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## Prediction Models for Clinical Outcome After a Carotid Revascularization Procedure An External Validation Study

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**Background and Purpose**—Prediction models may help physicians to stratify patients with high and low risk for periprocedural complications or long-term stroke risk after carotid artery stenting or carotid endarterectomy. We aimed to evaluate external performance of previously published prediction models for short- and long-term outcome after carotid revascularization in patients with symptomatic carotid artery stenosis.

**Methods**—From a literature review, we selected all prediction models that used only readily available patient characteristics known before procedure initiation. Follow-up data from 2184 carotid artery stenting and 2261 carotid endarterectomy patients from 4 randomized trials (EVA-3S [Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis], SPACE [Stent-Protected Angioplasty Versus Carotid Endarterectomy], ICSS [International Carotid Stenting Study], and CREST [Carotid Revascularization Endarterectomy Versus Stenting Trial]) were used to validate 23 short-term outcome models to estimate stroke or death risk  $\leq 30$  days after the procedure and the original outcome measure for which the model was developed. Additionally, we validated 7 long-term outcome models for the original outcome measure. Predictive performance of the models was assessed with C statistics and calibration plots.

**Results**—Stroke or death  $\leq 30$  days after the procedure occurred in 158 (7.2%) patients after carotid artery stenting and in 84 (3.7%) patients after carotid endarterectomy. Most models for short-term outcome after carotid artery stenting (n=4) or carotid endarterectomy (n=19) had poor discriminative performance (C statistics ranging from 0.49–0.64) and poor calibration with small absolute risk differences between the lowest and highest risk groups and overestimation of risk in the highest risk groups. Long-term outcome models (n=7) had a slightly better performance with C statistics ranging from 0.59 to 0.67 and reasonable calibration.

**Conclusions**—Current models did not reliably predict outcome after carotid revascularization in a trial population of patients with symptomatic carotid stenosis. In particular, prediction of short-term outcome seemed to be difficult. Further external validation of existing prediction models or development of new prediction models is needed before such models can be used to support treatment decisions in individual patients. (*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020486.)

**Key Words:** angioplasty ■ carotid endarterectomy ■ carotid stenosis ■ myocardial infarction ■ prognosis ■ thromboembolism

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In 2015, around 5.4 million patients worldwide suffered a first-ever ischemic stroke.<sup>1</sup> About 10% to 15% of these strokes are caused by thromboembolism from an atherosclerotic plaque at the carotid bifurcation or the internal carotid artery (ICA).<sup>2</sup> Such strokes can be prevented by surgical excision of the plaque with carotid endarterectomy (CEA) or by carotid artery stenting (CAS).<sup>3</sup> The benefit of carotid revascularization for an individual patient depends on the balance between the long-term risk of vascular complications on medical treatment and the periprocedural risk of these complications. Risk prediction models can be used to predict the absolute risk of periprocedural stroke or death after CEA or CAS in an individual patient.

Over the past decade, many prediction models for outcome after carotid revascularization have been developed. In a recent literature review, we identified 46 prediction models that can be applied to patients with symptomatic or asymptomatic ICA stenosis.<sup>4</sup> Only a few of these prediction models were validated in independent patient populations, although external validation is an essential step in prediction model development that should be performed before a model can be implemented in clinical practice.<sup>5,6</sup>

Therefore, we aimed to assess the external performance of prediction models for short-term and long-term outcome after carotid revascularization that were identified with our literature review. We selected prediction models that used readily available patient characteristics that were known before procedure initiation. We validated these models in patients with symptomatic ICA stenosis enrolled in randomized controlled trials comparing CAS versus CEA.

## Methods

### Selection of Prediction Models

In the literature review, we identified 46 prediction models for clinical outcome after CAS or CEA. Sixteen models were excluded from the current study; 10 of these models used procedural characteristics (eg, duration of procedure), 3 models predicted risk of myocardial infarction or other cardiac complications only, and 3 models did not contain sufficient information to validate the model (Figure). Details of the literature review and references of the excluded studies are provided in the [online-only Data Supplement](#).

