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Prediction of asymptomatic carotid artery stenosis in the general population: identification of high risk groups

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Abstract

Background and purpose—Because of a low prevalence of severe carotid stenosis in the general population screening for presence of asymptomatic carotid artery stenosis (ACAS) is not warranted. Possibly, for certain subgroups screening is worthwhile. The present study aims to develop prediction rules for the presence of ACAS (>50% and >70%).

Methods—Individual participant data from four population-based cohort studies (Malmö Diet and Cancer Study, Tromsø Study, Carotid Atherosclerosis Progression Study, and Cardiovascular Health Study; totaling 23,706 participants) were pooled. Multivariable logistic regression was performed to determine which variables predict presence of ACAS (>50% and >70%). Calibration and discrimination of the models was assessed and bootstrapping was used to correct for overfitting.

Results—Age, sex, history of vascular disease, systolic and diastolic blood pressure, TC/HDL ratio, diabetes mellitus and current smoking were predictors of stenosis (>50% and >70%). The calibration of the model was good confirmed by a non-significant Hosmer and Lemeshow test for moderate (p=0.59) and severe stenosis (p=0.07). The models discriminated well between participants with and without stenosis, with an AUC corrected for over optimism of 0.82 (95%CI 0.80–0.84) for moderate stenosis and of 0.87 (95% CI 0.85–0.90) for severe stenosis. The

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Conflicts of interest/Disclosures

None

regression coefficients of the predictors were converted into a score chart to facilitate practical application.

Conclusions—A clinical prediction rule was developed that allows identification of subgroups with high prevalence of moderate (>50%) ACAS and severe (>70%). When confirmed in comparable cohorts, application of the prediction rule may lead to a reduction in the number needed to screen for ACAS.

Keywords

Asymptomatic carotid artery stenosis; Prediction; Screening

Introduction

Stroke is among the leading causes of morbidity, long-term disability and mortality in both men and women in nearly all high, middle and low income countries.[1;2] As such stroke poses a substantial economic burden in terms of health care and societal costs worldwide.[3]

Stenosis of the internal carotid artery is a major risk factor for stroke. In individuals with symptoms of cerebral ischemia (i.e., transient ischemic attack or a minor disabling stroke) and with a carotid stenosis of 50% or over, high risks of a recurrent event have been reported: the risk of stroke was 21% at 2 weeks after the first TIA or stroke, and 32% at 12 weeks.[4] Treatment of symptomatic carotid stenosis has been well established. In general, symptomatic patients suitable for surgery with more than 70% carotid artery stenosis are recommend to have an carotid endarterectomy.[5]

Asymptomatic carotid artery stenosis (ACAS) is also related to a higher risk of stroke. Older studies among individuals not receiving optimal cardiovascular preventive treatment showed estimates for an annual risk for stroke of approximately 2–4% for patients with severe (>70%) carotid stenosis.[6–9] An observational study reported 10- and 15-year stroke risks being 10% and 17%, respectively.[10] These untreated risk estimates put individuals with an ACAS in the very high risk group based on the ESC/AHA guidelines on cardiovascular disease prevention.[11;12] As such ACAS individuals should receive best medical treatment involving antihypertensive and lipid-lowering drugs in addition to lifestyle advice (dietary measures, weight loss, quitting smoking, restriction alcohol consumption, increase exercise). Indeed, several studies have shown lower incidence rates among those with optimal cardiovascular preventive medications. A more recent study showed stroke risks of around 0.5% per year for 70% to 99% ACAS patients.[13]

Population screening for ACAS has been suggested as a way to reduce the burden of stroke. In earlier days this was based on the notion that revascularisation in combination with preventive therapy would be the most optimal treatment to reduce stroke risk. However, nowadays the lower risk estimates seems to favour a more conservative treatment choice as opposed to revascularisation.[14] And thus screening for ACAS is meant to identify those at high risk of stroke.

This study aims at developing prediction rules for identification of individuals with a high probability of having a moderate (>50%) or severe (>70%) asymptomatic carotid artery stenosis in the general population.

