Stroke

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Articles

We Need Stronger Predictors of Major Vascular Events in Patients With a Recent Transient Ischemic Attack or Nondisabling Stroke

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Abstract

Background It has been proposed that most prognostic factors in patients with transient ischemic attack or nondisabling stroke are weak and consequently that patients at high risk of recurrent major vascular events cannot be reliably identified.

Methods In the Dutch TIA trial, a multicenter, double-blind study of low-dose versus medium-dose aspirin, 3127 patients were included within 3 months after onset of a transient ischemic attack, amaurosis fugax, or nondisabling stroke. In a previous analysis, we developed a prediction model by means of Cox proportional hazards regression for the composite outcomes of fatal or nonfatal stroke and for myocardial infarction, stroke, or vascular death, based on clinical and demographic information as well as on the results of ancillary investigations. We assessed the discriminatory power and the calibration of the prediction models.

Results The median numbers of prognostic factors for stroke, myocardial infarction, or vascular death outcome and for stroke alone were 3 and 4, respectively. The proportion of patients with a predicted probability exceeding 30% was less than 5% for both models; here the calibration of the models was poor. Only four of the patients with stroke, myocardial infarction, or vascular death were assigned a probability of greater than 50% for that outcome, and only one of the patients with stroke was given such a high probability. The models' discriminatory ability was a little disappointing (areas under the curve of 0.73 and 0.75, respectively).

Conclusion This analysis indicates that we need stronger predictors of recurrence risk in patients with a transient ischemic attack or nondisabling stroke.

Key Words: cerebral ischemia • cerebral ischemia, transient • prognosis • risk factors

Introduction

Prognostic factors for recurrent stroke or myocardial infarction (MI) in patients with a transient ischemic attack (TIA) or nondisabling stroke are clinically important because they help to

identify patients in whom secondary prevention is particularly worthwhile and because they may be amenable to intervention.

We and others have investigated prognostic factors in large cohorts of patients by means of multiple regression techniques.[1,2] In both studies, relative risks were presented for each factor included in the final prediction model, but absolute risks and the dispersion of the risk estimates over the study population were not reported. Hankey et al,[3] however, reported the results of a prediction model for stroke or major vascular events based on a small cohort of 469 patients with a TIA. The model was validated on a sample of 1653 patients in the UK TIA Trial and on 107 patients in the Oxfordshire Community Stroke Project.[4] They concluded that most prognostic factors were weak and consequently that patients at high risk could not reliably be identified. We wondered whether these conclusions would hold in more detailed, previously published multiple regression models based on data from 3127 patients in the Dutch TIA Trial.[1]

Subjects and Methods

In the Dutch TIA Trial, a multicenter, double-blind study of low-dose (38 mg) versus medium-dose (283 mg) aspirin, 3127 patients were included within 3 months after onset of a TIA, amaurosis fugax, or nondisabling stroke. Recorded baseline characteristics included neurological history, vascular risk factors and prior vascular diseases, the results of CT scanning of the brain, and a standard 12-lead electrocardiogram. Outcome events were vascular death, MI, and stroke, the definitions of which have been described elsewhere.[5]

In a previous study we developed a prediction model by means of Cox proportional hazards regression for the composite outcomes of "fatal or nonfatal stroke" and for "myocardial infarction, stroke, or vascular death," whichever came first.[1] For each composite outcome a prediction model was developed that was based on clinical and demographic information, as well as on the results of ancillary investigations such as CT and electrocardiography. The two models contained 13 and 16 prognostic factors, respectively, all of which were statistically significant. The relative risks associated with these factors were typically in the range between 1 and 2 (Table), but a patient with all risk factors present would have a more than 99% risk of an outcome event.

