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ORIGINAL RESEARCH

European and US Guideline-Based Statin Eligibility, Genetically Predicted Coronary Artery Disease, and the Risk of Major Coronary Events

Hanjin Park, MD*; Daehoon Kim, MD;* Seng Chan You, MD; Eunsun Jang, MS; Hee Tae Yu, MD; Tae-Hoon Kim, MD; Dong-min Kim, MD; Jung-Hoon Sung, MD; Hui-Nam Pak, MD; Moon-Hyoung Lee, MD; Pil-Sung Yang, MD†; Boyoung Joung, MD, PhD†

BACKGROUND: A study was designed to investigate whether the coronary artery disease polygenic risk score (CAD-PRS) may guide lipid-lowering treatment initiation as well as deferral in primary prevention beyond established clinical risk scores.

METHODS AND RESULTS: Participants were 311 799 individuals from the UK Biobank free of atherosclerotic cardiovascular disease, diabetes, chronic kidney disease, and lipid-lowering treatment at baseline. Participants were categorized as statin indicated, statin indication unclear, or statin not indicated as defined by the European and US guidelines on statin use. For a median of 11.9 (11.2–12.6) years, 8196 major coronary events developed. CAD-PRS added to European-Systematic Coronary Risk Evaluation 2 (European-SCORE2) and US-Pooled Cohort Equation (US-PCE) identified 18% and 12% of statin-indication-unclear individuals whose risk of major coronary events were the same as or higher than the average risk of statin-indicated individuals and 16% and 12% of statin-indicated individuals whose major coronary event risks were the same as or lower than the average risk of statin-indication-unclear individuals. For major coronary and atherosclerotic cardiovascular disease events, CAD-PRS improved C-statistics greater among statin-indicated or statin-indication-unclear than statin-not-indicated individuals. For atherosclerotic cardiovascular disease events, CAD-PRS added to the European evaluation and US equation resulted in a net reclassification improvement of 13.6% (95% CI, 11.8–15.5) and 14.7% (95% CI, 13.1–16.3) among statin-indicated, 10.8% (95% CI, 9.6–12.0) and 15.3% (95% CI, 13.2–17.5) among statin-indication-unclear, and 0.9% (95% CI, 0.6–1.3) and 3.6% (95% CI, 3.0–4.2) among statin-not-indicated individuals.

CONCLUSIONS: CAD-PRS may guide statin initiation as well as deferral among statin-indication-unclear or statin-indicated individuals as defined by the European and US guidelines. CAD-PRS had little clinical utility among statin-not-indicated individuals.

Key Words: atherosclerotic cardiovascular disease ■ coronary artery disease ■ polygenic risk score ■ statin eligibility

Cardiovascular disease (CVD), including coronary artery disease (CAD), is a leading cause of death worldwide.[1] The European and US guidelines on primary prevention of CVD recommend lifestyle modification and lipid-lowering treatment for individuals at high risk of future CVD based on clinical risk scores including the European-Systematic Coronary Risk Evaluation 2 (European-SCORE2) and US-Pooled

Correspondence to: Boyoung Joung, MD, PhD, Yonsei University College of Medicine, 50-1 Yonseiro, Seodaemun-gu, Seoul 03722, Republic of Korea. Email: cby6908@yuhs.ac and Pil-Sung Yang, MD, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do 13496, Republic of Korea. Email: psyang01@cha.ac.kr

*H. Park and D. Kim contributed equally.

†P.-S. Yang and B. Joung are joint senior authors.

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CLINICAL PERSPECTIVE

What Is New?

- Coronary artery disease polygenic risk score identified statin-indication-unclear or statin-indicated individuals beyond the European-Systematic Coronary Risk Evaluation 2 and US-Pooled Cohort Equation models who might have been under- or overtreated for lipid-lowering treatment.
- Coronary artery disease polygenic risk score had little clinical utility among statin-not-indicated individuals.

What Are the Clinical Implications?

- Coronary artery disease polygenic risk score may affect clinical decision-making in primary prevention among statin-indication-unclear or statin-indicated individuals but not for statin-not-indicated individuals based on the European and US guidelines on statin use.

Nonstandard Abbreviations and Acronyms

CAD-PRS	coronary artery disease polygenic risk score
European-SCORE2	European-Systematic Coronary Risk Evaluation 2
PRS	polygenic risk score
US-PCE	United States-Pooled Cohort Equation

Cohort Equation (US-PCE) models.[2,3] However, many individuals who develop CVD have an estimated clinical risk score below the guideline-recommended thresholds whereas many of those who are judged to be at high risk of future CVD will not develop the disease.[4] Therefore, strategies to accurately identify those who will be over- or undertreated with lipid-lowering treatment are of clinical importance.[5]

Recently, common genetic variants have emerged as risk factors for CVD that provide information on disease predisposition from an earlier age.[6] By summing each of the common genetic variants in the form of polygenic risk scores (PRSs), genetic testing may significantly contribute to the prediction of disease onset that may outperform traditional risk factors.[7,8] However, the added value of PRS for CAD on established clinical risk scores has been modest and a broad genetic testing strategy has been discouraged.[9,10]

The most relevant questions in this context would be (1) is there a specific population in whom targeted genetic testing will impact contemporary management, and (2) if so, to what extent would the genetic testing added to established clinical risk scores prevent over- or undertreatment? To address these questions, we investigated the predictive power of CAD-PRS added to clinical risk scores across European and US guideline-based statin eligibility strata and assessed the extent to which over- or undertreatment would have been prevented.

METHODS

Study Population

The UK Biobank is a prospective cohort of 502 421 individuals recruited between 2006 and 2010. The study design and data collection have been described in detail previously.[11] Among a total of 502 421 participants in the UK Biobank, we included individuals aged ≥40 years between March 13, 2006, and October 1, 2010. We excluded participants without PRS data (n=16 263), Black race (n=7630), Asian race (n=10902), mixed, other, or unknown race or ethnicity (n=9476), missing data for European-SCORE2 and US-PCE (n=62 070) models, established atherosclerotic cardiovascular disease (ASCVD) (n=27 341), diabetes (n=15 052), chronic kidney disease or end-stage renal disease (n=2494), or receiving lipid-lowering medication (n=39 393). Finally, a total of 311 799 individuals were followed until a major coronary event, death, censoring, or March 31, 2021, whichever came first (Figure S1).

This study was approved by the institutional review board of the Yonsei University Health System (4-2022-0154). The requirement for informed consent was waived because personally identifying information was removed after cohort generation, in accordance with strict confidentiality guidelines. Restrictions apply to the availability of these data from the UK Biobank. All data and materials can be obtained upon direct application (http://ukbiobank.ac.uk).

