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Cardiovascular Risk Stratification Using Artificial Intelligence-Derived Retinal Imaging and SCORE2 in Untreated Dyslipidemia: A UK Biobank Prospective Cohort Study

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Abstract

We evaluated the prognostic performance of Dr. Noon CVD, an artificial intelligence (AI)-derived retinal imaging model, in 40,727 UK Biobank participants with untreated dyslipidemia. We assessed 5- and 10-year incident cardiovascular events and the model's incremental value beyond SCORE2. After adjustment for demographic, clinical, and metabolic risk factors, higher Dr. Noon CVD scores were independently associated with increased CVD risk; the hazard ratio was 1.51 (95% confidence interval 1.16–1.95) for the high-risk group and 1.75 (1.28–2.40) for an exploratory very-high-risk group. Adding the AI model to SCORE2 significantly improved discrimination (C-index improvement 0.025) and reclassification (net reclassification improvement 0.262; both $p <$ 0.001). Risk stratification remained effective even within the SCORE2 high-risk subgroup. These findings demonstrate that AI-derived retinal imaging independently predicts CVD outcomes and enhances standard risk assessment, offering a non-invasive strategy to guide treatment in individuals with dyslipidemia.

Introduction

Dyslipidemia is one of the most prevalent cardiovascular (CVD) risk factors worldwide.[1] Accurate stratification of absolute CVD risk in dyslipidemia individuals is essential for optimizing preventive strategies and guiding treatment thresholds.[2,3] However, a critical challenge in preventive cardiology remains the management of individuals with dyslipidemia who remain untreated. This population is heterogeneous, comprising individuals correctly identified as low-risk for whom treatment deferral is appropriate, as well as a substantial proportion of high-risk patients who remain unmedicated due to missed therapeutic opportunities, suboptimal adherence, or underestimation of risk.[4,5] In the latter group, this discordance between guideline recommendations and real-world practice emphasizes the need for objective strategies that can facilitate treatment initiation and ensure long-term compliance.

Current European Society of Cardiology (ESC) guidelines recommend the Systematic COronary Risk Evaluation 2 (SCORE2) algorithm, which provides 10-year estimates of fatal and non-fatal atherosclerotic events, calibrated for regional populations.[3,6] While SCORE2 represents a significant refinement over previous models,[7] limitations persist in its clinical application. Specifically, the reliance on laboratory lipid measurements necessitates invasive blood sampling, which can delay risk assessment and limit immediate accessibility at the point of care. Furthermore, even among patients identified as 'at-risk', the reliance on abstract numerical probabilities often fails to motivate medication adherence in asymptomatic individuals, emphasizing the need for strategies that bridge this implementation gap.[8–11]

To address the limitations of invasive blood-based risk assessment, retinal imaging has emerged as a unique, non-invasive window into systemic vascular health. Advances in oculomics initially focused on semi-automated platforms such as the Singapore “I” Vessel Assessment (SIVA) and Vessel Assessment and Measurement Platform for Images of the Retina (VAMPIRE).[12–14] These tools enabled objective measurement of vessel caliber, branching angles, and tortuosity but were constrained by reliance on manually predefined features and sensitivity to image quality.[15] More recently, deep learning approaches have revolutionized this field, allowing automated, end-to-end extraction of complex microvascular patterns directly from retinal images to predict CVD outcomes.[16]

Building upon this paradigm, Dr. Noon CVD (Mediwhale Inc., Seoul, South Korea) is an artificial intelligence (AI)-based software as a medical device that estimates coronary artery calcium (CAC) probability and derives individualized CVD risk directly from retinal fundus photographs.[17,18] The model was developed on 216,152 retinal images from multiple countries and validated against cardiac CT-derived CAC, demonstrating prognostic performance comparable to cardiac CT and superior to other non-invasive biomarkers such as carotid intima-media thickness or brachial-ankle pulse wave velocity.[17] Dr. Noon CVD has been adopted for clinical use in several countries like UAE, UK, Greece, Poland, Spain, Italy and South Korea, demonstrating its clinical utility in real-world.[18–23]

The clinical implementation of AI-based retinal imaging for untreated dyslipidemia hinges on addressing two key uncertainties regarding its performance and utility. First, it is essential to determine whether this non-invasive modality confers prognostic accuracy comparable to the established blood-based SCORE2 algorithm. Second, regarding clinical integration, the optimal strategy for combining these tools must be defined. Specifically, whether the retinal AI model serves to validate the safety of withholding treatment in lower-risk groups, or to provide the compelling evidence necessary to motivate adherence in high-risk individuals.

Therefore, in the present study, we aimed to validate the 5- and 10-year prognostic performance of Dr. Noon CVD in dyslipidemia participants of the UK Biobank (UKBB) who were not taking cholesterol-lowering medication, and to assess its complementary role to SCORE2 in stratifying risk among individuals for whom the decision to initiate cholesterol-lowering therapy is conditional.

Results

Baseline demographics and clinical characteristics.

The analysis included 40,727 participants with dyslipidemia not receiving cholesterol-lowering medication. As summarized in Table 1, participants in higher Dr. Noon CVD risk categories exhibited a progressively adverse clinical profile. Compared to the low-risk group, those in the high-risk group were older (mean 62.0 vs. 47.0 years), more frequently male (52.8% vs. 32.0%), and had a markedly higher prevalence of hypertension (68.7% vs. 34.1%) and diabetes (1.9% vs. 0.9%). Demographic characteristics stratified by the alternative risk classification are presented in **Table S1.**

Table 1

Baseline Characteristics of Participants With Dyslipidemia Without Cholesterol-Lowering Medication. Values are expressed as mean ± SD or n (%). Comparisons performed with Kruskal–Wallis tests or χ^2 tests. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; SCORE2, Systematic COronary Risk Evaluation 2.