The 30 models we selected for external validation included 23 short-term outcome models (4 CAS and 19 CEA models) and 7 long-term outcome models (2 CAS, 4 CEA, and 1 combined model). We classified models that predicted in-hospital risk or risk up to 30 days after the procedure as short-term outcome models, whereas models that predicted risk after longer follow-up were classified as long-term outcome models. Tables I and II in the [online-only Data Supplement](#) provide an overview of the predictors used in each prediction model, the predicted outcome measure, and a description and key baseline characteristics of the development cohorts. The most often predicted outcome measure was a composite of stroke or death for the short-term outcome models and mortality for the long-term outcome models.

### Validation Population

The validation population consisted of patients included in 4 randomized controlled trials that are pooled by the CSTC (Carotid Stenosis Trialists' Collaboration): the EVA-3S (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis) trial,<sup>7</sup> the SPACE (Stent-Protected Angioplasty versus Carotid Endarterectomy) trial,<sup>8</sup> the ICSS (International Carotid Stenting Study),<sup>9</sup> and the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial).<sup>10</sup> Collectively, these trials randomly allocated

4754 patients with symptomatic carotid artery stenosis of  $\geq 50\%$  according to the North American Symptomatic Carotid Endarterectomy Trial criteria<sup>11</sup> to undergo either CAS or CEA. Data on individual patient characteristics such as demographics, comorbidities, and degree of stenosis were collected at baseline in all 4 trials. Details on study design and methods are described elsewhere.<sup>7-10</sup> The CSTC welcomes other investigators to propose analyses of the pooled data. Such analyses could then be performed in close collaboration with the CSTC Steering Committee.

We excluded patients in whom the randomly allocated procedure was not completed or who suffered a stroke before procedure initiation. This resulted in 2184 patients who underwent CAS and 2261 patients who underwent CEA for analyses.

### Outcome Measures

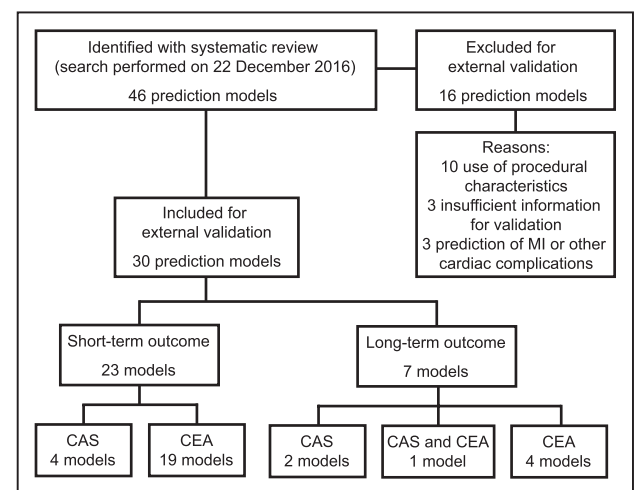
All patients in the validation population were followed up for the occurrence of stroke or death. Stroke was uniformly defined in all 4 trials as the occurrence of acute focal neurological deficit with symptoms that lasted for  $>24$  hours caused by ischemic or hemorrhagic cerebrovascular disturbance.

We used stroke or death risk within 30 days after the procedure as the primary outcome for all short-term outcome models. In addition, we externally validated all short-term outcome models for the original outcome measure that was used in the model development study, if data on this outcome measure were available in our validation population. We externally validated all long-term outcome models for the original outcome measure. Three long-term outcome models predicted death occurring within 5 years after the procedure (Hoke 2012, Conrad 2013, Wallaert 2013); we externally validated these models with data from EVA-3S and ICSS only, because sufficiently long-term follow-up data from these 2 trials were available to the CSTC.

### Statistical Analysis

We first matched predictors and outcome measures of each prediction model to variables in the validation population. Proxies were used in case a direct match was unavailable (Description of proxies is available in the [online-only Data Supplement](#)). A value of zero was assigned for predictors that were not available in any of the 4 trials (indicated with an asterisk in Table I in the [online-only Data Supplement](#)).