Methods

Study population

We used individual participant data from four observational studies on cardiovascular diseases (Tromsø Study, Malmö Diet and Cancer Study [MDCS], Carotid Atherosclerosis Progression Study [CAPS] and Cardiovascular Health Study [CHS]).[15–19] In brief, the *Tromsø Study* is a population-based prospective study in Tromsø, Norway. All inhabitants aged 55 to 74 years and 5% to 10% samples of other 5-year-age groups aged ≥ 25 years were invited. In total, 6,727 participants (attendance rate 77%) were screened with ultrasound examination of the right carotid artery and valid written informed consent was available in 6,659 participants.[15] In the population-based Malmö Diet and Cancer Study (MDCS), a total of 28 449 participants attended between 1991 and 1996 (attendance rate 41%). A random sample of 6,103 (20%) participants had an ultrasound examination.[16;17] In the *Carotid Atherosclerosis Progression Study* (CAPS), members of a German primary healthcare scheme were invited of whom 6,962 (attendance rate 21%) agreed to take part to be screened with ultrasound examination.[18] The *Cardiovascular Health Study* is a community-based, prospective study of people aged ≥ 65 years including 5,888 participants (attendance rate 57%) who were screened with ultrasound examination.[19] All studies excluded symptomatic patients and obtained information on degree of stenosis and potential determinants thereof.

Baseline characteristics

The following baseline characteristics were recorded in each study: age, sex, presence of diabetes mellitus, history of coronary and/or cerebrovascular disease, and information on medication use. In addition, data on blood pressure, lipid levels, current smoking, waist circumference and body mass index (BMI) were recorded.

Outcomes

Moderate ACAS was defined as ≥50% stenosis and severe ACAS as ≥70% stenosis, measured by Doppler ultrasonography supported by B-mode ultrasound imaging. When both carotid arteries were measured, we used the most severe stenosis grade observed.

Model development

Missing values were imputed with single regression techniques using information from all individuals without missing values on that variable, since deleting subjects with missing values often leads to biased findings and to a loss of statistical power.[20] The grade of stenosis was missing in 0.2% of the participants, predictors were missing for 0.1% to 5.2% of the participants. Restricted cubic spline functions and graphs were used to determine whether continuous variables could be analyzed as linear terms or required a transformation.[21]

For the continuous predictors age, systolic and diastolic blood pressure, and TC/HDL ratio, a linear relationship with outcome was found to be a good approximation after assessment of nonlinearity using restricted cubic splines. All candidate predictors for moderate stenosis were included in a multivariable logistic model and were step by step excluded using the likelihood ratio test with a p-value above 0.20. All analyses were stratified by study.

As most of the predictors to identify individuals with a high probability of ACAS being present, were similar to those used in the Framingham Risk Score (FRS), we additionally compared Number Needed to Screen (NNS) with the FRS.

Model performance

To study the performance of the final prediction model, we assessed its discrimination and calibration. Discrimination is the ability of the model to distinguish between participants with or without moderate (>50%) or severe (>70%) stenosis, and is quantified as the area under the receiver operating characteristic curve (AUC). An AUC ranges from 0.5 (no discrimination) to 1 (perfect discrimination). Calibration refers to the agreement between the predicted probabilities and observed frequencies of stenosis degree, which was tested with the Hosmer-Lemeshow statistic.[22] To create a good overview we selected the same predictors for moderate and severe stenosis.

Model validation

Prediction models derived with multivariable regression analysis are known for overestimated regression coefficients. These results in overestimated predictions when applied in new participants.[22;23] Therefore, we validated our model internally with bootstrapping techniques where in each bootstrap sample the entire modeling process was repeated.[23] This resulted in a shrinkage factor for the regression coefficients.[22] The bootstrap procedure was also used to estimate the AUC corrected for over-optimism. The corrected AUC may be considered as an estimate of discriminative ability expected in future similar participants.

Clinical application

To facilitate practical application of the model, the regression coefficients of the predictors in the model for severe stenosis were converted into points on a score chart. The total points (sum scores) were linked to the risk of the presence of moderate or severe stenosis.

