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ORIGINAL RESEARCH

Validation of Risk Prediction Models to Detect Asymptomatic Carotid Stenosis

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BACKGROUND: Significant asymptomatic carotid stenosis (ACS) is associated with higher risk of strokes. While the prevalence of moderate and severe ACS is low in the general population, prediction models may allow identification of individuals at increased risk, thereby enabling targeted screening. We identified established prediction models for ACS and externally validated them in a large screening population.

METHODS AND RESULTS: Prediction models for prevalent cases with ≥50% ACS were identified in a systematic review (975 studies reviewed and 6 prediction models identified [3 for moderate and 3 for severe ACS]) and then validated using data from 596 469 individuals who attended commercial vascular screening clinics in the United States and United Kingdom. We assessed discrimination and calibration. In the validation cohort, 11 178 (1.87%) participants had ≥50% ACS and 2033 (0.34%) had ≥70% ACS. The best model included age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, vascular and cerebrovascular disease, measured blood pressure, and blood lipids. The area under the receiver operating characteristic curve for this model was 0.75 (95% CI, 0.74–0.75) for ≥50% ACS and 0.78 (95% CI, 0.77–0.79) for ≥70% ACS. The prevalence of ≥50% ACS in the highest decile of risk was 6.51%, and 1.42% for ≥70% ACS. Targeted screening of the 10% highest risk identified 35% of cases with ≥50% ACS and 42% of cases with ≥70% ACS.

CONCLUSIONS: Individuals at high risk of significant ACS can be selected reliably using a prediction model. The best-performing prediction models identified over one third of all cases by targeted screening of individuals in the highest decile of risk only.

Key Words: atherosclerosis ■ carotid artery stenosis ■ external validation ■ ischemic stroke ■ prevention ■ risk prediction model ■ targeted screening

Transient ischemic attack (TIA) or ischemic stroke is the first presentation of cardiovascular disease in about 25% of the cases,[1,2] and 15% to 20% of ischemic stroke cases are associated with extracranial carotid artery stenosis.[3–5] Carotid stenosis is also a predictor for coronary events and vascular death.[6] The prevalence of moderate (≥50%) and severe (≥70%) asymptomatic carotid stenosis (ACS) in the general population has been estimated to be 2.0% and 0.5%, respectively.[7]

Because of this low overall prevalence, population-level screening for ACS with duplex ultrasound is not recommended in current guidelines.[8–11] However, targeted screening of high-risk individuals might be worthwhile,[11] and risk stratification tools or prediction models have been developed to provide individualized risk estimation for ACS. Before recommending targeted screening, risk prediction tools should be assessed for discrimination, calibration, and likely ability to detect false-positive and false-negative cases in an independent external population. We conducted a systematic review of published studies of prediction models for ACS and then externally validated these models in a large contemporary

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CLINICAL PERSPECTIVE

What Is New?

- Established risk prediction models to detect cases at high risk of asymptomatic carotid stenosis were validated in a contemporary screening population in the United States and United Kingdom.

What Are the Clinical Implications?

- Risk prediction models can be used for targeted screening for asymptomatic carotid stenosis, and cardiovascular risk management can be initiated or intensified to prevent complications of asymptomatic carotid stenosis.

Nonstandard Abbreviations and Acronyms

ACS	asymptomatic carotid stenosis
DBP	diastolic blood pressure
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
SBP	systolic blood pressure
TC	total cholesterol
TIA	transient ischemic attack

population of screenees in the United States and United Kingdom.

METHODS

Systematic review according to a predefined protocol to identify established risk prediction models. This protocol has been registered in an international registry for systematic reviews (PROSPERO [International Prospective Register of Systematic Reviews]): CRD42019108136. The study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations (Table S1) and the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS).[12,13]

Data Sharing

Data from large population-based studies conducted by the Nuffield Department of Population Health can be shared with bona fide researchers on application to the principal investigators of this study. Details of the departmental data access policy can be found at https://www.ndph.ox.ac.uk/data-access.

Search Strategy and Eligibility Criteria

We used comprehensive electronic strategies and incorporated a validated research search filter to search Medline (via PubMed interface) and EMBASE (via OVID EMBASE interface) on March 1, 2019, for studies reporting on development and validation of prediction models for risk of significant ACS in general or screened populations (Data S1).[14] We included studies that (1) addressed development and/or validation of diagnostic prediction models to detect ACS of 50% or greater, (2) assessed prediction models in both general and high-risk populations but not in diseased populations at higher risk of ACS, (3) involved a cross-sectional study design, and (4) were published in peer-reviewed journals without any language restrictions.

Screening Process and Data Extraction

Two authors (M.H.F.P. and M.S.M.) independently screened all titles and abstracts of the retrieved references and subsequently independently reviewed full-text copies for final inclusion in this study. We performed backward citation searching using the bibliographies of included studies.

Two authors (M.H.F.P. and M.S.M.) independently extracted the following data from the included studies reporting the development of a prediction model, based on the CHARMS checklist: source of data, setting study, geographic area (country and continent), study years, sample size, modeling method (eg, logistic model), number of participants with missing data, handling of missing data, investigation of satisfaction of modeling assumptions, selection methods for predictor selection, shrinkage of predictor weights, number of outcome events, number of participants, degree of stenosis, number and type of predictors (diagnostic variables) used in the final model, number of outcome events per variable, presentation of model, and model performance (calibration and validation). In studies that reported internal validation of prediction models, we extracted the following additional data: method of internal validation (eg, cross-validation, bootstrap), and whether the model was adjusted or updated after internal validation. In studies reporting external validation of a prediction model, we extracted the following additional data: type of external validation (eg, geographical and/or temporal distinct population), whether authors of the external validation also developed the original model, and performance of the model before or after model recalibration.

Critical Appraisal

Prediction modeling studies were assessed for risk of bias and applicability using the Prediction model Risk Of Bias Assessment Tool (PROBAST).[15] The assessment of risk of bias involved 4 domains: participants, predictors, outcome, and analysis. Risk of bias was judged as low, high, or uncertain for each domain. The assessment of applicability involved 3 domains:

participants, predictors, and outcome. Applicability was judged as low, high, or uncertain for each domain. Each distinct model included in the article was evaluated separately.[16]

External Validation Cohort

A cohort of 0.6 million self-referred and self-funded individuals who attended commercial vascular screening clinics between 2008 and 2013 in the United States and the United Kingdom was used for external validation. All individuals completed a standardized questionnaire including questions about their age; sex; height and weight; history of vascular disease (peripheral arterial disease, TIA, stroke, coronary artery disease, and congestive heart failure); history of hypertension; history of diabetes mellitus; smoking history; and use of antiplatelet, antihypertensive, and lipid-lowering medication. Standard blood pressure cuffs and sphygmomanometers were used, with systolic pressure measured using a Doppler probe, and peripheral arterial disease was assessed with ankle-brachial pressure index assessment.

Most participants underwent carotid duplex screening, conducted by trained staff using dedicated vascular ultrasound instruments (GE LOGIQ e). The highest peak systolic velocity and end-diastolic velocity of both the common carotid arteries and the internal carotid arteries were measured.

A blood sample was collected from a subset of participants for selected plasma biochemical measurements using point-of-care testing methods (Alere Cholestech LDX System, Alere Inc, Waltham, MA). Plasma levels of total cholesterol, high-density lipoprotein-cholesterol, and triglycerides were measured by enzymatic methods. Low-density lipoprotein-cholesterol was estimated using the Friedewald formula (low-density lipoprotein=total cholesterol–high-density lipoprotein–triglycerides / 5).

Predicted Outcomes

We externally validated the prediction models for both moderate or severe ACS:

1. Moderate or severe ACS; estimated stenosis of ≥50% (on the basis of peak systolic velocity ≥125 cm/s at either side or 0 cm/s for occluded arteries); and
2. Severe ACS, estimated stenosis of ≥70% (on the basis of peak systolic velocity ≥230 cm/s at either side or 0 cm/s for occluded arteries).

Statistical Analysis (External Validation)

Selected characteristics of the external validation cohort were summarized using standard methods. We used the same external validation population for all external validation analyses to enable comparisons between different prediction models. Participants who provided a blood sample and had a duplex ultrasound performed were included in analyses. For most predictors, the percentage of participants with missing data was <12%, except for measured diastolic blood pressure (31.8%) (Table S2). Missing data were imputed using chained equations and we created 20 imputed data sets with 200 iterations.[17] Total cholesterol/high-density lipoprotein cholesterol ratio was calculated before imputation.[18] Postimputation rounding was applied for limited-range variables (systolic blood pressure, diastolic blood pressure, total cholesterol/high-density lipoprotein cholesterol ratio, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and height), if needed.[19]

The regression formula reported for each model was applied to the external validation cohort to calculate the probability of ≥50% and ≥70% ACS per participant. These individual probabilities were used for assessing the predictive performance. We contacted authors to provide the regression formula if it was not reported. If the authors did not report or could not provide the regression formula, we calculated a sum score (total points) for each participant by summing the scores assigned to each predictor in the original reports (referred to as a "score chart"). We used the sum score to assess the predictive performance.

We examined the performance of discrimination and calibration in the different prediction models. Discrimination is the ability of the prediction model to distinguish between participants with and without the disease outcomes, assessed using the area under the receiver operating characteristic (AUROC) curve. AUROC curve values were calculated per imputed data set and results were subsequently pooled using Rubin's rules.[20,21]

Calibration is the agreement between predicted and observed risk and was assessed with calibration plots. For the models that provided the regression formula, we estimated the mean probability per participant across the 20 imputed data sets, and subsequently we split the predicted risks in deciles. We then calculated mean predicted and observed probability with corresponding 95% CIs per decile. In contrast, for the models that did not provide the regression formula, we used the predicted probability per sum score as reported in the original reports, and we calculated the observed probability with corresponding 95% CI in the validation cohort.

Differences between the prevalence of the predicted outcome in the development cohorts and the validation cohort are known to influence calibration. For this reason, we recalibrated the prediction models to the prevalence of the predicted outcome in the validation cohort by reestimating the intercept.[22] We fitted a logistic model with a fixed calibration slope and the intercept as the only free parameter.[22]

STATA version 15.1 was used for all statistical analyses, and R version 3.5.1 was used for constructing the figures.

Clinical Application

Clinical application of the prediction model with the best discrimination was assessed using 2 approaches. The first approach assessed targeted screening of the 10% and 20% cases at highest predicted risk of having significant ACS. For this, we calculated test characteristics for the highest decile and the highest 2 deciles of predicted risk. The second approach assessed targeted screening with a fixed level of sensitivity. For this, test characteristics were calculated for 2 levels of sensitivity (closest to sensitivity 80% and 90%).

Sensitivity Analyses

We performed additional external validation of the prediction models: (1) in complete cases, (2) participants without a history of prior TIA or stroke using imputed data sets, and (3) participants without a history of prior cardiovascular disease (ie, stroke, TIA, myocardial infarction, and peripheral arterial disease) using imputed data sets.

Ethical Approval

The University of Oxford Medical Sciences Inter-Divisional Research Ethics Committee approved the study. All individuals provided written consent for the data collected at the screening visit to be used for research purposes.

Role of the Funding Source

The study funders had no role in study design, data collection, analysis, or interpretation, drafting the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to publish the report.

RESULTS

We screened 923 unique reports identified by literature searching, assessed the full texts of 102 reports for eligibility, and included 5 studies (Figure 1 and Table S3). Four studies involved model development studies, of which 1 performed additional external validation of an existing prediction model.[23–26] One study was an external validation study.[27] Overall, 6 prediction models for the prevalence of significant ACS were developed.[23–26] Characteristics of model development are provided in Table 1 and Table S4.

Three prediction models were developed to detect ACS ≥50%,[23,24,26] 1 model was developed to detect ACS ≥60%,[25] and 2 models were developed to detect ACS ≥70%.[23,26] The risk predictors included age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, myocardial infarction, stroke or TIA, height, measured blood pressure, and blood lipids. The number of predictors included in the prediction models varied from 4 to 8. Two models used clinical characteristics, and 4 models used blood measurements in addition to clinical characteristics. An overview of the predictors used in prediction models is provided in Table S5. The number of cases used to develop the prediction models varied from 394 to 23 706; the number of events varied from 18 to 465, and the number of cases per predictor varied from 2.6 to 59.8.

The overall risk of bias was low in 2 models and high in 4 models. Concerns with the applicability of the prediction models was deemed low in 3 models, unclear in 2 models, and high in 1 model. An overview of the risk of bias and the applicability per model is provided in Table S6.

Predictive Performance

Discriminative performance, as assessed by the AUROC curves varied from 0.81 to 0.88 in the derivation cohorts, and from 0.71 to 0.87 in the internal validation cohorts, respectively (Figure 2).[23–27] Only 1 study provided calibration plots.[26]

In 2 studies, 10 external validation analyses were performed.[26,27] In Yan et al, 6 external validation analyses were performed using both ≥50% and ≥70% ACS as outcomes.[26] The number of cases used for external validation in their study was 5010, of which 64 (1.3%) had ≥50% ACS, and 38 (0.8%) had ≥70% ACS. The AUROC curve ranged from 0.63 to 0.68. No (re)calibration was performed. A cohort from China used for external validation was geographically and temporally distinct from the derivation cohorts. In Suri et al, 4 external validation analyses were performed using ≥50% and ≥75% ACS as predicted outcomes.[27] The number of cases used for external validation in their study was 5449, of which 227 (4.2%) had ≥50% ACS and 52 (1.0%) had ≥75% ACS. The AUROC curve ranged from 0.56 to 0.60. No (re) calibration was performed. The validation cohort was from the United States, as were the derivation cohorts of the validated models and the data of validation cohort were older than the derivation cohorts.

External Validation

The validation cohort consisted of 596 469 participants, of whom 11 178 (1.87%) participants had ≥50% ACS and 2033 (0.34%) participants had ≥70% ACS. Baseline characteristics of the validation cohort are provided in Table 2.

Discrimination for outcome ≥50% ACS

The model with the best discrimination showed an AUROC curve of 0.749 (95% CI, 0.744–0.753).[23] The

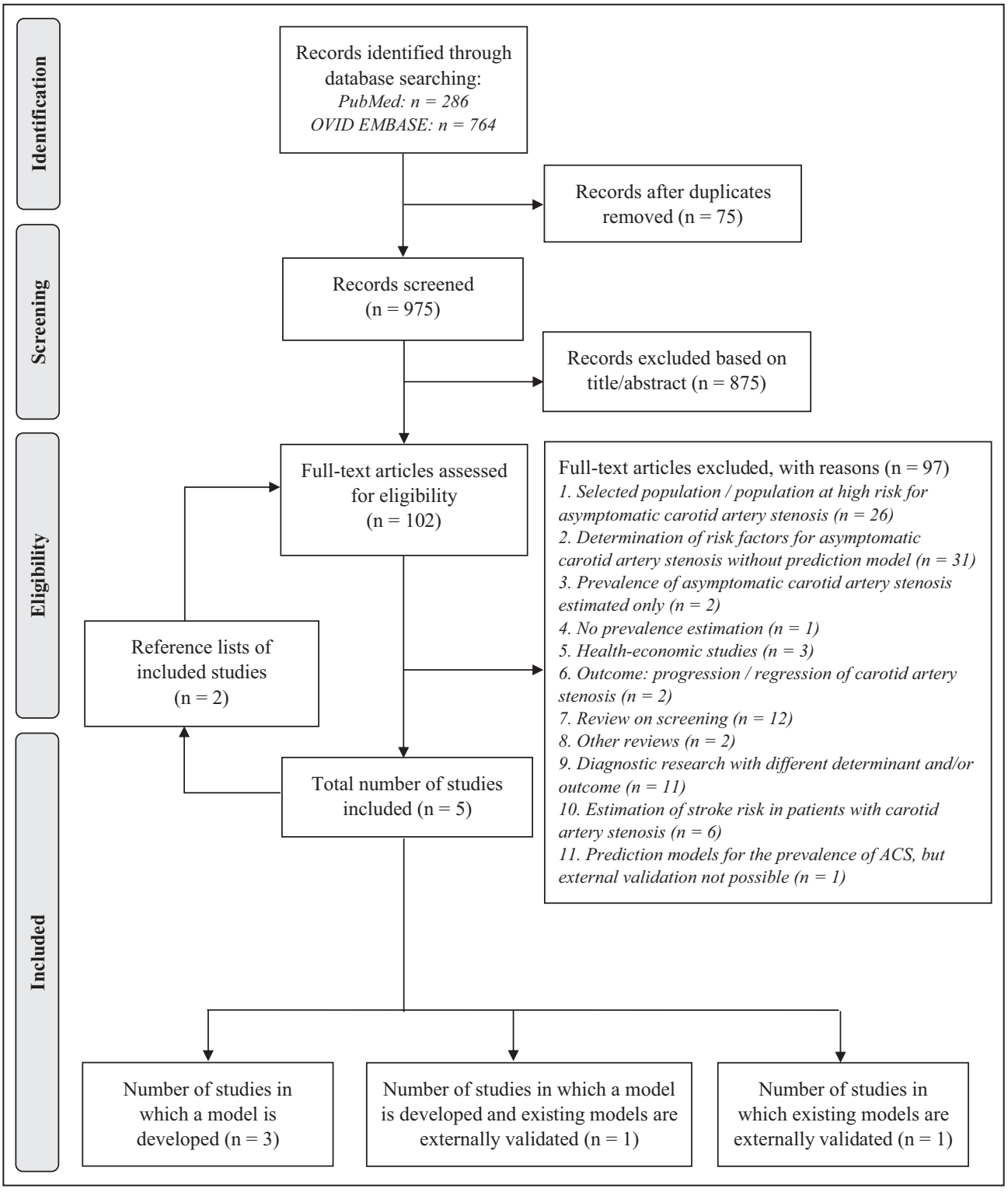

Figure 1. Flowchart of literature review to identify the included studies.

discriminative performance was fair in 3 other models with an AUROC curve of 0.727 (95% CI, 0.722–0.732), 0.704 (95% CI, 0.700–0.709) and 0.703 (95% CI, 0.699–0.708).[25,26] The discriminative performance was poor in 1 model with an AUROC curve of 0.673 (95% CI, 0.668–0.678).[24]

Table 1. Selected Characteristics of Studies Assessing Different Risk Prediction Models for Significant ACS

	Predicted Outcomes	Data Sources	Calendar Year of Recruitment	No. of Cases/Participants in Derivation Cohort	Number of Included Predictors	Number of Events Per Predictor	First Author, Year of Publication
1.	70%-100% ACS	Renqiu Stroke Screening Study, China	2012	18/3006 (0.6%)	7	2.6	Yan et al, 2018[26] *Model 1*
2.	50%-100% ACS			33/3006 (1.1%)	8	4.1	*Model 2*
3.	>70% ACS	Four observational studies: Sweden, Norway, Germany, four communities in the United States	Tromsø: 1994–1995; MDCS: 1991–1996; CAPS: NA; CHS: NA	127/23 706 (0.5%)	8	15.9	de Weerd et al, 2014[23] *Model 1*
4.	>50% ACS			465/23 706 (2.0%)	8	58.1	*Model 2*
5.	>50% ACS	Screening, NY, USA	2001–2002	38/394 (9.6%)	4	9.5	Jacobowitz et al, 2003[24]
6.	≥60% ACS	Screening, NY, USA	1997	239/1331 (18%)	4	59.8	Qureshi et al, 2001[25]

ACS indicates asymptomatic carotid stenosis; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; MDCS, Malmö Diet and Cancer Study; and NA, not available.

Discrimination for outcome ≥70% ACS

The model with the best discrimination showed an AUROC curve of 0.779 (95% CI, 0.770–0.789).[23] The discriminative performance was fair in 3 other models with an AUROC curve of 0.759 (95% CI, 0.749–0.770), 0.731 (95% CI, 0.721–0.742) and 0.701 (95% CI, 0.690–0.712).[25,26] The discriminative performance was poor in 1 model with an AUROC curve of 0.689 (95% CI, 0.677–0.701)[24] (Figure 2 and Table S7).

Calibration

In the model with the best discrimination, predicted probabilities (after recalibration with adjusting the intercept) showed good concordance between the predicted prevalence calculated with the prediction model and the observed prevalence in the external validation cohort. The predicted and observed prevalence of ≥50% ACS in the highest decile was 6.4% and 6.5%, respectively (Figure 3A).[23] The predicted and observed prevalence of ≥70% ACS in the highest 2 deciles was 1.7% and 1.4%, respectively (Figure S1). Other calibration plots are provided as Figures S1 and S2 for the outcomes ≥70% ACS and ≥50% ACS, respectively.

Application of the Prediction Model With the Best Discrimination

Application for outcome ≥50% ACS

First, we assessed targeted screening in the highest decile and highest 2 deciles of predicted risk. Prevalence of ≥50% ACS in the highest decile of predicted risk was 6.5% with a number needed to scan (NNS) of 15. Targeted screening of the highest decile identified 34.8% of cases with ≥50% ACS. Prevalence in the 2 highest deciles of predicted risk was 4.8% with an NNS of 21. Targeted screening of the 2 highest deciles identified 55.0% of cases with ≥50% ACS (Figure 3B and Table S8).

Second, we assessed targeted screening with fixed levels of sensitivity. For this, test characteristics were calculated for 2 levels of sensitivity (≈80% and 90%). Observed prevalences of ≥50% ACS were 2.78% and 3.38% for the sensitivity of 90.0% and 79.5%. The corresponding specificity was 40.0% and 56.6%, respectively (Table S8).

Application for outcome ≥70% ACS

Prevalence of ≥70% ACS in the highest decile of predicted risk was 1.4% with an NNS of 70. Targeted screening of the highest decile identified 41.7% of cases with ≥70% ACS. Prevalence in the 2 highest deciles of predicted risk was 0.98% with an NNS of 102. Targeted screening of the 2 highest deciles identified 62.1% of cases with ≥70% ACS (Figure S3 and Table S8).