For most predictors, the proportion of patients with missing data within each trial was low ( $<2\%$ ), although more missing values occurred for antiplatelet use (49%) and for presence of contralateral ICA occlusion (4%). However, some predictors have not been measured in one or more of the 4 trials and are thus systematically missing



**Figure.** Flowchart of prediction models selected for external validation from previous literature review. Models for short-term outcome predict risk  $\leq 30$  d after the procedure; models for long-term outcome predict risk  $>30$  d after the procedure. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and MI, myocardial infarction.

in some of the trials (Table III in the [online-only Data Supplement](#)). Also, the occurrence of myocardial infarction during follow-up was not available in CREST. Missing data were imputed with the MICE package in R using source trial as predictive variable in the imputation model and creating 10 imputed data sets.

Per model, we applied the original regression formula to calculate the risk of the outcome for each patient in the validation population. In case the original regression formula was unavailable despite contacting the authors, and a risk score was reported in the original publication, we assessed the performance of this risk score.

Predictive performance of the models was analyzed with discrimination and calibration. Discrimination describes the ability of a model to distinguish between someone with and without the outcome and was examined with the C statistic. A C statistic of 0.5 reflects a model with no discriminative ability, and a value of 1.0 indicates perfect discriminative ability. For each prediction model, we calculated the C statistic in each trial separately and performed a random-effects meta-analysis of the results to account for heterogeneity between the 4 trials. Subsequently, we pooled the C statistics of each multiply imputed data set with Rubin's rules.<sup>12</sup> Calibration indicates whether the predicted risks of the outcome correspond with the observed risks in the validation population. This was examined with calibration plots and calibration slopes. Differences between the incidence of the outcome in the validation population and the development cohorts are known to influence calibration. Therefore, we recalibrated the models for which we applied the original regression formula to the incidence of the outcome in the validation population by adjusting the original intercept (for logistic regression models) or baseline hazard (for Cox regression models).<sup>13,14</sup> Here, we present calibration of the models after recalibration. Calibration plots before recalibration are provided in Figure I in the [online-only Data Supplement](#).

We performed 2 sensitivity analyses. First, we externally validated each prediction model in each of the 4 trials separately. Second, we externally validated each model in complete cases (ie, patients who had data on all variables available that were used by the prediction model; a value of zero was assigned for predictors that were not available in any of the 4 trials). Statistical analyses were performed with SPSS version 22 and R-3.3.2.

## Results

### Validation Population and Occurrence of Outcome

Stroke or death within 30 days after revascularization occurred in 158 (7.2%) of the patients who underwent CAS and in 84 (3.7%) patients who underwent CEA. Stroke or death within 1 year occurred in 248 (11.4%) patients after CAS and in 163 (7.2%) patients after CEA.

Baseline characteristics of the development and validation populations are presented in Tables II and III in the [online-only Data Supplement](#). In both the development and validation populations, about two-thirds of patients were men and the mean age was 70 years. All patients in the validation population had symptomatic ICA stenosis, whereas only 2 models were specifically developed in symptomatic patients, 8 in asymptomatic patients, and 19 in both symptomatic and asymptomatic patients (Table II in the [online-only Data Supplement](#)).

We applied the original regression formula for 22 of the 30 models. Eight models did not report the original regression equation, and the authors were unable to provide additional information on request; therefore, we assessed performance of the risk scores.

### CAS Short-Term Outcome Models

C statistics for the 4 short-term outcome models after CAS ranged from 0.55 to 0.64 for our primary outcome in the validation population and were consistently lower than

the corresponding C statistics in the development cohorts (Table). The Hawkins 2012 model had the highest C statistic in the validation population. However, the calibration curves of all 4 models deviated from the ideal calibration slope for patients within the highest risk categories (Figure II in the [online-only Data Supplement](#)). Both age and history of stroke or symptomatic status were used as predictors in the 2 models with best model performance (Hawkins 2012, Wimmer 2012).

