there are unmet needs for CVD risk prediction, and the development of population-, disease-, and outcome-specific models is required.

Our goal was to use routinely obtained clinical and biochemical variables to generate a risk model for predicting MI in Korean people with type 2 diabetes. Previously, a 10-year CHD risk model from Koreans (Korean Heart Study) was reported [22]. The basic model included age, blood pressure, TC, smoking status and diabetes as risk variables, and the optimal model was created by adding other lipid parameters. The addition of high-density lipoprotein cholesterol (HDL-C; area under the curve=0.764) or triglyceride (area under the curve=0.815) levels produced the best discriminating model in men and women, respectively. Although this model had high predictive power, less than 10% of the study population had diabetes, suggesting that it might not be appropriate for people with diabetes. In addition, because people who underwent private health examinations comprised the cohort, it may not represent the general population. Another risk model using age, sex, BMI, HbA1c, blood pressure, HDL-C, albuminuria, creatinine, family history of CHD, and 2-way interaction terms between sex and other predictors was developed in Korean subjects with type 2 diabetes

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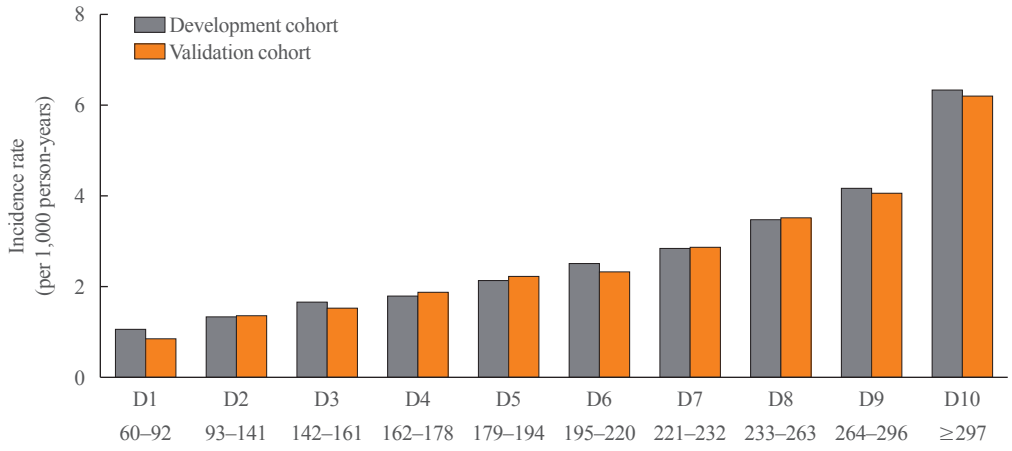

Fig. 3. Incidence rate (per 1,000 person-years) based on the decile groups of total risk score in the development and validation cohorts. The numbers on the x-axis represent the range of the total risk score according to each decile group.

[28]. This equation showed superior predictability for CHD risk compared to the UKPDS risk engine. However, it is limited because only 732 participants from one hospital were used for model generation. Our model is a risk engine optimized for people with type 2 diabetes and is generated based on the nationally representative database including more than one million Korean participants. The concordance index of this model was 0.682, with substantial discriminating power.

Interestingly, underweight people had a higher risk of MI than normal and overweight or obese people. The association between BMI and the risk of MI is inconclusive and might be affected by interactions with other factors. Although it is generally thought that a graded relationship exists between BMI and the risk of MI, a large case-control study from 52 countries showed that this association became nonsignificant after adjustment for multiple risk factors. Of note, the degree of association differed among ethnicities, with no significant relation in south Asians, Arabs, and mixed-race Africans [29]. A Norwegian study showed a sex-specific association, with obese men having an increased risk of MI and overweight women having a decreased risk compared with normal weight subjects [30]. Some other studies support evidence that underweight people are at higher risk of CVD or CVD mortality compared with normal weight people [31,32]. A study encompassing nearly 0.5 million United States adults concluded that the relative risk for CVD was elevated by 34% in the underweight population, whereas the obese group had a 15% elevated risk and was even insignificant in the overweight group [32]. Because BMI reflects total adiposity more than central adiposity and does not differentiate lean mass and fat mass, lower BMI may indicate less amount of beneficial fat or sarcopenia. In addition, a problem of poor nutritional status in underweight individuals can be another possible explanation for this unexpected finding.

Our study showed a J-shaped association between FBG and the risk of MI. There are several studies showing the J-shaped relationship between FBG and CVD or mortality, independent of diabetes status [33,34]. A Chinese population-based prospective cohort study demonstrated that this association was evident in participants including untreated diabetes [34]. We also found a similar pattern in subjects with or without use of anti-diabetic medications. Although the mechanistic explanation of this phenomenon needs further clarification, it is suggested that hypoglycemia leads to sympatho-adrenal activation and counter-regulatory hormone secretion. This condition can trigger vasoconstriction, platelet aggregation, vascular inflammation, and cardiac arrhythmia which might increase the risk for CVD [35].

AF was another significant contributing factor for increased risk of MI. MI and AF are closely related, and AF may precede or complicate the clinical course of MI [36]. At least three mechanisms may account for the association between AF and MI: (1) atherosclerosis and its associated inflammatory process, yielding a pro-thrombotic state; (2) direct coronary thromboembolism from the left atrial appendage; and (3) tachyarrhythmia episodes resulting in supply-demand mismatch [37]. Asians have a higher prevalence of diabetic kidney disease than Caucasians, accounting for 40% to 55% of those on dialysis, compared with less than 30% of those in Western countries [38]. Asian people with a low baseline eGFR have a higher risk of future stroke [39]. Both the MI and stroke risk equations, which included eGFR as a predictor, derived from the Hong Kong Di-

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abetes Registry performed better among Chinese patients with type 2 DM than the respective UKPDS risk engines, which did not include eGFR as a predictor; this difference suggests that renal dysfunction is an important risk factor for CVD, especially in Asian populations [26,38,39].

There are some limitations in this study. First, we did not have information on HbA1c levels or urine albumin-creatinine ratio, which were used as risk variables in other models. Instead of these variables, we used the duration of diabetes and the number of anti-diabetic medications to account for the severity of diabetes and the presence of CKD to account for the renal effect on CVD. Second, direct comparison of the performance with previous models was not possible due to the different risk variables used. However, we performed internal validation and showed that the actual incidence rate was similar to the predicted value. Third, because CKD was defined based on one measurement of eGFR, possibility of misclassification due to acute kidney injury remains. Fourth, the use of anti-hypertensive agents or lipid-lowering agents was not considered, which might have influence on the risk of MI. Lastly, because this is a Korean-specific model, its usefulness in other countries or ethnicities needs further investigation.

In conclusion, we expect that our risk model will be a useful tool for identifying individuals at a high risk of developing MI. Because 12 components of the risk model can be easily collected in routine clinical practice, this approach of risk assessment and intervention would improve the quality of care for patients with diabetes.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conception or design: S.H.L., K.H., M.K.K. Acquisition, analysis, or interpretation of data: S.H.L., K.H., H.S.K., J.H.C., K.H.Y., M.K.K. Drafting the work or revising: S.H.L., M.K.K. Final approval of the manuscript: S.H.L., K.H., H.S.K., J.H.C., K.H.Y., M.K.K.

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