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ORIGINAL RESEARCH

Incremental Predictive Value of Deep Learning–Quantified Coronary Atherosclerotic Volume

A SCAPIS Cohort Analysis

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ABSTRACT

BACKGROUND Coronary plaque volume assessed by coronary computed tomography angiography (CTA) may refine risk assessment beyond established risk models.

OBJECTIVES This study aims to evaluate whether deep learning-derived coronary plaque volume from coronary CTA improves prediction beyond established risk models and imaging markers in a general population.

METHODS Participants were randomly selected men and women 50-64 years of age from a population-based cohort, without prior atherosclerotic cardiovascular disease, with available SCORE2 (Systematic Coronary Risk Evaluation 2) data and coronary CTAs of acceptable quality. Total plaque volume (TPV) and noncalcified plaque volume (NCPV) were quantified using automated deep learning software and stratified into 6 categories. Participants were followed for coronary heart disease death or myocardial infarction over a median of 7.8 years.

RESULTS Among 23,314 participants, 287 coronary events occurred. Risk of events increased stepwise with increasing TPV and NCPV, including among participants with coronary artery calcium score = 0 and in those without manually detected atherosclerosis. In Cox regression analyses, adding TPV to a model including SCORE2 and segment involvement score significantly improved model performance (C-statistic: 0.798 vs 0.783; $P = 0.022$) and net reclassification index (0.093; 95% CI: 0.041-0.146). HRs increased with higher TPV categories, reaching 6.36 (95% CI: 3.00-13.52) in the highest category. Adding presence of stenosis ≥50% or any segment with only noncalcified plaque did not materially improve the C-statistic. Replacing TPV with NCPV yielded similar results.

CONCLUSIONS Automated deep learning–quantified TPV improved prediction of first coronary events beyond SCORE2, coronary artery calcium score, and manually derived coronary CTA measurements, and identified even small plaque volumes associated with increased risk in a general population without established atherosclerotic cardiovascular disease. (JACC Cardiovasc Imaging. 2026;■:■–■) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CACS = coronary artery calcium score

CTA = computed tomography angiography

NCPV = noncalcified plaque volume

NRI = net reclassification improvement

SIS = segment involvement score

TPV = total plaque volume

Coronary artery disease remains a leading cause of morbidity and mortality worldwide, underscoring the importance of accurately identifying individuals at elevated risk for ischemic heart disease to guide primary prevention with lifestyle interventions and lipid lowering therapies.[1] Clinical risk equations based on cardiovascular risk factors, such as the SCORE2 (Systematic Coronary Risk Evaluation 2), remain the cornerstone of cardiovascular risk assessment.[2] Cardiovascular imaging with carotid ultrasound, coronary artery calcium score (CACS) or coronary computed tomography angiography (CTA) can be utilized to further refine risk stratification.[3]

Coronary CTA enables noninvasive visualization of coronary plaques, allowing assessment of both degree of stenosis and overall atherosclerotic burden, parameters that have demonstrated prognostic value in population-based settings.[4,5] In a recently published analysis from the SCAPIS cohort, coronary CTA findings mainly driven by atherosclerotic burden quantified as the segment involvement score (SIS), were shown to predict future coronary events beyond recommended risk scores and coronary artery calcium scoring.[5]

Manual quantification of atherosclerotic burden is time-consuming and subject to substantial interobserver variability, limiting its reproducibility and clinical scalability. More recently, dedicated software tools have enabled fully or semiautomated quantification of coronary atherosclerosis, offering more granular and reproducible assessment of atherosclerotic burden and improved risk prediction.[6-11] However, automated volumetric plaque quantification has not yet been evaluated for risk prediction in a large general population without prior diagnosis of atherosclerotic cardiovascular disease (ASCVD).

Whether automated volumetric plaque quantification offers prognostic performance beyond CACS and manually derived SIS, when added to a model with SCORE2 in a general population-based cohort, remains to be established. We therefore investigated whether atherosclerotic burden, measured as deep learning-quantified plaque volume, improves risk prediction compared with SCORE2 combined with either CACS or manually assessed SIS at coronary CTA in a population-based sample of middle-aged individuals without established ASCVD.

METHODS

STUDY DESIGN AND POPULATION. SCAPIS (Swedish CArdioPulmonary bioImage Study) is a nationwide, population-based cohort study, aiming to improve the prediction and prevention of cardiovascular disease and pulmonary disease. Details about the study design and methods have been described previously.[12] In summary, 30,154 randomly selected men and women 50-64 years of age were included and examined between 2013 and 2018 at 6 university hospitals in Sweden, with extensive phenotyping that combined advanced cardiovascular and pulmonary imaging, functional testing, lifestyle data, and biological samples. All participants provided written informed consent when included in the SCAPIS study. The study was conducted in accordance with the Declaration of Helsinki and was approved by SCAPIS (petition 1146) and the Swedish Ethical Review Authority (Dnr 2010; 2010-228-31M, 2021-00549, 2022-00117-02, 2023-02237-01, and 2026-00082-02).

SCAPIS participants were excluded from the present analysis if they had: 1) declined registry follow-up; 2) a prior history of myocardial infarction, coronary artery revascularization, or stroke; 3) no available data to calculate SCORE2; 4) not undergone coronary CTA; 5) unacceptable image quality in proximal segments according to manual readers; 6) unacceptable image quality for deep learning-based plaque quantification; or 7) no available measurement of plaque volume.

CARDIOVASCULAR RISK ASSESSMENT. SCORE2 was calculated using data on sex, age, smoking status, systolic blood pressure, and non-high-density lipoprotein cholesterol. Smoking status was obtained from a health questionnaire. Systolic blood pressure was measured twice in each arm with the participant in the supine position using an automated device (Omron M10-IT, Omron Health Care Company). The mean systolic blood pressure from the arm with the higher mean value was used in the analysis. Total cholesterol and high-density lipoprotein cholesterol were measured in venous blood samples collected after an overnight fast.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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CORONARY CTA ACQUISITION AND MANUAL ASSESSMENT. The acquisition and analysis of cardiac images have been described elsewhere.[12] Imaging was performed using dual-source computed tomography (CT) scanners (Somatom Definition Flash, Siemens Medical Solutions). CACS images were acquired using electrocardiography-gated noncontrast CT at 120 kV. Coronary CTA was performed at 100 kV or 120 kV using 6 different protocols, selected according to heart rate, heart rhythm, and body weight. After image reconstruction, CACS was calculated according to the Agatston method. Coronary CTA images were evaluated in 3 steps using the 18-coronary-segment model. If all segments were healthy, this was noted in the electronic case report form, and no further questions were asked. In postprocessing, all 18 segments were set to "no atherosclerosis" in these participants. If there were any findings, the 11 most proximal segments (ie, S01, S02, S03, S05, S06, S07, S09, S11, S12, S13, and S17) were recorded individually, whereas the electronic case report form allowed findings from only 1 of the remaining distal segments to be recorded. Each segment was classified as having no atherosclerosis, 1%-49% stenosis, or ≥50% stenosis. Segments in which the degree of stenosis could not be assessed because of calcium blooming were classified as having 1%-49% stenosis in this analysis. The presence of calcified and noncalcified atherosclerosis was recorded for each segment. CACS was categorized as 0, 1-100, 101-300, or >300 Agatston Units. From coronary CTA, SIS, defined as the number of segments with any atherosclerosis, was calculated and categorized as 0, 1-2, 3-4, or >4 in accordance with current guidelines.[13]