Guideline-Defined Statin Eligibility

The European-SCORE2 model predicts 10-year risk of ASCVD events in apparently healthy individuals without established ASCVD, diabetes, or chronic kidney disease. With the estimated 10-year risk of ASCVD events by the European-SCORE2 model, the 2021 European Society of Cardiology guidelines[2] recommend age-specific treatment thresholds for statin use. For the calculation of the European-SCORE2, we used calibration coefficients developed for low-risk regions, which was intended for use in most Western European countries including the United Kingdom. Statin-indicated individuals were defined as those with low-density lipoprotein (LDL) ≥100 mg/dL and (1) patients aged 40 to 49 with European-SCORE2 ≥7.5%, (2) aged 50 to 69 with ≥10%, or (3) age ≥70 with ≥15%. Statin-indication-unclear individuals were defined as those with LDL ≥100 mg/dL and (1) those aged 40 to 49 with European-SCORE2 ≥2.5%, (2) aged 50 to 69 with ≥5%, or (3) age ≥70 with ≥7.5% in the presence of risk modifiers. Statin-not-indicated individuals were defined as those with LDL <100 mg/dL or (1) those aged 40 to 49 with European-SCORE2 <2.5%, (2) aged 50 to 69 with <5%, or (3) age ≥70 with <7.5%.

The US-PCE model[3] predicts 10-year ASCVD event risk in individuals without established ASCVD. With the estimated 10-year risk of ASCVD events by the US-PCE models, the 2019 American College of Cardiology/American Heart Association guidelines recommend a threshold of 7.5% for statin use. Statin-indicated individuals were defined as those with (1) LDL ≥70 mg/dL and US-PCE ≥7.5% or (2) LDL ≥190 mg/dL regardless of US-PCE. Because individuals with diabetes were excluded from our study sample, statin-indicated individuals with diabetes were not considered. Statin-indication-unclear individuals were defined as those with LDL ≥70 mg/dL and US-PCE ≥5% in the presence of risk enhancers. Statin-not-indicated individuals were defined as those with US-PCE <5% or LDL <70 mg/dL.

Polygenic Risk Score

We obtained CAD-PRS from the UK Biobank Polygenic Risk Score Release-Standard set. The performance of the CAD-PRS standard set has been validated in a previous study[12] and is reported to outperform its comparators.[9,13–15] Detailed information about the UK Biobank Polygenic Risk Score Release is provided in Data S1.

End Point

The primary end point was a major coronary event, which is the most specific and strongly associated outcome with CAD-PRS. A major coronary event was defined as any acute myocardial infarction, any coronary revascularization, or death due to CAD. The secondary end point was an ASCVD event, which is the most clinically relevant outcome. An ASCVD event was defined using the European and US guidelines on statin use, and we closely followed the ASCVD end point definitions used for each clinical risk score model (Table S1). Although the European and US guidelines define similar ASCVD end points, the European guideline also includes noncoronary, nonstroke cardiovascular deaths.[16]

The outcomes were extracted from the "first occurrence of health outcomes" field, which was obtained by linkage with primary care, hospital inpatient records, and the death register. Detailed information about the linkage procedure is publicly available online (https://www.ukbiobank.ac.uk). Detailed information about the definitions of outcomes and covariates is provided in Table S1.

Statistical Analysis

Baseline characteristics were reported as median (interquartile range) or count (percentage). Calibration of the European-SCORE2 and US-PCE models and their subsequent recalibration were assessed by plotting the observed probability against the mean predicted probability within tenths of the predicted probabilities of the ASCVD events. We recalibrated the European-SCORE2 and US-PCE models using simple logistic regression and tested the calibration using Greenwood–Nam–D'Agostino (GND) test (where a significant *P* value indicates presence of miscalibration). Logistic recalibration of prediction models has been used and validated in multiple studies.[17,18] All of the analyses in this study were carried out with the recalibrated European-SCORE2 and US-PCE models. We calculated the lifetime risk for major coronary events by adding CAD-PRS to the European and US guideline-based statin eligibility strata from the index age of 45 years to the attained age of 80 years, accounting for the competing risk of death (details in Data S1). In addition, a Fine–Gray subdistribution hazard model was used to assess the relative risk of major coronary events, adjusting for the competing risk of death.

We also calculated the predicted odds ratios (ORs) of major coronary events for each CAD-PRS percentile across statin eligibility strata with the median CAD-PRS percentile of statin-indicated individuals as the reference. The predicted probability of major coronary events was calculated using a logistic regression model with the CAD-PRS as the sole predictor because the European-SCORE2 and US-PCE model already accounts for sex, age, and traditional risk factors. The CAD-PRS percentile cutoff for statin-indication-unclear individuals that did not significantly differ from the average risk of statin-indicated individuals was determined by *F* statistics. Similarly, the CAD-PRS percentile cutoff for statin-indicated individuals that did not significantly differ from the average risk of statin-indication-unclear individuals was calculated. We repeated the same analysis among individuals aged <55 years.

The C-statistics for ASCVD events were calculated before and after adding CAD-PRS to the European-SCORE2 and US-PCE models for the overall population and the European and US guideline-defined statin eligibility subgroups. We also reported the *P* values of a *Z* score test based on a U statistics-based C estimator to assess the difference in C-index.

Net reclassification improvement (NRI) analysis for ASCVD events was performed to estimate the improvement in reclassification after adding CAD-PRS to the European-SCORE2 and US-PCE models. We used the 10-year ASCVD event risk thresholds provided in the European and US guidelines for the calculation of NRIs. For example, a 10% risk threshold was used for participants aged 50 to 69 according to the European guidelines (age-specific thresholds) and a 7.5% threshold was used according to the US guidelines. For the calculation of C-index and NRIs, we excluded individuals whose clinical risk scores would not affect therapy decision to reduce potential bias; those with (1) LDL <100 mg/dL based on the European and (2) LDL ≥190 and LDL <70 mg/dL based on the US guidelines. In addition, we estimated the observed 10-year rate of ASCVD and major coronary events to assess whether European and US guideline-based statin eligibility subgroups would result in different class of statin recommendation by CAD-PRS categories.

All analyses were performed using SAS version 9.4 for Windows (SAS Institute) and R statistics software version 4.0.2 (R Foundation for Statistical Computing), and a 2-sided *P* value <0.05 was considered statistically significant.

Sensitivity Analysis

Several sensitivity analyses were performed. First, because the European and US guidelines do not provide 10-year major coronary event risk thresholds for statin use, we performed NRI analysis for major coronary events using 10-year major coronary event risk threshold, which is equivalent to the 10-year ASCVD event risk threshold, by introducing a conversion factor[19] as previously performed by Lu et al.[20] Details of the 10-year major coronary event risk thresholds calculation are provided in Data S1. Second, we provided the results of the main analysis using the nonrecalibrated European-SCORE2 and US-PCE models for comparison. Third, the R^2 and *D*-statistics for ASCVD events before and after adding CAD-PRS to the European-SCORE2 and US-PCE models were performed as a complementary analysis.