The total points (sum scores) were linked to the risk of the presence of moderate or severe stenosis. Various cut off values were introduced, categorizing patients as having a very low risk, low risk, intermediate risk or high risk (see Table 4). The numbers needed to screen (NNS), sensitivities, specificities and the positive and negative predicted values of these thresholds were calculated. Additionally, we used the European Systematic COronary Risk Evaluation (SCORE) risk chart to estimate the number of individuals at high risk for developing vascular disease (10-year risk of ≥ 20%) and who are recommended antihypertensive and lipid-lowering drugs.[24]

Results

Study population

General characteristics of the study population are presented in Table 1. The mean age was 61 ± 12 years and 46% of the participants were men. Crude differences between studies are a consequence of different inclusion criteria across studies, in particular difference in age range. Overall, fifteen percent of the participants had a history of vascular disease (coronary heart disease and/or stroke). This prevalence of a history of vascular disease varied from 3% to 40% between the cohorts. Overall, 465 (2%) of the 23,706 participants had moderate stenosis and 127 (0.5%) had severe stenosis. The prevalence of severe stenosis among participants without a history of vascular disease 0.3% (95% CI 0.2–0.4%), among participants with a history of coronary heart disease 1.9% (95% CI 1.4–2.4%) and among participants with a history of stroke was 3.5% (95% CI 2.1–4.9%).

Model development

Table 2 presents the results from the multivariable analysis for severe stenosis. Age, sex, history of vascular disease, systolic and diastolic blood pressure, TC/HDL ratio, diabetes mellitus and current smoking were independent predictors of moderate and severe stenosis. The positive relation with systolic pressure in combination with an inverse relation with diastolic pressure in one regression model indicates the relevance of pulse pressure in the relation with risk of stenosis. As the fit of the model was better with systolic and diastolic pressure in the model as compared with pulse pressure alone, we decided to present the current model. The calibration of the model was good confirmed by a non-significant Hosmer and Lemeshow test for moderate stenosis (p=0.585), and for severe stenosis (p=0.071). The models discriminated well between participants with and without stenosis, with an AUC corrected for over optimism of 0.82 (95%CI 0.80–0.84) for moderate stenosis and of 0.87 (95% CI 0.85–0.90) for severe stenosis.

Clinical application

The regression coefficients of the predictors of the final model were converted into a score chart to facilitate practical application (Table 3). As an example how to use this chart, a 65-year-old men, non-smoker, presenting with a SBP of 160, a DBP of 80, with normal lipid levels, no diabetes and no history of vascular disease, will have a sum score of 14 (7+2+0+4+1+0+0+0). This corresponds to a risk of moderate stenosis of 3.1% and a risk of severe stenosis of 0.5% (Figure 1).

Table 4 shows the distribution of participants with and without moderate or severe stenosis across different risk categories. These results are of relevance to indicate the consequences of screening in particular groups. For participants at high stenosis risk (n=7247; 31% of the population), the prevalence of moderate stenosis is estimated to be 4.8% and the number needed to screen is 21. About 68% of the participants in this high-risk category who are initially free of vascular disease have a high cardiovascular risk (regardless of the degree of stenosis) and should receive lifestyle and drug interventions. When using a lower risk threshold for screening means that somewhat more participants with stenosis will be detected but against the expense of screening many more individuals. For example, in

participants at intermediate to high stenosis risk (n=11245; 47% of the population), the prevalence of moderate stenosis is estimated to be 3.6% and the number needed to screen is 28.

When we used the Framingham Risk Score estimate of 10 year risk of 20% or above, the number needed to screen for detection of one ACAS was 64. When a lower Framingham Risk Score cut point was used, e.g. 10 year risk of 7.5% as recently proposed, the number needed to screen was much higher.

Discussion

We developed a prediction model that allows identification of participants that might benefit from screening for asymptomatic carotid artery stenosis. We found that age, sex, TC/HDL ratio, systolic and diastolic blood pressure level, history of vascular disease, diabetes and smoking are strong predictors for the probability of having a moderate and severe ACAS. With the use of our prediction rule groups good be identified in whom the number needed to screen to detect one ACAS is between 21 and 35. When the Framingham risk score was used, with a cut point of a 10 year risk of 20% or above, 64 individuals would be needed to screen to detect one ACAS.