AUTOMATED PLAQUE QUANTIFICATION. The first author (J.M.) performed and supervised the plaque analysis using a graphics processing unit cluster comprising 8 NVIDIA V100 graphics processing units, with infrastructure provided by the Analytic Imaging Diagnostics Arena (Linköping University, Linköping, Sweden). All image analyses were performed blinded to outcome data and uploaded to the SCAPIS database before outcome data were made available to the research team. Following an initial manual review and exclusion of images of insufficient quality, no further manual corrections or repeat processing were performed.

Total plaque volume (TPV) and noncalcified plaque volume (NCPV) were quantified using fully automated deep learning software (QuantiPlaque), which was trained on coronary CTA datasets acquired across various CT scanners and scanning protocols and subsequently externally validated in 115 SCAPIS participants.[14] The software uses separate models for segmentation of total plaque and calcified plaque, whereas NCPV is derived by subtracting calcified plaque volume from TPV. If the software detected no plaques, TPV and NCPV were classified as 0. Among participants with any detectable plaque, values were categorized into quartiles based on the respective distribution of TPV and NCPV. The fourth quartile was further split into 2 equally sized categories to allow more granular assessment of high plaque burden. Hence there were 6 TPV and NCPV categories in total. As sensitivity analyses, TPV and NCPV were also analyzed as continuous variables after log-transformed as $\log(x + 1)$.

OUTCOME AND FOLLOW-UP. The primary outcome was defined as a composite of first nonfatal myocardial infarction or death from coronary heart disease, consistent with the outcome definition used in a prior SCAPIS publication.[5] Participants were followed from the date of baseline coronary CTA until the first occurrence of the primary outcome, death, loss to follow-up, or end of follow-up, whichever occurred first. We also followed individuals for coronary heart death and nonfatal myocardial infarction as separate endpoints. Clinical events were identified through linkage to the National Patient Register and the National Cause of Death Register maintained by the Swedish Board of Health and Welfare.

STATISTICAL ANALYSIS. Kaplan-Meier curves were generated to visualize cumulative event incidence across SIS, TPV and NCPV. To assess a potential nonlinear relationship with the time-dependent outcome, TPV, NCPV and SIS was modelled as restricted cubic splines in separate Cox models, and the resulting HR was plotted over the continuous variables. Time-to-event analyses examining the association between the exposure and outcome were performed using Cox proportional hazards models, and the results are presented as HRs with 95% CIs. The assumption of proportional hazards was evaluated using Schoenfeld residual plots. Due to strong collinearity between TPV and NCPV, we focused on TPV when modelling the risk of coronary events. Six models were examined:

1. SCORE2 alone as a continuous variable
2. SCORE2 and CACS (categorized)
3. SCORE2 and SIS (categorized)
4. SCORE2 and TPV (categorized)
5. SCORE2, CACS and TPV
6. SCORE2, SIS and TPV

Differences in model performance were assessed using Harrell's C-statistic. As sensitivity analyses, presence of any stenosis ≥50% and any segment with only noncalcified plaques were included in model 6. Models 1 to 6 were also compared including log(CACS+1), SIS and log (TPV+1) as continuous variables. The analyses were prespecified according to the analysis plan. In an additional leave-1-site-out analysis, models with SCORE2 + SIS and SCORE2 + SIS + log(TPV+1) were trained on all but one site and evaluated in the omitted site. To examine the effect of competing risk, we used a Fine-Gray subdistribution hazard regression, with noncoronary heart disease death treated as a competing event. We compared results from model 6 with and without the 115 individuals who had previously been used to validate the artificial intelligence (AI) algorithm. To assess whether the findings could be explained by differences between manual and AI-based assessment of distal segments, we also repeated the analysis after excluding individuals with manual findings in distal segments. Finally, we compared models 1 to 6, replacing TPV with NCPV. To compare discriminatory abilities, we also generated receiver-operating characteristic (ROC) curves after 4 and 8 years, and we compared area under curves with the test of DeLong.

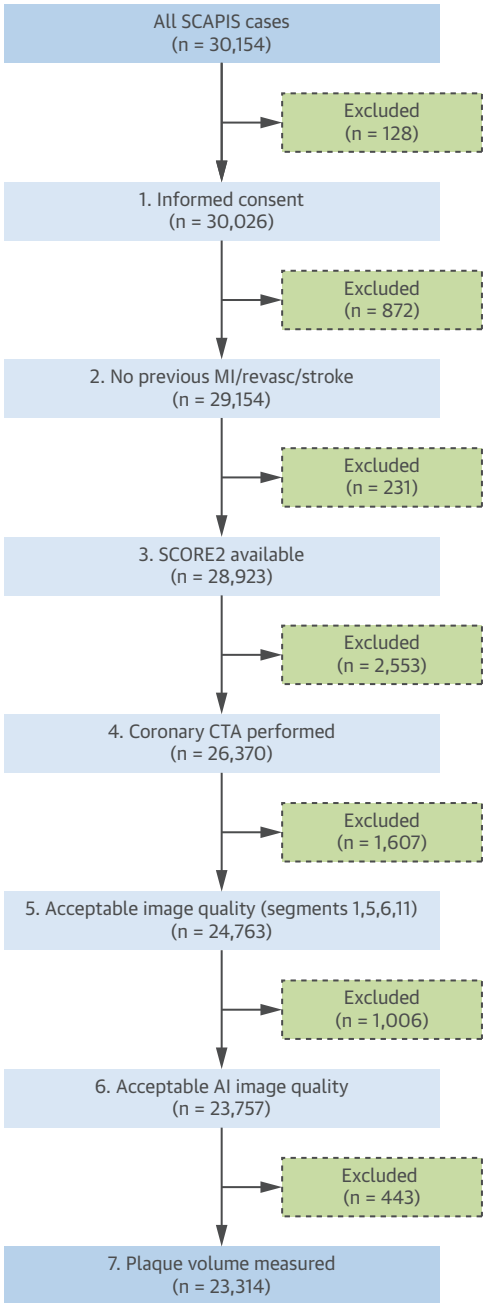
To illustrate the improvement in reclassification when going from a model with SCORE2 and SIS to a model with SCORE2, SIS and TPV, net reclassification improvement (NRI) was calculated. For the NRI analysis, we used a cut-off of <2% to define low risk, in accordance with recent ESC (European Society of Cardiology) guidelines on the management of dyslipidaemias.[3] Given the overall low-risk profile of the study population and a follow-up period of <10 years, we used a cut-off of ≥5% to define high risk, in line with the 2019 ESC cardiovascular disease guideline.[15]