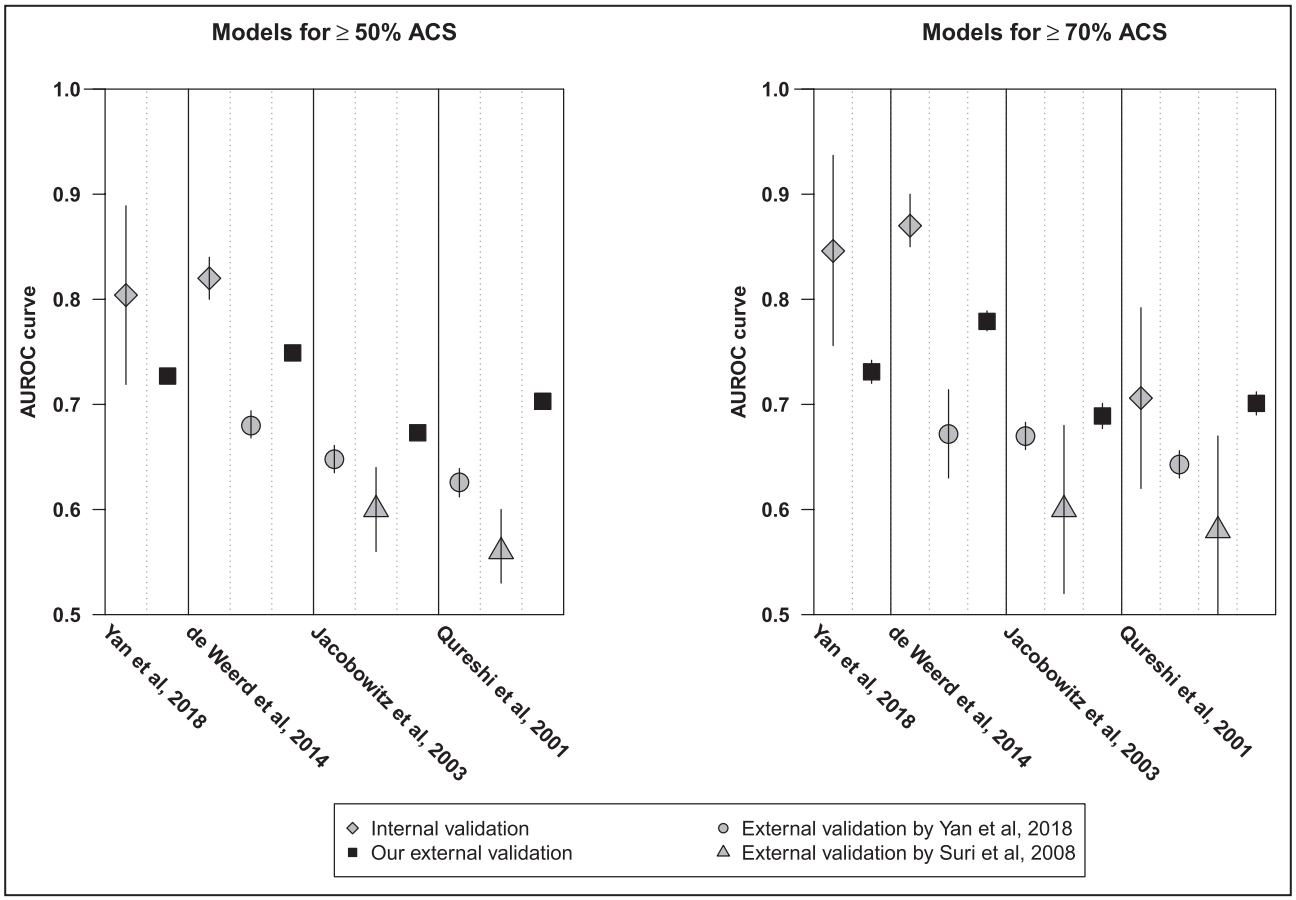

Figure 2. Discriminative performance of risk prediction models.
The symbols represent the AUROC curves of the included prediction models and the vertical bars represent the 95% CIs. The values of the AUROC curves and 95% CIs are provided in Table S6. The models of Jacobowitz et al[24] and Qureshi et al[25] were originally developed for >50% ACS and ≥60% ACS, respectively. Suri et al, 2008 used ≥50% ACS and ≥75% ACS as outcomes for the external validation.[27] The AUROC curves of 2 external validations for ≥50% ACS in the models developed for ≥70% ACS by de Weerd et al[23] and Yan et al[26] and 2 external validations for ≥70% ACS in the models developed for ≥50% ACS by the same authors are omitted in this figure. ACS indicates asymptomatic carotid stenosis; and AUROC, area under receiver operating characteristic.

Using fixed levels of sensitivity (≈80% and 90%), observed prevalences of ≥70% ACS were 0.8% and 0.5% for the sensitivity of 76.8% and 92.0%. The corresponding specificity was 65.1% and 40.0%, respectively (Table S8).

Sensitivity Analysis

Validation in subsets with complete cases, cases without a history of TIA or stroke, showed comparable results. Validation in the subset of cases without a history of cardiovascular disease showed a lower AUROC (Figure S4 and Table S9).

DISCUSSION

The present study validated prediction models in an external population to identify a cohort of individuals at high risk of asymptomatic carotid stenosis (ACS). In the model with the best discrimination, the observed prevalence of ACS in the decile at highest risk was 6.5% (≥50% ACS) and 1.4% (≥70% ACS) with an NNS of 15 and 70, respectively. Targeted screening of individuals in the highest decile of risk reliably identified 35% of cases with ≥50% ACS and 42% of cases with ≥70% ACS.

Early identification of ACS cases allows the initiation or intensification of cardiovascular risk management using triple medical therapy (ie, antithrombotic, antihypertensive, and lipid-lowering medication) to decrease the risk of cardiovascular disease. Carotid intervention might further decrease the risk of stroke in selected cases. Clinical and imaging features associated with an increased risk of stroke in patients with medically treated ACS, such as silent brain infarction, contralateral stroke, or TIA, plaque echolucency, intraplaque hemorrhage, microemboli, and reduced cerebrovascular reserve, have been identified.[10,28] Risk stratification tools, using a wide range of predictors, have been developed to estimate long-term stroke and cardiovascular disease risk in cases with ACS, but these have

Table 2. Selected Characteristics of Participants in the External Validation Cohort, by Severity of ACS

	Participants With <50% ACS (n=585 291)	Participants With 50% to 69% ACS (n=9145)	Participants With ≥70% ACS (n=2033)*	All Participants (n=596 469)
Age, y	62.0±10.0	68.7±8.9	68.3±8.8	62.2±10.1
Sex (male)	208 285 (35.6)	3442 (37.6)	1009 (49.6)	212 736 (35.7)
Current or former smoker	207 329 (40.0)	4865 (61.0)	1245 (69.2)	213 439 (40.4)
Never smoker	311 192 (60.0)	3112 (39.0)	555 (30.8)	314 859 (59.6)
Hypertension	202 768 (36.0)	5185 (58.9)	1166 (60.6)	209 119 (36.4)
Diabetes mellitus	44 986 (8.2)	1577 (18.3)	312 (16.4)	46 875 (8.4)
Coronary heart disease†	26 997 (5.1)	1262 (14.9)	344 (18.6)	28 603 (5.3)
Stroke/TIA	17 154 (3.3)	758 (9.0)	274 (15.0)	18 186 (3.4)
Peripheral arterial disease	16 370 (2.8)	1184 (13.4)	424 (21.8)	17 978 (3.1%)
Height, m	1.68±0.1	1.67±0.1	1.69±0.1	1.68±0.1
SBP, mm Hg	132±19.5	142±21.8	146±23.5	132±19.6
DBP, mm Hg	78±9.8	76±10.2	78±11.5	78±9.8
HDL-C, mmol/L	1.4±0.5	1.3±0.5	1.3±0.4	1.4±0.5
LDL-C, mmol/L	3.0±0.9	3.0±1.1	3.0±1.1	3.0±0.9
TC/HDL-ratio	4.0±1.6	4.2±1.7	4.4±2.0	4.0±1.6

Values are mean±SD for continuous variables and n (%) for categorical variables. DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TIA, transient ischemic attack.

*In this group, 500 participants had a presumed occlusion.

†Coronary heart disease is defined as previous myocardial infarction or a coronary intervention (bypass, angioplasty, or stenting).

not been validated with current medical treatment.[29,30] Reliable and validated risk stratification tools might help further refine the use of targeted screening for ACS by identifying cases at higher risk for stroke and cardiovascular disease.

We found that discrimination was less for participants without cardiovascular disease, but targeted screening could also include participants with a history of cerebrovascular or cardiovascular disease, since not all of these participants were taking adequate preventive treatments. Annual ipsilateral risk of stroke in ACS cases on medical therapy in previous randomized controlled trials varied between 1.4% and 2.4%.[31–33] More recent studies have reported lower risks attributable to improving risk factor management.[29] Annual risk of ipsilateral ischemic stroke and TIA in cases with >50% ACS and a history of TIA or minor stroke in another territory with consequent use of secondary prophylaxis was as low as 0.34% and 1.78%, respectively.[34]

The discrimination of the best model was fair and calibration good, despite differences between the original derivation and our validation cohort. Differences in duplex protocols, (eg, unilateral or bilateral screening), and differences in the methods of measurement of degree of stenosis between populations may have contributed to lower external performance in this large external validation cohort. Duplex screening does not assess intracranial stenosis, and extracranial calcified vessels can hamper reliable assessment. Different criteria for assessment of stenosis are available, but validity of duplex ultrasound performed by experienced sonographers is good,[35] and peak systolic velocity, while it is a simple measurement, may be useful as a screening tool to identify cases for more intensive evaluation.

The present study had several strengths. We conducted an extensive literature search to identify existing models and previous external validation according to a prespecified protocol. We used a large cohort for external validation and all models were validated using the same participants, allowing us to directly compare their predictive performance. Missing data in the validation population were limited for most variables, and our findings were unaffected by missing values. Multiple imputation was used to handle missing data, which is preferred to complete-case analysis. A direct match between predictors in the models and the external validation cohort was available for all predictors of externally validated models. Bilateral examination of the carotid arteries was performed and stenoses of either side were used as outcome. Our sensitivity analyses showed that exclusion of participants with previous stroke or TIA and exclusion of participants with previous cardiovascular disease did not influence the findings of the main analysis substantially.

The present study also had several limitations. First, even though the external validation data were prospectively collected, it was not primarily designed for research purposes. Second, participants were self-referred and self-funded, which may limit

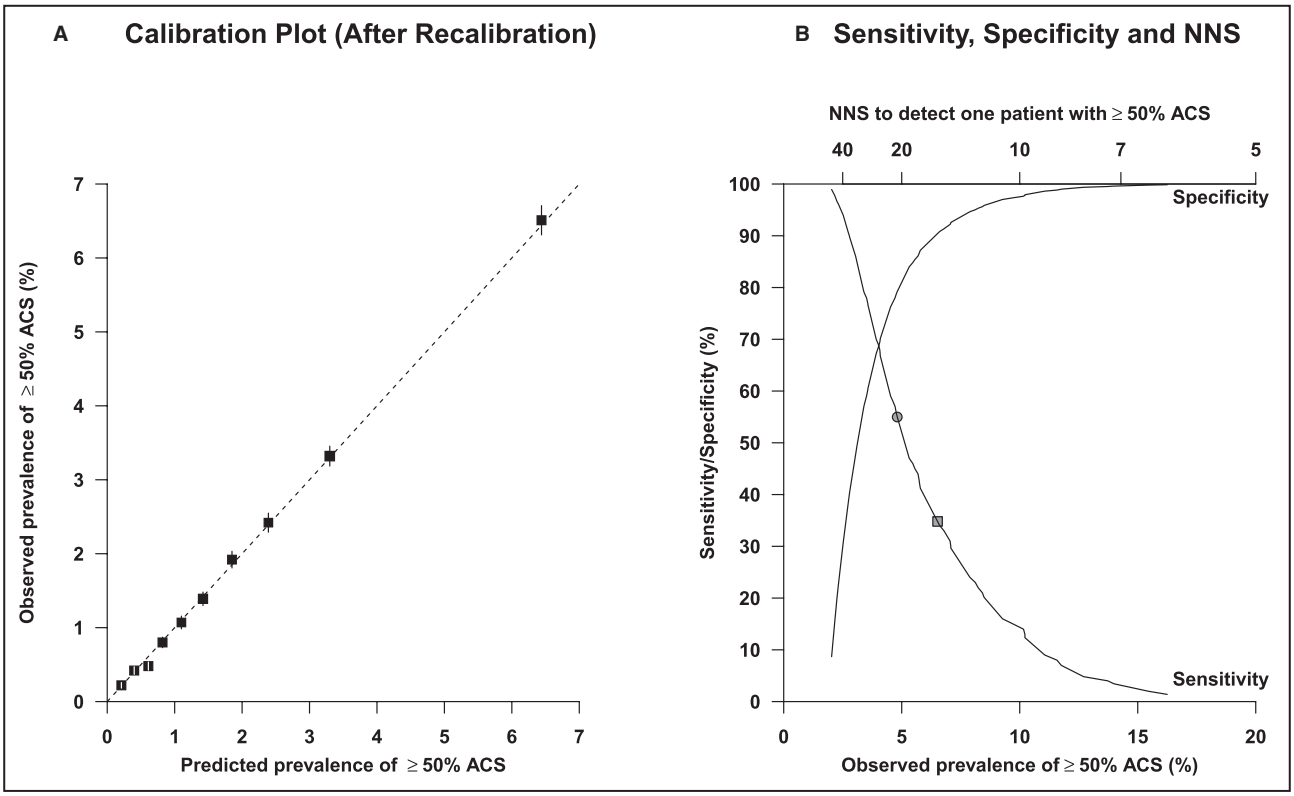

Figure 3. Clinical application of the prediction model of de Weerd et al[23] for ≥50% ACS.
A, Calibration plot of external validation of the prediction model developed by de Weerd et al.[23] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk, and the vertical lines represent the 95% CIs. **B**, Graph showing the sensitivity and specificity and corresponding observed prevalence and number needed to screen to detect 1 participant with ≥50% ACS using the prediction model developed by de Weerd et al.[23] The square corresponds to targeted screening of participants in the highest decile of predicted risk. The prevalence in this decile is 6.5% with a number needed to screen of 15, and sensitivity is 34.8%. The circle corresponds to targeted screening of participants in the highest two deciles of predicted risk. The prevalence in these deciles is 4.8% with a number needed to screen of 21 and sensitivity of 55.0%. ACS indicates asymptomatic carotid stenosis; and NNS, number needed to scan.

the generalizability to other (screened) populations. In addition, some predictors were not included in established risk prediction models, such as social status, possibly hampering reliable prediction in specific groups of patients. Third, data on medical history and height were assessed by self-reporting and, hence, may be susceptible to recall bias. Fourth, data from duplex measurement of the internal carotid artery and common carotid artery were not recorded separately.

Risk prediction models with good calibration are needed to improve the efficiency of targeted screening programs by identifying those at greatest risk, but future research should determine the long-term predictors of stroke and cardiovascular disease and determine the number of events that could be prevented by using more intensive medical treatment.

In conclusion, the present study showed that most prediction models had modest discrimination but could reliably identify a cohort of cases at high risk of ACS. The prevalence of ACS in the decile(s) at highest predicted risk of ACS was considerably higher than the overall prevalence, thereby substantially reducing the number of individuals needed to screen to detect ACS. Further research should determine the optimum thresholds required for a targeted screening by considering the number needed to screen, the diagnostic yield, the absolute reduction of stroke risk by prophylactic treatment, and cost-effectiveness of different approaches.

ARTICLE INFORMATION

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Author contributions: Prof Halliday and Mr Bulbulia, and Prof Lewington obtained the data and considered the clinical applicability of Life Line Screening. Mr Poorthuis designed the study. Mr Poorthuis, Mr Sherliker and Ms Clack cleaned the data. Mr Poorthuis designed the search strategy, performed literature searches, and removed duplicates. Mr Poorthuis and Dr Massa screened titles and abstracts and assessed full-text articles and reference lists of included studies. Mr Poorthuis performed the statistical analyses, supervised by Dr Massa, Mr Sherliker, and Prof Lewington. The manuscript was drafted by Mr Poorthuis. All authors interpreted the data, contributed to revision and editing of the manuscript, and approved the final version of the manuscript for submission for publication.

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Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S9
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REFERENCES

1. George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett E, Smeeth L, Timmis A, Hemingway H. How does cardiovascular disease first present in women and men? *Circulation*. 2015;132:1320–1328.
2. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, Gondrie MJA, Steyerberg EW, Ridker PM, Cook NR, van der Graaf Y. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart*. 2013;99:866–872.
3. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke*. 2000;31:1062–1068.
4. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. *Stroke*. 2003;34:2050–2059.
5. Bogiatzi C, Wannarong T, McLeod AI, Heisel M, Hackam D, Spence JD. SPARKLE (Subtypes of Ischaemic Stroke Classification System), incorporating measurement of carotid plaque burden: a new validated tool for the classification of ischemic stroke subtypes. *Neuroepidemiology*. 2014;42:243–251.
6. Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der Graaf Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. *Stroke*. 2007;38:1470–1475.
7. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, Rosvall M, Sitzer M, Buskens E, Bots ML. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. *Stroke*. 2010;41:1294–1297.
8. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832.
9. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1–e31.
10. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, Hamilton G, Kakisis J, Kakkos S, Lepidi S, et al. Editor's Choice—management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:3–81.
11. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2011;57:e16–e94.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
13. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, Reitsma JB, Collins GS. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med*. 2014;11:e1001744.
14. Ingui BJ, Rogers MA. Searching for clinical prediction rules in MEDLINE. *J Am Med Inform Assoc*. 2001;8:391–397.
15. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. *Ann Intern Med*. 2019;170:51–58.
16. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med*. 2019;170:W1–W33.
17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
18. Morris TP, White IR, Royston P, Seaman SR, Wood AM. Multiple imputation for an incomplete covariate that is a ratio. *Stat Med*. 2014;33:88–104.
19. Rodwell L, Lee KJ, Romaniuk H, Carlin JB. Comparison of methods for imputing limited-range variables: a simulation study. *BMC Med Res Methodol*. 2014;14:57.
20. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9:57.
21. Rubin DB. Inference and missing data. *Biometrika*. 1976;63:581–592.
22. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York: Springer-Verlag; 2009.
23. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, Rosvall M, Sitzer M, de Borst GJ, Buskens E, et al. Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups. *Stroke*. 2014;45:2366–2371.
24. Jacobowitz GR, Rockman CB, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, Riles TS. A model for predicting occult carotid artery stenosis: screening is justified in a selected population. *J Vasc Surg*. 2003;38:705–709.
25. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterman LR. Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York Stroke Screening Program. *J Neuroimaging*. 2001;11:105–111.
26. Yan Y, Gao S, Yang H, Qin S, Li F, Zhang G, Yang B, He Y, Zhao Y, Li E, et al. ECAS score: a web-based risk model to predict moderate and severe extracranial carotid artery stenosis. *Neurol Res*. 2018;40:249–257.
27. Suri MFK, Ezzeddine MA, Lakshminarayan K, Divani AA, Qureshi AI. Validation of two different grading schemes to identify patients with asymptomatic carotid artery stenosis in general population. *J Neuroimaging*. 2008;18:142–147.
28. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in

collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763–816.
29. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, Thomas DJ, Giannoukas A, Geroulakos G, Georgiou N, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. *Eur J Vasc Endovasc Surg*. 2005;30:275–284.
30. Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, Tegos T, Geroulakos G, Labropoulos N, Dore CJ, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*. 2010;52:1486–1496.
31. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421–1428.
32. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet*. 2010;376:1074–1084.
33. Hobson RW II, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1993;328:221–227.
34. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke*. 2010;41:e11–e17.
35. Jahromi AS, Cina CS, Liu Y, Clase CM. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. *J Vasc Surg*. 2005;41:962–972.
36. Abd Allah F, Baligh E, Ibrahim M. Clinical relevance of carotid atherosclerosis among Egyptians: a 5-year retrospective analysis of 4,733 subjects. *Neuroepidemiology*. 2010;35:275–279.
37. Aboyans V, Lacroix P. Indications for carotid screening in patients with coronary artery disease. *Presse Med*. 2009;38:977–986.
38. Admani AK, Mangion DM, Naik DR. Extracranial carotid artery stenosis: prevalence and associated risk factors in elderly stroke patients. *Atherosclerosis*. 1991;86:31–37.
39. Ahn SS, Baker JD, Walden K, Moore WS. Which asymptomatic patients should undergo routine screening carotid duplex scan? *Am J Surg*. 1991;162:180–183; discussion 183-4.
40. Aizenberg DJ. Cardiovascular testing in asymptomatic patients: carotid duplex, cardiac stress testing, screen for peripheral arterial disease. *Med Clin North Am*. 2016;100:971–979.
41. Alexandrov AV. Ultrasound and angiography in the selection of patients for carotid endarterectomy. *Curr Cardiol Rep*. 2003;5:141–147.
42. Ansari S, Tan JY, Larcos GS, Paterson H. Low prevalence of significant carotid artery disease on ultrasound in patients proceeding to coronary artery bypass surgery. *Intern Med J*. 2011;41:658–661.
43. Archbold RA, Barakat K, Magee P, Curzen N. Screening for carotid artery disease before cardiac surgery: is current clinical practice evidence based? *Clin Cardiol*. 2001;24:26–32.
44. Ascher E, Hingorani A, Yorkovich W, Ramsey PJ, Salles-Cunha S. Routine preoperative carotid duplex scanning in patients undergoing open heart surgery: is it worthwhile? *Ann Vasc Surg*. 2001;15:669–678.
45. Ballard JL, Mazeroll R, Weitzman R, Harward TR, Flanigan DP. Medical benefits of a peripheral vascular screening program. *Ann Vasc Surg*. 2007;21:159–162.
46. Barvalia M, Silber D, DiVita M, Joshi A, Wasty N, Cohen M. Utility of carotid duplex ultrasonography in a general inner-city hospital. *Cardiovasc Ultrasound*. 2014;12:48.
47. Belcaro G, Nicolaides AN, Cesarone MR, De Sanctis MT, Geroulakos G, Lennox A, Griffin M, Incandela L. Vascular screening in andropause: non-invasive investigations in vascular disease screening. *Curr Med Res Opin*. 2000;16(suppl 1):s68–s71.
48. Berens ES, Kouchoukos NT, Murphy SF, Wareing TH. Preoperative carotid artery screening in elderly patients undergoing cardiac surgery. *J Vasc Surg*. 1992;15:313–321; discussion 322-3.
49. Berger JS, Hochman J, Lobach I, Adelman MA, Riles TS, Rockman CB. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–681.e1.
50. Bosevski M, Borozanov V, Georgievska-Ismail L. Influence of metabolic risk factors on the presence of carotid artery disease in patients with type 2 diabetes and coronary artery disease. *Diab Vasc Dis Res*. 2007;4:49–52.
51. Bosevski M, Lazarova-Trajkovska E. Carotid artery disease in patients with type 2 diabetes. *Angiol Vasc Surg*. 2015;21:17–26.
52. Carnicelli AP, Stone JJ, Doyle A, Chowdhry A, Gillespie DL, Chandra A. Predictive multivariate regression to increase the specificity of carotid duplex ultrasound for high-grade stenosis in asymptomatic patients. *Ann Vasc Surg*. 2014;28:1548–1555.
53. Carnicelli AP, Stone JJ, Doyle A, Chowdhry AK, Mix D, Ellis J, Gillespie DL, Chandra A. Cross-sectional area for the calculation of carotid artery stenosis on computed tomographic angiography. *J Vasc Surg*. 2013;58:659–665.
54. Carsten CG III, Elmore JR, Franklin DP, Thomas DD, Mordan F, Wood GC. Use of limited color-flow duplex for a carotid screening project. *Am J Surg*. 1999;178:173–176.
55. Chiquete E, Torres-Octavo B, Cano-Nigenda V, Valle-Rojas D, Dominguez-Moreno R, Tolosa-Tort P, Florez-Cardona JA, Flores-Silva F, Reyes-Melo I, Higuera-Calleja J, et al. Characterisation of factors associated with carotid stenosis in a population at high risk. *Rev Neurol*. 2014;58:541–547.
56. Chua HC, Sitoh YY, Earnest A, Venketasubramanian N. Detection of internal carotid artery stenosis with duplex velocity criteria using receiver operating characteristic analysis. *Ann Acad Med Singapore*. 2007;36:247–252.
57. Chou CL, Wu YJ, Hung CL, Liu CC, Wang SD, Wu TW, Wang LY, Yeh HI. Segment-specific prevalence of carotid artery plaque and stenosis in middle-aged adults and elders in Taiwan: a community-based study. *J Formos Med Assoc*. 2019;118:64–71.
58. Colgan MP, Strode GR, Sommer JD, Gibbs JL, Sumner DS. Prevalence of asymptomatic carotid disease: results of duplex scanning in 348 unselected volunteers. *J Vasc Surg*. 1988;8:674–678.
59. Cull DL, Cole T, Miller B, Johnson B, Rawlinson D, Walker E, Taylor SM. The value of a carotid duplex surveillance program for stroke prevention. *Ann Vasc Surg*. 2011;25:887–894.
60. Derdeyn CP, Powers WJ. Cost-effectiveness of screening for asymptomatic carotid atherosclerotic disease. *Stroke*. 1996;27:1944–1950.
61. Derdeyn CP, Powers WJ, Moran CJ, DeWitte ITC, Allen BT. Role of Doppler US in screening for carotid atherosclerotic disease. *Radiology*. 1995;197:635–643.
62. Di Carli MF, Hachamovitch R. Should we screen for occult coronary artery disease among asymptomatic patients with diabetes? *J Am Coll Cardiol*. 2005;45:50–53.
63. Duval M, Altman JJ. When should ultrasonography be used to detect asymptomatic carotid atheroma in diabetic patients? *Diabetes Metab*. 2006;32:638–642.
64. Ellis MR, Franks PJ, Cuming R, Powell JT, Greenhalgh RM. Prevalence, progression and natural history of asymptomatic carotid stenosis: is there a place for carotid endarterectomy? *Eur J Vasc Surg*. 1992;6:172–177.
65. Elmore EM, Mosquera A, Weinberger J. The prevalence of asymptomatic intracranial large-vessel occlusive disease: the role of diabetes. *J Neuroimaging*. 2003;13:224–227.
66. Engelhardt M, Bruijnen H, Schnur C, Pfadenhauer K, Bohndorf K, Wolfe KD. Duplex scanning criteria for selection of patients for internal carotid artery endarterectomy. *Vasa*. 2005;34:36–40.
67. Eugene JR, Abdallah M, Miglietta M, Vernenkar VV, Pascual R, Briones R, Barnes T, Hager J. Carotid occlusive disease: primary care of patients with or without symptoms. *Geriatrics*. 1999;54:24–41.
68. Fabris F, Zanocchi M, Bo M, Scarafiotti C. Carotid plaques, aging, and risk factors for atherosclerosis. *Arch Gerontol Geriatr*. 1994;18:45–50.
69. Felberg RA, Christou I, Demchuk AM, Malkoff M, Alexandrov AV. Screening for intracranial stenosis with transcranial Doppler: the accuracy of mean flow velocity thresholds. *J Neuroimaging*. 2002;12:9–14.
70. Fernandes M, Keerthiraj B, Mahale AR, Kumar A, Dudekula A. Evaluation of carotid arteries in stroke patients using color Doppler sonography: a prospective study conducted in a tertiary care hospital in South India. *Int J Appl Basic Med Res*. 2016;6:38–44.