	Dyslipidemia without medication	Dr. Noon CVD risk groups			
		Low (< 31)	Moderate (31–40)	High (≥ 41)	*p*-value
Variable, n (%)	**40,727 (100)**	**11,560 (28.4)**	**15,678 (38.5)**	**13,489 (33.1)**	
Age, mean ± SD, years	56.00 ± 14.00	47.00 ± 18.00	56.00 ± 11.00	62.00 ± 7.00	< 0.001
40–49, n (%)	11,790 (28.9)	7,680 (66.4)	3,522 (22.5)	588 (4.4)	< 0.001
50–59, n (%)	13,910 (34.2)	3,245 (28.1)	7,038 (44.9)	3,627 (26.9)	< 0.001
60–69, n (%)	15,027 (36.9)	635 (5.5)	5,118 (32.6)	9,274 (68.8)	< 0.001
Male, n (%)	17,128 (42.1)	3,702 (32.0)	6,307 (40.2)	7,119 (52.8)	< 0.001
Smokers, n (%)	23,853 (58.6)	6,232 (53.9)	9,045 (57.7)	8,576 (63.6)	< 0.001
Diabetes, n (%)	541 (1.3)	103 (0.9)	180 (1.1)	258 (1.9)	< 0.001
Hypertension, n (%)	21,597 (53.03)	3,937 (34.1)	8,393 (53.5)	9,267 (68.7)	< 0.001
SBP, mean ± SD, mmHg	134.00 ± 24.50	126.00 ± 20.50	134.00 ± 23.00	141.00 ± 24.50	< 0.001
DBP, mean ± SD, mmHg	81.00 ± 13.50	78.50 ± 13.00	81.50 ± 13.50	83.00 ± 13.50	< 0.001
Triglyceride, mean ± SD, mg/dL	322.75 ± 94.06	304.50 ± 92.67	326.29 ± 92.64	333.91 ± 90.61	< 0.001
TC, mean ± SD, mg/dL	225.68 ± 53.36	215.35 ± 52.44	228.40 ± 52.77	231.87 ± 52.55	< 0.001
LDL-C, mean ± SD, mg/dl	140.91 ± 41.07	132.95 ± 40.46	142.46 ± 40.45	145.79 ± 39.56	< 0.001
HDL-C, mean ± SD, mg/dl	56.77 ± 19.84	56.88 ± 19.03	57.35 ± 20.38	56.07 ± 19.92	< 0.001
eGFR, mean ± SD, ml/min/1.73m^2	92.90 ± 17.00	98.70 ± 17.20	93.00 ± 16.40	89.70 ± 15.60	< 0.001
BMI, mean ± SD, kg/m^2	26.22 ± 5.51	25.60 ± 5.48	26.17 ± 5.44	26.80 ± 5.38	< 0.001
SCORE2, mean ± SD, %	4.80 ± 4.80	2.50 ± 2.40	4.70 ± 3.90	7.40 ± 4.90	< 0.001
CVD events, n (%)					
10-year CVD events, n (%)	2,531 (6.21)	279 (2.4)	875 (5.6)	1,377 (10.2)	< 0.001
5-year CVD events, n (%)	944 (2.3)	103 (0.9)	319 (2.0)	522 (3.9)	< 0.001

Dr. Noon CVD risk categories demonstrated distinct patterns of concordance and discordance with the SCORE2 algorithm (**Table S2**). The median SCORE2 probability increased substantially across Dr. Noon CVD risk groups. Regarding concordance, 64.5% of the Dr. Noon low risk group were consistently classified as low risk by SCORE2. Conversely, in the Dr. Noon CVD high risk group, the majority (79.6%) fell into the SCORE2 high to very-high risk categories.

Association between Dr. Noon CVD scores and longitudinal cardiovascular events

During the 5-year follow-up, 944 CVD events occurred. Kaplan-Meier survival analysis revealed a clear, progressive divergence in event-free survival across risk groups (Fig. 1). This gradient was reflected in incidence rates, which rose from 1.79 per 1,000 person-years in Dr. Noon CVD low-risk group to 7.85 in the high-risk group (p for trend $<$ 0.001). In the fully-adjusted model (controlling for age group per decade, sex, hypertension, diabetes, smoking status, estimated glomerular filtration rate [eGFR], and body mass index [BMI]), the high-risk group remained significantly associated with an increased risk of CVD events compared to the low-risk group (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.16–1.95, $p < 0.001$). Under the alternative classification, the exploratory very-high risk group identified individuals with a substantially elevated incidence rate of 11.11 per 1,000 person-years, corresponding to a fully-adjusted HR of 1.75 (1.28–2.40) (Table 2). These associations remained robust across sequential covariate adjustments (**Table S3**). Furthermore, the results were consistently replicated over the 10-year horizon, demonstrating similar prognostic gradients and stability across models (**Tables S4** and **Table S5**).

Table 2

Association Between Dr. Noon CVD Risk Groups and 5-Year Cardiovascular Events in Participants With Dyslipidemia Without Cholesterol-Lowering Medication. Demographic-adjusted model included age and sex. Traditional risk-adjusted model additionally adjusted for systolic blood pressure, smoking status, diabetes, total cholesterol, and high-density lipoprotein cholesterol. Fully-adjusted model further included estimated glomerular filtration rate and body mass index. Original classification comprised low, moderate, and high-risk groups. The alternative classification further divided the original high-risk group to define an additional very-high risk category representing the upper extreme of risk. Incidence rates were calculated per 1,000 person-years. *p* for trend was estimated by modeling Dr. Noon CVD risk group as an ordinal variable. CI, confidence interval; PY, person-years; HR, hazard ratio.

