Original Contribution

Prediction of Asymptomatic Carotid Artery Stenosis in the General Population
Identification of High-Risk Groups

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

Methods—Individual participant data from 4 population-based cohort studies (Malmö Diet and Cancer Study, Tromsø Study, Carotid Atherosclerosis Progression Study, and Cardiovascular Health Study; totaling 23,706 participants) were pooled. Multivariable logistic regression was performed to determine which variables predict presence of ACAS (>50% and >70%). Calibration and discrimination of the models were assessed, and bootstrapping was used to correct for overfitting.

Results—Age, sex, history of vascular disease, systolic and diastolic blood pressure, total cholesterol/high-density lipoprotein ratio, diabetes mellitus, and current smoking were predictors of stenosis (>50% and >70%). The calibration of the model was good confirmed by a nonsignificant Hosmer and Lemeshow test for moderate (P=0.59) and severe stenosis (P=0.07). The models discriminated well between participants with and without stenosis, with an area under the receiver operating characteristic curve corrected for over optimism of 0.82 (95% confidence interval, 0.80–0.84) for moderate stenosis and of 0.87 (95% confidence interval, 0.85–0.90) for severe stenosis. The regression coefficients of the predictors were converted into a score chart to facilitate practical application.

Conclusions—A clinical prediction rule was developed that allows identification of subgroups with high prevalence of moderate (>50%) and severe (>70%) ACAS. When confirmed in comparable cohorts, application of the prediction rule may lead to a reduction in the number needed to screen for ACAS. (Stroke. 2014;45:00-00.)

Key Words: asymptomatic diseases ■ carotid artery stenosis ■ clinical prediction rule ■ screening

Stroke is among the leading causes of morbidity, long-term disability, and mortality in both men and women in nearly all high-, middle-, and low-income countries. As such, stroke poses a substantial economic burden in terms of healthcare and societal costs worldwide. Stenosis of the internal carotid artery is a major risk factor for stroke. In individuals with symptoms of cerebral ischemia (ie, transient ischemic attack or a minor disabling stroke) and with a carotid stenosis of ≥50%, high risks of a recurrent event have been reported: the risk of stroke was 21% at 2 weeks after the first transient ischemic attack or stroke and 32% at 12 weeks. Treatment of symptomatic carotid stenosis has been well established. In general, symptomatic patients suitable for surgery with >70% carotid artery stenosis are recommended to have a carotid endarterectomy. Asymptomatic carotid artery stenosis (ACAS) is also related to a higher risk of stroke. Older studies among individuals not receiving optimal cardiovascular preventive treatment showed estimates for an annual risk for stroke of ≥2% to 4% for patients with severe (>70%) carotid stenosis. An observational study reported 10- and 15-year stroke risks being 10% and 17%, respectively. These untreated risk estimates put...
individuals with an ACAS in the high-risk group based on the European Society of Cardiology/American Heart Association guidelines on cardiovascular disease prevention.\(^\text{11,12}\) As such, ACAS individuals should receive best medical treatment involving antihypertensive and lipid-lowering drugs in addition to lifestyle advice (dietary measures, weight loss, quitting smoking, restriction alcohol consumption, increase exercise). Several studies have shown lower incidence rates among those with optimal cardiovascular preventive medications. A more recent study showed stroke risks of ≈0.5% per year for 70% to 99% patients with ACAS.\(^\text{13}\)

Population screening for ACAS has been suggested as a way to reduce the burden of stroke. In earlier days, this was based on the notion that revascularization in combination with preventive therapy would be the most optimal treatment to reduce stroke risk. However, nowadays the lower risk estimates seem to favor a more conservative treatment choice as opposed to revascularization.\(^\text{14}\) And thus, screening for ACAS is meant to identify those at high risk of stroke.

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

### Methods

#### Study Population

We used individual participant data from 4 observational studies on cardiovascular diseases (Tromsø Study, Malmö Diet and Cancer Study [MDCS], Carotid Atherosclerosis Progression Study [CAPS], and Cardiovascular Health Study [CHS]).\(^\text{15-19}\) In brief, the Tromsø Study is a population-based prospective study in Tromsø, Norway. All inhabitants aged 55 to 74 years and 5% to 10% samples of other 5-year age groups aged ≥25 years were invited. In total, 6727 participants (attendance rate, 41%) agreed to take part to be screened with ultrasound examination.\(^\text{16,17}\) In the population-based MDCS, primary healthcare scheme were invited, of whom 6962 (attendance ≥50%) or severe (>70%) ACAS in the general population.