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Table 1. Prognostic Factors for Stroke, Myocardial Infarction, or Vascular Death and for Fatal or Nonfatal Stroke Based on a Cox Proportional Hazards Multiple Regression Model[1]

In the present study we examined the aggregation of prognostic factors in this study population, the discriminatory power of the two prediction models by means of receiver operating characteristic analysis, and the calibration (ie, the concordance of the predicted probabilities with observed probabilities) of the models.[6]

Results

This analysis concerns the 3126 patients who were entered into the Dutch TIA Trial and had complete baseline information. A stroke occurred in 272 patients and was fatal in 57. Two hundred patients had a major cardiac event (nonfatal MI in 67, sudden death in 84, and other cardiac death in 49). The combined outcome of stroke, MI, or vascular death (whichever came first) occurred in 469 patients. The 2-year risk of stroke was 7.2% (95% confidence interval [CI], 6.3% to 8.2%), and the 2-year risk of stroke, MI, or vascular death was 11.8% (95% CI, 10.7% to 13.0%), estimated by Kaplan-Meier survival analysis. The calibration of the two models was reasonable in the range of probabilities lower than 40%. The proportion of patients with a predicted probability exceeding 30% was less than 5% for both models; in this respect the calibration of the models was poor (Fig 1). The median number of prognostic factors for stroke, MI, or vascular death outcome was 3, and in only 2.5% of the patients were more than 6 prognostic factors present. The median number of prognostic factors for stroke was 4, and only 1.5% of the patients had more than 6 factors (Fig 1). Only four of the patients with stroke, MI, or vascular death were assigned a probability of more than 50% of that outcome, and only one of

the patients with stroke was given such a high probability. The discriminatory ability of the models was disappointing (Fig 2).

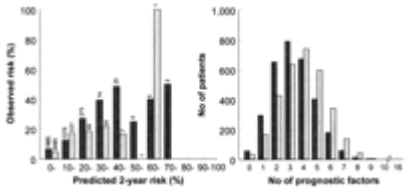

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Figure 1. Left, Calibration of the prediction model: comparison of predicted (*x* axis) and actual (*y* axis) 2-year risks of the two outcome events. The total number of patients in that decile is shown on top of the bars. Right, Distribution of the number of prognostic factors in the study population for each of the two outcomes. Black bars indicate stroke, myocardial infarction, or vascular death; gray bars, stroke.

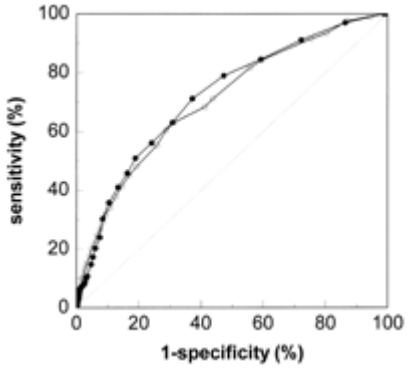

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Figure 2. Discriminatory ability of the multiple regression model for the prediction of myocardial infarction, stroke, or vascular death (○) and fatal or nonfatal stroke (•) by a receiver operator characteristic curve. The diagonal line shows the theoretical curve of a noninformative test. The areas under the curve are 0.73 and 0.75, respectively.

Discussion

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When the evaluation of any prediction model is based on the data from which the model was derived, the results tend to be overoptimistic. Nevertheless, the calibration and discriminatory power of our prediction models for recurrent stroke and vascular events in patients with a recent TIA or nondisabling stroke, based on more than 3000 patients and several hundreds of outcome events occurring during more than 2 years of follow-up, was less than satisfactory. Further external validation is therefore not necessary to prove our main conclusion that we need stronger predictors of major outcome events in patients with a TIA or nondisabling stroke. This rather disappointing result can be explained by the fact that most patients had no more than three or four relatively weak prognostic factors, in combination with the low baseline risk. We tested for the presence of complex interactions in the data, but the relative risk of each of the two outcomes increased linearly with the number of predictors present in each patient, with a factor of 1.4 (95% CI, 1.3 to 1.5) for stroke, MI, and vascular death and a factor of 1.5 (95% CI, 1.4 to 1.7) for fatal and nonfatal stroke, which are equal in magnitude to the relative risks associated with the individual predictors.

The patients in this study constitute a selected sample of all patients with a TIA or nondisabling stroke because they had been entered into a randomized clinical trial. Thus, most patients who were candidates for endarterectomy because they had a severe symptomatic carotid stenosis were excluded from this sample. We therefore did not take carotid stenosis and plaque morphology into account.[7] Nevertheless, this analysis shows that we need stronger predictors of risk of recurrence. To be clinically useful, such prognostic information should be easily obtainable at low cost and at low risk to the patient. In our opinion, potentially useful prognostic factors that deserve further prospective evaluation may be provided by transcranial Doppler monitoring,[8] carotid intima-media thickness,[9] coagulation disturbances,[10] and transesophageal echocardiography.[11] [12] [13]

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