71. Ghanaati H, Golchin N, Motevalli M, Shakiba M, Jalali AH, Firouznia K. Carotid Doppler ultrasonography in preoperative assessment of coronary artery bypass graft surgery in an Iranian population: association between atherosclerosis risk factors and carotid stenosis. *Iran J Radiol*. 2009;6:125–129.
72. Giral P, Bruckert E, Dairou F, Boubrit K, Drobinski G, Chapman JM, Beucler I, Turpin G. Usefulness in predicting coronary artery disease by ultrasonic evaluation of the carotid arteries in asymptomatic hypercholesterolemic patients with positive exercise stress tests. *Am J Cardiol*. 1999;84:14–17.
73. Gao MJ, Hua Y, Jia LY, Ling C, Duan C. Characteristics of large vascular lesions detected by trancranial Doppler in diabetic patients complicated with hypertension. [Chinese]. *Chin J Cerebrovasc Dis*. 2011;8:298–302.
74. Greco G, Egorova NN, Moskowitz AJ, Gelijns AC, Kent KC, Manganaro AJ, Zwolak RM, Riles TS. A model for predicting the risk of carotid artery disease. *Ann Surg*. 2013;257:1168–1173.
75. Hedblad B, Janzon L, Jungquist G, Ogren M. Factors modifying the prognosis in men with asymptomatic carotid artery disease. *J Intern Med*. 1998;243:57–64.
76. Helfre M, Grange C, Riche B, Maucort-Boulch D, Thivolet C, Vouillarmet J. Usefulness of a systematic screening of carotid atherosclerosis in asymptomatic people with type 2 diabetes for cardiovascular risk reclassification. *Ann Endocrinol (Paris)*. 2017;78:14–19.
77. Hogberg D, Kragsterman B, Bjorck M, Tjarnstrom J, Wanhainen A. Carotid artery atherosclerosis among 65-year-old Swedish men—a population-based screening study. *Eur J Vasc Endovasc Surg*. 2014;48:5–10.
78. Hoshino T, Sissani L, Labreuche J, Ducrocq G, Lavallee PC, Meseguer E, Guidoux C, Cabrejo L, Hobeanu C, Gongora-Rivera F, et al. Prevalence of systemic atherosclerosis burdens and overlapping stroke etiologies and their associations with long-term vascular prognosis in stroke with intracranial atherosclerotic disease. *JAMA Neurol*. 2018;75:203–211.
79. Howard G, Baker WH, Chambless LE, Howard VJ, Jones AM, Toole JF. An approach for the use of Doppler ultrasound as a screening tool for hemodynamically significant stenosis (despite heterogeneity of Doppler performance). A multicenter experience. Asymptomatic Carotid Atherosclerosis Study Investigators. *Stroke*. 1996;27:1951–1957.
80. Hua Y, Tao YL, Li M, Yong Q, He W, Zhao H, Luo Y, Zhang Y, Peng T, Yu DL, et al. Multicenter ultrasound screening for the results of carotid atherosclerotic lesions in a Chinese population with high-risk of stroke: a preliminary analysis. [Chinese]. *Chin J Cerebrovasc Dis*. 2014;11:617–623.
81. Hughes JP, Dubin R, Rodriguez-Wong A, Porreca FJ. Risk focused screening for vascular disease: one University Hospital's experience. *J Vasc Ultrasound*. 2010;34:118–123.
82. Joakimsen O, Bonaa KH, Mathiesen EB, Stensland-Bugge E, Arnesen E. Prediction of mortality by ultrasound screening of a general population for carotid stenosis: the Tromso Study. *Stroke*. 2000;31:1871–1876.
83. Jonas DE, Feltner C, Amick HR, Sheridan S, Zheng ZJ, Watford DJ, Carter JL, Rowe CJ, Harris R. Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;161:336–346.
84. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, Geroulakos G, Abbott AL, Adovasio R, Ziani B, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014;59:956–967.e1.
85. Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, Madan J. A review and critique of modelling in prioritising and designing screening programmes. *Health Technol Assess*. 2007;11:1–145.
86. Kazemi-Bajestani SMR, van der Vlugt M, de Leeuw FE, Blankensteijn JD, Bredie SJH. A high prevalence of carotid artery stenosis in male patients older than 65 years, irrespective of presenting clinical manifestation of atherosclerotic diseases. *Angiology*. 2013;64:281–286.
87. Kazum S, Eisen A, Lev EI, Iakobishvili Z, Solodky A, Hasdai D, Kornowski R, Mager A. Prevalence of carotid artery disease among ambulatory patients with coronary artery disease. *Isr Med Assoc J*. 2016;18:100–103.
88. Lacroix P, Aboyans V, Criqui MH, Bertin F, Bouhamed T, Archambeaud F, Laskar M. Type-2 diabetes and carotid stenosis: a proposal for a screening strategy in asymptomatic patients. *Vasc Med*. 2006;11:93–99.
89. Lassila HC, Tyrrell KS, Matthews KA, Wolfson SK, Kuller LH. Prevalence and determinants of carotid atherosclerosis in healthy postmenopausal women. *Stroke*. 1997;28:513–517.
90. Lee TT, Solomon NA, Heidenreich PA, Oehlert J, Garber AM. Cost-effectiveness of screening for carotid stenosis in asymptomatic persons. *Ann Intern Med*. 1997;126:337–346.
91. LeFevre ML. Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161:356–362.
92. Li Q, Zhang Y, Wang M, Zhu X. Study on the screening program and risk factors of carotid artery stenosis with coronary artery disease. [Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2013;34:626–629.
93. Liang Y, Yan Z, Sun B, Cai C, Jiang H, Song A, Qiu C. Cardiovascular risk factor profiles for peripheral artery disease and carotid atherosclerosis among Chinese older people: a population-based study. *PLoS One*. 2014;9:e85927.
94. Lim LS, Haq N, Mahmood S, Hoeksema L, Surricchio M, Abraham-Katz RB, Bergeisen G, Compton MT, Guillory VJ, et al. Atherosclerotic cardiovascular disease screening in adults: American College of Preventive Medicine position statement on preventive practice. *Am J Prev Med*. 2011;40:381.e1–381.e10.
95. Lim YJ, Kim YW, Choe YH, Ki CS, Park SK. Risk factor analysis for development of asymptomatic carotid stenosis in Koreans. *J Korean Med Sci*. 2006;21:15–19.
96. Martin MJ, Mullenix PS, Crawford JV, Cuadrado DS, Andersen CA. Focused high-risk population screening for carotid arterial stenosis after radiation therapy for head and neck cancer. *Am J Surg*. 2004;187:594–598.
97. Mathiesen EB, Joakimsen O, Bonaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromso Study. *Cerebrovasc Dis*. 2001;12:44–51.
98. Meng X, Liu G, Wang X, Xu Q. Analysis of carotid atherosclerosis and related risk factors in a university physical examination population in Beijing. [Chinese]. *Natl Med J China*. 2017;97:2620–2624.
99. Moneta GL, Taylor DC, Zierler RE, Kazmers A, Beach K, Strandness DE Jr. Asymptomatic high-grade internal carotid artery stenosis: is stratification according to risk factors or duplex spectral analysis possible? *J Vasc Surg*. 1989;10:475–483.
100. Mostaza JM, Gonzalez-Juanatey JR, Castillo J, Lahoz C, Fernandez-Villaverde JM, Maestro-Saavedra FJ. Prevalence of carotid stenosis and silent myocardial ischemia in asymptomatic subjects with a low ankle-brachial index. *J Vasc Surg*. 2009;49:104–108.
101. Niederkorn K, Horner S, Schmidt R, Fazekas F, Lechner H. Ultrasonic assessment of the prevalence of carotid artery stenosis in asymptomatic volunteers. *J Neuroimaging*. 1991;1:119–122.
102. Obuchowski NA, Modic MT, Magdinec M, Masaryk TJ. Assessment of the efficacy of noninvasive screening for patients with asymptomatic neck bruits. *Stroke*. 1997;28:1330–1339.
103. O'Leary DH, Kronmal RA, Wolfson SK, Bond MG, Tracy RP, Gardin JM, Kittner SJ, Price TR, Savage PJ. Sonographic evaluation of carotid artery atherosclerosis in the elderly: relationship of disease severity to stroke and transient ischemic attack. *Radiology*. 1993;188:363–370.
104. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK Jr, Bommer W, Price TR, Gardin JM, Savage PJ. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke*. 1992;23:1752–1760.
105. Paprottka KJ, Saam D, Rubenthaler J, Schindler A, Sommer NN, Paprottka PM, Clevert DA, Reiser M, Saam T, Helck A. Prevalence and distribution of calcified nodules in carotid arteries in correlation with clinical symptoms. *Radiol Med*. 2017;122:449–457.
106. Park JH, Kim WH, Kim JH, Park TS, Baek HS. Prevalence of and risk factors for extracranial internal carotid artery stenosis in Korean Type 2 diabetic patients. *Diabet Med*. 2006;23:1377–1380.
107. Prati P, Vanuzzo D, Casaroli M, Di Chiara A, De Biasi F, Feruglio GA, Touboul PJ. Prevalence and determinants of carotid atherosclerosis in a general population. *Stroke*. 1992;23:1705–1711.
108. Prati P, Vanuzzo D, Casaroli M, Bader G, Mos L, Pilotto L, Canciani L, Ruscio M, Touboul PJ. Determinants of carotid plaque occurrence. A long-term prospective population study: the San Daniele Project. *Cerebrovasc Dis*. 2006;22:416–422.

109. Qiu J, Zhou Y, Yang X, Zhang Y, Li Z, Yan N, Wang Y, Ge S, Wu S, Zhao X, et al. The association between ankle-brachial index and asymptomatic cranial-carotid stenosis: a population-based, cross-sectional study of 5440 Han Chinese. *Eur J Neurol*. 2016;23:757–762.
110. Rockman CB, Hoang H, Guo Y, Maldonado TS, Jacobowitz GR, Talishinskiy T, Riles TS, Berger JS. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg*. 2013;57:327–337.
111. Rockman CB, Jacobowitz GR, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, Riles TS. Focused screening for occult carotid artery disease: patients with known heart disease are at high risk. *J Vasc Surg*. 2004;39:44–51.
112. Roh YN, Woo SY, Kim N, Kim S, Kim YW, Kim DI. Prevalence of asymptomatic carotid stenosis in Korea based on health screening population. *J Korean Med Sci*. 2011;26:1173–1177.
113. Ryglewicz D, Rozenfeld A, Baranska-Gieruszczak M, Czyrny M, Lechowicz W. Carotid artery disease in patients with ischemic stroke. Results of year-long observation conducted within the framework of prospective epidemiological studies, Warsaw, 1991–1992. [Polish]. *Neurol Neurochir Pol*. 1998;32:255–264.
114. Saleem MA, Sadat U, Walsh SR, Young VE, Gillard JH, Cooper DG, Gaunt ME. Role of carotid duplex imaging in carotid screening programmes—an overview. *Cardiovasc Ultrasound*. 2008;6:1–3.
115. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, Berger JS. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol*. 2013;61:1736–1743.
116. Shah B, Rockman CB, Guo Y, Chesner J, Schwartzbard AZ, Weintraub HS, Adelman MA, Riles TS, Berger JS. Diabetes and vascular disease in different arterial territories. *Diabetes Care*. 2014;37:1636–1642.
117. Silaghi CN, Fodor D, Craciun AM. Circulating matrix Gla protein: a potential tool to identify minor carotid stenosis with calcification in a risk population. *Clin Chem Lab Med*. 2013;51:1115–1123.
118. Smolen HJ, Cohen DJ, Samsa GP, Toole JF, Klein RW, Furiak NM, Lorell BH. Development, validation, and application of a microsimulation model to predict stroke and mortality in medically managed asymptomatic patients with significant carotid artery stenosis. *Value Health*. 2007;10:489–497.
119. Solomon NA, Heidenreich PA, Oehlert J, Garber AM. Cost-effectiveness of screening for carotid stenosis in asymptomatic persons. *Ann Intern Med*. 1997;126:337–346.
120. Stein RA, Rockman CB, Guo Y, Adelman MA, Riles T, Hiatt WR, Berger JS. Association between physical activity and peripheral artery disease and carotid artery stenosis in a self-referred population of 3 million adults. *Arterioscler Thromb Vasc Biol*. 2015;35:206–212.
121. Sutton-Tyrrell K, Alcorn HG, Wolfson SK Jr, Kelsey SF, Kuller LH. Predictors of carotid stenosis in older adults with and without isolated systolic hypertension. *Stroke*. 1993;24:355–361.
122. Touze E. Natural history of asymptomatic carotid artery stenosis. *Rev Neurol (Paris)*. 2008;164:793–800.
123. Walters GK, Jones CE, Meyd CJ, Cavaluzzi JA, Chachich BM. The role of carotid duplex ultrasonography in the therapeutic algorithm of extracranial carotid disease. *J Vasc Technol*. 1993;17:177–182.
124. Weisman SM, Brooks EA. Costs and benefits of bundled community-based screening for carotid artery stenosis, peripheral artery disease, and abdominal aortic aneurysm. *Manag Care*. 2015;24:45–53.
125. Whitty CJM, Sudlow CLM, Warlow CP. Investigating individual subjects and screening populations for asymptomatic carotid stenosis can be harmful. *J Neurol Neurosurg Psychiatry*. 1998;64:619–623.
126. Willeit J, Kiechl S. Prevalence and risk factors of asymptomatic extracranial carotid artery atherosclerosis: a population-based study. *Arterioscler Thromb*. 1993;13:661–668.
127. Woo SY, Joh JH, Han SA, Park HC. Prevalence and risk factors for atherosclerotic carotid stenosis and plaque a population-based screening study. *Medicine (Baltimore)*. 2017;96:e5999.
128. Wyman RA, Mays ME, McBride PE, Stein JM. Ultrasound-detected carotid plaque as a predictor of cardiovascular events. *Vasc Med*. 2006;11:123–130.
129. Yin D, Carpenter JP. Cost-effectiveness of screening for asymptomatic carotid stenosis. *J Vasc Surg*. 1998;27:245–255.
130. Yu RHY, Ho SC, Ho SSY, Chan SSG, Woo JLF, Ahuja AT. Carotid atherosclerosis and the risk factors in early postmenopausal Chinese women. *Maturitas*. 2009;63:233–239.
131. Zorach BB, Arpin PA, Nelson J, MacKey WC. Progression of moderate-to-severe carotid disease. *J Vasc Surg*. 2016;63:1505–1510.

Supplemental Material

Data S1.

Supplemental Methods. Search strategy Medline

(via PubMed interface)

1. "Carotid Stenosis"[Mesh]

2. "Carotid stenosis"[tiab] OR "Carotid artery stenosis"[tiab] OR "Carotid artery occlusion"[tiab] OR "Carotid artery stenoses"[tiab]

3. #1 OR #2

4. (Validat$ OR Predict$.ti. OR Rule$) OR (Predict$ AND (Outcome$ OR Risk$ OR Model$)) OR ((History OR Variable$ OR Criteria OR Scor$ OR Scoring$ OR Characteristic$ OR Finding$ OR Factor$) AND (Predict$ OR System$ OR Model$ OR Decision$ OR Identif$ OR Prognos$)) OR (Decision$ AND (Model$ OR Clinical$ OR Logistic Models/)) OR (Prognostic AND (History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$ OR Model$))[14]

5. "Mass Screening"[Mesh] OR Screen*[tiab]

6. Prevalence[Mesh] OR prevalenc* OR communit*[tiab]

7. "Population"[MeSH Terms] OR population*[tiab]

8. #5 OR #6 OR #7

9. #3 AND #4 AND #8

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286 references identified on March 1, 2019

EMBASE (via OVID EMBASE interface) *

1. exp carotid artery stenosis/

2. (carotid artery or carotid artery atherosclerosis or carotid artery disease or carotid artery diseases).ti,ab,kw.

3. stenos*.ti,ab,tw.

4. 2 AND 3

5. 1 OR 4

6. predict.ti.

7. (validat* or rule*).ti,ab.

8. (predict* and (outcome* or risk* or model*)).ti,ab.

9. ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.

10. decision*.ti,ab. and statistical model/

*https://www.nice.org.uk/guidance/ng50/documents/search-strategies

11. (decision* and (model* or clinical*)).ti,ab.

12. (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.

13. (stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.

14. receiver operating characteristic/

15. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14

16. exp mass screening/

17. Screening.ab,ti,kw.

18. exp prevalence/

19. Prevalence.ab,ti,kw.

20. 16 OR 17 OR 18 OR 19

21. 5 AND 15 AND 20

22. letter.pt. or letter/

23. note.pt.

24. conference abstract.pt.

25. editorial.pt.

26. case report/ or case study/

27. (letter or comment*).ti.

28. 22 OR 23 OR 24 OR 25 OR 26 OR 27

29. animal/ not human/

30. nonhuman/

31. exp animal experiment/

32. exp experimental animal/

33. animal model/

34. exp rodent/

35. (rat or rats or mouse or mice).ti.

36. 29 or 30 or 31 or 32 or 33 or 34 OR 35

37. 28 OR 36

38. 21 NOT 37

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764 references identified on March 1, 2019

Table S1. PRISMA checklist [12]

Section/topic	#	Checklist item	Reported
TITLE			
Title	1	Identification as a systematic review, meta-analysis, or both.	NA
ABSTRACT			
Structured summary	2	Structured abstract including background, objectives, data sources, study eligibility criteria, methodological assessment, synthesis method, results, conclusions and implications of key findings.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, outcomes (PICO design).	✓
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, and where it can be accessed.	✓
Eligibility criteria	6	Specify study characteristics and report characteristics (such as years considered, language, publication status) used as criteria for eligibility.	✓
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors, experts) in the search, and the date of last search.	✓
Search	8	Present full electronic search strategy, including limits used, such that it could be repeated.	✓
Study selection	9	State the process for selecting studies (i.e., screening, eligibility) and make sure that this is done by 2 authors.	✓
Data collection	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	✓
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	✓
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	✓
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	✓
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	✓
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, illustrated with a flow diagram.	✓
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	✓
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	✓
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression).	✓
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	✓

Table S2. Missing data per variable

Variable	Percentage of participants with missing
Age	0
Sex	0
Current or former smoker	11.4
Never smoked	11.4
Hypertension	3.69
Diabetes mellitus	6.22
Coronary heart disease	8.91
Stroke/TIA	9.90
Peripheral arterial disease	1.70
Height	1.79
SBP	0.48
DBP	31.8
HDL-C	0.3
LDL-C	8.6
TC/HDL-ratio	0.3

DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack.