Dr. Noon CVD risk groups	N	Cases	Person-years (PY)	Incidence rate (per 1,000 PY)	Unadjusted HR (95% CI)	Demographic-adjusted HR (95% CI)	Traditional risk-adjusted HR (95% CI)	Fully-adjusted HR (95% CI)
Dr. Noon CVD groups stratified by original risk categories								
Low	11,560	103	57,624	1.7875	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Moderate	15,678	319	77,835	4.0984	2.30 (1.84, 2.87)	1.36 (1.07, 1.74)	1.28 (1.00, 1.63)	1.26 (0.99, 1.61)
High	13,489	522	66,461	7.8543	4.41 (3.57, 5.45)	1.74 (1.34, 2.25)	1.55 (1.20, 2.01)	1.51 (1.16, 1.95)
HR trend (per group increase)					**2.04 (1.86, 2.24)**	**1.30 (1.16, 1.46)**	**1.23 (1.10, 1.38)**	**1.23 (1.10, 1.38)**
p for trend					**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Dr. Noon CVD groups stratified by alternative risk categories								
Low	11,560	103	57,624	1.7875	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Moderate	15,678	319	77,835	4.0984	2.30 (1.84, 2.87)	1.37 (1.07, 1.76)	1.29 (1.01, 1.64)	1.27 (0.99, 1.62)
High	11,300	403	55,754	7.23	4.06 (3.27, 5.04)	1.68 (1.30, 2.18)	1.51 (1.16, 1.96)	1.47 (1.13, 1.91)
Very high	2,189	119	10,707	11.11	6.26 (4.81, 8.15)	2.11 (1.55, 2.88)	1.84 (1.34, 2.51)	1.75 (1.28, 2.40)
HR trend (per group increase)					**1.82 (1.69, 1.96)**	**1.26 (1.15, 1.38)**	**1.21 (1.10, 1.32)**	**1.19 (1.08, 1.30)**
p for trend					**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

To confirm that the discriminative ability of the model was not driven solely by demographic differences such as age or sex, we performed a stratified analysis for 10-year CVD events using age- and sex-specific Dr. Noon CVD score percentiles (**Table S6**). In this analysis, risk categories were re-defined within each subgroup based on relative distribution: Q1-2 (< 50th percentile), Q3 (50–75th percentile), and Q4 (≥ 75th percentile). Given that the independent prognostic value of the model was already established in the fully-adjusted main analysis, unadjusted HRs were calculated for subgroups to directly assess the intrinsic discriminative power and actual relative risk gradient within each subgroup. Consequently, Dr. Noon CVD scores consistently stratified risk across demographic profiles. A significant graded association (p for trend < 0.05) was observed in 5 out of 6 subgroups over the 10-year follow-up. Moreover, in the youngest subgroup (40–49 years), individuals in the top quartile (Q4) showed a roughly twofold increase in unadjusted hazard risk compared to the lower half (Q1-2) (HR 2.35 for females; 1.98 for males).

Incremental predictive value of Dr. Noon CVD over SCORE2

Comparative discrimination metrics for 5- and 10-year CVD event prediction are shown in Table 3. The demographic-adjusted Dr. Noon CVD model yielded a C-index of 0.696 (95% CI 0.680–0.704). SCORE2 alone

showed a C-index of 0.680 (0.664–0.695). Combining Dr. Noon CVD with SCORE2 significantly improved the C-index to 0.705 (0.689–0.721), with an absolute improvement of 2.5% (0.025; 95% CI 0.017 to 0.032; $p < 0.001$). The continuous net reclassification improvement (NRI) was 0.262 (95% CI 0.212–0.319; $p < 0.001$), indicating a modest, statistically significant improvement in CVD risk classification.

Table 3

Comparative Discrimination and Incremental Predictive Value of the Dr. Noon CVD Original Risk Classification and SCORE2 for 5- and 10-Year Cardiovascular Events. C-index values were calculated from Cox proportional hazards models for 5- and 10-year cardiovascular event prediction. Each discrimination model was fitted separately using the prespecified Dr. Noon CVD model (age and sex adjusted) and SCORE2, and then refitted as a combined model to quantify the incremental discrimination and reclassification improvement gained by adding Dr. Noon CVD to SCORE2. Both the Dr. Noon CVD original risk classification (low, moderate, high) and SCORE2 (low-moderate, high, very-high) were entered as categorical variables. C-index, *p*-values, and net reclassification index are presented across incrementally adjusted models: demographic (age and sex), traditional risk (plus systolic blood pressure, smoking, diabetes, total cholesterol, and high-density lipoprotein cholesterol), and fully adjusted (further including estimated glomerular filtration rate and body mass index). CI, confidence interval; CVD, cardiovascular disease; NRI, net reclassification improvement; SCORE2, Systematic Coronary Risk Evaluation 2.

Models	Prediction of 5-year CVD events		Prediction of 10-year CVD events	
	C-index (95% CI)	*p*-value	C-index (95% CI)	*p*-value
Demographic-adjusted Dr. Noon CVD	0.696 (0.680, 0.704)	-	0.690 (0.681, 0.700)	-
Traditional risk-adjusted Dr. Noon CVD	0.710 (0.695, 0.726)	-	0.703 (0.693, 0.712)	-
Fully-adjusted Dr. Noon CVD	0.716 (0.702, 0.732)	-	0.707 (0.698, 0.717)	-
SCORE2	0.680 (0.664, 0.695)	-	0.667 (0.657, 0.676)	-
Dr. Noon CVD plus SCORE2	0.705 (0.689, 0.721)	-	0.696 (0.686, 0.705)	-
ΔDr. Noon CVD plus SCORE2 versus SCORE2	0.025 (0.018, 0.032)	< 0.001	0.029 (0.024, 0.033)	< 0.001
Continuous NRI (95% CI)	0.262 (0.210, 0.323)	< 0.001	0.272 (0.237, 0.311)	< 0.001
CVD event NRI (95% CI)	0.256 (0.207, 0.647)	< 0.001	0.256 (0.222, 0.627)	< 0.001
Non-CVD event NRI (95% CI)	0.005 (-0.365, 0.014)	0.957	0.016 (-0.346, 0.026)	0.776

Prognostic value of Dr. Noon CVD within SCORE2 risk groups for conditional therapy

The prognostic performance of Dr. Noon CVD was evaluated within the SCORE2 high risk subgroup, a population for whom statin therapy is a Class IIa recommendation (Fig. 2 and Table 4).[3,6] In this clinically relevant subgroup, the original classification (3-group) successfully stratified residual risk, demonstrating a clear graded relationship (p for trend < 0.001) with a fully-adjusted HR of 1.54 (95% CI 1.24–1.92) for the high-risk category. This risk discrimination was further refined by the alternative risk classification (4-group), which extended the risk gradient within the same SCORE2 subgroup (**Figure S1** and **Table S7**). Specifically, the alternative model identified an even higher risk subset, reaching an adjusted HR of 1.94 (1.48–2.55) for the very-high risk category.