RESULTS

The baseline characteristics of the study population and excluded individuals are presented in Table 1 and Table S2, respectively. During a median follow-up of 11.9 (11.2–12.6) years, 8196 individuals experienced major coronary events, and 12 429 and 11 837 individuals experienced European and US guideline-defined ASCVD events, respectively. Individuals who experienced major coronary events were older, had higher blood pressure, and higher blood lipid levels. The baseline characteristics of the study population by European and US guideline-based statin eligibility strata and by the CAD-PRS are provided in Tables S3 and S4, respectively. Among the traditional cardiovascular risk factors, age and systolic blood pressure had the highest discriminative value for

Table 1. Baseline Characteristics of the Study Population

	Total	No major coronary events	Major coronary event
Total no.	311 799	303 603	8196
Follow-up duration, y	11.9 (11.2 to 12.6)	11.9 (11.2 to 12.6)	11.8 (10.8 to 12.6)
Age, y	57 (50 to 63)	57.0 (49.0 to 63.0)	61.0 (56.0 to 65.0)
Female sex	178 476 (57.2)	176 414 (58.1)	2062 (25.2)
Townsend deprivation index	−2.3 (−3.7 to −0.1)	−2.3 (−3.7 to −0.1)	−2.1 (−3.6 to −0.5)
Systolic blood pressure, mm Hg	136 (124 to 149)	135.0 (123.5 to 148.5)	145.0 (133.5 to 158.5)
Diastolic blood pressure, mm Hg	82 (75 to 89)	81.5 (75.0 to 89.0)	86.0 (79.0 to 92.5)
Body mass index, kg/m^2	26.3 (23.8 to 29.3)	26.2 (23.8 to 29.2)	27.4 (25.1 to 30.1)
Waist circumference, cm	88 (79 to 97)	88 (79 to 97)	95 (87 to 102)
Hypertension	58 521 (18.8)	55 991 (18.4)	2530 (30.9)
Blood pressure-lowering medication	34 765 (11.1)	33 236 (10.9)	1529 (18.7)
Fasting glucose, mg/dL	88.1 (82.4 to 94.3)	88 (82 to 94)	89 (83 to 95)
Total cholesterol, mg/dL	227 (201 to 255)	227 (201 to 254)	238 (212 to 267)
High-density lipoprotein, mg/dL	56 (47 to 66)	56 (47 to 67)	49 (42 to 57)
Low-density lipoprotein, mg/dL	143 (123 to 164)	142 (122 to 164)	156 (136 to 177)
Triglyceride, mg/dL	128 (91 to 184)	127 (90 to 183)	164 (117 to 233)
European-SCORE2, %*	2.7 (1.7 to 4.7)	2.7 (1.7 to 4.6)	6.0 (3.6 to 9.7)
US-Pooled Cohort Equation, %	2.6 (1.7 to 4.5)	2.6 (1.7 to 4.3)	5.6 (3.3 to 9.2)
Cigarette smoking			
Never	175 816 (56.4)	172 189 (56.7)	3627 (44.3)
Previous	103 828 (33.3)	100 811 (33.2)	3017 (36.8)
Current	32 155 (10.3)	30 603 (10.1)	1552 (18.9)

Values are presented as the median (first quartile, third quartile) or n (%). SCORE2 indicates Systemic Coronary Risk Evaluation 2.
*European-SCORE2 was calculated using calibration coefficients for low-risk regions.

ASCVD events for both the European-SCORE2 and US-PCE models (Figure S2).

Calibration of CAD-PRS

The nonrecalibrated European-SCORE2 model was fairly calibrated (calibration slope, β=1.26; GND test, P_{GND}=0.061) whereas the nonrecalibrated US-PCE model overestimated (β=0.64; P_{GND}<0.001) the 10-year ASCVD event risk in our study sample. After recalibration, both the European-SCORE2 (β=0.99; P_{GND}=0.423) and US-PCE models (β=0.98; P_{GND}=0.145) were well calibrated (Figure 1).[21] The density plots by CAD-PRS, European-SCORE2, and US-PCE are presented in Figure S3. CAD-PRS was not strongly correlated or associated with European-SCORE2, US-PCE, or traditional risk factors for CVD (Figures S4 and S5).

Predictive Performance of CAD-PRS

The lifetime and relative risk of major coronary events largely overlapped across European and US guideline-based statin eligibility strata when CAD-PRS was considered (Table 2, Table S5). For example, the lifetime risk of major coronary events among statin-indicated individuals who had high CAD-PRS was 37.4% (95% CI, 29.3–45.8) based on the European-SCORE2 model. This decreased to 1.3% (95% CI 1.1 to 1.5) among statin-not-indicated individuals who had low CAD-PRS, thereby representing a 28-fold risk gradient.