### CEA Short-Term Outcome Models

For the 19 short-term outcome models after CEA, C statistics ranged from 0.49 to 0.60 for our primary outcome, which indicates poor discriminative performance (Table). The Bekelis 2013b model had reasonable calibration with a calibration slope (0.88) near the ideal value of 1.0. However, the curve was narrow with an absolute risk difference of only 5% between patients in the lowest and highest risk groups, similar to most other short-term outcome models after CEA. This indicates that these models cannot distinguish between patients with a low or high risk of the outcome (Figure II in the [online-only Data Supplement](#)). The Kuhan 2001 and Bennett 2015 models were probably overfitted to the original development population, which is reflected by the rather flat calibration curves with too low predictions for patients in the lowest risk categories and too high predictions for patients in the highest risk categories. The calibration curves of the other models deviated from the ideal calibration curve for predicted risks >5%. Most frequently used predictors in the models with most reasonable performance (Calvillo-King 2010a, Bekelis 2013b) were history of transient ischemic attack or stroke and history of coronary artery disease.

### CAS or CEA Long-Term Outcome Models

We externally validated 7 prediction models for long-term outcome after CAS or CEA. C statistics ranged from 0.59 to 0.67 and were clearly higher compared with those of the short-term outcome models (Table). All calibration plots showed increasing observed risk of the outcome with increasing predicted risk (Figure II in the [online-only Data Supplement](#)). For the long-term outcome models after CAS, the Hoke 2012 model had the highest C statistic in combination with a reasonable calibration curve; for the long-term outcome models after CEA, the Wallaert 2013 model had best discrimination and calibration. Age, diabetes mellitus, and heart failure were used as predictors in both models with best external performance.

### Sensitivity Analyses

External validation in each of the 4 trials separately yielded results comparable to our main analyses, although results were less precise. C statistics and calibration curves varied more between the trials for the prediction models after CEA than for the models after CAS, which may be caused by the low number of outcome events per trial after CEA (data not shown). Performance of the prediction models in a complete case analysis also showed results comparable to our main results (Table IV in the [online-only Data Supplement](#)).

**Table. Discrimination (C Statistic) of Each Prediction Model in the Validation Population and in the Original Model Development Study**

Prediction Model	Model Development Study		External Validation	
	C Statistic (95% CI) in Development Cohort	Original Outcome Measure	C Statistic (95% CI) for Original Outcome Measure	C Statistic (95% CI) for Stroke or Death
<b>CAS short-term models</b>				
Hofmann 2006a	0.69 (NR)	Stroke, MI, or death	0.55 (0.50–0.60)	0.55 (0.50–0.59)
Hofmann 2006b	0.73 (NR)	Stroke, MI, or death	0.55 (0.50–0.60)	0.55 (0.50–0.59)
Hawkins 2012	0.71 (NR)	Stroke or death	0.64 (0.60–0.69)	0.64 (0.60–0.69)
Wimmer 2012	0.69 (NR)	Stroke or death	0.60 (0.56–0.65)	0.60 (0.56–0.65)
<b>CEA short-term models</b>				
McCrary 1993	NR	Stroke, MI, or death	0.53 (0.47–0.60)	0.54 (0.48–0.61)
Kucey 1998	0.58 (NR)	Stroke or death	0.53 (0.47–0.59)	0.53 (0.47–0.59)
Rothwell 1999	NR	Major stroke or death	0.46 (0.28–0.64)	0.52 (0.44–0.61)
Kuhan 2001	NR	Major stroke or death	0.40 (0.14–0.66)	0.56 (0.48–0.64)
Tu 2003	NR	Stroke or death	0.53 (0.47–0.59)	0.53 (0.47–0.59)
Matsen 2005	0.66 (NR)	Mortality	0.51 (0.18–0.84)	0.49 (0.42–0.56)
Goodney 2008	0.71 (NR)	Stroke or death	0.55 (0.47–0.63)	0.55 (0.47–0.63)
Calvillo-King 2010a	0.62 (NR)	Stroke or death	0.60 (0.54–0.66)	0.60 (0.54–0.66)
Calvillo-King 2010b	0.64 (NR)	Stroke	0.60 (0.54–0.66)	0.60 (0.54–0.66)
Calvillo-King 2010c	NR	Stroke or death	0.59 (0.54–0.65)	0.59 (0.54–0.65)
Bekelis 2013a	0.64 (0.62–0.66)	Stroke, MI, or death	0.55 (0.48–0.63)	0.55 (0.48–0.62)
Bekelis 2013b	0.63 (0.61–0.65)	Stroke	0.57 (0.49–0.65)	0.57 (0.49–0.65)
Bekelis 2013c	0.74 (0.71–0.77)	Mortality	0.50 (0.07–0.93)	0.55 (0.47–0.62)
Gupta 2013	0.64 (NR)	Stroke, MI, or death	0.56 (0.49–0.64)	0.55 (0.47–0.63)
Wimmer 2014	0.65 (NR)	Stroke or death	0.53 (0.46–0.60)	0.53 (0.46–0.60)
Bennett 2015a	0.70 (NR)	Stroke or death	0.56 (0.47–0.65)	0.56 (0.47–0.65)
Bennett 2015b	0.74 (NR)	Stroke or death	0.52 (0.47–0.57)	0.52 (0.47–0.57)
Chaudhry 2016	NR	Stroke, cardiac complications, or death	0.49 (0.42–0.57)	0.49 (0.43–0.56)
Eslami 2016	0.71 (NR)	Stroke, MI, death, or discharge to rehabilitation facility	0.54 (0.48–0.61)	0.52 (0.46–0.59)
<b>CAS long-term models</b>				
Hoke 2012*	0.79 (NR)	Mortality	0.67 (0.63–0.71)	NA
Cheng 2016	0.66 (NR)	Stroke, MI, or death	0.61 (0.57–0.65)	NA
<b>CEA long-term models</b>				
van Lammeren 2012	0.69 (0.64–0.73)	Stroke, MI, or death from cardiovascular causes	0.59 (0.54–0.63)	NA
Conrad 2013*	0.74 (NR)	Mortality	0.67 (0.63–0.71)	NA
Wallaert 2013*	NR	Mortality	0.66 (0.59–0.73)	NA
Gates 2015	NR	Short-term stroke, MI, or death, long-term ipsilateral stroke or death from neurological causes	0.60 (0.55–0.65)	NA
<b>CAS and CEA long-term model</b>				
Alcocer 2013	NR	Mortality	0.60 (0.57–0.64)	NA