Statistical significance was defined as a 2-sided value of $P < 0.05$. Statistical software used was R, version 4.6.1 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION. After applying the exclusion criteria, 23,314 participants were included in the analyses (Figure 1). Those performing coronary CTA but excluded because of insufficient image quality had

FIGURE 1 Study Flowchart Showing Participant Inclusion and Exclusion



AI = artificial intelligence; CTA = computed tomography angiography; MI = myocardial infarction; revasc = revascularization; SCAPIS = Swedish CArdioPulmonary bio-Image Study; SCORE2 = Systematic Coronary Risk Evaluation 2.

TABLE 1 Baseline Characteristics of the Study Population, Overall and Stratified by Incident Coronary Event Status

		By Event Status	
	Overall (N = 23,314)	Coronary Event (n = 287)	No Coronary Event (n = 23,027)
Age, y	57.3 (53.6-61.1)	59.0 (55.1-62.7)	57.3 (53.6-61.1)
Sex			
Female	11,809 (50.7)	64 (22.3)	11,745 (51.0)
Male	11,505 (49.3)	223 (77.7)	11,282 (49.0)
Education, university degree	10,419 (45.7)	104 (38.0)	10,315 (45.8)
Family history of myocardial infarction	6,297 (28.6)	88 (33.5)	6,209 (28.5)
Body mass index, kg/m^2	26.1 (23.8-29.0)	27.7 (25.1-30.5)	26.1 (23.8-29.0)
Waist circumference, cm	93.0 (85.0-102.0)	99.0 (92.0-107.0)	93.0 (85.0-102.0)
Current smoking	2,839 (12.6)	63 (23.0)	2,776 (12.5)
Treated hyperlipidemia	1,488 (6.6)	20 (7.4)	1,468 (6.6)
Treated hypertension	4,054 (18.0)	64 (23.6)	3,990 (17.9)
Treated diabetes mellitus	655 (2.9)	13 (4.8)	642 (2.9)
Total cholesterol, mmol/L	5.5 (4.8-6.2)	5.7 (5.0-6.5)	5.5 (4.8-6.2)
HDL-cholesterol, mmol/L	1.6 (1.3-1.9)	1.3 (1.1-1.7)	1.6 (1.3-1.9)
Triglycerides, mmol/L	1.0 (0.8-1.5)	1.3 (1.0-2.0)	1.0 (0.8-1.4)
Systolic blood pressure, mm Hg	124.0 (114.0-136.0)	132.0 (120.0-143.0)	124.0 (114.0-136.0)
Diastolic blood pressure, mm Hg	77.0 (70.0-84.0)	80.0 (74.0-87.0)	77.0 (70.0-84.0)
HbA_{1c}, mmol/mol	36.0 (33.0-38.0)	36.0 (33.0-39.0)	36.0 (33.0-38.0)
SCORE2 risk, %	4.1 (2.6-6.1)	6.7 (4.7-9.2)	4.1 (2.6-6.1)
SCORE2 risk category			
Low/moderate (<5%)	14,594 (62.6)	84 (29.3)	14,510 (63.0)
High/very high (≥5%)	8,720 (37.4)	203 (70.7)	8,517 (37.0)
CACS, Agatston Unit	0.0 (0.0-19.0)	52.0 (1.0-235.0)	0.0 (0.0-18.0)
CACS category			
0	13,871 (59.9)	69 (24.2)	13,802 (60.4)
1-100	6,554 (28.3)	101 (35.4)	6,453 (28.2)
101-300	1,613 (7.0)	57 (20.0)	1,556 (6.8)
>300	1,112 (4.8)	58 (20.4)	1,054 (4.6)
SIS			
0	13,504 (57.9)	60 (20.9)	13,444 (58.4)
1-2	5,660 (24.3)	66 (23.0)	5,594 (24.3)
3-4	2,242 (9.6)	53 (18.5)	2,189 (9.5)
>4	1,908 (8.2)	108 (37.6)	1,800 (7.8)
Stenosis ≥50%	1,236 (5.3)	66 (23.0)	1,170 (5.1)
Any noncalcified plaque	1,963 (8.4)	80 (27.9)	1,883 (8.2)
Any plaque (auto)	19,243 (82.5)	277 (96.5)	18,966 (82.4)
TPV, mm^3	21.4 (3.2-70.9)	148.7 (41.9-338.0)	21.0 (3.1-69.0)
TPV category			
0	4,071 (17.5)	10 (3.5)	4,061 (17.6)
Q1 (>0-11.1 mm^3)	4,811 (20.6)	24 (8.4)	4,787 (20.8)
Q2 (>11.1-32.1 mm^3)	4,813 (20.6)	25 (8.7)	4,788 (20.8)
Q3 (>32.1-88.2 mm^3)	4,808 (20.6)	48 (16.7)	4,760 (20.7)
Q4a (>88.2-177.1 mm^3)	2,405 (10.3)	56 (19.5)	2,349 (10.2)
Q4b (>177.1 mm^3)	2,406 (10.3)	124 (43.2)	2,282 (9.9)
Calcified plaque volume, mm^3	0.0 (0.0-4.2)	10.5 (0.0-52.3)	0.0 (0.0-3.9)
NCPV, mm^3	19.9 (3.1-62.3)	124.5 (37.7-274.0)	19.5 (3.0-60.8)

Values are median (Q1-Q3) or n (%).