Table S3. Full-text evaluation

	First author, year of publication	Selected population/ diseased population at high risk for ACS	Determination of risk factors of ACS without prediction model	Prevalence of ACS estimated only	No prevalence estimation of ACS	Health-economic research on ACS	Outcome: progression/regression of carotid artery stenosis	Review on screening	Other reviews	Diagnostic research with different determinant and/or outcome	Estimation of stroke risk or mortality in patients with ACS	External validation not possible	**Included studies**
1.	Abd Allah et al, 2010[36]		*										
2.	Aboyans et al, 2009[37]	*											
3.	Admani et al, 1991[38]		*										
4.	Ahn et al, 1991[39]	*											
5.	Aizenberg, 2016[40]							*					
6.	Alexandrov, 2003[41]								*				
7.	Ansari et al, 2011[42]	*											
8.	Archbold et al, 2001[43]	*											
9.	Ascher et al, 2001[44]	*											
10.	Ballard et al, 2007[45]			*									
11.	Barvalia et al, 2014[46]	*											
12.	Belcaro et al, 2000[47]							*					
13.	Berens et al, 1992[48]	*											
14.	Berger et al, 2013[49]		*										
15.	Bosevski et al, 2007[50]	*											
16.	Bosevski et al, 2015[51]	*											
17.	Carnicelli et al, 2014[52]									*			
18.	Carnicelli et al, 2013[53]									*			
19.	Carsten et al, 1999[54]									*			
20.	Chiquete et al, 2014[55]	*											
21.	Chua et al, 2007[56]									*			
22.	Chou et al, 2018[57]		*										
23.	Colgan et al, 1988[58] †		*										
24.	Cull et al, 2011[59]				*								
25.	de Weerd et al, 2014[23]												*
26.	Derdeyn et al, 1996[60]					*							
27.	Derdeyn et al, 1995[61]									*			
28.	Di Carli et al, 2005[62]	*											
29.	Duval et al, 2006[63]	*											
30.	Ellis et al, 1992[64]	*											
31.	Elmore et al, 2003[65]		*										
32.	Engelhardt et al, 2005[66]									*			
33.	Eugene et al, 1999[67]								*				
34.	Fabris et al, 1994[68]		*										
35.	Felberg et al, 2002[69]									*			
36.	Fernandes et al, 2016[70]										*		
37.	Ghanaati et al, 2009[71]	*											
38.	Giral et al, 1999[72]									*			
39.	Gao et al, 2011[73]	*											
40.	Greco et al, 2013[74]											*	
41.	Hedblad et al, 1998[75]										*		
42.	Helfre et al, 2017[76]	*											
43.	Hogberg et al, 2014[77]		*										
44.	Hoshino et al, 2018[78]	*											
45.	Howard et al, 1996[79]									*			
46.	Hua et al, 2014[80]												
47.	Hughes et al, 2010[81]		*										

	First author, year of publication	Selected population/ diseased population at high risk for ACS	Determination of risk factors of ACS without prediction model	Prevalence of ACS estimated only	No prevalence estimation of ACS	Health-economic research on ACS	Outcome: progression/regression of carotid artery stenosis	Review on screening	Other reviews	Diagnostic research with different determinant and/or outcome	Estimation of stroke risk or mortality in patients with ACS	External validation not possible	**Included studies**
48.	Jacobowitz et al, 2003[24]												*
49.	Joakimsen et al, 2000[82]										*		
50.	Jonas et al, 2014[83]							*					
51.	Kakkos et al, 2014[84]						*						
52.	Karnon et al, 2007[85]							*					
53.	Kazemi-Bajestani et al, 2013[86]	*											
54.	Kazum et al, 2016[87]	*											
55.	Lacroix et al, 2006[88]	*											
56.	Lassila et al, 1997[89]		*										
57.	Lee et al, 1997[90]							*					
58.	LeFevre et al, 2014[91]							*					
59.	Li et al, 2013[92]	*											
60.	Liang et al, 2014[93]		*										
61.	Lim et al, 2011[94]							*					
62.	Lim et al, 2006[95]		*										
63.	Martin et al, 2004[96]	*											
64.	Mathiesen et al, 2001[97]		*										
65.	Meng et al, 2017[98]		*										
66.	Moneta et al, 1989[99]										*		
67.	Mostaza et al, 2009[100]	*											
68.	Niederkorn et al, 1991[101]		*										
69.	Obuchowski et al, 1997[102]							*					
70.	O'Leary et al, 1993[103]										*		
71.	O'Leary et al, 1992[104]		*										
72.	Paprottka et al, 2017[105]	*											
73.	Park et al, 2006[106]	*											
74.	Prati et al, 1992[107] †		*										
75.	Prati et al, 2006[108]		*										
76.	Qiu et al, 2016[109]		*										
77.	Qureshi et al, 2001[25]												*
78.	Rockman et al, 2013[110]		*										
79.	Rockman et al, 2004[111]		*										
80.	Rodriguez Saldana et al, 1998			*									
81.	Roh et al, 2011[112]		*										
82.	Ryglewicz et al, 1998[113]	*											
83.	Saleem et al, 2008[114]							*					
84.	Savji et al, 2013[115]		*										
85.	Shah et al, 2014[116]		*										
86.	Silaghi et al, 2013[117]		*										
87.	Smolen et al, 2007[118]										*		
88.	Solomon et al, 1997[119]							*					
89.	Stein et al, 2015[120]		*										
90.	Suri et al, 2008[27]												*
91.	Sutton-Tyrrel et al, 1993[121]		*										
92.	Touzé et al, 2008[122]							*					
93.	Walters et al, 1993[123]									*			
94.	Weisman et al, 2015[124]					*							
95.	Whitty et al, 1998[125]									*			
96.	Willeit et al, 1993[126]		*										
97.	Woo et al, 2017[127]		*										

	First author, year of publication	Selected population/ diseased population at high risk for ACS	Determination of risk factors of ACS without prediction model	Prevalence of ACS estimated only	No prevalence estimation of ACS	Health-economic research on ACS	Outcome: progression/regression of carotid artery stenosis	Review on screening	Other reviews	Diagnostic research with different determinant and/or outcome	Estimation of stroke risk or mortality in patients with ACS	External validation not possible	**Included studies**
98.	Wyman et al, 2006[128]							*					
99.	Yan et al, 2018[26]												*
100	Yin et al, 1998[129]					*							
101	Yu et al, 2009[130]		*										
102	Zorach et al, 2016[131]						*						

† These articles were identified through cross-checking the reference lists of the studies included.
ACS indicates asymptomatic carotid artery stenosis.

Table S4. Characteristics of included model derivation and/or internal validation studies

	Predicted outcome	Data source	No. events / No. total patients	Modelling method	Handling of missing data	Selection methods for predictor selection	Correction for overoptimism	Number of predictive factors	Presentation of risk model	First author, year of publication
1.	≥70% ACS	Renqiu Stroke Screening Study, China	18 / 3006 (0.6%)	Logistic	No details provided	Backward	No	7	Regression coefficients and web calculator	Yan et al, 2018[26] *Model 1*
2.	≥50% ACS		33 / 3006 (1.1%)	Logistic	No details provided	Backward	No	8	Regression coefficients and web calculator	*Model 2*
3.	≥70% ACS	4 observational studies: Sweden, Norway, Germany, 4 communities in the US	127 / 23706 (0.5%)	Logistic	Imputation (single regression technique)	Based on the predictors for moderate stenosis	Yes	8	Original model, scoring chart	de Weerd et al, 2014[23] *Model 1*
4.	≥50% ACS		465 / 23706 (2.0%)	Logistic	Imputation (single regression technique)	Backward	Yes	8	Original model, scoring chart	*Model 2*
5.	>50% ACS	Screening, NY, US	38 / 394 (9.6%)	Logistic and X^2 analysis*	Not stated	Based on univariate analysis	No	4	Original model	Jacobowitz et al, 2003[24]
6.	≥60% ACS	Screening, NY, US	239 / 1331 (18%)	Logistic	Not stated	Based on univariate analysis	No	4	Original model	Qureshi et al, 2001[25]

ACS indicates asymptomatic carotid artery stenosis.

* Logistic regression and X^2 analysis were not used to weight the diagnostic variables in the prediction model.

Table S4. Characteristics of included model derivation and/or internal validation studies (continued)

	Discrimination		Calibration			First author, year of publication
	AUROC curve	Sensitivity / specificity	Calibration plot	Hosmer-Lemeshow test	Observed-expected ratio	
1.	0.806 (95% CI 0.724-0.889)	-	Yes	P > 0.05	High correlation between observed and predicted risk: r = 0.924, P < 0.001	Yan et al, 2018[26] *Model 1*†
2.	0.785 (95% CI 0.705-0.864)	-	Yes	P > 0.05	High correlation between observed and predicted risk: r = 0.955, P < 0.001	*Model 2*†
3.	0.87 (0.85-0.90)*	Yes	-	P = 0.071	-	de Weerd et al, 2014[23] *Model 1*‡
4.	0.82 (0.80-0.84)*	Yes	-	P = 0.585	-	*Model 2*‡
5.	-	-	-	-	-	Jacobowitz et al, 2003[24]
6.	0.706 (0.620-0.792)	-	-	-	-	Qureshi et al, 2001[25]

AUROC curve indicates area under receiver operating characteristic curve.
* This AUROC curve was calculated after bootstrapping techniques were applied. † Model 1 refers to the model that was developed with predicted outcome 70-100% ACS and model 2 refers to the model that was developed with predicted outcome 50-100% ACS. ‡ Model 1 refers to the model that was developed with predicted outcome >70% ACS and model 2 refers to the model that was developed with predicted outcome >50% ACS.

Table S5. Predictors (diagnostic variables) used in the prediction models

Risk predictors	Yan et al, 2018[26] (Model: ≥50% ACS)	Yan et al, 2018[26] (Model: ≥70% ACS)	De Weerd et al, 2014[23] (Both models)	Jacobowitz et al, 2003[24]	Qureshi et al, 2001[25]
Age*	*	*	*		*
Sex	*	*	*		
Current smoking			*	*	*
Hypertension				*	
Hypercholesterolemia				*	*
Diabetes mellitus			*		
History of stroke/TIA	*	*			
Coronary artery disease					*
Cardiac disease				*	
History of vascular disease†			*		
History of peripheral arterial disease	*	*			
Height (per cm increase)	*	*			
SBP‡	*		*		
DBP§	*		*		
HDL (per mmol/L increase)	*	*			
LDL (per mmol/L increase)		*			
TC/HDL ratio			*		

ACS indicates asymptomatic carotid stenosis; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack.

* Age was defined as per year increase (in Yan et al, 2018), categorized in four groups (in de Weerd et al, 2014) and dichotomized in >65 years and ≤65 years (in Qureshi et al, 2001). † History of vascular disease is defined as a medical history of either coronary heart disease or stroke. ‡ SBP was defined as per mmHg increase (in Yan et al, 2018), categorized in three groups (in de Weerd et al, 2014). § DBP was defined as per mmHg increase (in Yan et al, 2018), categorized in three groups (in de Weerd et al, 2014).

Table S6. Risk of bias assessment using PROBAST

First author, year of publication	Risk of bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
1. Yan et al, 2018[26] *Model 1**	-	?	?	-	+	+	?	-	?
2. *Model 2**	-	?	?	-	+	+	?	-	?
3. de Weerd et al, 2014[23] *Model 1*†	+	+	+	+	+	+	+	+	+
4. *Model 2*†	+	+	+	+	+	+	+	+	+
5. Jacobowitz et al, 2003[24]	-	?	+	-	-	+	+	-	-
6. Qureshi et al, 2001[25]	+	+	+	-	+	+	+	-	+

PROBAST indicates Prediction model Risk Of Bias ASessement Tool.

+ indicates low risk of bias / low concern regarding applicability; - indicates high risk of bias / high concern regarding applicability; and ? indicates unclear risk of bias / unclear concern regarding applicability.

An overview of all steps per prediction model is available on request.

* Model 1 refers to the model that was developed with predicted outcome 70-100% ACS and model 2 refers to the model that was developed with predicted outcome 50-100% ACS. † Model 1 refers to the model that was developed with predicted outcome >70% ACS and model 2 refers to the model that was developed with predicted outcome >50% ACS.

Table S7. Discrimination of each prediction model in the original cohort and validation cohorts

	First author, year of publication	Predicted outcome in original model	Model development study		Previous external validations	
			AUROC curve (95% CI) in derivation cohort	AUROC curve (95% CI) in internal validation cohort	Predicted outcome of external validation	AUROC curve (95% CI)
1.	Yan et al, 2018[26] *Model 1**	70-100% ACS	0.785 (0.705-0.864)	0.846 (0.756-0.937)‡	-	-
2.	*Model 2**	50-100% ACS	0.806 (0.724-0.889)	0.804 (0.719-0.889)‡	-	-
3.	de Weerd et al, 2014[23] *Model 1*†	>70% ACS	-	0.87 (0.85-0.90)§	70-100% ACS	0.672 (0.630-0.657)[26]
4.	*Model 2*†	>50% ACS	-	0.82 (0.80-0.84)§	50-100% ACS	0.680 (0.668-0.694)[26]
5.	Jacobowitz et al, 2003[24]	>50% ACS	-	-	70-100% ACS	0.670 (0.657-0.683)[26]
					50-100% ACS	0.648 (0.635-0.661)[26]
					75-100% ACS	0.60 (0.52-0.68)[27]
					50-100% ACS	0.60 (0.56-0.64)[27]
6.	Qureshi et al, 2001[25]	≥60% ACS	-	0.706 (0.620-0.792)‖	70-100% ACS	0.643 (0.630-0.656)[26]
					50-100% ACS	0.626 (0.612-0.639)[26]
					75-100% ACS	0.58 (0.50-0.67)[27]
					50-100% ACS	0.56 (0.53-0.60)[27]

ACS indicates asymptomatic carotid artery stenosis; AUROC curve, area under receiver operating characteristic curve; CI, confidence interval.

* Model 1 refers to the model that was developed with predicted outcome 70-100% ACS and model 2 refers to the model that was developed with predicted outcome 50-100% ACS. † Model 1 refers to the model that was developed with predicted outcome >70% ACS and model 2 refers to the model that was developed with predicted outcome >50% ACS. ‡ Model was internally validated using split sample with random division of participants: 60% was assigned to the derivation cohort and 40% was assigned to the validation cohort. § Model was internally validated with bootstrapping techniques to correct for overoptimism. ‖ Model was internally validated using split sample with random division of participants after excluding patients with history of transient ischemic attack, stroke, or carotid artery surgery: 66% was used for the derivation cohort and 33% was used for the validation cohort.

Table S7. Discrimination of each prediction model in the original cohort and validation cohorts (continued)

	First author, year of publication	Predicted outcome in original model	Our external validation			
			Predicted outcome of our external validation	AUROC curve (95% CI)	Predicted outcome of our external validation	AUROC curve (95% CI)
1.	Yan et al, 2018[26] *Model 1**	70-100% ACS	≥50% ACS	0.704 (0.700-0.709)	≥70% ACS	0.731 (0.720-0.742)
2.	*Model 2**	50-100% ACS	≥50% ACS	0.727 (0.722-0.732)	≥70% ACS	0.759 (0.749-0.770)
3.	de Weerd et al, 2014[23] *Model 1*†	>70% ACS	≥50% ACS	0.749 (0.744-0.753)	≥70% ACS	0.779 (0.770-0.789)
4.	*Model 2*†	>50% ACS	≥50% ACS	0.749 (0.744-0.753)	≥70% ACS	0.779 (0.770-0.789)
5.	Jacobowitz et al, 2003[24]	>50% ACS	≥50% ACS	0.673 (0.668-0.678)	≥70% ACS	0.689 (0.677-0.701)
6.	Qureshi et al, 2001[25]	≥60% ACS	≥50% ACS	0.703 (0.699-0.708)	≥70% ACS	0.701 (0.690-0.712)

ACS indicates asymptomatic carotid artery stenosis; AUROC curve, area under receiver operating characteristic curve; CI, confidence interval.

* Model 1 refers to the model that was developed with predicted outcome 70-100% ACS and model 2 refers to the model that was developed with predicted outcome 50-100% ACS. † Model 1 refers to the model that was developed with predicted outcome >70% ACS and model 2 refers to the model that was developed with predicted outcome >50% ACS.

Table S8. Clinical application of the prediction model with the best discrimination ***Outcome ≥50% ACS***

Sensitivity	Specificity	PPV	NPV	True positive	False negative	False positive	True negative	Observed prevalence	NNS
Highest decile of predicted risk of ≥50% ACS									
34.8%	90.5%	6.51%	98.6%	3,885	7,293	55,762	529,529	6.51%	15
Highest two deciles of predicted risk of ≥50% ACS									
55.0%	79.2%	4.81%	98.9%	6,149	5,029	121,676	463,615	4.81%	21
Two different levels of sensitivity for the outcome ≥50% ACS									
79.5%	56.6%	3.38%	99.3%	8,882	2,296	254,033	331,258	3.38%	30
90.0%	40.0%	2.78%	99.5%	10,060	1,118	351,171	234,120	2.78%	36

ACS indicates asymptomatic carotid artery stenosis; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value.

Table S8. Clinical application of the prediction model with the best discrimination (continued)

Outcome ≥70% ACS

Sensitivity	Specificity	PPV	NPV	True positive	False negative	False positive	True negative	Observed prevalence	NNS
Highest decile of predicted risk of ≥70% ACS									
41.7%	90.1%	1.42%	99.8%	848	1,185	58,799	535,637	1.42%	70
Highest two deciles of predicted risk of ≥70% ACS									
62.1%	78.5%	0.98%	99.8%	1,263	770	127,566	466,870	0.98%	102
Two different levels of sensitivity for the outcome ≥70% ACS									
76.8%	65.1%	0.75%	99.9%	1,561	472	207,361	387,075	0.75%	133
92.0%	40.0%	0.52%	99.9%	1,870	163	356,506	237,930	0.52%	192

ACS indicates asymptomatic carotid artery stenosis; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value.

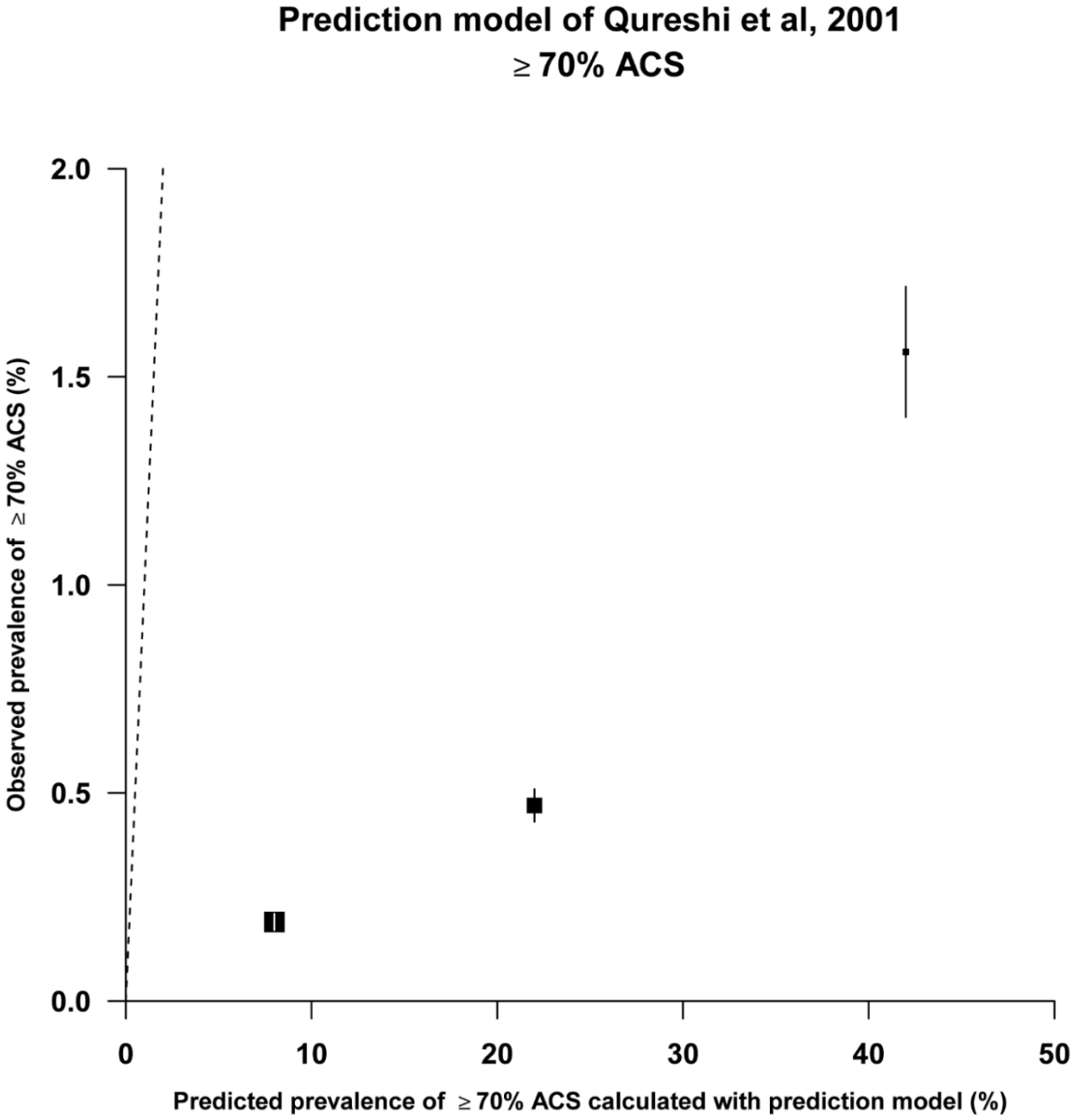
Table S9. Sensitivity analyses

	Prediction model	AUROC (95% CI) for ≥50% ACS			AUROC (95% CI) for ≥70% ACS		
		Complete-case analysis	Without patients with previous TIA or stroke	Without patients with previous CVD	Complete-case analysis	Without patients with previous TIA or stroke	Without patients with previous CVD
1	Yan et al, 2018[26] *Model 1**	0.697 (0.692-0.702)	0.692 (0.687-0.698)	0.668 (0.662-0.675)	0.723 (0.711-0.735)	0.715 (0.703-0.728)	0.686 (0.670-0.702)
2	*Model 2**	0.715 (0.708-0.720)	0.714 (0.709-0.720)	0.687 (0.680-0.693)	0.758 (0.744-0.771)	0.743 (0.731-0.755)	0.708 (0.692-0.724)
3	De Weerd et al, 2014[23] *Model 1*†	0.745 (0.739-0.751)	0.740 (0.735-0.745)	0.719 (0.713-0.724)	0.783 (0.770-0.795)	0.770 (0.759-0.781)	0.747 (0.733-0.761)
4	*Model 2*†	0.745 (0.739-0.751)	0.740 (0.735-0.745)	0.719 (0.713-0.724)	0.783 (0.770-0.795)	0.770 (0.759-0.781)	0.747 (0.733-0.761)
5	Jacobowitz et al, 2003[24]	0.673 (0.667-0.678)	0.668 (0.662-0.673)	0.644 (0.638-0.651)	0.689 (0.675-0.702)	0.680 (0.667-0.694)	0.647 (0.629-0.664)
6	Qureshi et al, 2001[25]	0.702 (0.696-0.707)	0.699 (0.694-0.704)	0.679 (0.673-0.685)	0.698 (0.686-0.710)	0.695 (0.683-0.707)	0.668 (0.652-0.683)

ACS indicates asymptomatic carotid artery stenosis; AUROC curve, area under receiver operating characteristic curve; CI, confidence interval; CVD, cardiovascular disease; TIA, transient ischemic attack.