Table 4
Hazard Ratios for 10-Year Cardiovascular Events Stratified by Dr. Noon CVD Risk Classification Within the SCORE2 High Risk Subgroup.

Dr. Noon CVD risk groups	Prediction of 10-year CVD events							
	Unadjusted HR (95% CI)	*p*-value	Demographic-adjusted HR (95% CI)	*p*-value	Traditional risk-adjusted HR (95% CI)	*p*-value	Fully-adjusted HR (95% CI)	*p*-value
Low	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Moderate	1.90 (1.57, 2.30)	**< 0.001**	1.34 (1.08, 1.65)	0.007	1.31 (1.07, 1.62)	**0.011**	1.30 (1.06, 1.61)	**0.013**
High	2.78 (2.31, 3.34)	**< 0.001**	1.62 (1.30, 2.02)	**< 0.001**	1.57 (1.26, 1.95)	**< 0.001**	1.54 (1.24, 1.92)	**< 0.001**
HR trend	1.60 (1.48, 1.73)	**< 0.001**	1.25 (1.14, 1.37)	**< 0.001**	1.23 (1.12, 1.35)	**< 0.001**	1.22 (1.11, 1.34)	**< 0.001**

Data are hazard ratios (95% CIs) unless otherwise stated. Models were sequentially adjusted to evaluate the stability of the association. The demographic-adjusted model controlled for age and sex. The traditional risk-adjusted model additionally controlled for systolic blood pressure, smoking status, diabetes, total cholesterol, and high-density lipoprotein cholesterol. The fully-adjusted model further included estimated glomerular filtration rate and body mass index. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; SCORE2, Systematic Coronary Risk Evaluation 2.

Discussion

In this study of 40,727 UKBB participants with dyslipidemia not receiving cholesterol-lowering therapy, higher Dr. Noon CVD scores were consistently associated with increased 5-year CVD event incidence (p for trend < 0.001) and reduced event-free survival. Fully-adjusted HRs were 1.26 (95% CI, 0.99–1.61) for the moderate-risk group and 1.51 (1.16–1.95) for the high-risk group, indicating an independent, graded association. An exploratory high-risk tier yielded an HR of 1.75 (1.28–2.40). Dr. Noon CVD showed discrimination comparable to SCORE2 (C-index 0.696 [0.680–0.704] vs. 0.680 [0.664–0.695]) and significantly improved performance when combined with SCORE2 (ΔC-index 0.025 [0.018–0.032]; $p < 0.001$), with an NRI of 0.262 ($p < 0.001$). Furthermore, Dr. Noon CVD effectively stratified residual risk among participants classified as high risk by SCORE2 (fully-adjusted HR 1.54; p for trend $<$ 0.001), a pattern consistently observed over the 10-year follow-up horizon. These findings demonstrate that AI-derived retinal CVD risk estimation might provide complementary prognostic information beyond conventional clinical calculators.

While the absolute increase in the C-index (ΔC-index 0.025) upon adding Dr. Noon CVD to SCORE2 might initially appear modest, it represents a clinically meaningful improvement that elevates the model's discriminative power above the 0.70 threshold. Importantly, the C-index is known to be relatively insensitive to the addition of new markers to robust baseline models. In contrast, reclassification metrics provided a clearer picture of clinical utility: our analysis revealed a substantial Continuous NRI of 0.262 ($p < 0.001$). This improvement was primarily driven by the event NRI (up to 0.256) indicating a superior ability to identify true high-risk patients. Regarding clinical implementation, retinal photography is non-invasive, scalable, and low-cost compared to other imaging modalities. Therefore, even a modest incremental gain in prediction accuracy, when combined with high accessibility and significant risk reclassification, points toward a favorable cost-benefit profile for integrating Dr. Noon CVD into routine screening workflows.

This work was the first validation of the Dr. Noon CVD outside Korea, aligned with its intended-use population (individuals with dyslipidemia not receiving cholesterol-lowering medication, a group at risk of CVD), and might therefore be directly informative for real-world implementation. Earlier studies supported the evolution of the model by assessing performance in more heterogeneous populations and by establishing clinical validity and

technical repeatability in Korean cohorts that included high-risk of CVD patients,[17–19,22,30,31] and the present study builds on this foundation by demonstrating performance in a large non-Korean cohort that reflects the intended use population at risk of CVD and not receiving cholesterol-lowering therapy, showing that the algorithm generalizes to those most likely to benefit in practice.

Within this context, the evaluation of an expanded stratification scheme offers an additional advantage because risk categorization based on CAC has long been standardized into four tiers that capture progressively greater atherosclerotic burden, and a particularly meaningful rise in risk is consistently observed beyond 300 Agatston units.[32,33] The three-tier Dr. Noon CVD framework, rooted in CAC 0 and CAC $\geq$ 100 analogs, already shows incidence gradients similar to CAC-based classification, which supports its clinical validity.[18] The absence of an upper tier analogous to CAC $\geq$ 300 could, however, restrict its ability to represent the very-high risk range, so we examined an expanded scheme that added a new very-high risk category. Incidence rates rose stepwise across these higher risk categories, reaching 4.10, 7.23, and 11.11 per 1,000 person-years, with a fully-adjusted HR of 1.19 (1.09 to 1.30) and a significant trend (p for trend < 0.001). The emergence of a distinct very-high group indicates that a higher threshold may enhance alignment with established CAC-based frameworks and improve the granularity and clinical interpretability of AI-derived retinal CVD risk stratification.