Risk of stroke or death within 30 d after the procedure was used as primary outcome for all short-term outcome models; the original outcome measure was used for all long-term outcome models. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; NA, not applicable; and NR, not reported.

\*Externally validated with data from EVA-3S (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis) and ICSS (International Carotid Stenting Study) only.

## Discussion

In this study, we assessed predictive performance of 30 existing prediction models for short-term and long-term outcome after carotid revascularization in a large population of patients with symptomatic ICA stenosis. Most prediction models for short-term outcome after CAS or CEA had poor ability to discriminate between patients who will and will not get an event. In addition, most calibration curves were narrow (ie, absolute risk difference between patients in the lowest and highest risk groups was small), and risk was overestimated in the highest risk categories. The long-term outcome models showed slightly better external performance compared with short-term outcome models, but most of them were originally developed to predict mortality. Hence, these prediction models cannot predict which patients have a higher long-term stroke risk despite CAS or CEA, and therefore, are not specific for outcome prediction after carotid revascularization.

Differences in study population characteristics between the development cohorts and the validation population may have contributed to the poor external performance of most models. Most models were developed in observational cohorts of both symptomatic and asymptomatic patients, whereas they were validated in a trial population of symptomatic patients. Trial populations are probably more homogenous and might have lower mean absolute complication risks than study populations from observational cohort studies because of strict inclusion and exclusion criteria and are therefore less representative for the total patient population undergoing CAS or CEA. Also, the proportion of patients with vascular risk factors or (cardiac) comorbidities might have been different in the validation population, which reduces usefulness of such characteristics to distinguish between someone with and without the outcome. However, most models showed only moderate discrimination in the development cohorts (Table); thus, we did not expect to find a model with excellent predictive performance in the validation population.

Another reason for the poor external performance could be that clinicians have already identified the high-risk patients for CAS or CEA and have avoided treating these patients. Consequently, the risk difference in the remaining eligible patients who undergo the intervention is small, which makes it difficult to identify a high-risk subset. It is mathematically impossible to assess this explanation because data on the outcome of patients that did not undergo CAS or CEA are absent. Nevertheless, our results suggest that among those eligible for CAS or CEA, identification of a high-risk subset is currently impossible.