* Model 1 refers to the model that was developed with predicted outcome 70-100% ACS and model 2 refers to the model that was developed with predicted outcome 50-100% ACS. † Model 1 refers to the model that was developed with predicted outcome >70% ACS and model 2 refers to the model that was developed with predicted outcome >50% ACS.

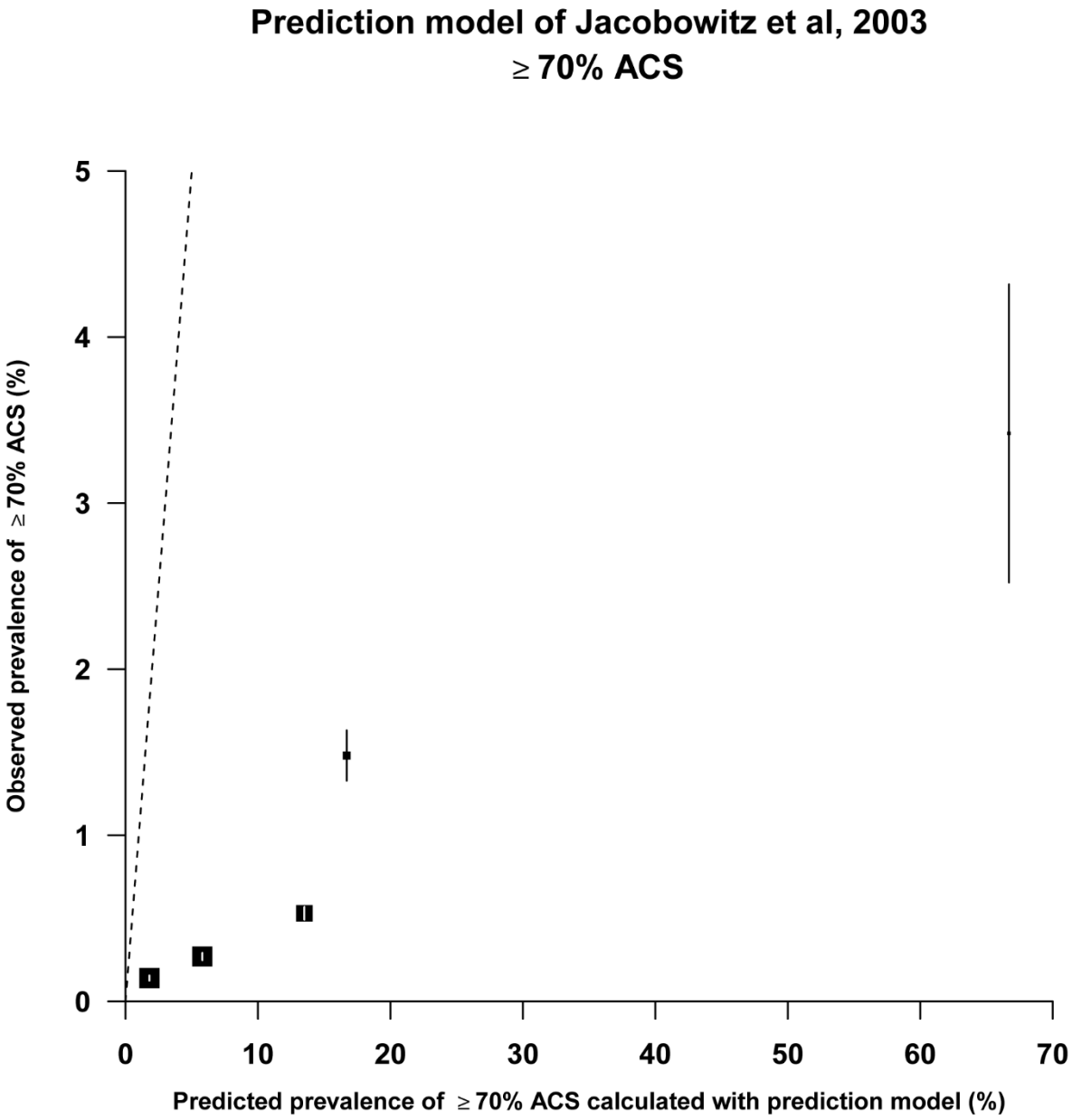
Figure S1. Calibration plots for outcome ≥70% ACS



	Risk groups		
Predicted prevalence (%)	8	22	42
Number of patients with ≥50% ACS	702	960	371
Observed prevalence in validation cohort (%)	0.19	0.47	1.56

ACS indicates asymptomatic carotid artery stenosis.

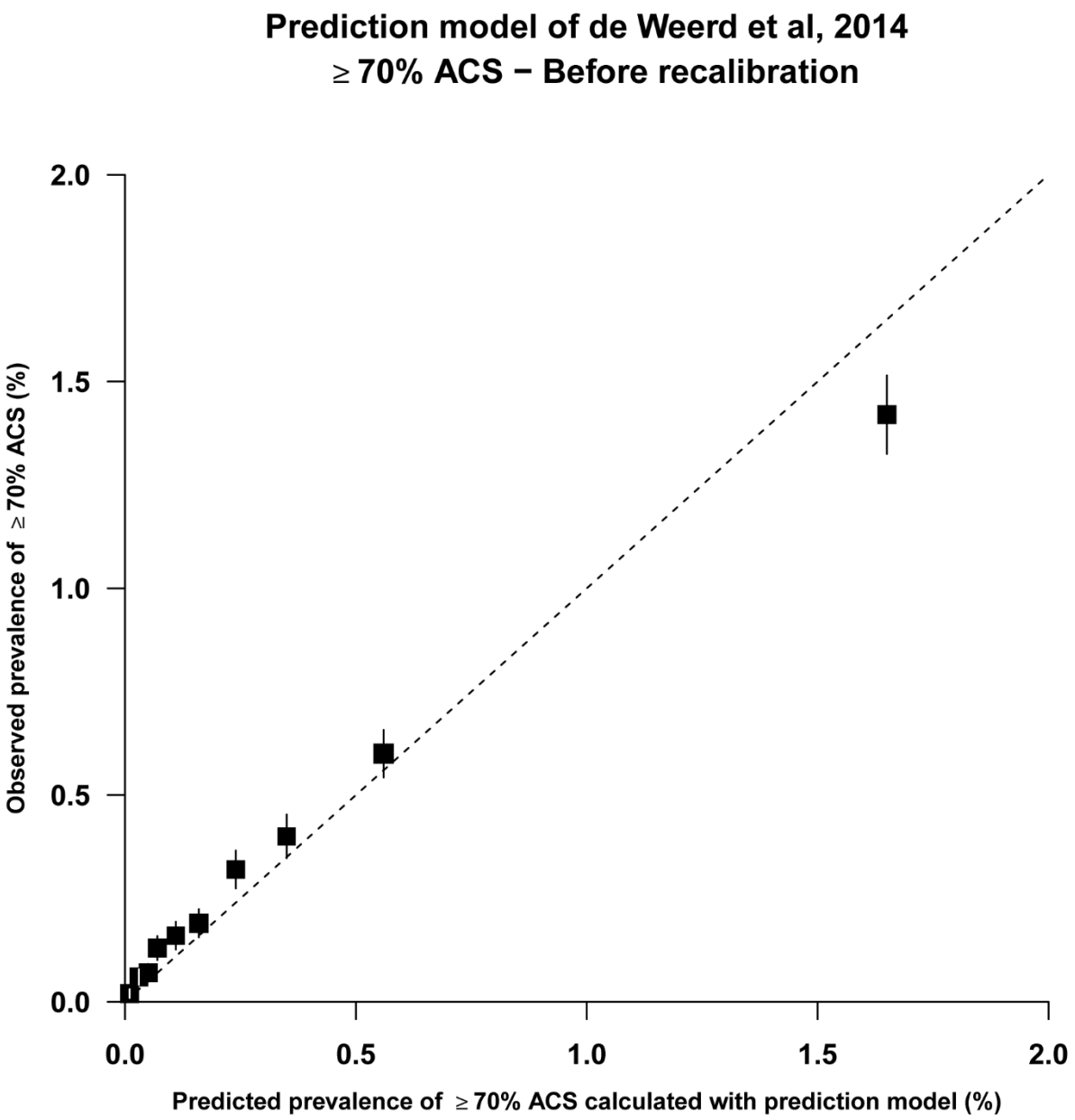
Figure S2. A Calibration plot of external validation of the prediction model developed by Qureshi et al, 2001 (originally developed for ≥60% ACS).[25] It shows the predicted and observed prevalence of ≥70% ACS. The boxes represent the risk groups as provided in the original article and vertical lines represent the 95% confidence intervals.



	Risk groups				
Predicted prevalence (%)	1.8	5.8	13.5	16.7	66.7
Number of patients with ≥50% ACS	308	585	724	362	54
Observed prevalence in validation cohort (%)	0.14	0.27	0.53	1.48	3.42

ACS indicates asymptomatic carotid artery stenosis.

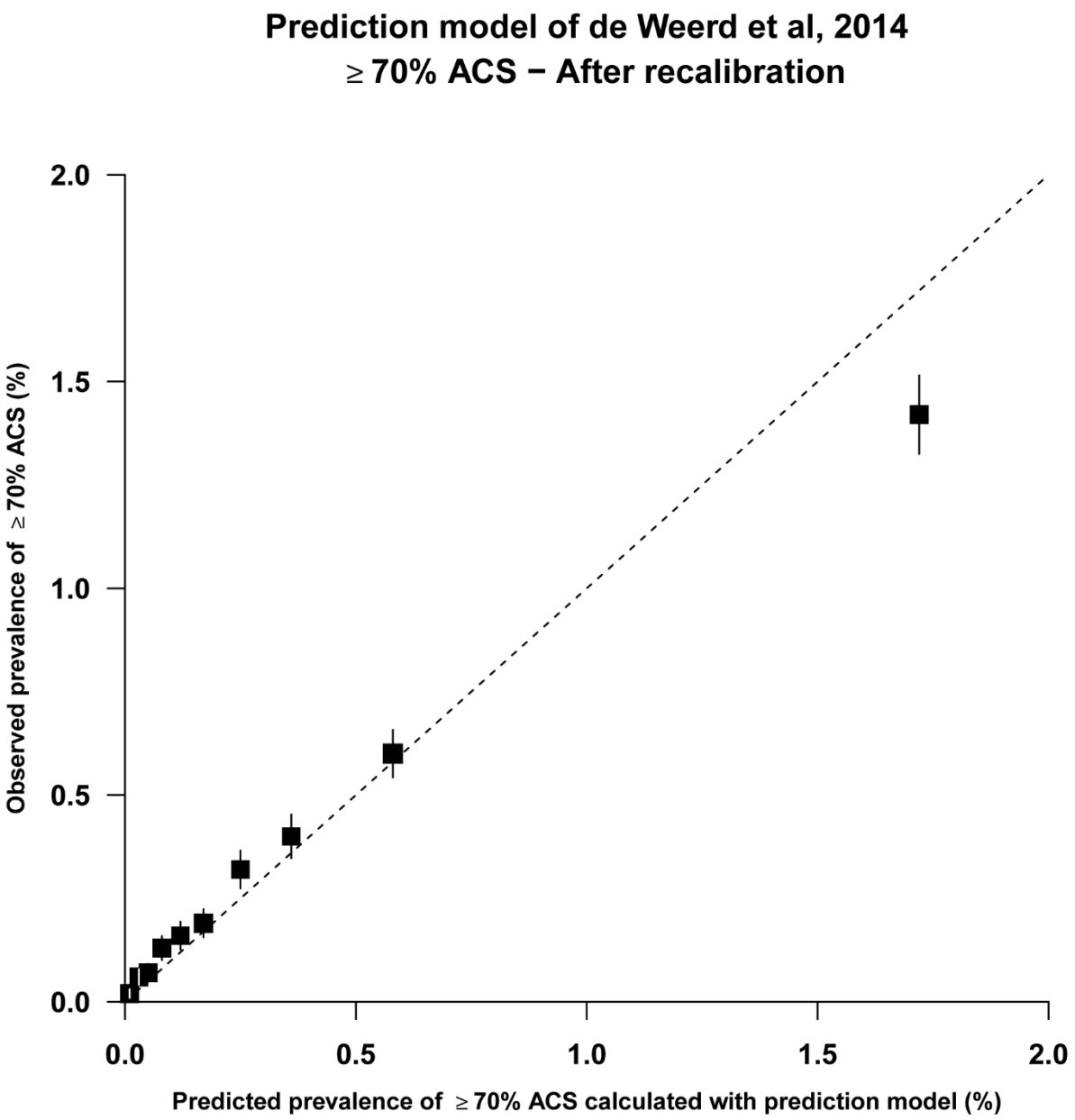
Figure S2. B Calibration plot of external validation of the prediction model developed by Jacobowitz et al, 2003 (originally developed for >50% ACS).[24] It shows the predicted and observed prevalence of ≥70% ACS. The boxes represent the risk groups as provided in the original article and vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.03	0.05	0.07	0.11	0.16	0.24	0.35	0.56	1.65
Number of patients with ≥50% ACS	10	33	43	77	88	120	181	218	414	849
Observed prevalence in validation cohort (%)	0.02	0.06	0.07	0.13	0.16	0.19	0.32	0.40	0.60	1.42

ACS indicates asymptomatic carotid artery stenosis.

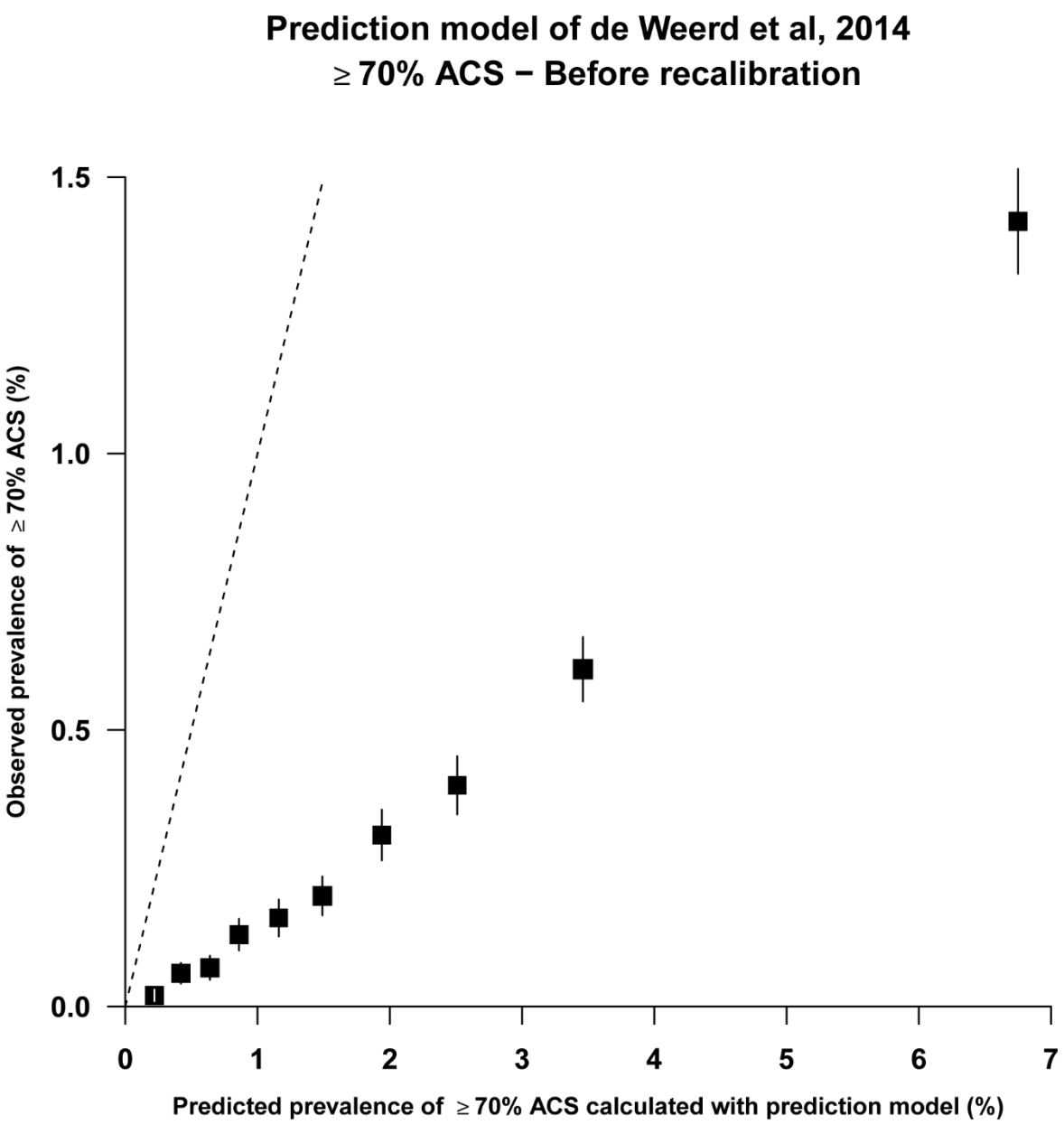
Figure S2. C Calibration plot of external validation of the prediction model (originally developed for ≥70% ACS) developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥70% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.03	0.05	0.08	0.12	0.17	0.25	0.36	0.58	1.72
Number of patients with ≥50% ACS	10	33	43	77	88	120	181	218	415	848
Observed prevalence in validation cohort (%)	0.02	0.06	0.07	0.13	0.16	0.19	0.32	0.40	0.60	1.42

ACS indicates asymptomatic carotid artery stenosis.

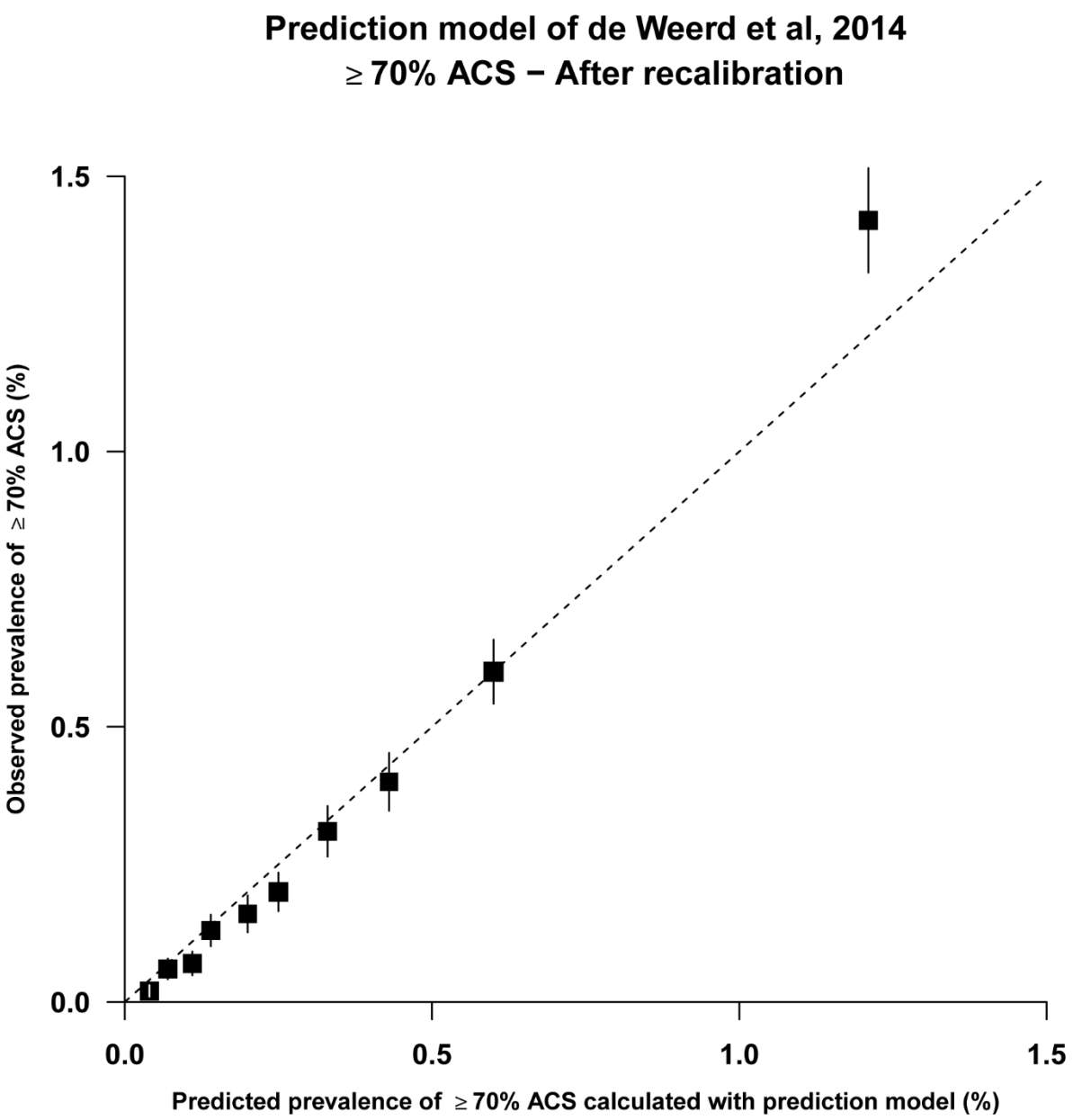
Figure S2. D Calibration plot of external validation of the prediction model for ≥70% ACS developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥70% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.22	0.42	0.64	0.86	1.16	1.49	1.94	2.51	3.46	6.75
Number of patients with ≥50% ACS	10	33	44	76	88	128	180	216	413	845
Observed prevalence in validation cohort (%)	0.02	0.06	0.07	0.13	0.16	0.20	0.31	0.40	0.61	1.42

ACS indicates asymptomatic carotid artery stenosis.