#### Baseline Characteristics

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

#### Outcomes

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

### Model Development

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

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

To create a good overview, we selected the same predictors for moderate and severe stenosis. Because most of the predictors to identify individuals with a high probability of ACAS being present were expected to be similar to those used in the Framingham Risk Score, we additionally compared number needed to screen with the Framingham Risk Score.

#### Model Performance

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

#### Model Validation

Prediction models derived with multivariable regression analysis are known for overestimated regression coefficients. These results in overestimated predictions when applied in new participants.\(^\text{21,23}\) Therefore, we validated our model internally with bootstrapping techniques where in each bootstrap sample the entire modeling process was repeated.\(^\text{24}\) This resulted in a shrinkage factor for the regression coefficients.\(^\text{24}\) The bootstrap procedure was also used to estimate the AUC corrected for overoptimism. The corrected AUC may be considered as an estimate of discriminative ability expected in future similar participants.

#### Clinical Application

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

The total points (sum scores) were linked to the risk of the presence of moderate or severe stenosis. Various cutoff values were introduced, categorizing patients as having a very low risk, low risk, intermediate risk, or high risk. The numbers needed to screen, sensitivities, specificities, and the positive and negative predicted values of these thresholds were calculated.

#### Study Population

General characteristics of the study population are presented in Table 1. The mean age was 61±12 years, and 46% of the participants were men. Crude differences between studies are a consequence of different inclusion criteria across studies, in particular difference in age range. Overall, 15% of the participants had a history of vascular disease (coronary heart disease and stroke). This prevalence of a history of vascular disease varied from 3% to 40% between the cohorts. Overall, 465
(2%) of the 23,706 participants had moderate stenosis and 127 (0.5%) had severe stenosis. The prevalence of severe stenosis among participants without a history of vascular disease was 0.3% (95% confidence interval [CI], 0.2%–0.4%), among participants with a history of coronary heart disease 1.9% (95% CI, 1.4%–2.4%), and among participants with a history of stroke 3.5% (95% CI, 2.1%–4.9%).

Model Development

Table 1 presents the results from the multivariable analysis for severe stenosis. Age, sex, history of vascular disease, systolic and diastolic blood pressure, total cholesterol/high-density lipoprotein ratio, diabetes mellitus, and current smoking were independent predictors of moderate and severe stenosis. The positive relationship with systolic pressure in combination with an inverse relationship with diastolic pressure in one regression model indicates the relevance of pulse pressure in the relationship with risk of stenosis. Because the fit of the model was better with systolic and diastolic pressure in the model compared with pulse pressure alone, we decided to present the current model. The calibration of the model was good confirmed by a nonsignificant Hosmer and Lemeshow test for moderate stenosis (P=0.585) and for severe stenosis (P=0.071). The models discriminated well between participants with and without stenosis, with an AUC corrected for over optimism of 0.82 (95% CI, 0.80–0.84) for moderate stenosis and of 0.87 (95% CI, 0.85–0.90) for severe stenosis.

Clinical Application

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

Table 4 shows the distribution of participants with and without moderate or severe stenosis across different risk categories. These results are of relevance to indicate the consequences of screening in particular groups. For participants at high stenosis risk (n=7247; 31% of the population), the prevalence of moderate stenosis is estimated to be 4.8% and the number needed to screen is 21. When using a lower risk threshold for screening means that somewhat more participants with...
Predictors and Severe and Stenosis

This gave us the opportunity to present a precise and accurate study of individuals who were included in our population-based cohorts.

Strengths and Limitations

These observations are compatible with our findings. Presence of a bruit over the carotid artery has been evaluated as a means to identify individuals at high risk of a carotid stenosis but was found to be unreliable.

Discussion

We developed a prediction model that allows identification of participants that might benefit from screening for ACAS. We found that age, sex, total cholesterol/high-density lipoprotein ratio, systolic and diastolic blood pressure level, history of vascular disease, diabetes mellitus, and smoking are strong predictors for the probability of having a moderate and severe ACAS.