CACS = coronary artery calcium score; HBA_{1c} = glycosylated hemoglobin; HDL = high density lipoprotein; NCPV = noncalcified plaque volume; SCORE2 = Systematic Coronary Risk Evaluation 2; SIS = segment involvement score; TPV = total plaque volume.

somewhat higher body mass index and waist circumference and more often hypertension and diabetes (Supplemental Table 1). Over a median follow-up of 7.8 years (182,857 person-years), 287 first coronary events occurred, yielding an incidence rate of 1.6 per 1,000 person-years. Participants who experienced an event were older, more often male, and had a higher baseline cardiovascular risk profile

(SCORE2), coronary calcium burden, and coronary atherosclerotic burden than those who remained event-free (**Table 1**).

PLAQUE VOLUME AND CORONARY EVENTS. The distribution of and correlation between TPV, NCPV, and SIS, and their relation to coronary events are illustrated in Supplemental Figure 1 and Supplemental Table 2. The correlation between TPV and NCPV was strong (r = 0.973). The relation between TPV categories, baseline characteristics, CACS and SIS is shown in Supplemental Table 3. The proportion of individuals with TPV >0 but no manually detected plaques (SIS = 0), stratified by site, tube voltage, image quality, and coronary CTA protocol, is shown in Supplemental Table 4. Examples of images in which no plaques were detected by the manual readers but were identified by the AI algorithm are shown in Supplemental Figure 2. The risk of coronary events increased with increasing TPV, NCPV, and SIS (**Figures 2 and 3**, Supplemental Figure 3, Supplemental Figure 4, Supplemental Table 5). Among individuals with CACS = 0 (n = 13,870), a TPV of >0 to 32.1 mm^3 (n = 7,236) was associated with a 2.63-fold increased risk of coronary events (95% CI: 1.17-5.92), whereas a TPV of >32.1 mm^3 (n = 2,859) was associated with a 5.26-fold increased risk (95% CI: 2.29-12.07) (Supplemental Figure 5A). Also in individuals without any manually detected atherosclerosis at coronary CTA (n = 13,504), a TPV of >0 to 32.1 mm^3 (n = 7,069) and >32.1 mm^3 (n = 2,690) was associated with a 2.36 (95% CI: 1.04-5.37) and 4.50 (95% CI: 1.92-10.55) fold increased risk of coronary events, respectively (Supplemental Figure 5B).

INCREMENTAL PREDICTIVE VALUE OF TPV. In Cox regression analyses, model 4 (SCORE2 + TPV) demonstrated significantly better discriminative performance than model 2 (SCORE2 + CACS; P = 0.024), whereas there was a trend toward improved discriminative performance for model 3 (SCORE2 + SIS) compared with model 2 (P = 0.051) (**Table 2**). No significant difference was observed between models 3 and 4 (P = 0.292). Model 5 (SCORE2 + CACS + TPV) showed significantly better discrimination than model 2 (P = 0.006) but not compared with model 4 (P = 0.954). Model 6 (SCORE2 + SIS + TPV) showed significantly better performance than model 3 (SCORE2 + SIS) (P = 0.022), but not than model 4 (SCORE2 + TPV) (P = 0.176). In model 6, both SIS and TPV remained significantly associated with coronary events. In the sensitivity analyses, adding presence of any stenosis ≥50% and any segment with only noncalcified plaques to model 6 did not materially change the C-statistic, and both SIS and TPV remained significantly associated with coronary events (Supplemental Table 6). Stenosis ≥50% was not associated with the outcome, whereas the presence of any segment containing only noncalcified plaques was (HR: 1.66 [95% CI: 1.25-2.19]). When CACS, SIS, and TPV were modelled as continuous variables in models 2 to 6, the overall results were consistent with primary models (Supplemental Table 7). In the leave-1-site-out analysis comparing SCORE2 + SIS with SCORE2 + SIS + log(TPV+1), the estimated difference in the C-statistic was similar to that observed in the main analysis (Supplemental Table 8). For model 6, Fine-Gray competing-risk analyses yielded similar estimates to the primary Cox regression analyses (Supplemental Table 9). Similarly, excluding individuals previously used to validate the AI algorithm (Supplemental Table 10) or those with findings in distal segments (Supplemental Table 11) yielded similar estimates. Finally, substituting NCPV for TPV in models 4-6 did not materially change the results (Supplemental Table 12).

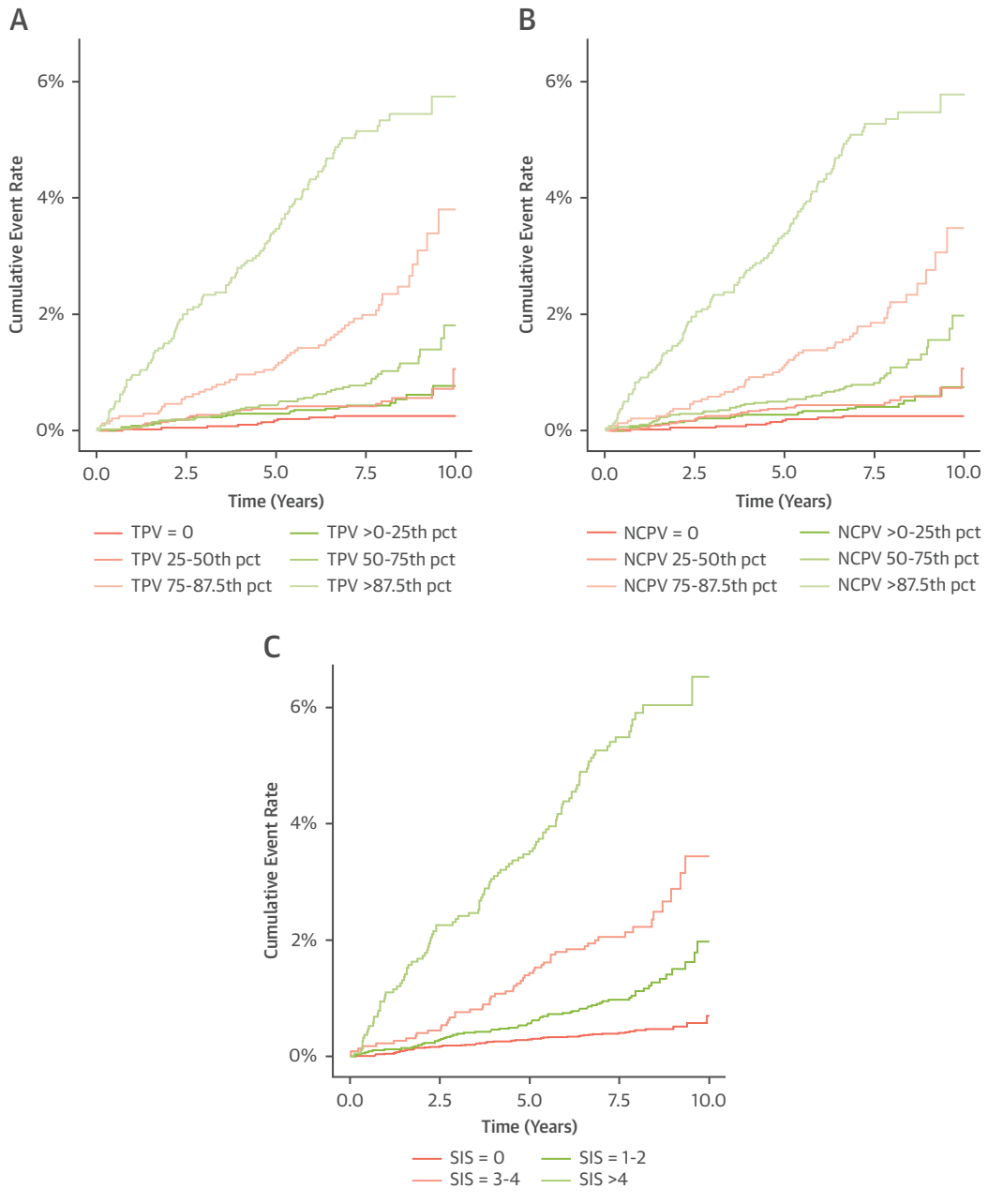
When comparing discriminatory ability using ROC curves at 4 and 8 years, a model including SCORE2 and TPV showed a numerically higher, though not statistically significant, area under the curve compared with a model including SCORE2 and SIS (**Figure 4A**). Adding TPV to a model with SCORE2 and SIS resulted in a significantly larger area under the curve (**Figure 4B**).