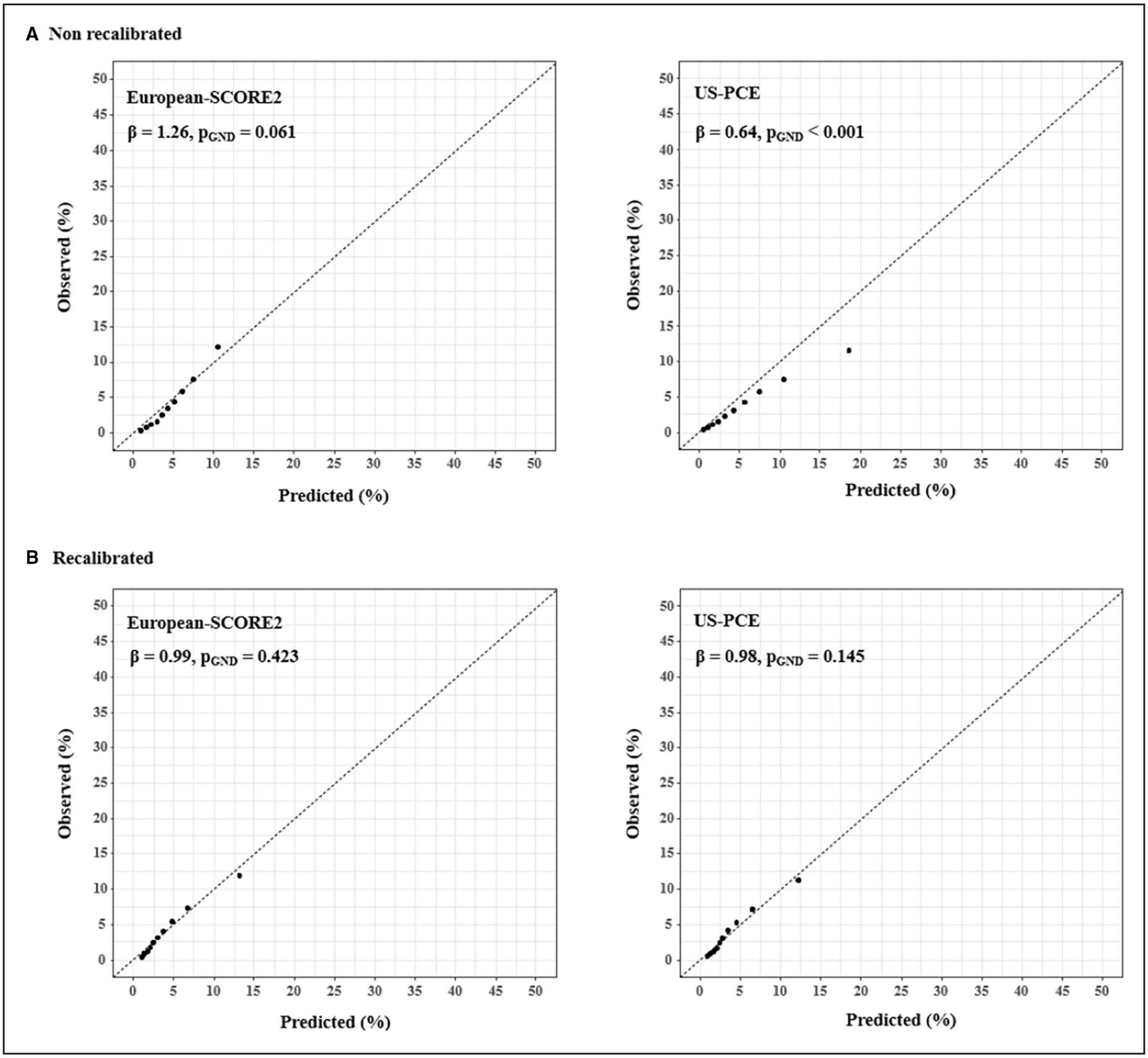

Figure 1. Calibration plots of the European-SCORE2 and US-PCE models before and after recalibration.
PCE indicates pooled cohort equation; P_{GND}, P value for Greenwood–Nam–D'Agostino test; SCORE2, Systemic Coronary Risk Evaluation 2; and β, the calibration slope.

Table 2. Lifetime and Relative Risk of Major Coronary Events by Adding CAD-PRS Across European and US Guideline-Based Statin Eligibility Strata, After Adjusting for the Competing Risk of Death

	European-SCORE2			US-PCE		
	Lifetime risk (45 to 80 y)	Relative risk		Lifetime risk (45 to 80 y)	Relative risk	
		HR (95% CI)	*P* value		HR (95% CI)	*P* value
Statin-indicated*						
High genetic risk†	37.4 (29.3–45.8)	38.4 (32.8–45.0)	<0.001	21.3 (19.8–22.7)	23.9 (20.7–27.7)	<0.001
Intermediate genetic risk	21.9 (16.2–27.8)	20.9 (18.1–24.2)	<0.001	12.1 (11.4–12.8)	13.6 (11.8–15.6)	<0.001
Low genetic risk	19.9 (7.6–32.3)	11.4 (9.4–13.8)	<0.001	6.2 (5.2–7.1)	7.1 (6.0–8.4)	<0.001
Statin-indication-unclear						
High genetic risk	22.0 (20.7–23.3)	22.3 (19.3–25.8)	<0.001	18.0 (15.6–20.4)	22.2 (18.9–26.0)	<0.001
Intermediate genetic risk	10.3 (9.7–10.8)	10.4 (9.0–12.0)	<0.001	10.9 (7.3–14.5)	10.21 (8.8–11.9)	<0.001
Low genetic risk	4.8 (4.1–5.5)	4.8 (4.0–5.7)	<0.001	5.7 (1.9–9.5)	4.3 (3.4–5.3)	<0.001
Statin-not-indicated						
High genetic risk	7.5 (7.0–8.1)	6.1 (5.3–7.0)	<0.001	7.9 (7.3–8.4)	6.3 (5.5–7.3)	<0.001
Intermediate genetic risk	3.3 (3.1–3.6)	2.5 (2.2–2.9)	<0.001	3.3 (3.0–3.5)	2.4 (2.1–2.8)	<0.001
Low genetic risk	1.3 (1.1–1.5)	Reference		1.3 (1.1–1.5)	Reference	

CAD indicates coronary artery disease; HR, hazard ratio; PCE, pooled cohort equation; PRS, polygenic risk score; and SCORE2, Systemic Coronary Risk Evaluation 2.

*Statin eligibility was categorized according to the 2021 European Society of Cardiology and 2019 American College of Cardiology/American Heart Association guidelines on statin use.

†Genetic risk was categorized into low, intermediate, and high-risk groups by <20th, ≥20 to <80th, ≥80th percentiles of the polygenic risk score for coronary artery disease.

In contrast, no overlap in the lifetime and relative risk of major coronary events was identified when CAD-PRS was not considered (Table S6).

Across all European and US guideline-defined statin eligibility strata, individuals with higher CAD-PRS had higher predicted ORs for major coronary events. However, the impact of higher CAD-PRS was insignificant among statin-indication-unclear individuals (Figure 2). European and US guideline-defined statin-indication-unclear individuals with CAD-PRS ≥82nd