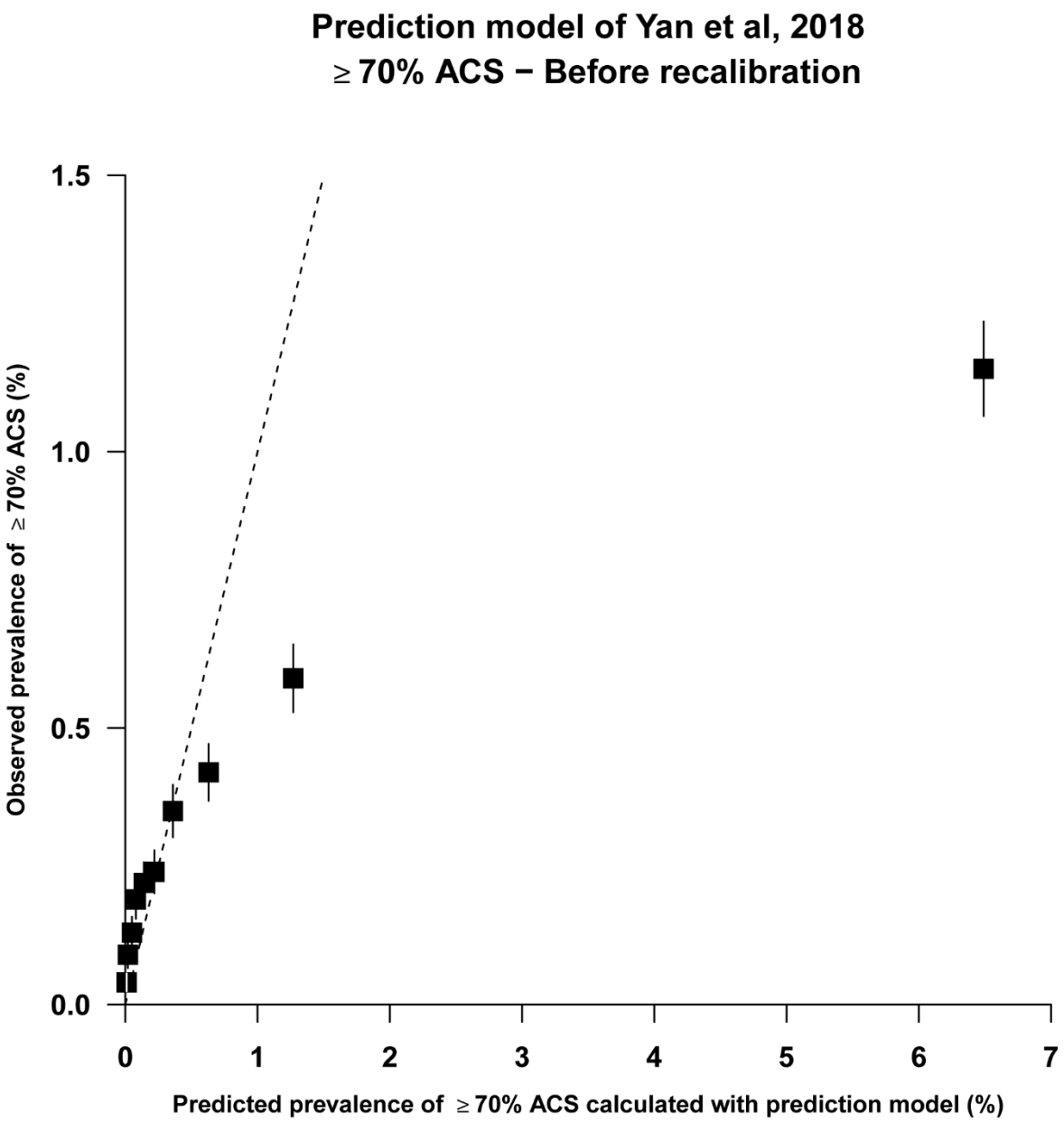
Figure S2. E Calibration plot of external validation of the prediction model (originally developed for ≥50% ACS) developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥70% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.04	0.07	0.11	0.14	0.20	0.25	0.33	0.43	0.60	1.21
Number of patients with ≥50% ACS	10	33	44	76	88	128	180	216	412	846
Observed prevalence in validation cohort (%)	0.02	0.06	0.07	0.13	0.16	0.20	0.31	0.40	0.60	1.42

ACS indicates asymptomatic carotid artery stenosis.

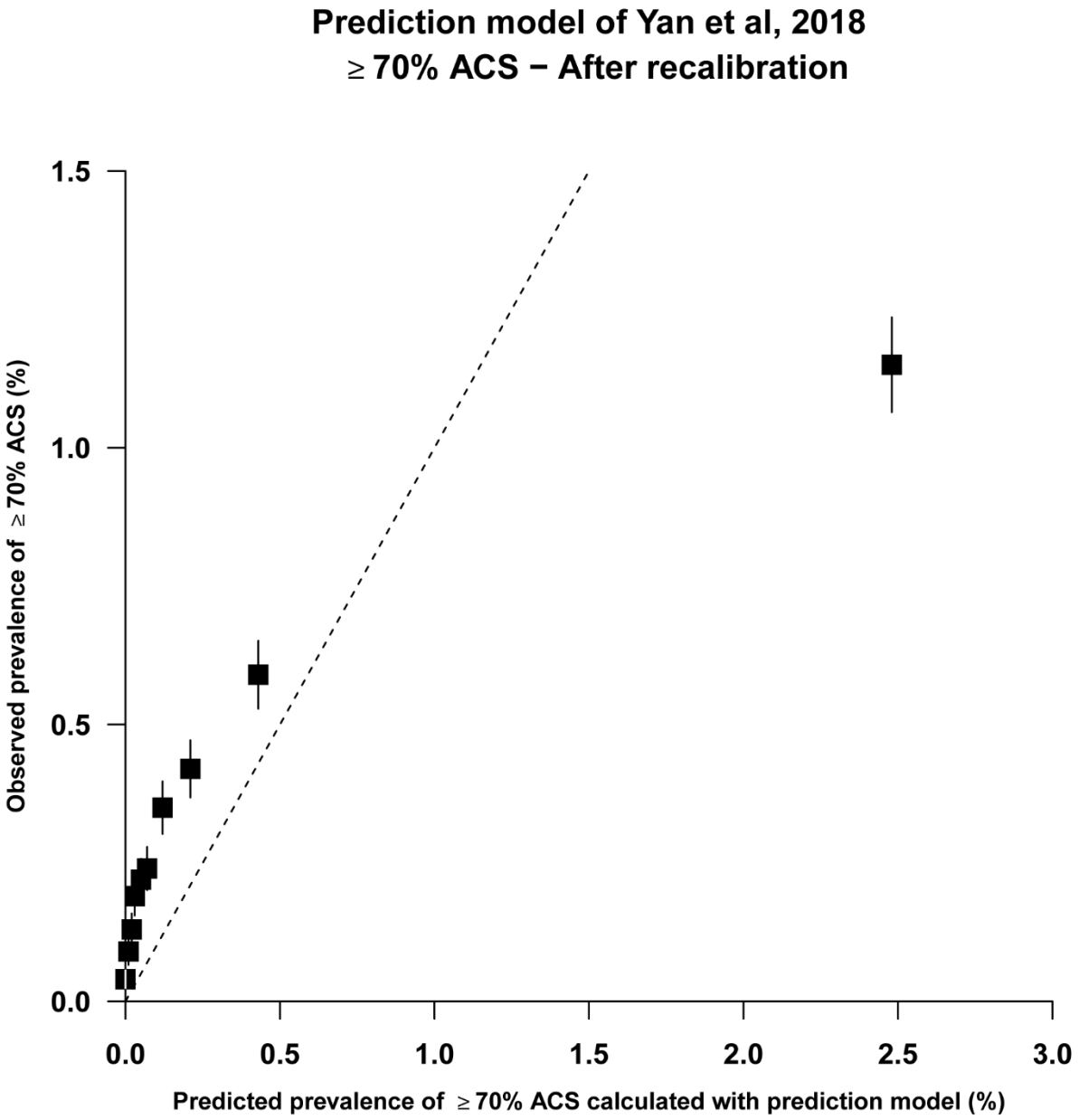
Figure S2. F Calibration plot of external validation of the prediction model (originally developed for ≥50% ACS) developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥70% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.02	0.05	0.08	0.14	0.22	0.36	0.63	1.27	6.49
Number of patients with ≥50% ACS	24	54	76	114	129	141	209	248	351	688
Observed prevalence in validation cohort (%)	0.04	0.09	0.13	0.19	0.22	0.24	0.35	0.42	0.59	1.15

ACS indicates asymptomatic carotid artery stenosis.

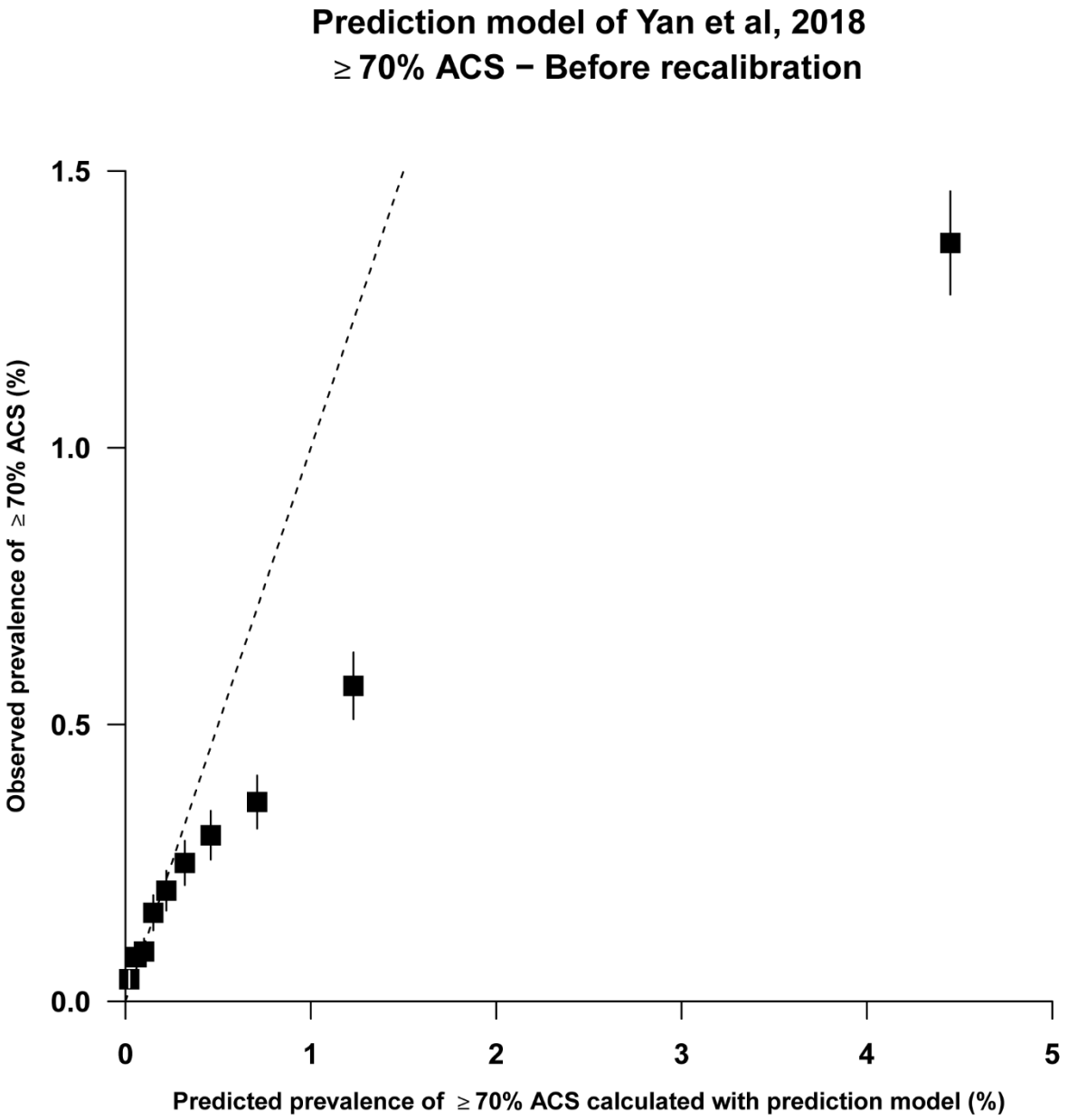
Figure S2. G. Calibration plot of external validation of the prediction model (originally developed for ≥70% ACS) developed by de Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥70% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.00	0.01	0.02	0.03	0.05	0.07	0.12	0.21	0.43	2.48
Number of patients with ≥50% ACS	24	54	76	114	129	141	209	248	351	687
Observed prevalence in validation cohort (%)	0.04	0.09	0.13	0.19	0.22	0.24	0.35	0.42	0.59	1.15

ACS indicates asymptomatic carotid artery stenosis.

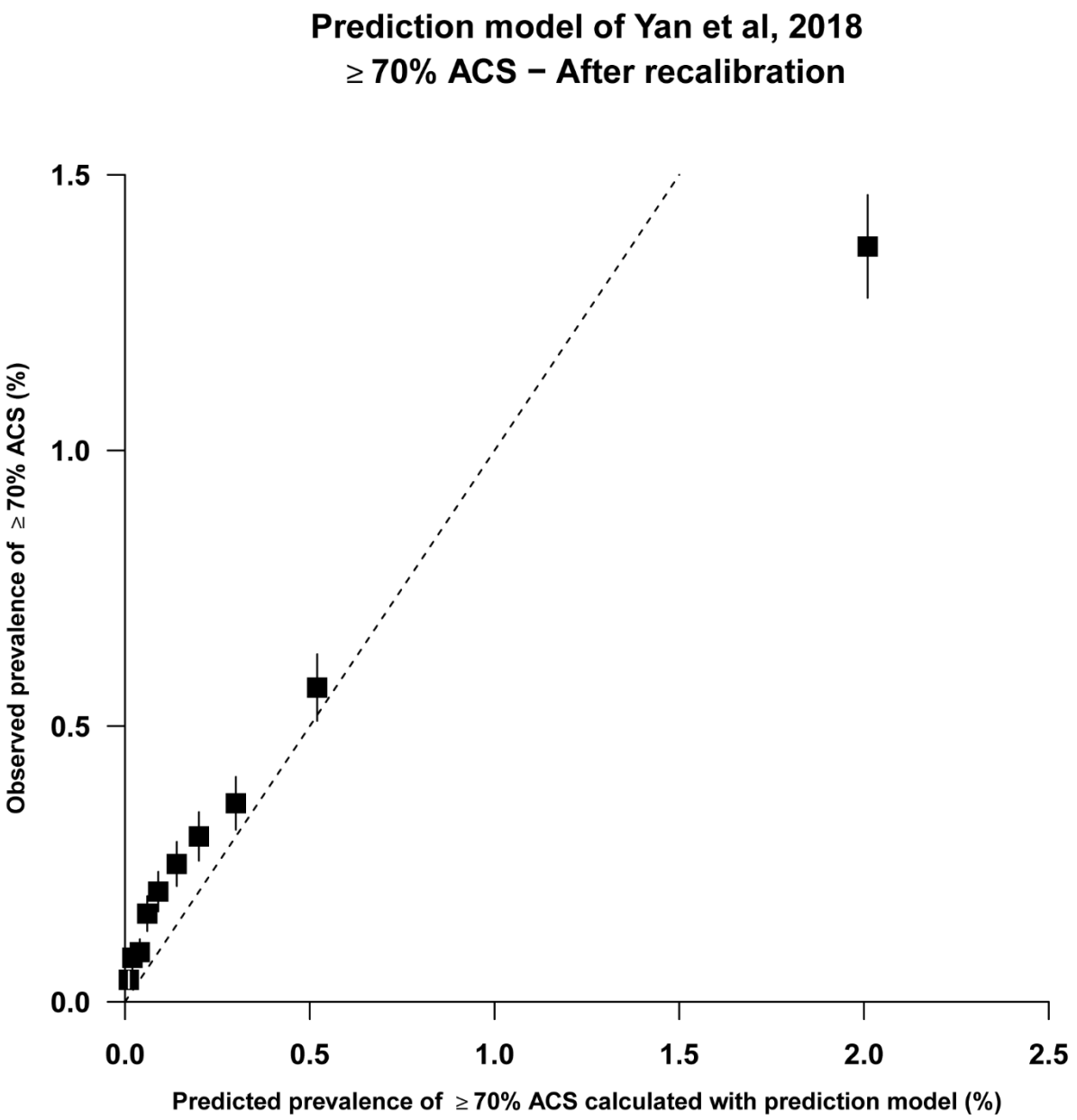
Figure S2. H Calibration plot of external validation of the prediction model (originally developed for ≥70% ACS) developed by de Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥70% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.02	0.06	0.10	0.15	0.22	0.32	0.46	0.71	1.23	4.45
Number of patients with ≥50% ACS	21	49	51	93	120	149	180	214	338	818
Observed prevalence in validation cohort (%)	0.04	0.08	0.09	0.16	0.20	0.25	0.30	0.36	0.57	1.37

ACS indicates asymptomatic carotid artery stenosis.

Figure S2. I Calibration plot of external validation of the prediction model (originally developed for ≥50% ACS) developed by de Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥70% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.

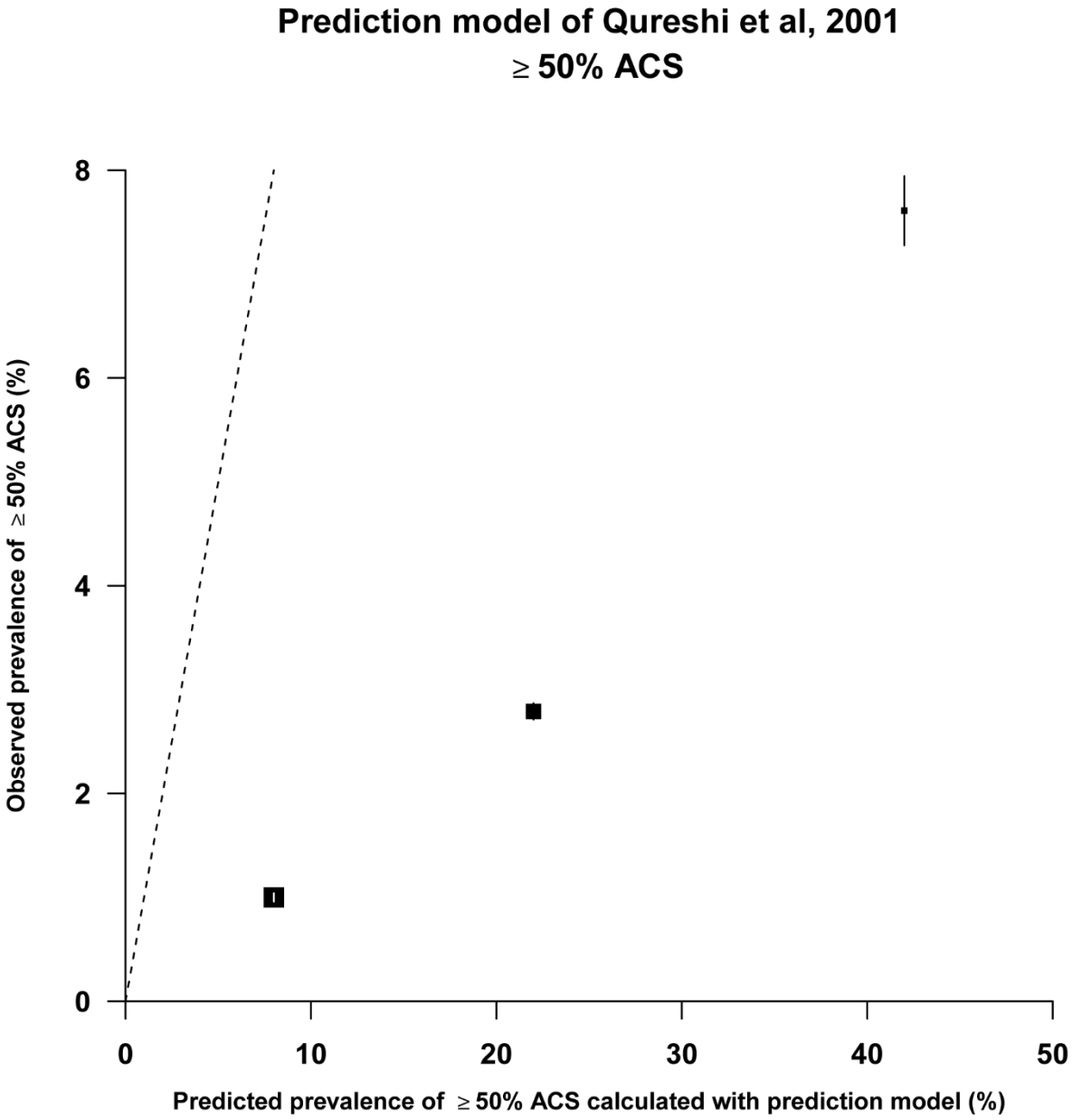


	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.02	0.04	0.06	0.09	0.14	0.20	0.30	0.52	2.01
Number of patients with ≥50% ACS	21	49	51	93	120	149	180	214	338	818
Observed prevalence in validation cohort (%)	0.04	0.08	0.09	0.16	0.20	0.25	0.30	0.35	0.57	1.37

ACS indicates asymptomatic carotid artery stenosis.

Figure S2. J Calibration plot of external validation of the prediction model (originally developed for ≥50% ACS) developed by de Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥70% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.

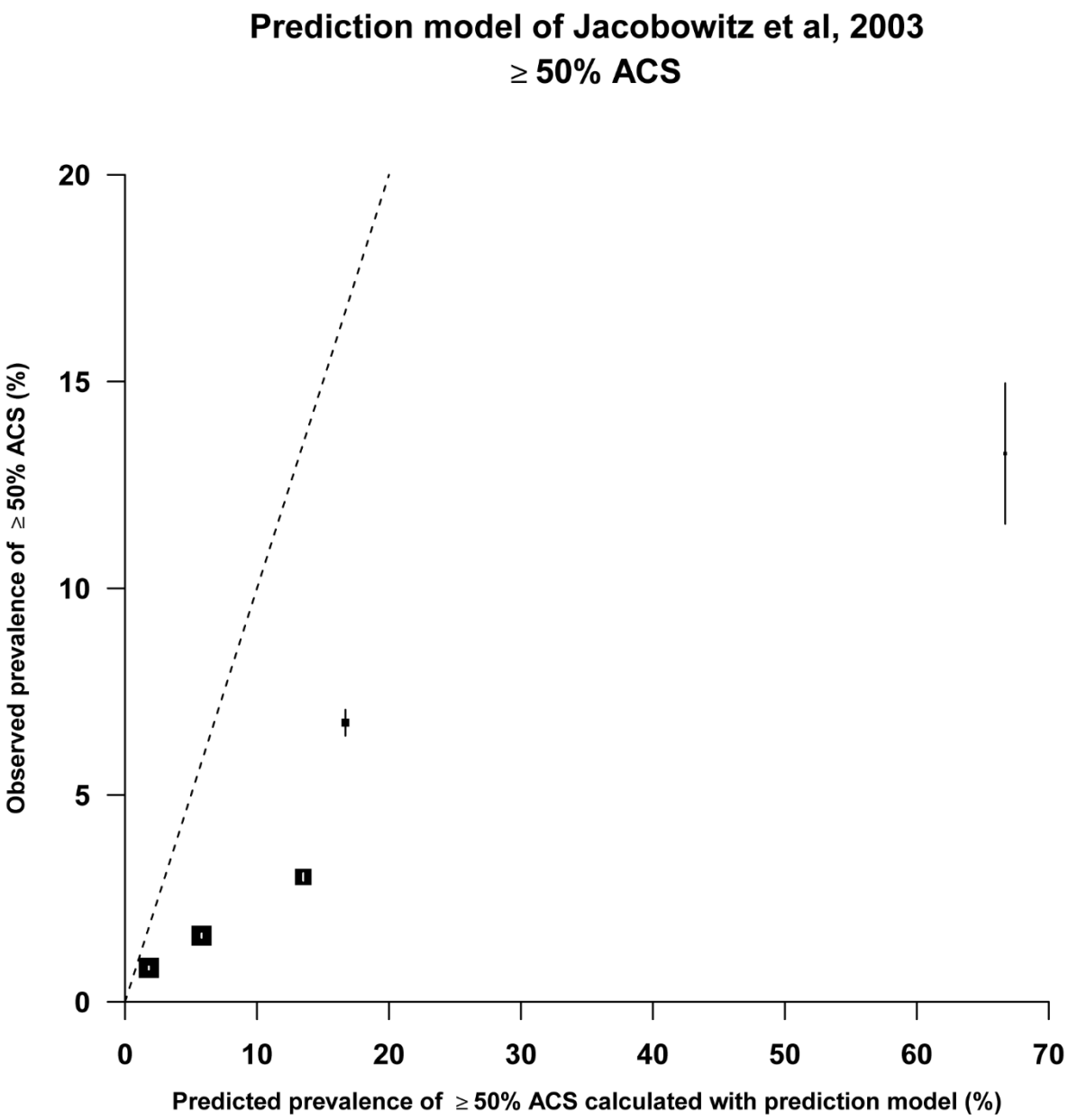
Figure S2. Calibration plots for outcome ≥50% ACS



	Risk groups		
Predicted prevalence (%)	8	22	42
Number of patients with ≥50% ACS	3713	5658	1807
Observed prevalence in validation cohort (%)	1.00	2.79	7.61

ACS indicates asymptomatic carotid artery stenosis.