Dr. Noon CVD model demonstrated a clear gradient of CVD risk across categories in both unadjusted and sequentially adjusted analyses, including after controlling for BMI and eGFR, two variables emphasized in the PREVENT framework as key cardio-kidney-metabolic determinants.[34,35] Prior studies have shown that reduced kidney function is associated with retinal microvascular abnormalities, including choroidal and retinal thinning and hypertensive retinopathy,[36,37] suggesting partial overlap between renal impairment and microvascular injury. In our analysis, however, risk discrimination remained significant after full adjustment for eGFR, demonstrating that kidney filtration markers alone do not fully explain the retinal vascular signal. Together, these findings support the interpretation that AI-derived retinal CVD risk capture residual microvascular information relevant to CVD risk within the wider context of cardiovascular-kidney-metabolic health, a framework increasingly adopted to reflect the interconnected nature of these systems, and the most substantial clinical implication remains the strong association with incident cardiovascular events and cardiovascular mortality.[35]

European guidelines have recommended risk-based lipid-lowering therapy since 2003,[38,39] yet a substantial proportion of individuals with dyslipidemia in the UKBB (2006–2010) remained untreated. This pattern likely reflects persistent barriers to therapy initiation.[4,5] This 'treatment gap' is particularly relevant to the SCORE2 'high-risk' category. Currently classified as a Class IIa recommendation ('should be considered'), this group occupies a clinical grey zone where the decision to initiate lifelong medication is discretionary.[3,6] Consequently, clinical hesitancy regarding the absolute benefit, combined with patient reluctance to medicate in the absence of symptoms, often leads to conservative prescribing patterns in this group.

In this context, Dr. Noon CVD successfully stratified residual risk within these untreated high-risk individuals (fully-adjusted HR 1.54; $p < 0.001$), identifying a subset with significantly elevated event rates. This finding has important implications for patient engagement. Consistent with prior evidence that AI-supported clinical tools can enhance medication adherence,[40] the delivery of such precise risk information, specifically by isolating the 'highest risk' individuals within the heterogeneous high-risk group, offers a robust strategy to resolve clinical hesitancy. By validating the need for intervention with objective data, this approach helps both patients and clinicians recognize the urgency of initiating or intensifying cholesterol-lowering therapy.

Mechanistically, Dr. Noon CVD model demonstrated robust performance in these SCORE2 high risk individuals, where hypertension and metabolic comorbidities are prevalent. In an independent validation, Dr. Noon CVD captures chronic vascular burden in conditions like hypertensive retinopathy and retinal vein occlusion, whereas conventional calculators often fail to distinguish these high-risk phenotypes.[19,23] This confirms the model's sensitivity to arteriolar remodeling driven by hemodynamic stress. Thus, the attenuation in low-risk individuals in this study reflects the absence of detectable arteriolar pathology rather than algorithmic failure, while the high-risk results validate the model's clinical utility in identifying overt microvascular disease.

We acknowledge several limitations of our study. Several limitations should be acknowledged. First, this study used data from the UKBB, a well-characterized but predominantly White ethnicity cohort, which may limit generalizability to other ethnicities or healthcare settings. Retrospective, observational design also precludes causal inference, and residual confounding from unmeasured factors such as socioeconomic status, lifestyle, or medication adherence cannot be excluded.

Second, several aspects of data ascertainment and exposure definition may introduce bias. CVD events were identified from linked hospital and mortality registries rather than adjudicated review, although prior validations of the UKBB event coding support its accuracy.[41] Participants taking cholesterol-lowering medication were excluded according to self-reported questionnaire data, not prescription records, raising the possibility of misclassification due to underreporting or recall error. Moreover, all measurements including retinal images, laboratory variables, and comorbidities were obtained at a single baseline time point, preventing assessment of interval changes that might affect risk estimates. Furthermore, this exclusion criterion naturally resulted in a paucity of participants classified as 'very-high risk' by SCORE2 (0.3%) and those with established diabetes (1.3%), as these individuals are typically prioritized for pharmacological treatment under current guidelines. Consequently, the statistical power to evaluate model performance specifically within these highest-risk or diabetic subgroups was limited.

Third, limitations related to the modeling approach should be considered. The Dr. Noon CVD algorithm was developed using retinal images from multiple camera systems, whereas the UKBB used a single device (Topcon 3D OCT-1000 Mark II) not included in model training. Although this strengthens external validity, device-specific imaging characteristics could influence performance. In addition, Dr. Noon CVD was designed and authorized as a categorical, three-tier device classifier, conceptually distinct from population-based continuous calculators such as SCORE2. Therefore, direct calibration or decision-curve comparisons were not performed, as these would extend beyond the model’s approved regulatory and clinical framework.

Fourth, a potential limitation is the mismatch in risk horizons between Dr. Noon CVD (5-year category-based stratification) and SCORE2 (10-year risk categories), which may introduce conceptual discordance when comparing or integrating categorical risk tiers. Although our findings were consistent across both 5- and 10-year outcomes, differences in the underlying time horizons could affect the interpretability of cross-tool reclassification and subgroup comparisons.

Finally, Dr. Noon CVD cutoffs were applied as approved in the Korean regulatory framework to examine external validity. The 5-year incidence gradients confirmed that original thresholds preserved discriminative value in this UK cohort; however, they were not recalibrated to local event rates. An exploratory "very-high" tier showed statistically significant separation (HR 1.77; 95% CI 1.29–2.42) but requires confirmation in independent populations. As this was an observational study, findings should be validated prospectively before informing treatment decisions.

In conclusion, in this large UK Biobank cohort of individuals with dyslipidemia not receiving cholesterol-lowering therapy, an AI-derived retinal CVD risk categories demonstrated consistent prognostic performance over both 5- and 10-year horizons, with discrimination that was independent of established clinical risk factors. Associations remained significant after adjustment for conventional, metabolic, and renal variables, suggesting that retinal imaging-derived biomarkers capture vascular risk information beyond routine clinical indices. The model also provided incremental value beyond SCORE2, particularly by further stratifying individuals classified at high risk, supporting its potential role as a non-invasive complement to guideline-based prevention strategies. These findings might support the clinical utility of AI-derived retinal CVD risk assessment and warrant prospective validation in more diverse populations.