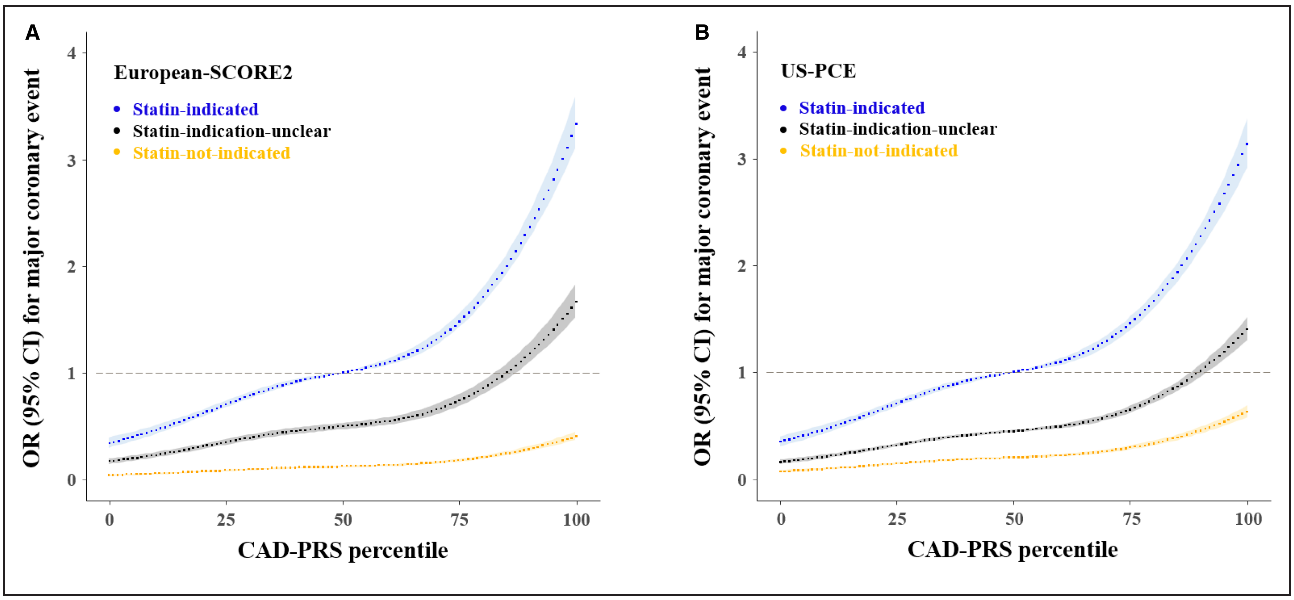

Figure 2. CAD-PRS predicted odds ratios for major coronary events by statin eligibility.
Predicted odds ratios for each CAD-PRS percentile across statin eligibility strata (median CAD-PRS percentile of statin-indicated individuals as the reference) are presented. The predicted probability of major coronary events was calculated using a logistic regression model with CAD-PRS as the sole predictor. *Statin eligibility was categorized according to the 2021 European Society of Cardiology and 2019 American College of Cardiology/American Heart Association guidelines on statin use. CAD indicates coronary artery disease; OR, odds ratio; PCE, pooled cohort equation; PRS, polygenic risk score; and SCORE2, Systemic Coronary Risk Evaluation 2.

and 88th percentile had comparable predicted ORs of major coronary events with statin-indicated individuals (Figure S6A). Similarly, European and US guideline-defined statin-indicated individuals with CAD-PRS ≤16th and 12th percentile had comparable predicted ORs of major coronary events with statin-indication-unclear individuals (Figure S6B). In contrast, there were no statin-not-indicated individuals who had comparable major coronary event risk compared with statin-indicated individuals.

The predicted ORs of major coronary events among individuals aged <55 years showed similar trends and identified more individuals who would have been over- or undertreated for lipid-lowering treatment (Figure S7). For example, European and US guideline-defined statin-indication-unclear individuals with CAD-PRS ≥81st and 75th percentile did not significantly differ from the average predicted risk of that among statin-indicated individuals (Figure S8A). Likewise, European and US guideline-defined statin-indicated individuals with CAD-PRS ≤18th and 24th percentile did not significantly differ from the average major coronary event risk of statin-indication-unclear individuals (Figure S8B).

Figure 3 shows the observed 10-year rate of ASCVD and major coronary events by statin eligibility and CAD-PRS. Among the European or US guideline-based statin-indication-unclear individuals with high CAD-PRS, the 10-year rates for ASCVD and major coronary events were higher than the statin initiation thresholds whereas lower than among statin-indicated individuals with low CAD-PRS.