Comparison with existing literature

We did not come across studies that specifically aimed at developing a prediction rule for the presence of ACAS. Etiologic focused studies reported determinants of carotid artery stenosis. These studies suggested that elevated blood pressure, smoking, cholesterol levels, increasing age and male sex were associated with presence of carotid artery stenosis.[15;25;26] These observations are compatible with our findings. Presence of a bruit over the carotid artery has been evaluated as a means to identify individuals at high risk of a carotid stenosis, but was found to be unreliable.[27]

Strengths and limitations

The major strength of this study is the large number of individuals that were included in our population-based cohorts. This gave us the opportunity to present a precise and accurate prediction rule. Using bootstrapping techniques, we demonstrated that the prediction rule was robust. The shrinkage factor was close to 1, suggesting a stable model and the calibration after correction for over optimism also was very good (AUC 0.87 for severe (>70%) stenosis). In addition, not all data were available for each participant. With imputation techniques, we were able to use all participants instead of only complete cases. This results in a prediction rule with increased precision. Although there are differences in the methods of measurement of degree of stenosis between studies we are not concerned about the validity of our prediction model. The Tromsø study measured only the right carotid artery. We believe that this had little effect on the prediction rule. Those with a stenosis are the cases, and in Tromsø some of the cases will be in the ‘reference’ population. As the prevalence of stenosis is rather low, the effect of having some few cases in the much larger reference population will not affect the magnitudes and direction of the risk factor relations. Having only one side does however affect the prevalence of stenosis in the

population. This means that the prevalence of stenosis is underestimated to some extent. Furthermore, the discrimination between presence and absence of ACAS may be affected by the variation in diagnostic criteria. Unfortunately, there is no easy way to reclassify study participants using uniform stenosis criteria.

Clinical implication

Due to the improvement in drug therapy the annual rate of ipsilateral stroke associated with asymptomatic carotid stenosis has fallen from 2–4% to <1% in the last 20 years.[28] Therefore, the balance between benefit and risk for surgery in patients with ACAS has changed. So carotid revascularization as mainly underlying reason for screening for ACAS seems not applicable anymore. Yet, individuals with an ACAS are at very high risk of any future cardiovascular events, and should be considered for best medical treatment following the cardiovascular risk management guidelines and should obtain lifestyle guidance. Our model may help in that respect.

Conclusions

In conclusion, our clinical prediction rule that allows identification of subgroups with relatively high prevalence of moderate (>50%) or severe (>70%) ACAS. When population based screening for ACAS is considered, use of the prediction rule is recommended to identify subgroups in order to reduce the number needed to screen substantially.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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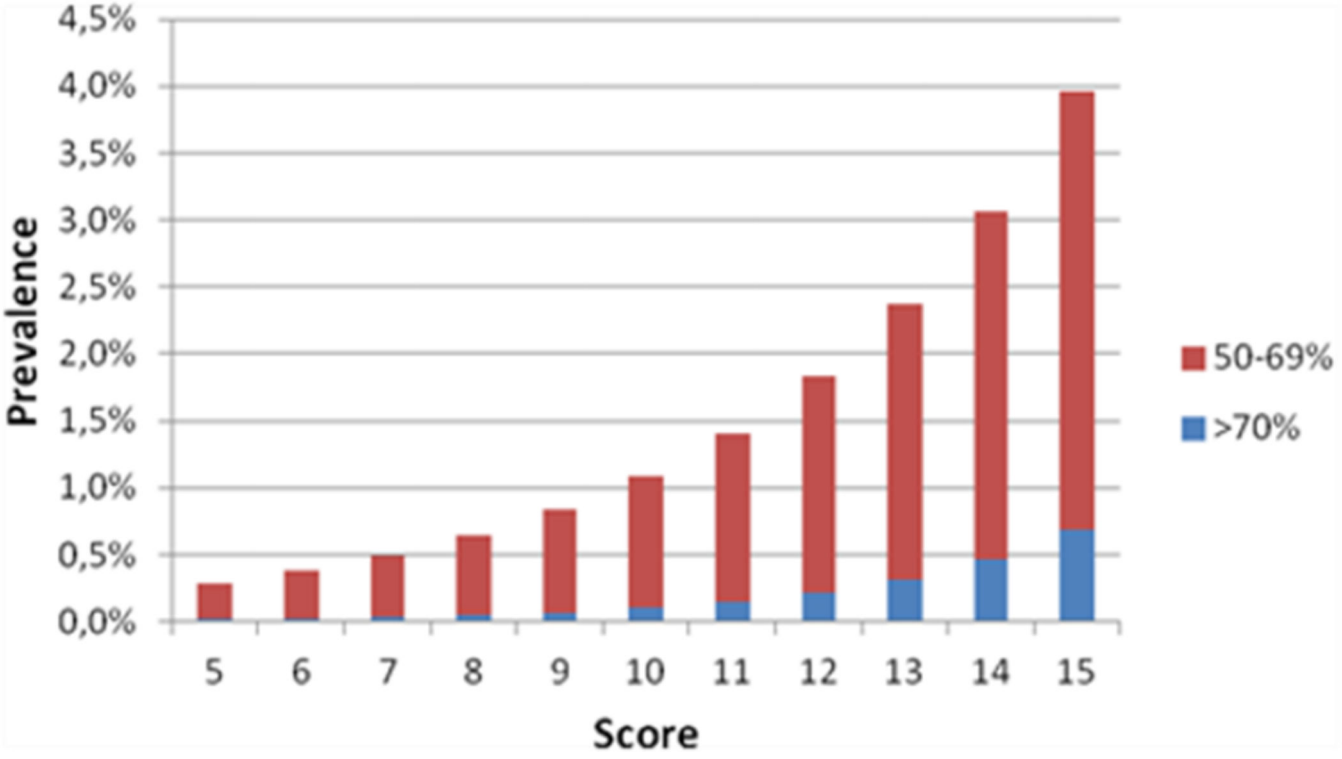