Comparison With Existing Literature

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

Strengths and Limitations

The major strength of this study is the large number of individuals who were included in our population-based cohorts. This gave us the opportunity to present a precise and accurate prediction rule. Using bootstrapping techniques, we demonstrated that the prediction rule was robust. The shrinkage factor was >1, suggesting a stable model and the calibration after correction for over optimism also was good (AUC 0.87 for severe >70% stenosis). In addition, not all data were available for each participant. With imputation techniques, we were able to use all participants instead of only complete cases. This results in a prediction rule with increased precision. Although there are differences in the methods of measurement of degree of stenosis between studies, we are not concerned about the validity of our prediction model. The Tromsø study measured only the right carotid artery. We think that this had little effect on the prediction rule. Those with a stenosis are the cases, and in Tromsø, some of the cases will be in the reference population. Because the prevalence of stenosis is rather low, the effect of having some few cases in the much larger reference population will not affect the magnitudes and direction of the risk factor relationships. Having only one side does, however, affect the prevalence of stenosis in the population. This means that the prevalence of stenosis is underestimated to some extent. Furthermore, the discrimination between presence and absence of ACAS may be affected by the variation in the population.
Clinical Implication
Because of the improvement in drug therapy, the annual rate of ipsilateral stroke associated with asymptomatic carotid stenosis has fallen from 2% to 4% to <1% in the past 20 years.28 Therefore, the balance between benefit and risk for surgery in patients with ACAS has changed. So carotid revascularization as mainly underlying reason for screening for ACAS seems not applicable anymore. Yet, individuals with an ACAS are at high risk of any future cardiovascular events and should be considered for best medical treatment following the cardiovascular risk management guidelines and should obtain lifestyle guidance. Our model may help in that respect.

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

Acknowledgments
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Sources of Funding
This study is supported by an unconditional grant from The Netherlands Organization for Health Research and Development (ZonMW, project No. 6230.0046).

Table 4. Model Performance for Severe and Moderate Stenosis

<table>
<thead>
<tr>
<th>Prediction Score</th>
<th>Total No. of Participants</th>
<th>No. of Participants</th>
<th>Prevalence</th>
<th>SE (%)</th>
<th>SP (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>NNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate stenosis</td>
<td>Very low risk ≤9 points</td>
<td>8417</td>
<td>26</td>
<td>0.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk 10–11 points</td>
<td>4044</td>
<td>36</td>
<td>0.9%</td>
<td>94.4%</td>
<td>36.1%</td>
<td>2.9%</td>
<td>99.7%</td>
<td>35</td>
</tr>
<tr>
<td>Intermediate risk 12–13 points</td>
<td>3998</td>
<td>57</td>
<td>1.4%</td>
<td>86.7%</td>
<td>53.3%</td>
<td>3.6%</td>
<td>99.5%</td>
<td>28</td>
</tr>
<tr>
<td>High risk ≥14 points</td>
<td>7247</td>
<td>346</td>
<td>4.8%</td>
<td>74.4%</td>
<td>70.3%</td>
<td>4.8%</td>
<td>99.3%</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>23706</td>
<td>465</td>
<td>2.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>Very low risk ≤9 points</td>
<td>8417</td>
<td>2</td>
<td>0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk 10–11 points</td>
<td>4044</td>
<td>5</td>
<td>0.1%</td>
<td>98.4%</td>
<td>35.7%</td>
<td>0.8%</td>
<td>100.0%</td>
<td>122</td>
</tr>
<tr>
<td>Intermediate risk 12–13 points</td>
<td>3998</td>
<td>14</td>
<td>0.4%</td>
<td>94.5%</td>
<td>52.8%</td>
<td>1.1%</td>
<td>99.9%</td>
<td>94</td>
</tr>
<tr>
<td>High risk ≥14 points</td>
<td>7247</td>
<td>106</td>
<td>1.5%</td>
<td>83.5%</td>
<td>69.7%</td>
<td>1.5%</td>
<td>99.9%</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td>23706</td>
<td>127</td>
<td>0.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

None.

References

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## SUPPLEMENTAL MATERIAL

Table I. Intercept adjusted for prior probability

<table>
<thead>
<tr>
<th>Risk of moderate stenosis</th>
<th>Adjusted intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0%</td>
<td>-8.117</td>
</tr>
<tr>
<td>1.5%</td>
<td>-7.699</td>
</tr>
<tr>
<td>2.0%</td>
<td>-7.398</td>
</tr>
<tr>
<td>2.5%</td>
<td>-7.162</td>
</tr>
<tr>
<td>3.0%</td>
<td>-6.967</td>
</tr>
<tr>
<td>3.5%</td>
<td>-6.800</td>
</tr>
<tr>
<td>4.0%</td>
<td>-6.654</td>
</tr>
<tr>
<td>5.0%</td>
<td>-6.406</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of severe stenosis</th>
<th>Adjusted intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3%</td>
<td>-11.263</td>
</tr>
<tr>
<td>0.4%</td>
<td>-10.970</td>
</tr>
<tr>
<td>0.5%</td>
<td>-10.742</td>
</tr>
<tr>
<td>0.6%</td>
<td>-10.554</td>
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<tr>
<td>0.7%</td>
<td>-10.395</td>
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<tr>
<td>0.8%</td>
<td>-10.256</td>
</tr>
<tr>
<td>0.9%</td>
<td>-10.133</td>
</tr>
<tr>
<td>1.0%</td>
<td>-10.023</td>
</tr>
</tbody>
</table>