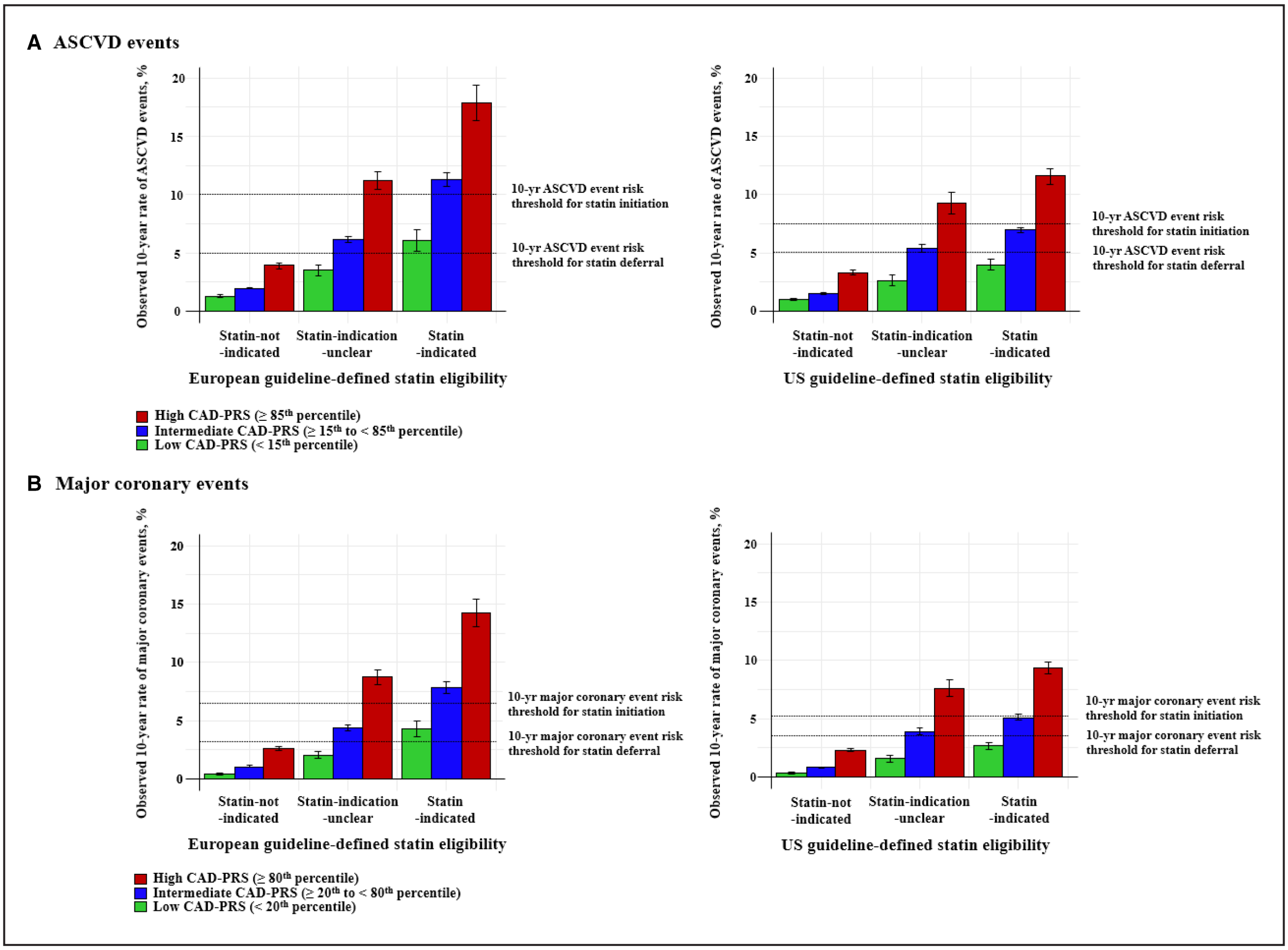

Figure 3. Observed 10-year rate of ASCVD and major coronary events by statin eligibility and CAD-PRS.
Error bars indicate Kaplan–Meier rate 95% CIs. The 10-year ASCVD event risk thresholds were based on the European and US guidelines on statin use. The 10-year major coronary event risk threshold for statin use was calculated using conversion factors as described in Data S1. For the European guideline-based statin eligibility, data are shown for the group of 50 to 69 years (who represent 229 763 out of 311 799 of the study population) because of multiple age-specific statin initiation thresholds. For the US guideline-based statin eligibility, data are shown for all age groups. High CAD-PRS was defined as ≥85th percentile for ASCVD events and ≥80th percentile for major coronary events because NRI analysis for ASCVD and major coronary events revealed about 10% to 15% and 15% to 20% reclassification among statin-indication-unclear individuals, respectively (Table 4 and Table S8). ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; NRI, net reclassification improvement; and PRS, polygenic risk score.

Table 3. C-Statistics for ASCVD Events by Adding CAD-PRS to the European-SCORE2 and US-PCE Models

	C-index (SE)		*P* value for difference in C-index†	C-index (SE)		*P* value for difference in C-index
	European-SCORE2	European-SCORE2+CAD-PRS		US-PCE	US-PCE+CAD-PRS	
Overall	0.72 (0.002)	0.74 (0.002)	<0.001	0.72 (0.003)	0.74 (0.002)	<0.001
Statin-indicated*	0.55 (0.006)	0.61 (0.006)	<0.001	0.57 (0.005)	0.62 (0.005)	<0.001
Statin-indication-unclear	0.59 (0.004)	0.65 (0.004)	<0.001	0.53 (0.006)	0.63 (0.006)	<0.001
Statin-not-indicated	0.70 (0.004)	0.72 (0.004)	<0.001	0.70 (0.004)	0.72 (0.004)	<0.001

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; PCE, pooled cohort equation; PRS, polygenic risk score; and SCORE2, Systemic Coronary Risk Evaluation 2.

*Statin eligibility was categorized according to the 2021 European Society of Cardiology and 2019 American College of Cardiology/American Heart Association guidelines on statin use.

†*P* values comparing the difference in C-index before and after adding CAD-PRS to the European-SCORE2 or US-PCE models (described in the Methods section).

Discriminative Performance of CAD-PRS

We assessed the C-statistics and NRI before and after adding CAD-PRS to the European-SCORE2 and US-PCE models. Improvement in discrimination for ASCVD events by C-statistics was small among individuals who were statin not indicated (C-index of 0.70; SE 0.004–0.72; 0.004 for European-SCORE2 and 0.70; 0.004–0.72; 0.004 for US-PCE models, Table 3 and Figure S9). In contrast, a greater improvement in C-statistics among statin-indicated and statin-indication-unclear individuals was identified (Table 3 and Figure S9). Similarly, the NRI for ASCVD events were 13.6% (95% CI, 11.8–15.5) and 14.7% (95% CI, 13.1–16.3) among statin-indicated individuals, 10.8% (95% CI, 9.6–12.0) and 15.3% (95% CI 13.2–17.5) among statin-indication-unclear individuals whereas among statin-not-indicated individuals, the NRIs were 0.9% (95% CI, 0.6–1.3) and 3.6% (95% CI, 3.0–4.2) based on the European-SCORE2 and US-PCE models, respectively (Table 4).

Sensitivity Analysis

The C statistics (Table S7 and Figure S10) and NRI (Table S8) for major coronary events showed better reclassification by adding CAD-PRS to the European-SCORE2 and US-PCE models than that for ASCVD events. The results of the sensitivity analysis using the nonrecalibrated European-SCORE2 and US-PCE models showed similar trends and results with the main analysis (Table S9, Figures S11 and S12). In addition, the R^2 and *D*-statistics for ASCVD events before and after adding CAD-PRS to European-SCORE2 and US-PCE models are provided in Table S10. The trends and results were similar to those of the C-statistics.

Table 4. Net Reclassification Improvement for ASCVD Events by Adding CAD-PRS to the European-SCORE2 and US-PCE Models

	European-SCORE2			US-PCE		
	Individuals reclassified			Individuals reclassified		
	Up, %	Down, %	NRI (95%CI), %	Up, %	Down, %	NRI (95% CI), %
Statin indicated*						
Cases	0.0	24.5	−24.4 (−26.1 to −22.7)	0.0	25.2	−25.2 (−26.6 to −23.7)
Noncases	0.0	38.1	38.1 (37.3 to 38.8)	0.0	39.9	39.9 (39.3 to 40.5)
All			13.6 (11.8 to 15.5)			14.7 (13.1 to 16.3)
Statin indication unclear						
Cases	19.4	0.3	19.1 (17.9 to 20.3)	33.4	0.1	33.3 (31.2 to 35.4)
Noncases	8.6	0.3	−8.3 (−8.5 to −8.0)	18.0	0.0	−17.9 (−18.4 to −17.5)
All			10.8 (9.6 to 12.0)			15.3 (13.2 to 17.5)
Statin not indicated						
Cases	1.1	0.0	1.1 (0.8 to 1.4)	4.4	0.0	4.4 (3.7 to 4.9)
Noncases	0.2	0.0	−0.2 (−0.2 to −0.1)	0.8	0.0	−0.8 (−0.8 to −0.7)
All			0.9 (0.6 to 1.3)			3.6 (3.0 to 4.2)

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; NRI, net reclassification improvement; PCE, pooled cohort equation; PRS, polygenic risk score; and SCORE2, Systemic Coronary Risk Evaluation 2.

*Statin eligibility was categorized according to the 2021 European Society of Cardiology and 2019 American College of Cardiology/American Heart Association guidelines on statin use.

DISCUSSION

In this longitudinal cohort study, we aimed to identify individuals who should be tested with CAD-PRS and to what extent CAD-PRS would affect clinical decision-making. For major coronary events, CAD-PRS added to European-SCORE2 and US-PCE models identified 18% and 12% of statin-indication-unclear individuals who might have been undertreated, and 16% and 12% of statin-indicated individuals who might have been overtreated for lipid-lowering treatment. We also found that genetic testing for statin-not-indicated individuals (73.6% and 72.3% of the overall study population based on the European-SCORE2 and US-PCE models) would have little impact in clinical decision-making, and these findings were largely consistent for ASCVD events.