Methods

Study design and population

Clinical and retinal imaging data were obtained from the UKBB, a nationwide prospective population-based cohort.[24] The full study protocol is accessible online.[25] Baseline data were collected during the initial assessment visit (2006–2010), with follow-up extending to February 2021. For this analysis, we specifically included treatment-naïve individuals with dyslipidemia who were not receiving cholesterol-lowering therapy. Dyslipidemia was defined by self-report, relevant ICD-9/10 codes, use of cholesterol-lowering agents, or laboratory criteria (definitions in **Table S8**) from the UKBB. Among 73,278 participants with analyzable fundus images and valid Dr. Noon CVD scores (**Figure S2** and **Table S9**), we additionally provide age- and sex-specific descriptive distributions of the score for all participants with retinal photography (**Figure S3**). These descriptive materials are distinct from the analytic cohort, which was restricted to ages 40–69 years with further exclusions detailed below.

Participants using cholesterol-lowering medications at baseline were excluded to ensure a treatment-naïve study population. Eligible participants had baseline non-mydriatic retinal photographs and sufficient data to compute both Dr. Noon CVD and SCORE2. We excluded individuals outside the age range of 40–69 years, with ungradable retinal images (AI-derived quality score < 0.2), prior CVD disease at baseline (ICD-9/10, OPCS-4, or self-report; **Table S8**), or missing key clinical variables (age, sex, smoking status, current status of diabetes or dyslipidemia, systolic and diastolic blood pressure, triglycerides, total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], eGFR, and BMI).

Retinal photographs were obtained at the UKBB assessment centers between December 2009 and July 2010 using the Topcon 3D OCT-1000 Mark II fundus camera (Topcon Corporation, Tokyo, Japan; 2048×1536 resolution; 45° field of view).[24] Cameras used to develop Dr. Noon CVD algorithm differed from those in this study which included AFP-210 (NIDEK Corporation, Aichi, Japan), TRC-NW8 (Topcon Corporation), and Nonmyd A-D (Kowa Co. Ltd., Shizuoka, Japan); the Topcon 3D OCT-1000 Mark II was not used for model training.[17]

Clinical and laboratory data

Demographic and clinical variables included age, sex, comorbidities, BMI, blood pressure, smoking status, and laboratory results (TC, HDL-C, triglycerides, LDL-C, and eGFR). Age was categorized by decade (40–49, 50–59, and 60–69 years). Blood pressure was measured twice after a 10-minute rest, and the mean value was recorded according to the UK Biobank assessment protocol. Hypertension and diabetes were defined by self-report, ICD-9/10 diagnostic codes, or standard laboratory/measurement criteria (**Table S8**). eGFR was calculated using the CKD-EPI equation and dichotomized as < 60 versus ≥ 60mL/min/1.73m^2.[26] BMI was classified as < 30 versus ≥ 30kg/m^2. Smoking status was defined as current or noncurrent (former smokers included as noncurrent).

Cardiovascular risk scores

Dr. Noon CVD is an AI-based DL model that estimates 5-year CVD risk from bilateral non-mydriatic fundus photographs. A convolutional neural network trained on retinal images linked to CAC scores produces a 0–100 numeric value representing CAC probability.[17,18] Participants were classified into predefined risk groups based on AI-derived CAC probability values, defined as low risk for scores < 31 points, moderate risk for scores from 31 to < 41 points, and high risk for scores ≥ 41 points, based on predicted 5-year risk (**Figure S4**).[17,18] For the exploratory analysis using a four-group classification, the high-risk group was further stratified, with a 'very-high risk' category defined as Dr. Noon CVD scores ≥ 51 points.

SCORE2 is the ESC model for estimating the 10-year risk of first-onset atherosclerotic CVD disease, including nonfatal myocardial infarction, nonfatal stroke, and CVD death, in apparently healthy adults. SCORE2 risk was calculated using the *RiskScorescvd* R package, incorporating age, sex, smoking status, SBP, and non-HDL-C.[7] According to the 2021 ESC guideline thresholds, individuals aged 40–49 years were classified as low-moderate ($< 2.5\%$), high (2.5–7.5%), or very-high ($\geq 7.5\%$) risk, and those aged 50–69 years as low-moderate ($< 5\%$), high (5–10%), or very-high ($\geq 10\%$) risk.[6,27]

Cardiovascular outcomes

The primary outcome was incident CVD events, defined identically to the composite used for baseline exclusions and aligned with the endpoint structure of the pivotal trial supporting Korean Ministry of Food and Drug Safety authorization of Dr. Noon CVD.[18] CVD events included fatal or nonfatal coronary heart disease (myocardial infarction, angina, and coronary revascularization), cerebrovascular disease (ischemic or hemorrhagic stroke and transient ischemic attack), and heart failure. Outcomes were evaluated over both 5-year and 10-year follow-up horizons. Events were identified through linked National Health Service hospital admission and death registry records using ICD-9, ICD-10, and OPCS-4 codes, supplemented by self-reported diagnoses (**Table S8**). Participants were censored at the relevant horizon (5 or 10 years), non-CVD death, or loss to follow-up, whichever occurred first. To reduce reverse causation, a 1-year landmark was applied, and analyses were restricted to participants who were alive and event-free 1 year after baseline.

Statistical analysis

Longitudinal associations between Dr. Noon CVD risk categories and incident CVD outcomes were evaluated using Cox proportional hazards models to estimate HRs with 95% CIs. HR trends across ordered categories were tested by modeling risk groups as ordinal variables. Event-free survival was illustrated using unadjusted and multivariable adjusted curves, with between group differences compared by the log-rank test and multivariable Cox regression. All analyses were performed separately for the 5-year and 10-year follow up horizons. Model discrimination was quantified using Harrell's C-index with 2,000 bootstrap replicates. Reclassification performance was evaluated using the continuous NRI, with separate estimates for event and non-event components.[28] Comparable analyses were conducted for the SCORE2 algorithm, and incremental prognostic value was assessed by incorporating Dr. Noon CVD risk categories into SCORE2 based models. All risk scores, including SCORE2 and Dr. Noon CVD, were evaluated as categorical variables for all primary and exploratory analyses.