Missing data in the validation population may be a third reason for the poor external performance. In the validation population, zeros were inserted for predictors that were unavailable. Also, proxies were used if no direct match was available in the validation population. Therefore, not all prediction models could completely be applied to the validation population, which may have influenced predictive performance adversely.

Although external validation is an essential step in prediction model development, only 4 of the 30 included models had been externally validated in an independent patient population before; 2 were externally validated in the same article

in which their development was described (Alcocer 2013 and Cheng 2016),<sup>15,16</sup> and the other 2 had each been validated twice in independent validation studies (Rothwell 1999 and Tu 2003).<sup>17–20</sup> Our findings are similar to the findings of these previous studies, except that the discriminative performance of the Tu 2003 and Cheng 2016 models was slightly better in the previous external validations. A calibration plot was reported for only one of the previous external validation studies,<sup>18</sup> whereas we reported calibration plots for each prediction model that we validated.

Our study has several strengths. We performed an extensive external validation study of all existing prediction models for clinical outcome after carotid revascularization that we identified with a literature review. Moreover, all models were validated in the same study population, which allows for direct comparison of their predictive performance. Furthermore, multiple imputation was used to handle missing data, which is preferable to complete case analysis.<sup>21</sup>

Nevertheless, some limitations need to be mentioned. First, our validation population consisted of symptomatic ICA stenosis patients, whereas the majority of the models was developed for both symptomatic and asymptomatic patients. Symptomatic and asymptomatic patients have a different absolute complication risk after CAS or CEA and have different characteristics that may influence this risk (eg, type of most recent ipsilateral ischemic event, time between most recent event and procedure). Moreover, study populations that consist of both symptomatic and asymptomatic patients have more variation in patient characteristics and absolute complication risk compared with our validation population. External validation of prediction models developed for asymptomatic patients or both symptomatic and asymptomatic patients in a population of symptomatic patients may have reduced predictive performance of these models. Second, the amount of systematically missing predictors was considerable in some of the individual trials. However, we performed multiple imputation to account for these missing variables. Moreover, predictive performance in the total population after multiple imputation was comparable to the performance in the complete case analysis. Third, some variables were unavailable in the validation population and were assigned a value of zero for all patients; consequently, these variables could not add to the predictive ability of the models. Last, we could not externally validate 3 prediction models, because insufficient information was reported or insufficient data were available to externally validate these models.

The aim of this study was to assess external performance of prediction models for clinical outcome after carotid revascularization based on readily available patient characteristics. Yet, none of the prediction models showed good discrimination and consistently good calibration in our validation population, whereas calibration is especially important if the aim of the model is to identify patients at different levels of risk. Consequently, we cannot recommend the use of any of these models in clinical practice. External validation of the prediction models in other study populations is demanded, preferably in observational cohorts of patients undergoing CAS or CEA and with sufficient information available on predictors

and outcomes. In case external performance of the existing prediction models in other study populations would remain poor, new prediction models for short-term outcome after CAS or CEA need to be developed considering the most important predictors from our previous literature review<sup>4</sup> as candidate predictors. Such models may eventually be combined with long-term outcome models to estimate absolute risk of postprocedural complications after carotid revascularization and optimize decision-making between CAS and CEA in individual patients.

### Conclusions

In this external validation study, prediction models with readily available patient characteristics poorly predicted short-term and long-term outcome after carotid revascularization in a trial population of patients with symptomatic carotid stenosis. Further external validation of existing prediction models or development of new prediction models—preferably in a more heterogeneous study population with sufficient information on predictors and outcomes—is needed to accurately estimate risks after CAS or CEA in individual patients with carotid stenosis.

### Appendix

Involvement of the authors in the CSTC Steering Committee is as follows: Dr Algra (independent chair); EVA-3S: Dr Becquemin, Dr Calvet, Dr Mas; ICSS: Dr Bonati (coordinator), Dr Brown, Dr Hendrikse; SPACE and SPACE-2: Dr Eckstein, Dr Fraedrich, Dr Jansen, Dr Ringleb; CREST and CREST-2: Dr Brott, Dr Howard, Dr Roubin; ACST-1 and ACST-2: Dr Bulbulia, Dr Halliday; trial statistician: Dr Gregson. The members of the Steering Committees and a list of Investigators contributing data to the trials including those in this pooled analysis can be found in earlier publications.