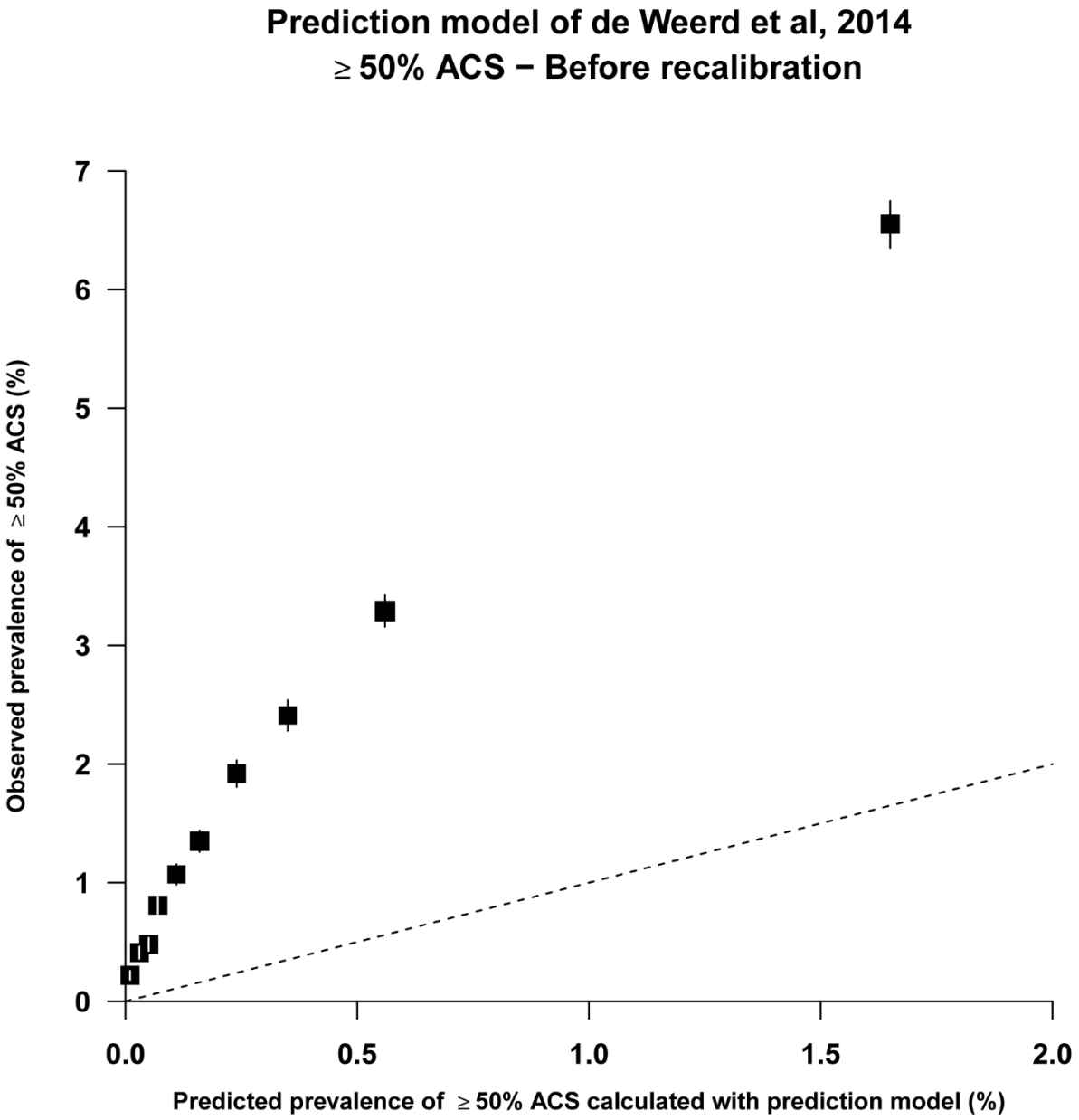
Figure S2. A Calibration plot of external validation of the prediction model developed by Qureshi et al, 2001 (originally developed for ≥60% ACS).[25] It shows the predicted and observed prevalence of ≥50% ACS. The boxes represent the risk groups as provided in the original article and vertical lines represent the 95% confidence intervals.



	Risk groups				
Predicted prevalence (%)	1.8	5.8	13.5	16.7	66.7
Number of patients with ≥50% ACS	1798	3419	4100	1658	203
Observed prevalence in validation cohort (%)	0.82	1.60	3.02	6.75	13.26

ACS indicates asymptomatic carotid artery stenosis.

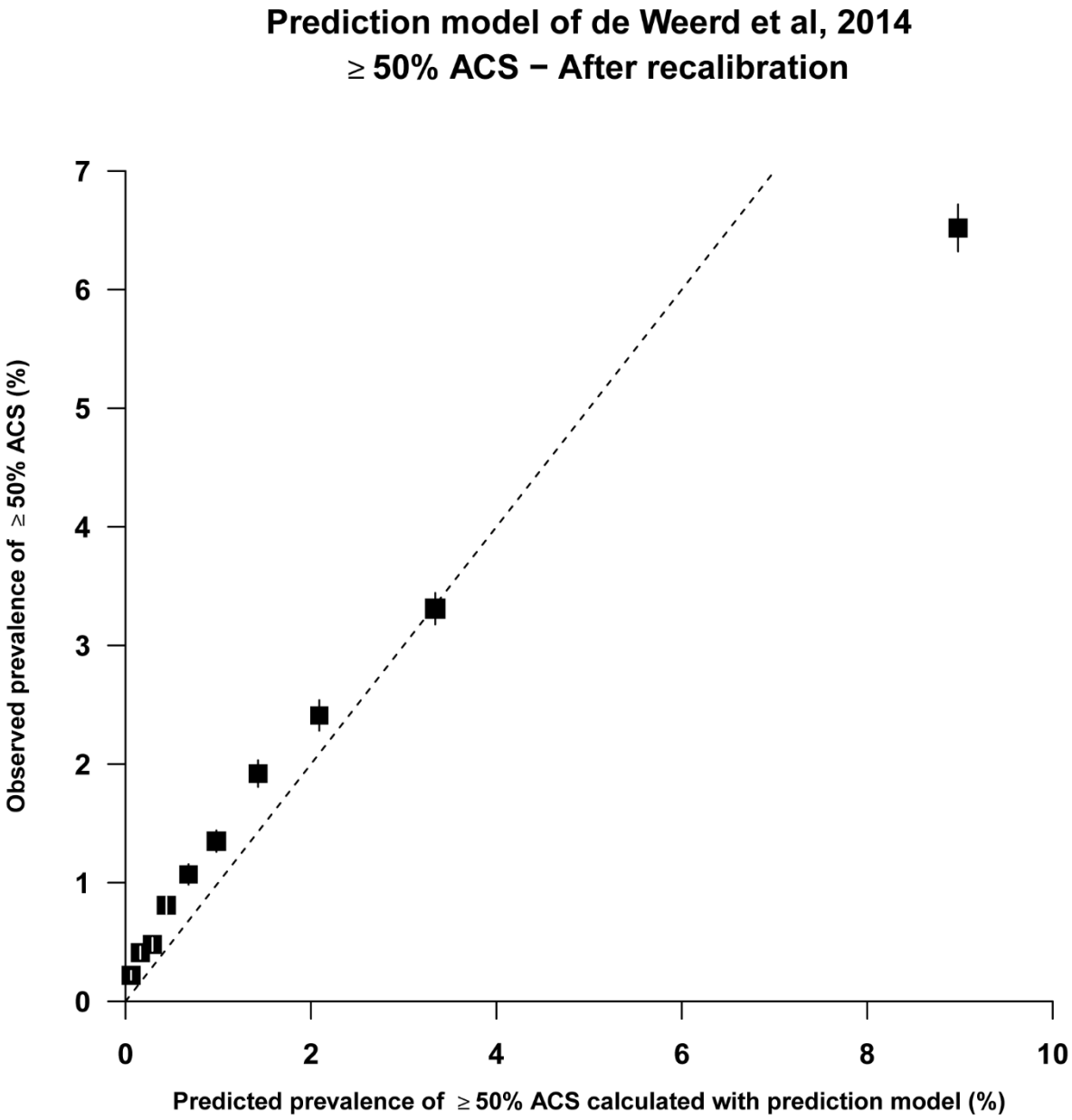
Figure S2. B Calibration plot of external validation of the prediction model developed by Jacobowitz et al, 2003 (originally developed for >50% ACS).[24] It shows the predicted and observed prevalence of ≥50% ACS. The boxes represent the risk groups as provided in the original article and vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.03	0.05	0.07	0.11	0.16	0.24	0.35	0.56	1.65
Number of patients with ≥50% ACS	130	246	285	480	583	851	1103	1316	2273	3911
Observed prevalence in validation cohort (%)	0.22	0.41	0.48	0.81	1.07	1.35	1.92	2.41	3.29	6.55

ACS indicates asymptomatic carotid artery stenosis.

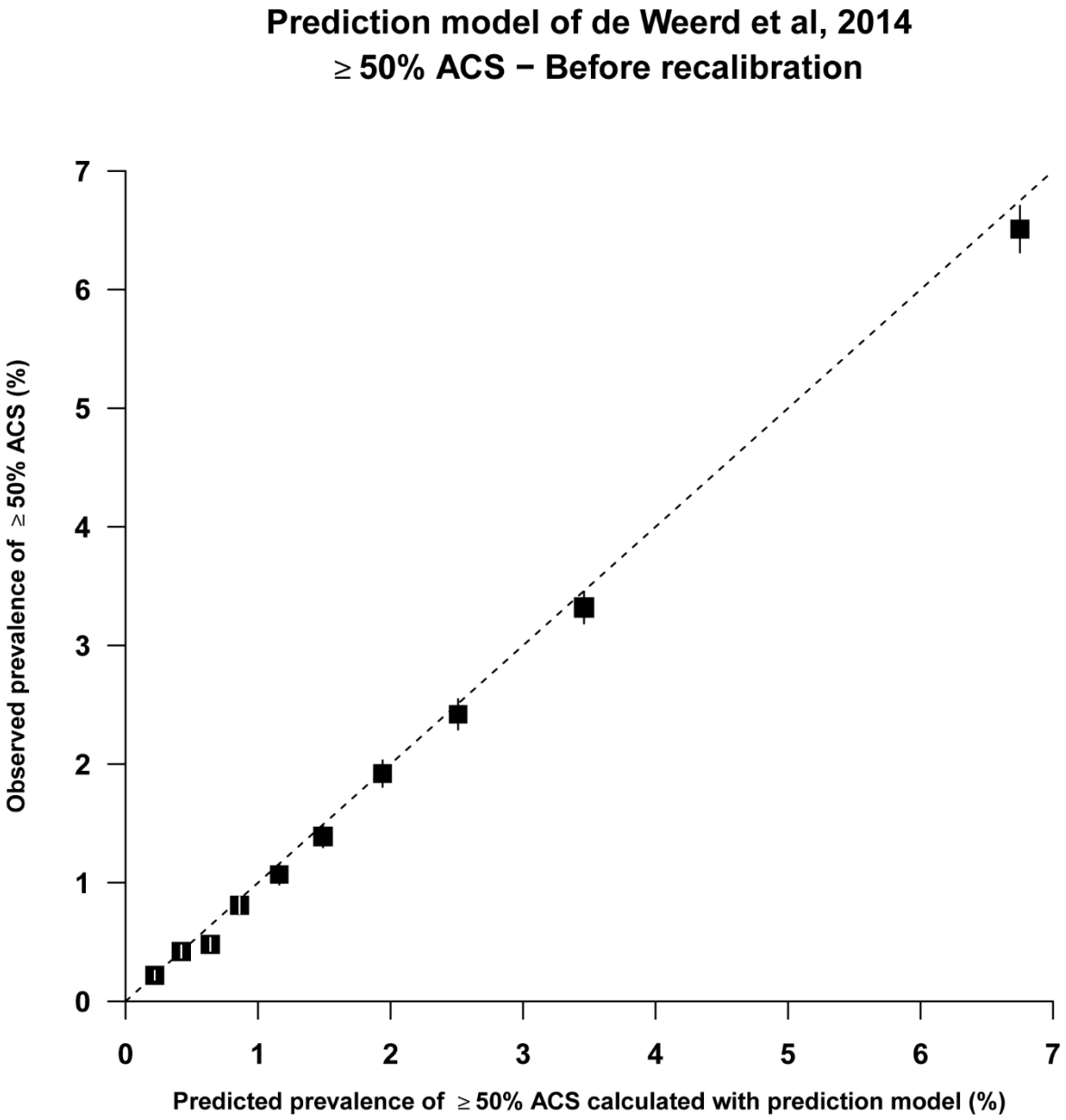
Figure S2. C Calibration plot of external validation of the prediction model developed by de Weerd et al, 2014 (originally developed for ≥70% ACS).[23] It shows the predicted and observed prevalence of ≥50% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.06	0.16	0.29	0.44	0.68	0.98	1.43	2.09	3.34	8.98
Number of patients with ≥50% ACS	130	246	285	480	584	851	1103	1317	2291	3891
Observed prevalence in validation cohort (%)	0.22	0.41	0.48	0.81	1.07	1.35	1.92	2.41	3.31	6.52

ACS indicates asymptomatic carotid artery stenosis.

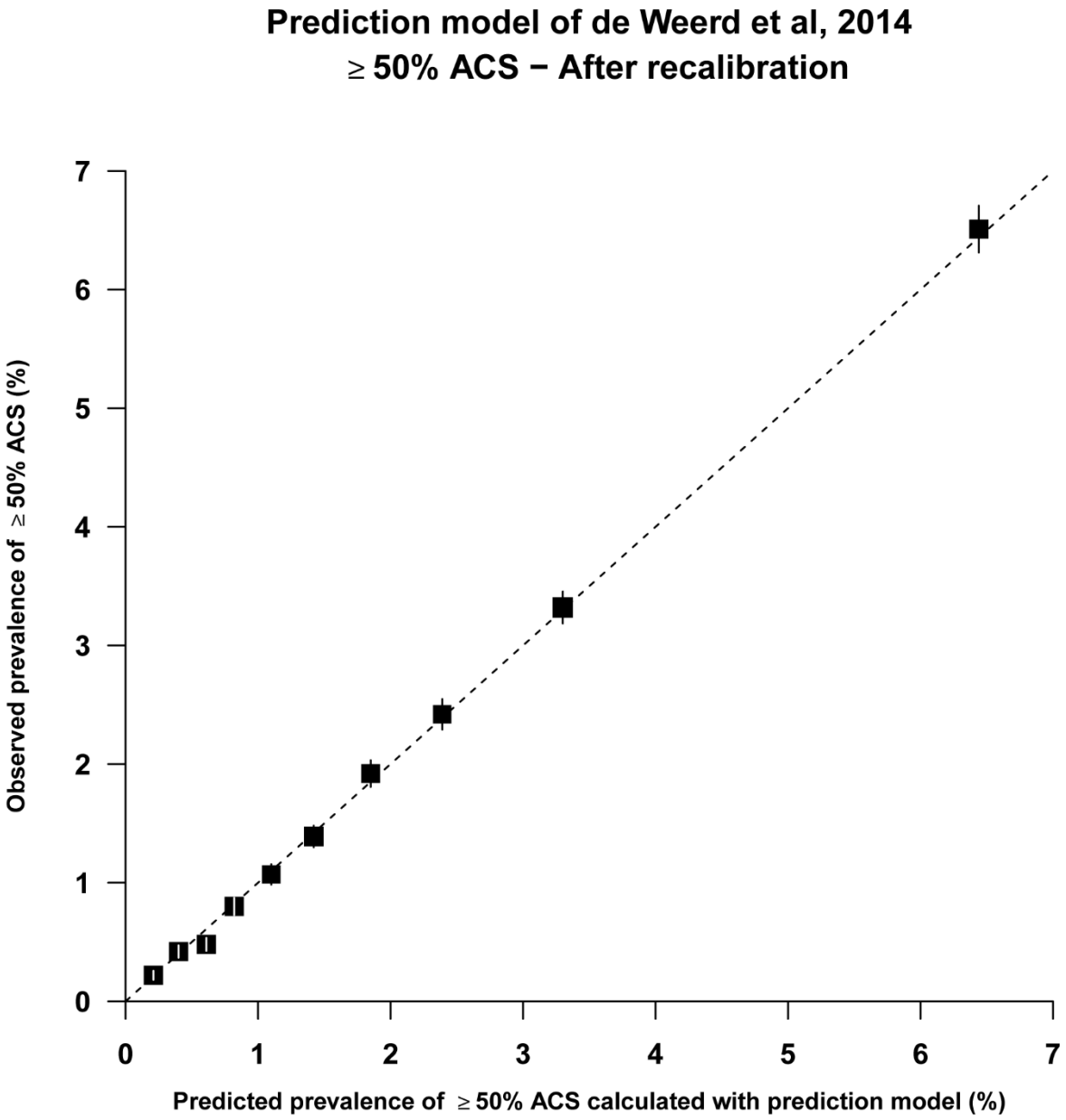
Figure S2. D Calibration plot of external validation of the prediction model developed by de Weerd et al, 2014 (originally developed for ≥70% ACS).[23] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.22	0.42	0.64	0.86	1.16	1.49	1.94	2.51	3.46	6.75
Number of patients with ≥50% ACS	130	251	284	480	589	879	1096	1320	2263	3886
Observed prevalence in validation cohort (%)	0.22	0.42	0.48	0.81	1.07	1.39	1.92	2.42	3.32	6.51

ACS indicates asymptomatic carotid artery stenosis.

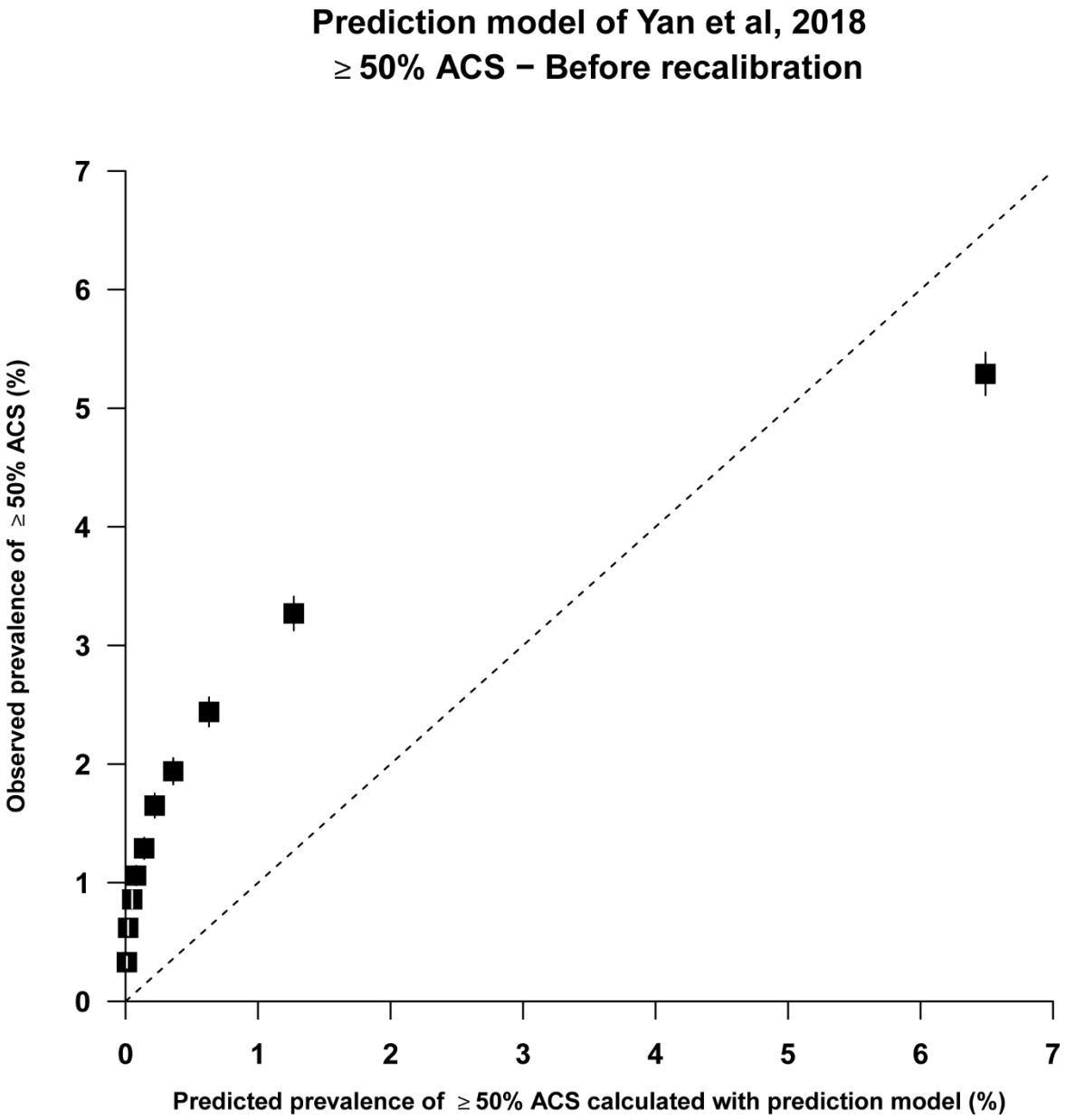
Figure S2. E Calibration plot of external validation of the prediction model for ≥50% ACS developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥50% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.21	0.40	0.61	0.82	1.10	1.42	1.85	2.39	3.30	6.44
Number of patients with ≥50% ACS	131	250	284	480	589	879	1096	1320	2264	3885
Observed prevalence in validation cohort (%)	0.22	0.42	0.48	0.80	1.07	1.39	1.92	2.42	3.32	6.51

ACS indicates asymptomatic carotid artery stenosis.