Four hierarchical Cox models were constructed for Dr. Noon CVD: an *unadjusted model* with no covariates; a *demographic-adjusted model* adjusted for age group (per decade) and sex; a *traditional risk-adjusted model* further including hypertension, diabetes, and smoking status; a *fully-adjusted model* additionally incorporating eGFR (< 60 vs ≥ 60mL/min/1.73m^2) and BMI (≥ 30 vs < 30kg/m^2). Analyses were performed in three analytic sets. The primary analysis evaluated 5- and 10-year associations across all hierarchical adjustment levels, from the demographic-adjusted to the fully-adjusted model. Exploratory analyses re-evaluated the associations using alternative Dr. Noon CVD thresholds (low, moderate, high, and very-high cutoffs) under identical model structures. Stratified analyses were performed across all SCORE2 risk categories (low-to-moderate, high, and very-high risk), applying the fully-adjusted model framework to evaluate the stratification of residual risk.

All analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and two-sided p-values < 0.05 were considered statistically significant.

Declarations

Ethics

UKBB received ethical approval from the North West Multi-Centre Research Ethics Committee.[29] All participants provided informed consent. This secondary analysis was conducted under the UKBB application framework under ID:68428.

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Contributors

DN, THR, and SH conceptualized the study and were responsible for project administration. DN, JS, MJ, ST, SN, THP, TKY, THR, and SH developed the methodology. JS and SN were responsible for data curation. DN, JS, and SN performed the formal analysis. DN, THR, and SH conducted the investigation. THR provided resources. DN and SH were responsible for visualization. DN wrote the original draft. All authors were involved in validation and writing (review and editing). MJ, ST, SN, THP, TKY, THR, AB, SLP, VS, KM, IR, HK, ML, HKK, CJL, HKh, SP, YHL, and SH provided supervision. DN, JS, and SN had direct access to and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and accepted responsibility to submit for publication.

Conflicts of interest

D. Nam, J. Seo, S. Thakur, S. Nusinovici, and T. H. Rim are employees of Mediwhale Inc. T. H. Rim owns stock in Mediwhale Inc. T. K. Yoo and M. Jang have served as consultants for Mediwhale Inc. T. H. Park was formerly an employee of Mediwhale Inc. C. J. Lee and S. Park received stock options from Mediwhale Inc. All other authors declare no competing interests.

Data availability

The data used in this study are available from the UK Biobank (https://www.ukbiobank.ac.uk/) upon application. Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

Code availability

The deep learning algorithm (Dr. Noon CVD) is a proprietary medical device software and is not publicly available. However, the code used for statistical analysis and result generation in this study is available from the corresponding author upon reasonable request.