RISK RECLASSIFICATION. Adding TPV to a model comprising SCORE2 and SIS improved risk reclassification (NRI: 0.093 [95% CI: 0.041-0.146]) (**Table 3**). Among those who experienced a coronary event, there was a net correct reclassification to higher risk group for 10.2% (95% CI: 5.0%-15.6%) and among event-free participants, there was a net incorrect upward reclassification for 0.9% (95% CI: 0.4%-1.5%).

DISCUSSION

PRINCIPAL FINDINGS. This study yielded several key findings. First, it was feasible to apply a fully automatic deep learning-based software to detect and quantify coronary atherosclerosis on most coronary CTAs acquired from a large general population without established ASCVD. Second, deep learning-based TPV improved risk stratification when added to models including SCORE2 and SIS, and this was also the case when presence of stenosis ≥50% and any segment with only noncalcified atherosclerosis were included in the model. Third, in a model including both SIS and TPV, both variables remained

FIGURE 2 Kaplan-Meier Curves for Incident Coronary Events

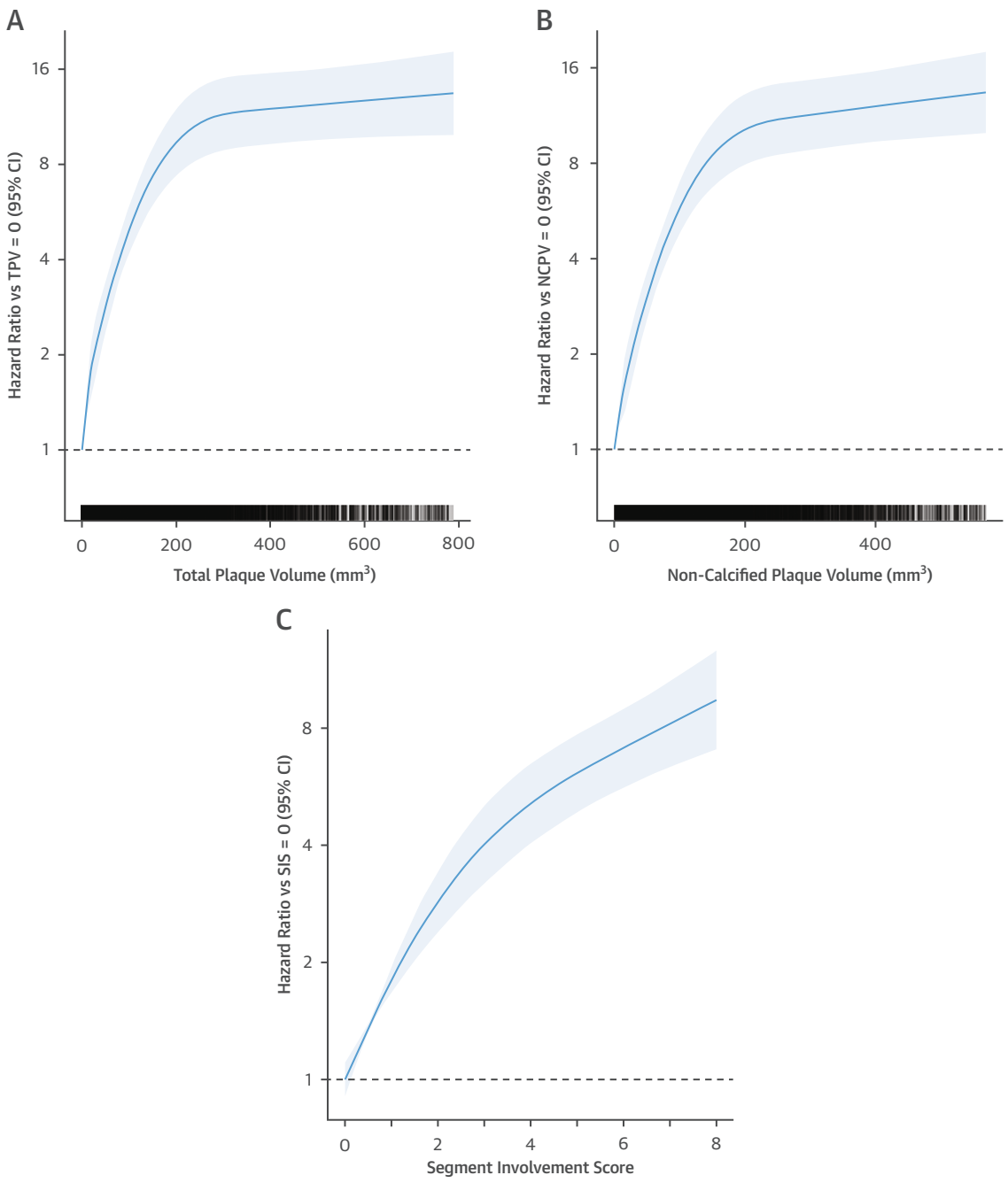


Kaplan-Meier curves for incident coronary events stratified by TPV category (A), NCPV category (B), and SIS category (C).
NCPV = noncalcified plaque volume; SIS = segment involvement score; TPV = total plaque volume.

significantly associated with the outcome, suggesting that they capture partially different aspects of coronary atherosclerotic burden. Fourth, even very small plaque volumes detected by the software, such as >0 to 11 mm^3, tended to be associated with an ~2-fold increase in the risk of coronary events. Fifth, among individuals with a CACS of 0 and those without any manually detected atherosclerosis, the deep learning-based software identified 73% and 72%, respectively, in whom risk increased stepwise with increasing plaque volume.