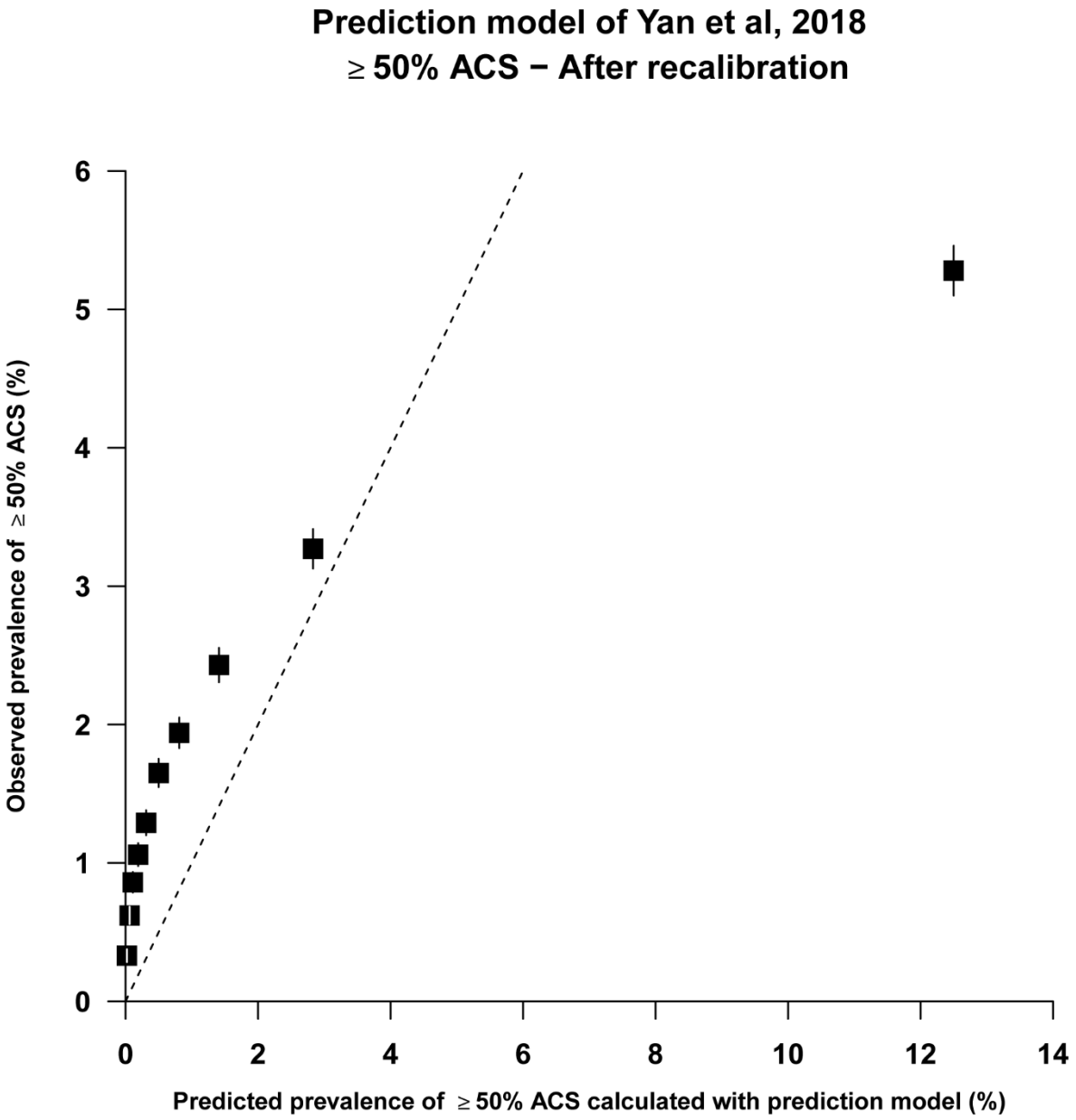
Figure S2 F Calibration plot of external validation of the prediction model for ≥50% ACS developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals. Figure also shown as Figure 3A in the manuscript.



	Deciles of predicted risk									
Predicted prevalence (%)	0.01	0.02	0.05	0.08	0.14	0.22	0.36	0.63	1.27	6.49
Number of patients with ≥50% ACS	198	368	511	633	771	983	1156	1453	1952	3153
Observed prevalence in validation cohort (%)	0.33	0.62	0.86	1.06	1.29	1.65	1.94	2.44	3.27	5.29

ACS indicates asymptomatic carotid artery stenosis.

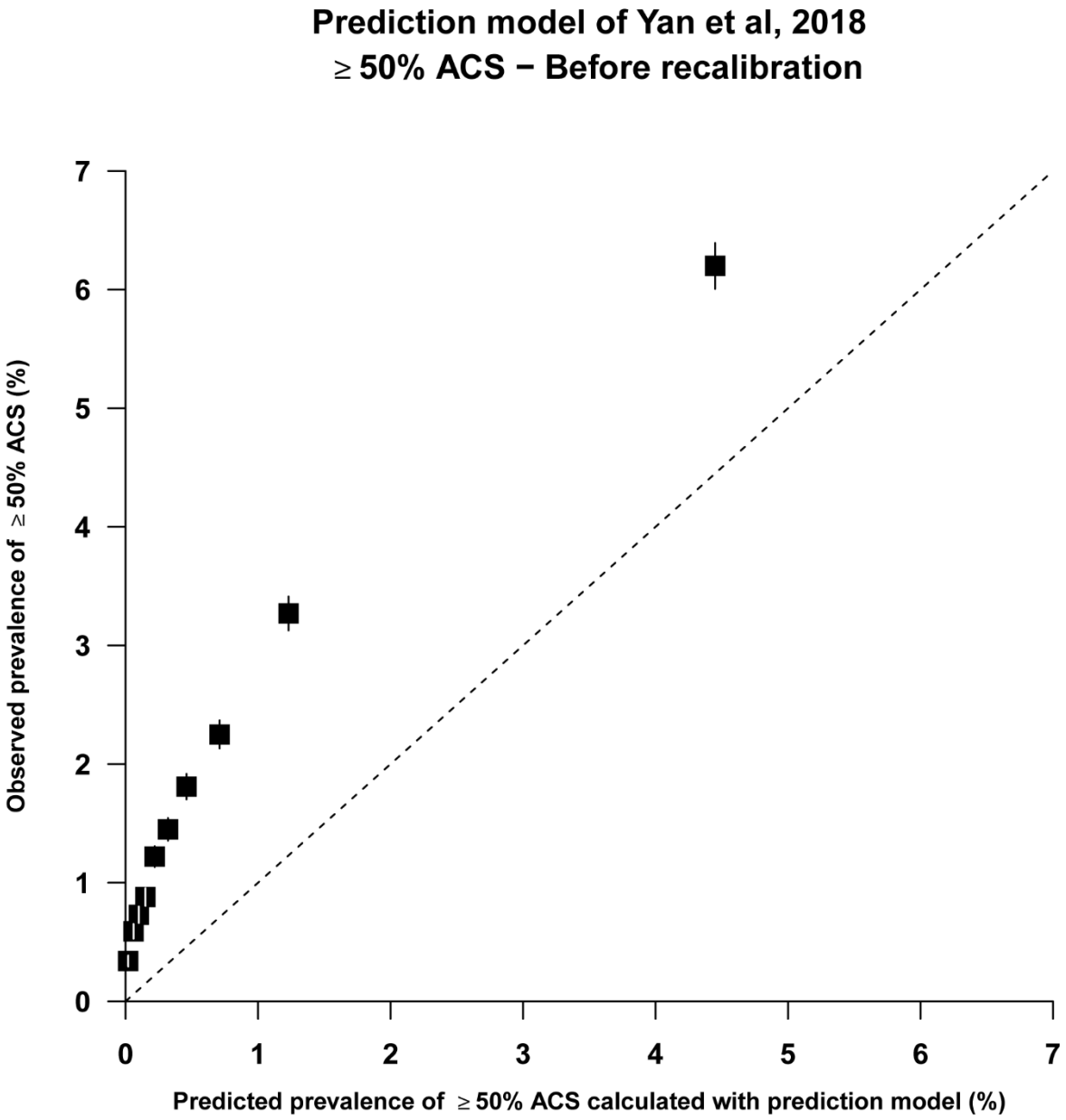
Figure S2 G Calibration plot of external validation of the prediction model developed by Yan et al, 2018 (originally developed for ≥70% ACS).[26] It shows the predicted and observed prevalence of ≥50% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.02	0.06	0.11	0.19	0.31	0.50	0.81	1.41	2.83	12.50
Number of patients with ≥50% ACS	198	369	511	632	772	983	1156	1452	1953	3152
Observed prevalence in validation cohort (%)	0.33	0.62	0.86	1.06	1.29	1.65	1.94	2.43	3.27	5.28

ACS indicates asymptomatic carotid artery stenosis.

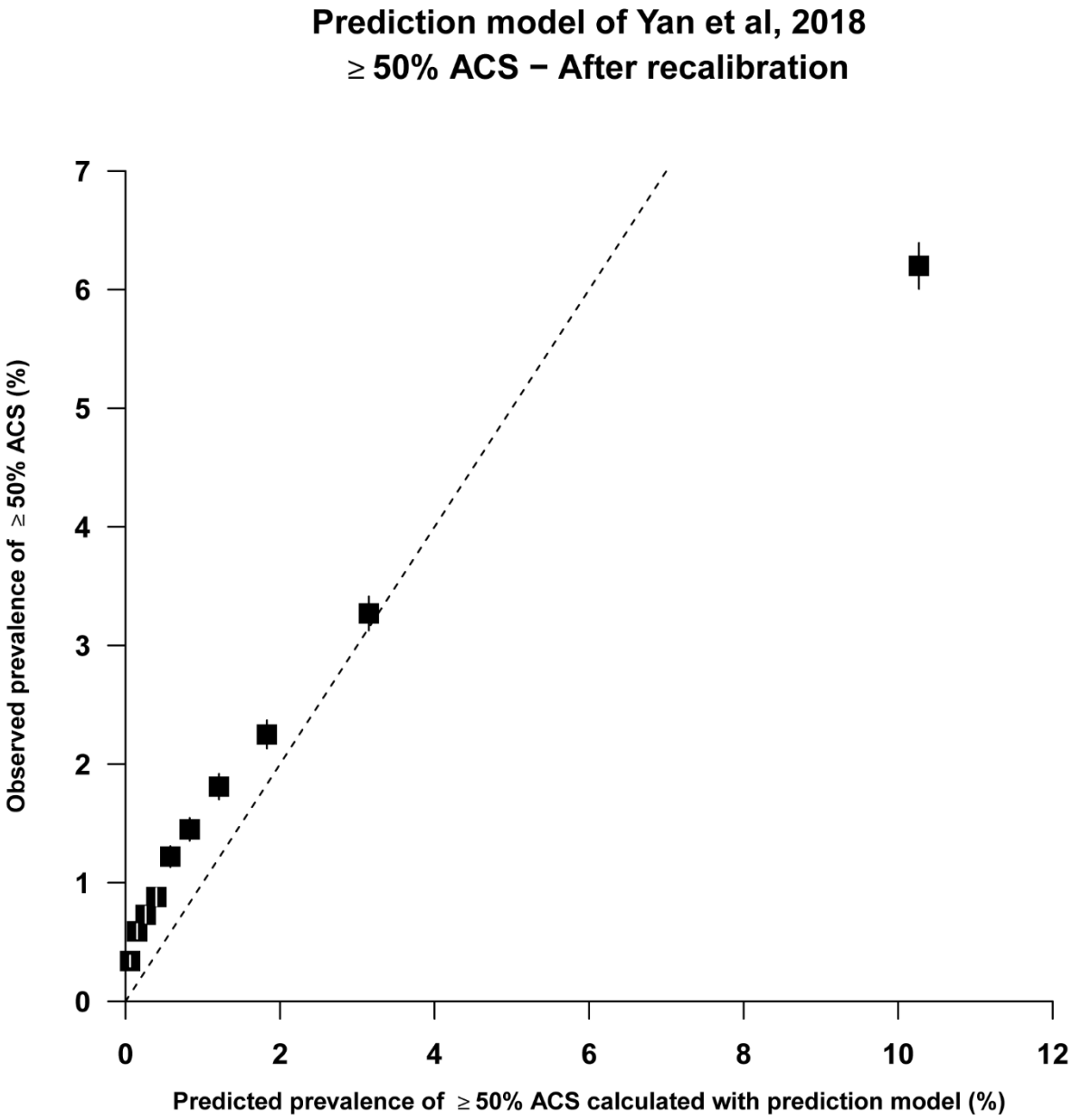
Figure S2 H Calibration plot of external validation of the prediction model developed by de Yan et al, 2018 (originally developed for ≥70% ACS).[26] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.



	Deciles of predicted risk									
Predicted prevalence (%)	0.02	0.06	0.10	0.15	0.22	0.32	0.46	0.71	1.23	4.45
Number of patients with ≥50% ACS	202	351	438	523	729	863	1081	1345	1950	3696
Observed prevalence in validation cohort (%)	0.34	0.59	0.73	0.88	1.22	1.45	1.81	2.25	3.27	6.20

ACS indicates asymptomatic carotid artery stenosis.

Figure S2 I Calibration plot of external validation of the prediction model for ≥50% developed by de Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥50% ACS (before recalibration). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.

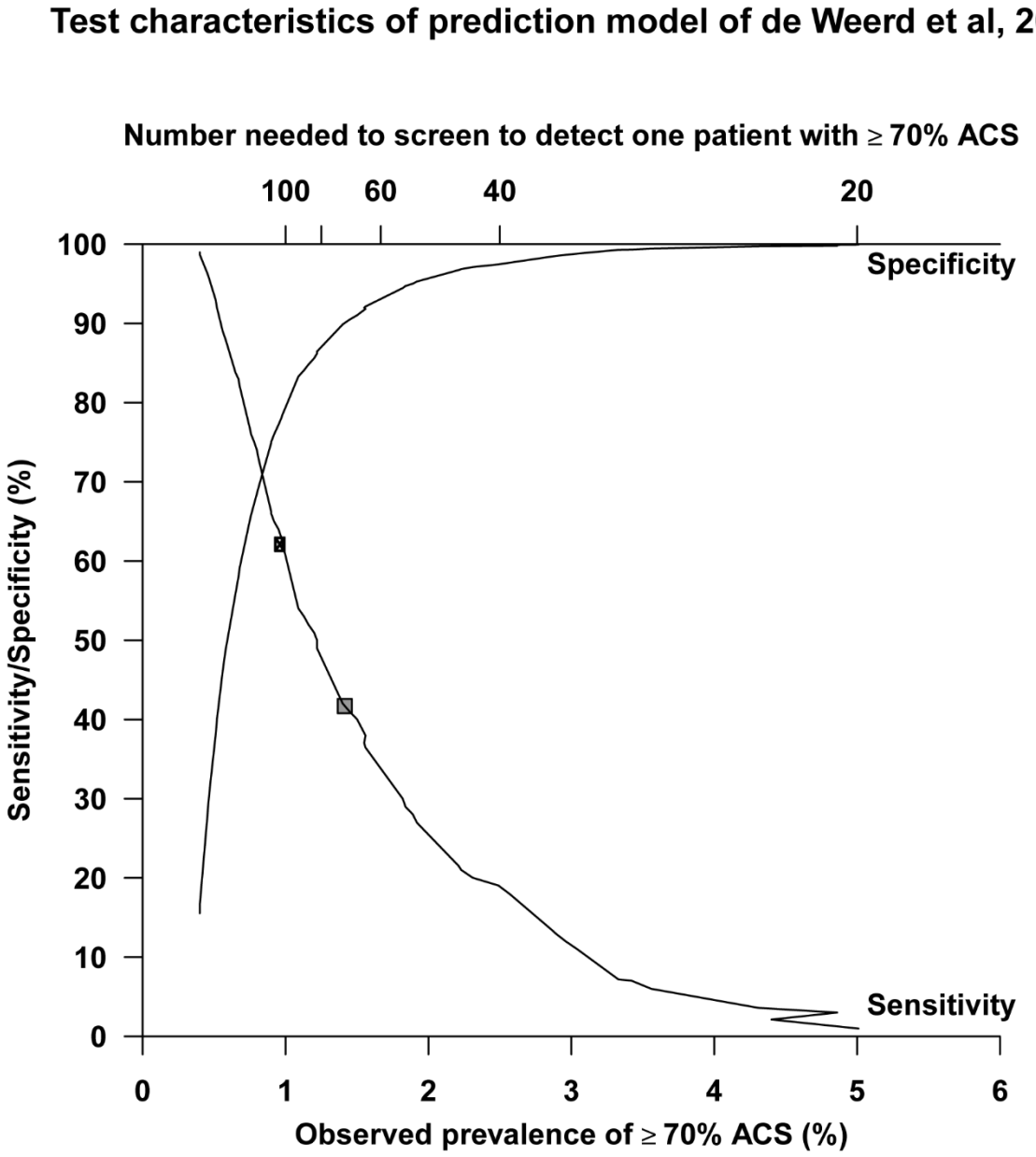


	Deciles of predicted risk									
Predicted prevalence (%)	0.06	0.15	0.26	0.40	0.58	0.83	1.21	1.83	3.15	10.27
Number of patients with ≥50% ACS	202	351	437	524	729	863	1082	1344	1948	3698
Observed prevalence in validation cohort (%)	0.34	0.59	0.73	0.88	1.22	1.45	1.81	2.25	3.27	6.20

ACS indicates asymptomatic carotid artery stenosis.

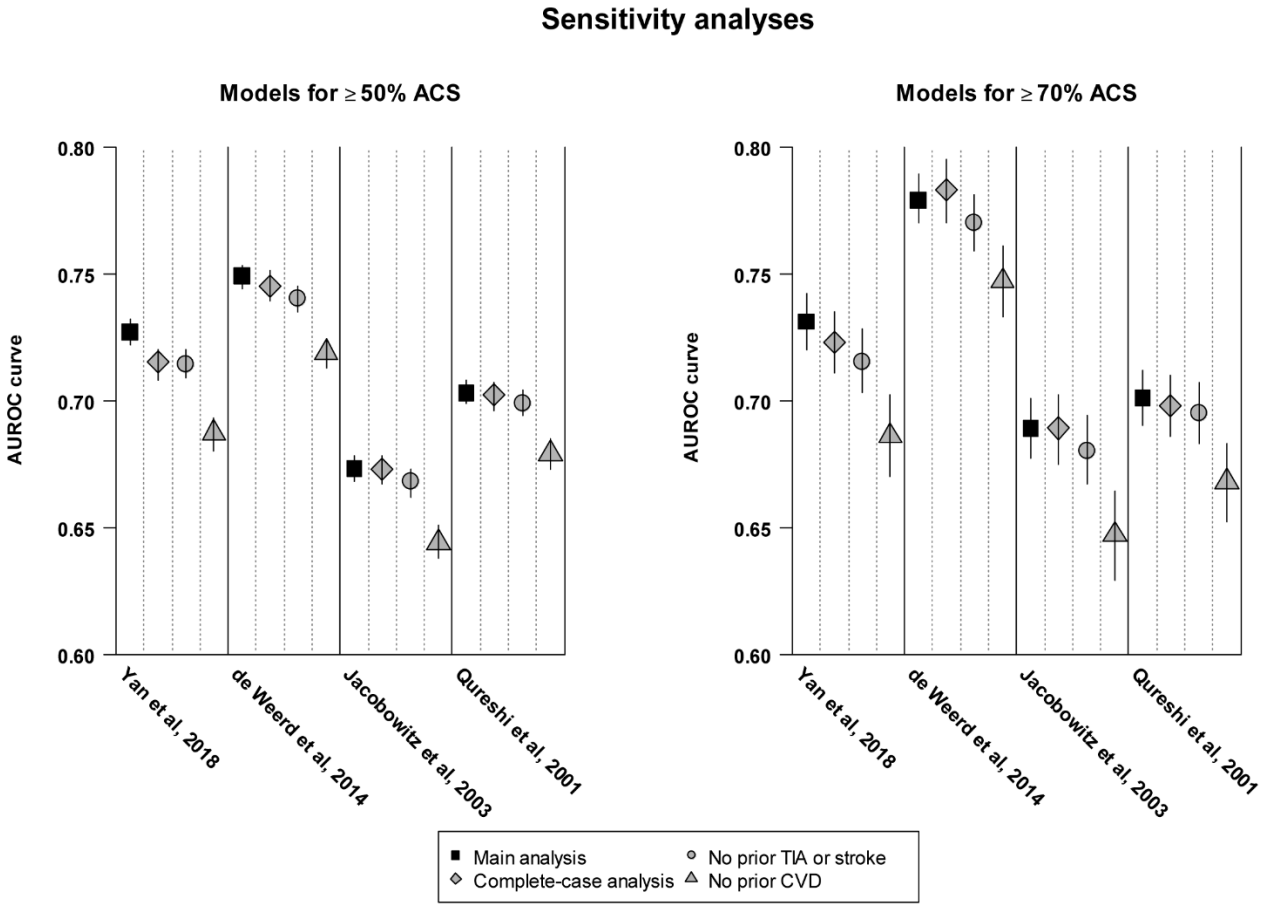
Figure S2 J Calibration plot of external validation of the prediction model for ≥50% ACS developed by Yan et al, 2018.[26] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.

Figure S3. Clinical application of the prediction model with the best discrimination



Graph showing the sensitivity and specificity and corresponding observed prevalence and number needed to screen to detect one patient with ≥70% ACS using the prediction model developed by de Weerd et al, 2014.[23] The square corresponds to targeted screening of patients in the highest decile of predicted risk. The prevalence in this decile is 1.42% with a number needed to screen of 70 and sensitivity is 41.7%. The circle corresponds to targeted screening of patients in the highest two deciles of predicted risk. The prevalence in these deciles is 0.98% with a number needed to screen of 102 and sensitivity of 62.1%.

Figure S4. Sensitivity analyses



The boxes represent the AUROC curve of the analyses and the vertical lines represent the 95% confidence intervals.

ACS indicates asymptomatic carotid artery stenosis; AUROC curve, area under receiver operating characteristic curve.