Figure 1.
Predicted probability of stenosis according to score categories.

Table 1

General characteristics of the study population, by cohort.

	Tromsø		MDCS		CAPS		CHS		Total	
No. of participants	6659		6103		5056		5888		23706	
Age (years)	60.2	± 10.2	57.5	± 5.9	50.1	± 13.1	72.8[§]	± 5.6	60.5	± 12.1
Male sex	3298	(49.5%)	2572	(42.1%)	2471	(48.9%)	2495	(42.4%)	10836	(45.7%)
History of vascular disease	954	(14.3%)	167	(2.7%)	155	(3.1%)	2213	(37.6%)	3489	(14.7%)
Coronary heart disease	825	(12.4%)	102	(1.7%)	108	(2.1%)	1997	(33.9%)	3032	(12.8%)
Stroke	182	(2.7%)	69	(1.1%)	52	(1.0%)	349	(5.9%)	652	(2.8%)
Body mass index (kg/m^2)	26.1	± 4.0	25.9	± 4.0	26.6	± 4.1	26.7	± 4.7	26.3	± 4.2
Waist-hip ratio	0.87	± 0.08	0.85	± 0.09	0.95	± 0.11	0.93	± 0.09	0.90	± 0.10
Hypertension[*]	4006	(60.2%)	3891	(63.8%)	1320	(26.1%)	3681	(62.5%)	12898	(54.4%)
Systolic blood pressure (mmHg)	145	± 23	141	± 19	128	± 17	137	± 22	138	± 21
Diastolic blood pressure (mmHg)	83	± 13	87	± 9	77	± 10	71	± 11	80	± 13
Diabetes mellitus[†]	217	(3.3%)	277	(4.5%)	134	(2.7%)	722	(12.3%)	1350	(5.7%)
Current smoking	2118	(31.8%)	1724	(28.2%)	1057	(20.9%)	700	(11.9%)	5599	(23.6%)
Hyperlipidemia[‡]	2518	(37.8%)	2447	(40.1%)	720[//]	(14.2%)	1563	(26.5%)	7248	(30.6%)
TC/HDL ratio	4.7	± 1.6	4.8	± 1.5	3.8	± 1.1	4.2	± 1.3	4.4	± 1.4
Moderate stenosis										
Observed prevalence	1.8%		0.6%		0.8%		4.4%		2.0%	
Expected prevalence[#]	1.9%		1.3%		2.6%		2.1%		2.0%	
Severe stenosis										
Observed prevalence	0.7%		0.1%		0.2%		1.1%		0.5%	
Expected prevalence[#]	0.8%		0.3%		0.8%		0.5%		0.5%	

[*] Hypertension is defined as a systolic blood pressure above 140mmHg or an diastolic blood pressure above 90mmHg.

[†] Diabetes mellitus is defined as a glucose level above 6.9mmol/l or anti diabetic medicine use.

[‡] Hyperlipidemia defined as an TC/HDL ratio above 5mmol/l or statin use.

[§] inclusion criteria: age 65 and older.