Previous studies demonstrated that broad genetic testing for CAD-PRS would reclassify about 4% or less of the individuals as statin eligible whereas others reported more.[9,10,22–25] Because of the modest and contentious predictive performance of CAD-PRS when added to a clinical risk score, genetic testing for everyone has been discouraged. This led to the question of who would benefit from CAD-PRS. Recent evidence suggested younger or intermediate clinical risk individuals would benefit more from CAD-PRS.[26–28] However, those studies were exclusively based on US-PCE models, did not assess for baseline ASCVD risk score calibration, or were limited by small sample size.[20,26–28] Our results are valuable in that we assessed and corrected for miscalibration of US-PCE and extended the applicability of CAD-PRS using European-SCORE2 models in a large population-based, longitudinal cohort.

Predicted ORs for major coronary events in this study suggest that statin-not-indicated individuals would not be reclassified to statin-indicated individuals regardless of the CAD-PRS percentile. Consistently, the NRI for ASCVD events was insignificant among statin-not-indicated individuals. This is important because the majority of individuals in the primary prevention setting would be classified as statin not indicated and excluding statin-not-indicated individuals as candidates for genetic testing would prevent excessive health care costs. The predicted ORs of CAD-PRS 99th to 1st percentile was about 2 for statin-not-indicated, 9 for statin-indication-unclear, and 20 for statin-indicated individuals based on the European-SCORE2 models (Figure 1). A predicted OR of 10 is typically required for a new biomarker to substantially improve discrimination,[10] and our results that genetic testing among statin-indication-unclear or statin-indicated and not testing among statin-not-indicated individuals might be reasonable.

The 2021 European Society of Cardiology and 2019 American College of Cardiology/American Heart Association guidelines on statin use suggest statin-indication-unclear individuals may be further risk stratified by risk modifiers such as coronary artery calcium score or carotid ultrasound.[2,3] However, neither guideline suggests PRS as a risk modifier. According to the results of this study, the addition of CAD-PRS as a risk modifier in the European and US guidelines on statin use might be reasonable. Although this study suggested that more than 12% of statin-indicated individuals may potentially defer for lipid-lowering treatment, about 25% of ASCVD event cases among statin-indicated individuals were falsely downclassified (Table 4). Because the potential harm associated with statin use is considered small, lipid-lowering treatment deferral based on CAD-PRS alone might be too premature to be justified at this point. Conversely, statin-indication-unclear individuals whose major coronary or ASCVD event risk were reclassified to statin-indicated individuals by adding CAD-PRS might be justified for statin initiation. For example, NRI for ASCVD events suggests that among the 62 539 and 29 954 statin-indication-unclear individuals defined by the European-SCORE2 and US-PCE models, 17 511 (12 133 correctly and 5378 incorrectly) and 15 396 (10 004 correctly and 5392 incorrectly) would be encouraged to receive statins (Table 4 and Table S3).

This study addressed the most relevant question in the field using standardized validated PRS data from a prospective cohort by combining PRS data with 2 different clinical risk score models from Europe and the United States and by implementing multiple analytic methods with sensitivity analyses that are consistent with standard reporting on PRS.[29] A future health economic study that assesses the costs and benefits of implementing CAD-PRS in clinical practice across various geographic regions using multiple ASCVD risk scores (including European-SCORE2, US-PCE, and QRISK3 score) might be beneficial.

LIMITATIONS

This study has potential limitations. First, this study included participants of European descent and the performance of PRS is known to depend on ancestry. Therefore, caution is needed when our results are applied to individuals of non-European descent. Second, the nonrecalibrated US-PCE model largely overestimated the 10-year ASCVD event risk in our study sample and the predictive performance of CAD-PRS added to US-PCE might have been overestimated. Systematic overestimation of 10-year ASCVD event risk by the US-PCE models has been reported in multiple studies.[30,31] Nonetheless, we corrected for miscalibration by recalibration and provides a reasonable estimation. Third, this study included individuals aged

40 to 73 and further conclusions cannot be drawn for other age groups. Fourth, the NRIs for major coronary events were based on 10-year major coronary event risk thresholds equivalent to 10-year ASCVD event risk thresholds by implementing a conversion factor. Such a conversion assumes that the associated clinical implications are similar for different outcome definitions, which might not always be true. However, NRI calculation for major coronary events using the 10-year ASCVD event risk thresholds would be problematic and our analytic method is in line with the guidelines on NRI computation.[19] Fifth, because the UK Biobank consists of healthy volunteers, the results of this study applied to individuals or regions with high cardiovascular risk requires careful consideration. Sixth, because this study used European-SCORE2 and US-PCE models to assess the baseline ASCVD risk, further studies on the utility of CAD-PRS when added to other 10-year ASCVD risk score such as QRISK 3 score might be useful.

CONCLUSIONS

CAD-PRS may guide statin initiation as well as deferral among statin-indication-unclear or statin-indicated individuals as defined by the European and US guidelines. CAD-PRS had little clinical utility among statin-not-indicated individuals.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, Department of Internal Medicine (H.P., D.K., E.J., H.T.Y., T.-H.K., H.-N.P., M.-H.L., B.J.) and Department of Biomedical Systems Informatics (S.C.Y.), Yonsei University College of Medicine, Seoul, Republic of Korea; Division of Cardiology, Department of Internal Medicine, College of Medicine, Dankook University, Cheonan, Republic of Korea (D.-m.K.); and Division of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea (J.-H.S., P.-S.Y.).