COMPARISON WITH PREVIOUS STUDIES. Several studies have shown that CACS provides incremental prognostic information beyond established clinical risk

FIGURE 3 **Associations of TPV, NCPV, and SIS With Coronary Event Risk**



Restricted cubic spline showing the association between TPV (A), NCPV (B), and SIS (C) and risk of coronary events. Abbreviations as in Figure 2.

scores, such as the Framingham risk score, the pooled cohort equation, and SCORE, in primary prevention in general populations.[16-20] Recently, a study from the SCAPIS cohort reported that coronary CTA-derived data improved discrimination for coronary events when added to a model including the pooled cohort equation (or SCORE2) and CACS.[5] The discriminatory ability of the coronary CTA data was primarily driven by SIS. In the final model, stenosis ≥50% was not significantly associated with

coronary events, and only 8.3% of the population had any segment containing exclusively noncalcified atherosclerosis on visual assessment.

INCREMENTAL VALUE OF AUTOMATED PLAQUE QUANTIFICATION. In the present study, we showed that TPV quantified by a deep-learning algorithm significantly improved discriminative performance when added to a model including SCORE2 and SIS, with a 2.6-fold higher risk in individuals with TPV 32.1-88.2 mm^3 and a 4.4- to 6.4-fold higher risk in those with higher TPV values. Further addition of stenosis ≥50% and the presence of any segment containing exclusively noncalcified atherosclerosis did not alter the association between TPV and outcome and resulted in almost no change in the C-statistic. Any segment containing exclusively noncalcified atherosclerosis was, however, significantly associated with outcome indicating that presence of noncalcified plaques does add value in addition to plaque volume. When the addition of TPV to SCORE2 and SIS was tested in ROC analysis at 4 years and 8 years of follow-up, the results were in line with the comparison of the C-statistic of the Cox regression models.

Previous studies have demonstrated an incremental prognostic value of quantitative measurements of plaque volumes compared with surrogate markers of atherosclerotic burden, such as CACS and SIS.[8,11,21,22] These studies have been performed in smaller clinical cohorts of patients with suspected or confirmed coronary artery disease and in many cases used relatively time-consuming semiautomatic methods. In this study, we used a fully automated method without manual adjustments in a large sample from a general population without prior diagnosis of ASCVD. A recent study evaluating the predictive value of TPV in the SCOT-HEART (Scottish Computed Tomography of the Heart) cohort found lower HRs in groups with corresponding atherosclerotic burden compared to the present study, possibly reflecting that the SCOT-HEART cohort consists of symptomatic patients with higher baseline risk.[23]

In sensitivity analyses, replacing TPV with NCPV in the models did not materially change the HRs or C-statistic. These findings are consistent with those of previous studies,[6,9] although some studies have reported NCPV to be a slightly stronger predictor of outcomes.[7] In the present study, NCPV was derived by subtracting calcified plaque volume from TPV, whereas other studies have estimated NCPV directly. Model 4 (SCORE2 + TPV) was not significantly better than model 3 (SCORE2 + SIS), and both TPV and SIS were independently associated with coronary events when included in the same model. These results may suggest that both the area and the thickness of atherosclerosis confer independent risk that is not fully captured by a summary measure of plaque volume.

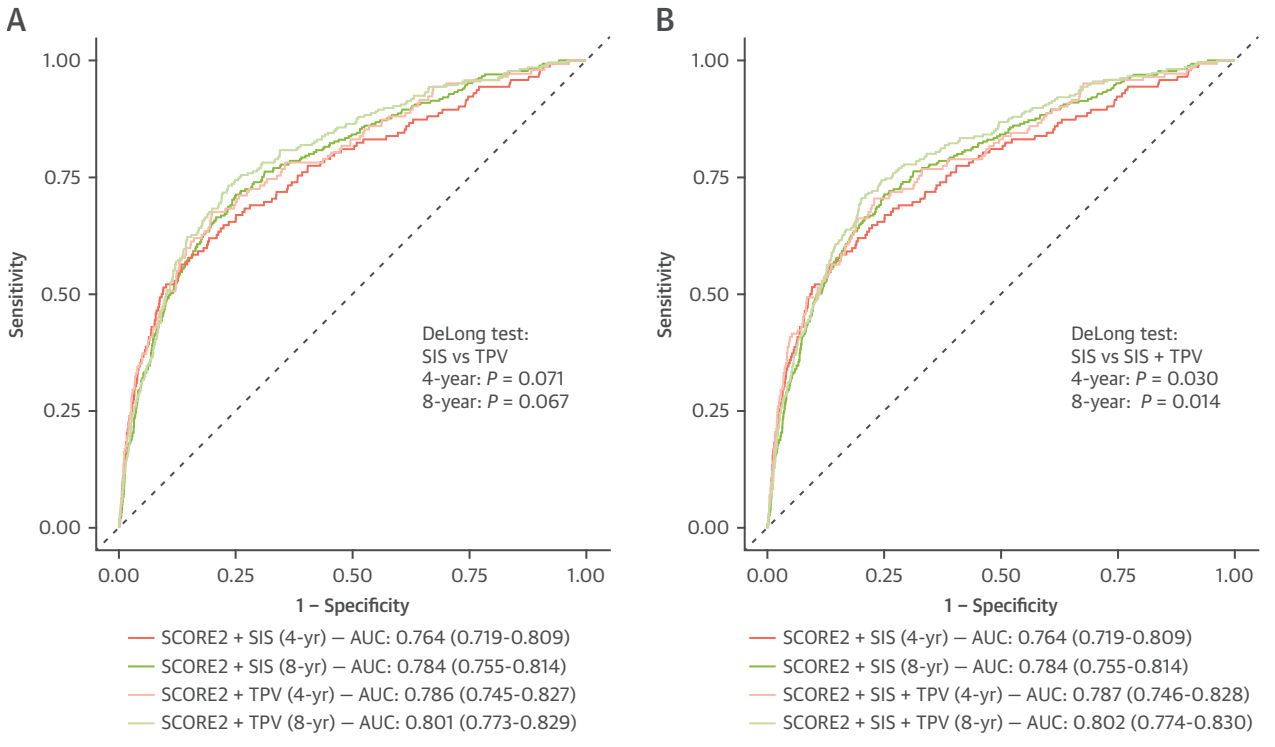
TABLE 2 HRs (95% CI) from SCORE2-Adjusted Cox Models With Categorical Coronary CTA Predictors (SIS Categories, TPV Categories, Stenosis ≥50%, Any Noncalcified Plaque) and CACS-Based Models