[//] classification method: peak systolic velocity ratio method (Tromso), lumen diameter reduction (MDCS), cross sectional area reduction method (CAPS), peak systolic velocity (CHS).

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given the risk factor distribution of the total study population.

Table 2

Multivariable predictors for presence of moderate and severe and stenosis

	Odds ratio (95% confidence interval)*	
Predictors	**Moderate stenosis (>50%)**	**Severe stenosis (>70%)**
Age (per 10 years)	1.8 (1.6–2.1)	2.2 (1.7–2.8)
Male sex	1.5 (1.2–1.8)	2.5 (1.7–3.6)
History of vascular disease	1.9 (1.6–2.3)	2.5 (1.7–3.5)
Systolic blood pressure (per 10 mmHg)	1.3 (1.2–1.4)	1.3 (1.2–1.5)
Diastolic blood pressure (per 10 mmHg)	0.7 (0.6–0.7)	0.7 (0.6–0.8)
TC/HDL ratio (per point)	1.2 (1.1–1.3)	1.2 (1.1–1.4)
Diabetes mellitus	1.3 (1.0–1.8)	1.6 (1.0–2.5)
Current smoking	2.3 (1.8–2.8)	3.0 (2.1–4.4)
Area under the ROC curve†	0.82 (0.80–0.84)	0.87 (0.85–0.90)

TC, TC, total cholesterol; HDL, high-density lipoprotein

*Adjusted for overoptimism (regression coefficients were shrunk by 7% in model for severe stenosis and 2% in model for moderate stenosis).

†Adjusted for optimism with bootstrapping techniques.

Table 3

Stenosis score chart

Characteristic	Value	Stenosis score
Age (years)	< 50	0
	50–59	4
	60–69	7
	70+	9
Sex	male	2
	female	0
History of vascular disease	no	0
	yes	3
Systolic blood pressure (mmHg)	< 125	0
	125–139	2
	140+	4
Diastolic blood pressure (mmHg)	< 75	2
	75–84	1
	85+	0
TCHDL ratio	< 5	0
	5+	1
Diabetes mellitus	no	0
	yes	1
Current smoking	no	0
	yes	3

The stenosis score ranges from 0 to 25 points. The predicted prevalence of stenosis is defined as $1 / (1+e^{-LP})$, where LP refers to the linear predictor in a logistic regression model. Two LPs were defined as follows:

$$LP_{\text{severe stenosis}} = -10.74 + 0.384 \times \text{sum score};$$

$$LP_{\text{moderate stenosis}} = -7.16 + 0.265 \times \text{sum score}.$$

Using these models, the mean predicted probability of severe stenosis was 0.5% and the mean predicted probability of moderate stenosis was 2.0%. We estimated the intercepts for other prevalence figures, so when the model is applied in a population with other prevalence rates of stenosis, the intercept of the model can be adjusted (Webtable 1). When the prevalence of stenosis is lower, the intercept needs to be more negative, leading to lower predicted prevalences.

Table 4

Model performance for severe and moderate stenosis

Moderate stenosis

	Prediction score	Total no. of participants	No. of participants with moderate stenosis	prevalence	SE (%)	SP (%)	PPV (%)	NPV (%)	NNS
Very low risk	≤ 9 points	8417	26	0.3%					
Low risk	10–11 points	4044	36	0.9%	94.4%	36.1%	2.9%	99.7%	35
Intermediate risk	12–13 points	3998	57	1.4%	86.7%	53.3%	3.6%	99.5%	28
High risk	≥ 14 points	7247	346	4.8%	74.4%	70.3%	4.8%	99.3%	21
Total		23706	465	2.0%					

Severe stenosis

	Prediction score	Total no. of participants	No. of participants with severe stenosis	prevalence	SE (%)	SP (%)	PPV (%)	NPV (%)	NNS
Very low risk	≤ 9 points	8417	2	0.0%					
Low risk	10–11 points	4044	5	0.1%	98.4%	35.7%	0.8%	100.0%	122
Intermediate risk	12–13 points	3998	14	0.4%	94.5%	52.8%	1.1%	99.9%	94
High risk	≥ 14 points	7247	106	1.5%	83.5%	69.7%	1.5%	99.9%	68
Total		23706	127	0.5%					

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; NNS, number needed to screen.