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Supplemental Material

Data S1
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REFERENCES

1. Global Cardiovascular Risk C, Magnussen C, Ojeda FM, Leong DP, Alegre-Diaz J, Amouyel P, Aviles-Santa L, De Bacquer D, Ballantyne CM, Bernabe-Ortiz A, et al. Global effect of modifiable risk factors on cardiovascular disease and mortality. *N Engl J Med*. 2023;389:1273–1285. doi: 10.1056/NEJMoa2206916
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, Benetos A, Biffi A, Boavida JM, Capodanno D, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337. doi: 10.1093/eurheartj/ehab484
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
4. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. *JAMA*. 2014;311:1406–1415. doi: 10.1001/jama.2014.2630
5. Greenland P, Hassan S. Precision preventive medicine-ready for prime time? *JAMA Intern Med*. 2019;179:605–606. doi: 10.1001/jamainternmed.2019.0142
6. Musunuru K, Kathiresan S. Genetics of common, complex coronary artery disease. *Cell*. 2019;177:132–145. doi: 10.1016/j.cell.2019.02.015
7. Marston NA, Patel PN, Kamanu FK, Nordio F, Melloni GM, Roselli C, Gurmu Y, Weng LC, Bonaca MP, Giugliano RP, et al. Clinical application of a novel genetic risk score for ischemic stroke in patients with cardiometabolic disease. *Circulation*. 2021;143:470–478. doi: 10.1161/CIRCULATIONAHA.120.051927
8. Marston NA, Melloni GEM, Gurmu Y, Bonaca MP, Kamanu FK, Roselli C, Lee C, Cavallari I, Giugliano RP, Scirica BM, et al. Genetic risk score to identify risk of venous thromboembolism in patients with cardiometabolic disease. *Circ Genom Precis Med*. 2021;14:e003006. doi: 10.1161/CIRCGEN.120.003006
9. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease. *JAMA*. 2020;323:636–645. doi: 10.1001/jama.2019.22241
10. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *JAMA*. 2020;323:627–635. doi: 10.1001/jama.2019.21782
11. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779
12. Thompson DJ, Wells D, Selzam S, Peneva I, Moore R, Sharp K, Tarran WA, Beard EJ, Riveros-Mckay F, Giner-Delgado C, et al. UK biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. *medRxiv*2022:2022.2006.2016.22276246. doi: 10.1101/2022.06.16.22276246.
13. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50:1219–1224. doi: 10.1038/s41588-018-0183-z
14. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. *J Am Coll Cardiol*. 2018;72:1883–1893. doi: 10.1016/j.jacc.2018.07.079
15. Wang M, Menon R, Mishra S, Patel AP, Chaffin M, Tanneeru D, Deshmukh M, Mathew O, Apte S, Devanboo CS, et al. Validation of a genome-wide polygenic score for coronary artery disease in south Asians. *J Am Coll Cardiol*. 2020;76:703–714. doi: 10.1016/j.jacc.2020.06.024
16. Mortensen MB, Tybjaerg-Hansen A, Nordestgaard BG. Statin eligibility for primary prevention of cardiovascular disease according to 2021 European prevention guidelines compared with other

international guidelines. *JAMA Cardiol*. 2022;7:836–843. doi: 10.1001/jamacardio.2022.1876
17. Lamain-de Ruiter M, Kwee A, Naaktgeboren CA, de Groot I, Evers IM, Groenendaal F, Hering YR, Huisjes AJ, Kirpestein C, Monincx WM, et al. External validation of prognostic models to predict risk of gestational diabetes mellitus in one Dutch cohort: prospective multicentre cohort study. *BMJ*. 2016;354:i4338. doi: 10.1136/bmj.i4338
18. Levy TJ, Coppa K, Cang J, Barnaby DP, Paradis MD, Cohen SL, Makhnevich A, van Klaveren D, Kent DM, Davidson KW, et al. Development and validation of self-monitoring auto-updating prognostic models of survival for hospitalized COVID-19 patients. *Nat Commun*. 2022;13:6812. doi: 10.1038/s41467-022-34646-2
19. Leening MJ, Vedder MM, Witteman JC, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Ann Intern Med*. 2014;160:122–131. doi: 10.7326/M13-1522
20. Lu X, Liu Z, Cui Q, Liu F, Li J, Niu X, Shen C, Hu D, Huang K, Chen J, et al. A polygenic risk score improves risk stratification of coronary artery disease: a large-scale prospective Chinese cohort study. *Eur Heart J*. 2022;43:1702–1711. doi: 10.1093/eurheartj/ehac093
21. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21:128–138. doi: 10.1097/EDE.0b013e3181c30fb2
22. O'Sullivan JW, Raghavan S, Marquez-Luna C, Luzum JA, Damrauer SM, Ashley EA, O'Donnell CJ, Willer CJ, Natarajan P; American Heart Association Council on G, et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e93–e118. doi: 10.1161/CIR.0000000000001077
23. Riveros-Mckay F, Weale ME, Moore R, Selzam S, Krapohl E, Sivley RM, Tarran WA, Sorensen P, Lachapelle AS, Griffiths JA, et al. Integrated polygenic tool substantially enhances coronary artery disease prediction. *Circ Genom Precis Med*. 2021;14:e003304. doi: 10.1161/CIRCGEN.120.003304
24. Klarin D, Natarajan P. Clinical utility of polygenic risk scores for coronary artery disease. *Nat Rev Cardiol*. 2022;19:291–301. doi: 10.1038/s41569-021-00638-w
25. O'Sullivan JW, Ashley EA, Elliott PM. Polygenic risk scores for the prediction of cardiometabolic disease. *Eur Heart J*. 2023;44:89–99. doi: 10.1093/eurheartj/ehac648
26. Mars N, Koskela JT, Ripatti P, Kiiskinen TJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med*. 2020;26:549–557. doi: 10.1038/s41591-020-0800-0
27. Marston NA, Pirruccello JP, Melloni GEM, Koyama S, Kamanu FK, Weng LC, Roselli C, Kamatani Y, Komuro I, Aragam KG, et al. Predictive utility of a coronary artery disease polygenic risk score in primary prevention. *JAMA Cardiol*. 2023;8:130–137. doi: 10.1001/jamacardio.2022.4466
28. de La Harpe R, Thorball CW, Redin C, Fournier S, Muller O, Strambo D, Michel P, Vollenweider P, Marques-Vidal P, Fellay J, et al. Combining European and U.S. risk prediction models with polygenic risk scores to refine cardiovascular prevention: the CoLaus|PsyCoLaus study. *Eur J Prev Cardiol*. 2023;30:561–571. doi: 10.1093/eurjpc/zwad012
29. Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, Kullo IJ, Rowley R, Dron JS, Brockman D, et al. Improving reporting standards for polygenic scores in risk prediction studies. *Nature*. 2021;591:211–219. doi: 10.1038/s41586-021-03243-6
30. Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. *Ann Intern Med*. 2016;165:786–794. doi: 10.7326/M16-1739
31. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A, Franco OH. Comparison of application of the ACC/AHA guidelines, adult treatment panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA*. 2014;311:1416–1423. doi: 10.1001/jama.2014.2632
32. Pasaniuc B, Zaitlen N, Shi H, Bhatia G, Gusev A, Pickrell J, Hirschhorn J, Strachan DP, Patterson N, Price AL. Fast and accurate imputation of summary statistics enhances evidence of functional enrichment. *Bioinformatics*. 2014;30:2906–2914. doi: 10.1093/bioinformatics/btu416
33. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Dreyer R, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. *Circulation*. 2019;139:1593–1602. doi: 10.1161/CIRCULATIONAHA.118.035658
34. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38:904–909. doi: 10.1038/ng1847
35. Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, D'Agostino RB. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham study. *Neurology*. 1997;49:1498–1504. doi: 10.1212/wnl.49.6.1498
36. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham heart study. *BMJ*. 2018;361:k1453. doi: 10.1136/bmj.k1453
37. Beiser A, D'Agostino RB Sr, Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham study. The practical incidence estimators (PIE) macro. *Stat Med*. 2000;19:1495–1522. doi: 10.1002/(sici)1097-0258(20000615/30)19:11/12<1495::aid-sim441>3.0.co;2-e