	HR (95% CI)	C-Statistic (95% CI)
Model 1		0.734 (0.705-0.763)
SCORE2	1.21 (1.19-1.24)	
Model 2		0.772 (0.743-0.801)
SCORE2	1.16 (1.13-1.20)	
CACS 1-100	2.38 (1.74-3.26)	
CACS 101-300	4.84 (3.37-6.94)	
CACS >300	6.61 (4.60-9.51)	
Model 3		0.783 (0.754-0.813)
SCORE2	1.15 (1.11-1.18)	
SIS 1-2	2.15 (1.51-3.06)	
SIS 3-4	3.80 (2.60-5.55)	
SIS >4	8.28 (5.92-11.58)	
Model 4		0.793 (0.765-0.821)
SCORE2	1.15 (1.11-1.18)	
TPV Q1 (>0-11.1 mm^3)	1.95 (0.93-4.08)	
TPV Q2 (>11.1-32.1 mm^3)	1.94 (0.93-4.03)	
TPV Q3 (>32.1-88.2 mm^3)	3.37 (1.70-6.66)	
TPV Q4a (>88.2-177.1 mm^3)	6.92 (3.51-13.62)	
TPV Q4b (>177.1 mm^3)	13.49 (7.01-25.95)	
Model 5		0.792 (0.763-0.820)
SCORE2	1.14 (1.10-1.18)	
CACS 1-100	1.45 (1.02-2.06)	
CACS 101-300	1.34 (0.85-2.13)	
CACS >300	1.39 (0.84-2.30)	
TPV Q1 (>0-11.1 mm^3)	1.87 (0.90-3.93)	
TPV Q2 (>11.1-32.1 mm^3)	1.74 (0.83-3.65)	
TPV Q3 (>32.1-88.2 mm^3)	2.82 (1.39-5.72)	
TPV Q4a (>88.2-177.1 mm^3)	5.49 (2.67-11.31)	
TPV Q4b (>177.1 mm^3)	10.41 (4.94-21.96)	
Model 6		0.798 (0.769-0.826)
SCORE2	1.13 (1.10-1.17)	
SIS 1-2	1.51 (1.03-2.22)	
SIS 3-4	1.73 (1.09-2.74)	
SIS >4	2.81 (1.75-4.52)	
TPV Q1 (>0-11.1 mm^3)	1.86 (0.89-3.89)	
TPV Q2 (>11.1-32.1 mm^3)	1.69 (0.80-3.55)	
TPV Q3 (>32.1-88.2 mm^3)	2.60 (1.27-5.29)	
TPV Q4a (>88.2-177.1 mm^3)	4.43 (2.13-9.24)	
TPV Q4b (>177.1 mm^3)	6.36 (3.00-13.52)	

Model comparisons: model 2 vs 1: $P < 0.001$; model 3 vs 2: $P = 0.051$; model 4 vs 2: $P = 0.024$; model 4 vs 3: $P = 0.292$; model 5 vs 2: $P = 0.006$; model 5 vs 4: $P = 0.954$; model 6 vs 3: $P = 0.022$; model 6 vs 4: $P = 0.176$.
CTA = computed tomography angiography; other abbreviations as in Table 1.

CLINICAL IMPLICATIONS. Notably, in this low-risk population, with an incidence rate of 1.6 per 1,000 person-years, the automated deep-learning algorithm classified only 17.5% of individuals as free of

FIGURE 4 **Discrimination of Risk Models Including SIS and TPV**



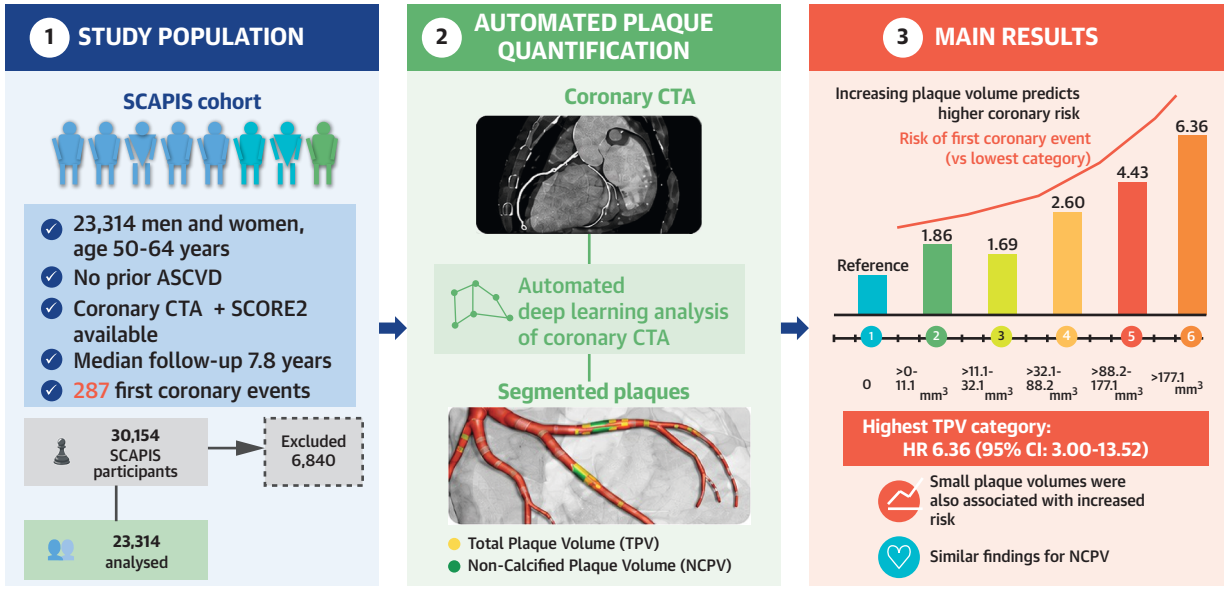
Receiver-operating characteristic (ROC) curves comparing discrimination of models including SCORE2 and SIS vs SCORE2 and TPV (A) and SCORE2 and SIS vs SCORE2, SIS and TPV (B), at 4 and 8 years of follow-up. Abbreviations as in Figures 1 and 2.