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Figures

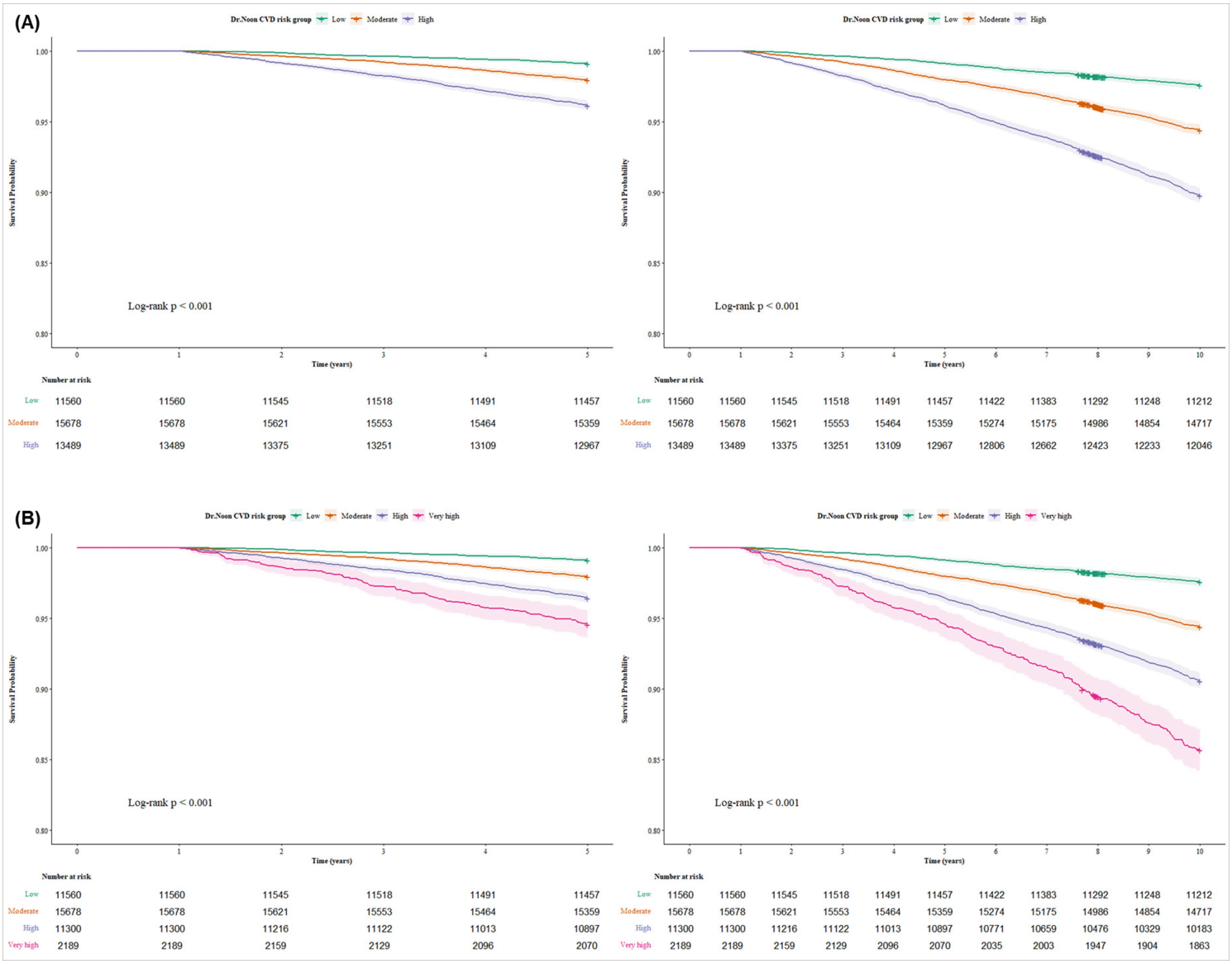


Figure 1

Kaplan-Meier Curves for 5-Year And 10-Year Cardiovascular Event-Free Survival According to Dr. Noon CVD Risk Categories in Participants With Dyslipidemia Without Cholesterol-Lowering Medication: (A) Original and (B) Alternative Risk Classifications.

Curves represent unadjusted Kaplan-Meier estimates of cardiovascular event-free survival across Dr. Noon CVD risk groups. Original classification comprised low, moderate, and high-risk groups. The alternative classification further divided the original high-risk group to define an additional very-high risk category representing the upper extreme of risk. Number at risk is presented below each panel.

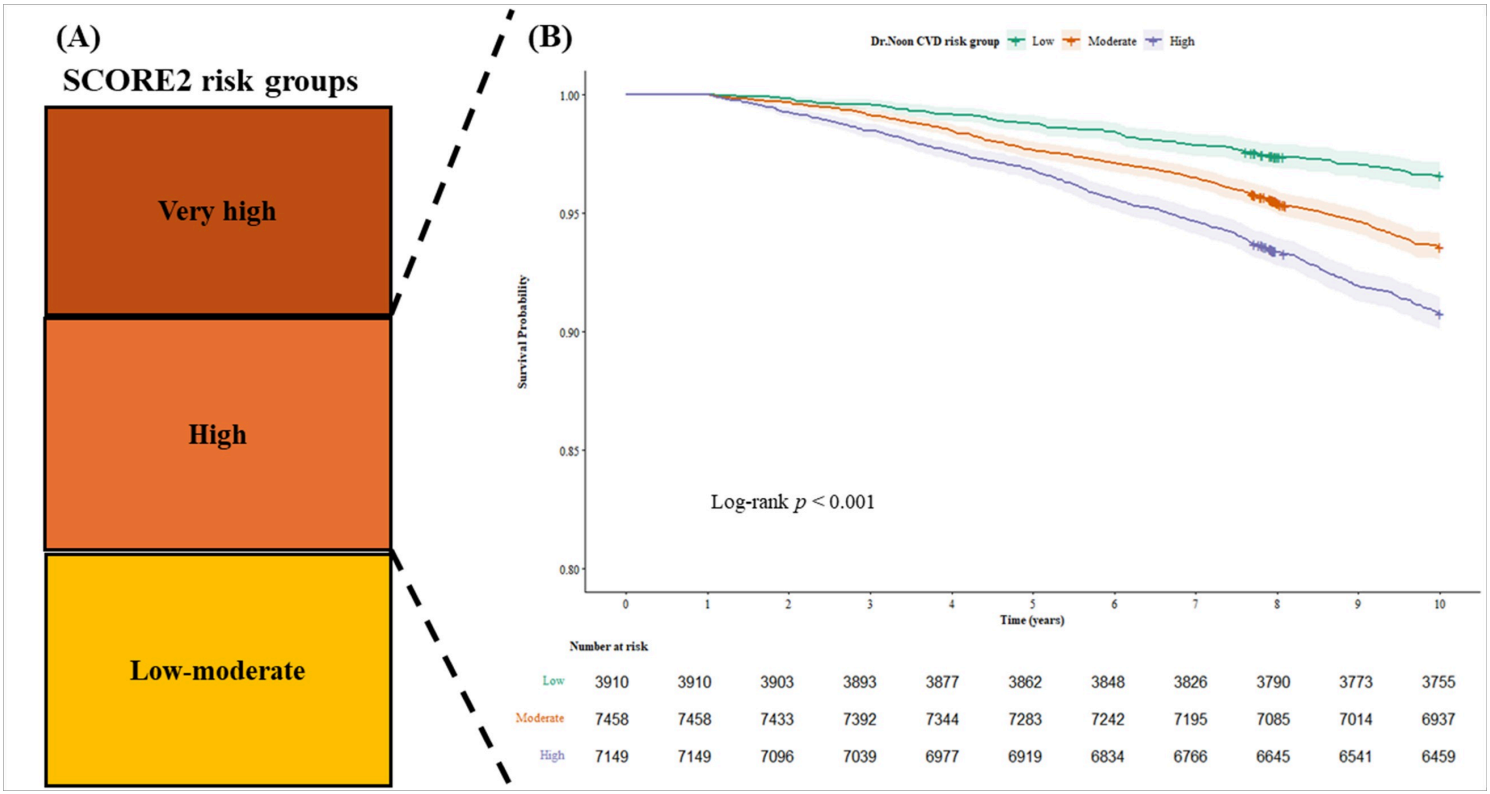


Figure 2

Subgroup Analysis Showing Cardiovascular Risk Stratification by Dr. Noon CVD (Original Risk Categories) Within the SCORE2 High Risk Group.

(A) Schematic representation of SCORE2 risk categories (low-moderate, high, very-high), highlighting the 'High' risk subgroup selected for this analysis. (B) Kaplan-Meier estimates of 10-year cardiovascular event-free survival for participants within this SCORE2 high-risk subgroup, stratified by Dr. Noon CVD original risk classification (low, moderate, high). The number at risk is provided below the graph. SCORE2, Systematic Coronary Risk Evaluation 2.

Supplementary Files

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- SupplementarymaterialsDRNSCORE2Dyslipidemiav5npjdm.docx