detectable atherosclerosis, compared with 57.9% by manual assessment and 59.9% by CACS-based classification. This is consistent with findings from the Miami Heart Study, in which 88.9% of cardiovascularly healthy men and women 40-65 years of age had detectable plaques when AI-supported software was used.[24] Our algorithm detected very small plaque volumes (>0-11 mm^3) that tended nonetheless to be associated with an increased risk of future coronary events, indicating that these findings may reflect true atherosclerosis rather than overestimation due to technical reasons. Furthermore, even among individuals with CACS = 0 and among those without any manually detected atherosclerosis at coronary CTA, who are generally considered to be at very low risk, the algorithm identified a subgroup at comparatively higher risk. These findings suggest that automated plaque quantification can improve risk stratification beyond CACS and manually read coronary CTA alone, including individuals traditionally regarded as being at very low risk. These findings require confirmation in future studies, and clinically meaningful thresholds need to be established.

Although coronary CTA with subsequent automated detection and quantification of plaque volume may improve early detection of coronary atherosclerosis and risk stratification beyond conventional risk scores, with or without CACS, these methods are resource-intensive and entail higher radiation exposure as well as the need for contrast administration. Moreover, although the differences were statistically significant, the incremental improvement in risk stratification was modest both when coronary CTA findings were compared with CACS[5] and when TPV was compared with SIS in the present study, and the clinical significance of these improvements remains uncertain. Randomized studies are therefore needed to evaluate the clinical impact and cost-effectiveness of implementing these methods in the general population.

STUDY LIMITATIONS. The analysis was based on an observational, population-based cohort and is, therefore, subject to residual confounding despite adjustment for baseline cardiovascular risk using SCORE2. However, the primary objective was to

CENTRAL ILLUSTRATION **Automated Coronary Plaque Quantification and Prediction of Coronary Events**



Automated deep learning-derived coronary plaque volume from coronary CTA improves prediction of first coronary events beyond established risk models, CACS, and manual coronary CTA measures in the general population.

Malmqvist J, et al. JACC Cardiovasc Imaging. 2026;■(■):■-■.

ASCVD = atherosclerotic cardiovascular disease; CACS = coronary artery calcium score; CTA = computed tomography angiography; NCPV = noncalcified plaque volume; SCAPIS = Swedish CArdioPulmonary bioImage Study; SCORE2 = Systematic Coronary Risk Evaluation 2; TPV = total plaque volume.

TABLE 3 **Classification of Risk of Coronary Events, Comparing a Model With SCORE2 and SIS (Model 3) and a Model With SCORE2, SIS and TPV (Model 6)**

	Estimate (95% CI)
Net reclassification index	0.093 (0.041-0.146)
Net correct reclassification in those with events, %	10.2 (5.0-15.6)
Net correct reclassification in those without events, %	−0.9 (−1.5 to −0.4)

	Model 6 Categories				
Model 3 Categories	**0-2%**	**2-5%**	**>5%**	**Total**	**% Reclassified**
Events					
0-2%	91	24	0	115	20.9
2-5%	8	49	18	75	34.7
>5%	0	7	68	75	9.3
Total	99	80	86	265	
Nonevents					
0-2%	8,030	297	0	8,327	3.6
2-5%	251	684	121	1,056	35.2
>5%	2	74	333	409	18.6
Total	8,283	1,055	454	9,792	

Abbreviations as in Table 1.

compare prediction models rather than to draw causal inferences. Although the cohort was large, the absolute number of first coronary events was relatively low (287 events among 23,314 participants), potentially limiting statistical power to detect modest differences in discrimination between models. The study population consisted of randomly selected Swedish men and women 50-64 years of age and the findings may therefore not be directly generalizable to other age groups or populations with different ethnic or clinical characteristics. Nevertheless, given that the distribution of cardiovascular risk factors in Sweden is similar to that in many developed countries within and outside Europe, the findings are likely generalizable to comparable populations. The analyses were restricted to participants with acceptable coronary CTA image quality for both manual SIS assessment and deep learning-based plaque quantification and may not be generalizable beyond this population. Manual readers could only record plaque findings from 1 distal segment, whereas the software analyzed the entire coronary tree. However, in a sensitivity analysis excluding individuals with distal findings, the estimates from the main analyses remained largely unchanged, suggesting that differences in the assessment of distal segments do not explain the main findings. As expected, median plaque volumes were lower in this study than in studies including clinical populations[6,8,20,23] but were also lower than in a study of healthy individuals with a similar age distribution.[24] This may indicate that TPV thresholds derived using QuantiPlaque are not directly generalizable to other software platforms. The coronary CTA results obtained at baseline were not withheld from clinicians, which may have contributed to early revascularizations and influenced the prognostic value of the findings. However, in a previous study, excluding participants who underwent early revascularization did not affect the results.[5] Finally, we lack information about other measures of coronary atherosclerosis, such as severity of stenosis beyond ≥50%, low-attenuation plaque volume, plaque burden (defined as plaque volume relative to vessel volume), or detailed morphological features of high-risk plaques. Whether these measures could further improve risk stratification in this population warrants further studies.

CONCLUSIONS

In a general middle-aged population, TPV, quantified using a deep-learning algorithm, improved prediction of first coronary events beyond SCORE2 alone and beyond CACS in models including SCORE2, and most importantly, provided incremental predictive value beyond a model including SCORE2 and SIS, resulting in improved net reclassification. The algorithm could also identify small plaque volumes associated with an increased risk of coronary events (Central Illustration).

DATA AVAILABILITY The data sets supporting the conclusions of this paper are available from SCAPIS upon reasonable request.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a middle-aged population without established ASCVD, fully automated deep learning-based quantification of total coronary plaque volume was feasible at scale, provided prognostic information beyond conventional risk scores, CACS, and manually assessed coronary CTA, and identified individuals at increased coronary risk despite CACS = 0 or no visually detected coronary atherosclerosis.

TRANSLATIONAL OUTLOOK: Standardization across software platforms, validation of clinically meaningful plaque-volume thresholds, and randomized studies evaluating effects on preventive treatment, clinical outcomes, and cost-effectiveness are warranted.

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KEY WORDS coronary computed tomography angiography, risk prediction, SCAPIS, SCORE2, segment involvement score, total plaque volume

APPENDIX For supplemental figures and tables, please see the online version of this paper.