### Acknowledgments

Drs Volkers, Greving, Kappelle, and Algra designed the study plan. Drs Volkers, Greving, and Algra undertook the statistical analysis and interpreted the results together with Dr Kappelle. Drs Mas, Ringleb, Bonati, and Howard extracted individual patient data from the contributing trials. Dr Volkers wrote the first version of the article. All authors contributed to data interpretation, critical revision of the article, and approved the final version. All authors gave final approval to submit for publication.

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### Disclosures

None.

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## Prediction Models for Clinical Outcome After a Carotid Revascularization Procedure: An External Validation Study

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## **SUPPLEMENTAL MATERIAL**

### **Prediction models for clinical outcome after a carotid revascularization procedure: an external validation study**

Description of literature review

Description of proxies used in the validation population

Table I. Predictors used in prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome

Table II. Description of development cohorts of prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome

Table III. Baseline characteristics and missings in validation population

Table IV. Discrimination (c-statistic) of each prediction model in complete cases

Figure I. Calibration plots before recalibration for the nine prediction models with known intercept or baseline hazard

Figure II. Calibration plots after recalibration

Supplemental references

## **Description of literature review<sup>1</sup>**

### Literature search

We performed a literature search in PubMed and Embase on December 22, 2016, for studies that described a prediction model for short-term or long-term outcome after carotid artery stenting (CAS) or carotid endarterectomy (CEA). The search syntax consisted of synonyms for ‘carotid artery stenting OR carotid endarterectomy’ AND ‘prediction model’ AND ‘vascular events’.

We included studies that described a prediction model that predicted risk of vascular events after CAS or CEA in patients with symptomatic or asymptomatic carotid artery stenosis. These studies had to present either a prediction model with regression coefficients and a measure of predictive performance or a risk score (not only a multivariable analysis of predictors), and had to include at least one baseline patient characteristic in the final prediction model.

Critical appraisal and data extraction was performed with a standardized form based on the CHARMS checklist.<sup>2</sup>

### Results

Our search yielded 37 records that described 46 unique prediction models; 11 models for patients who underwent CAS, 34 models for patients who underwent CEA, and 1 model for patients who underwent CAS or CEA. Thirty-six of these models predicted short-term outcome and 10 models predicted long-term outcome.

We excluded 13 of the 46 prediction models for the current analysis. Ten of these models used procedural characteristics,<sup>3-11</sup> three models predicted risk of myocardial infarction or other cardiac complications,<sup>12-14</sup> and three did not provide sufficient information to validate the model.<sup>15-17</sup>

## Description of proxies used in the validation population

### Predictors

We used proxies for 16 predictors. *Nonwhite race* (defined as blacks or Hispanics) was only collected in CREST, which was conducted in the USA. The other three trials were mainly conducted in Europe; therefore, we assigned a value of zero (absent) for the variable nonwhite race for patients from these three trials.

We used history of *insulin-dependent or non-insulin dependent diabetes mellitus* as proxy for the predictor diabetes or impaired glucose tolerance and for the predictor diabetes with inadequate glycemic control (HbA1c >7%). We used serum creatinine values to calculate glomerular filtration rates (GFR) with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and used a threshold of GFR <15 ml/min/1.73m<sup>2</sup> as need for *dialysis*.<sup>18</sup>

Occurrence of transient ischemic attack (TIA) as qualifying event before the procedure was used as proxy for *history of TIA*. We approximated *history of stroke with residual symptoms* by combining a history of stroke with a modified Ranking Scale (mRS) score at baseline of 1 or higher; *history of stroke without residual symptoms* was approximated by combining a history of stroke and an mRS score at baseline of 0. We used an mRS score at baseline  $\geq 3$  as proxy for *dependent functional status* and a score of 4 or 5 as proxy for *patient admission from nursing home*.

We used history of coronary heart disease (composite of history of angina, myocardial infarction, or coronary revascularization) as proxy for presence of *physiologic high-risk characteristics* (which included heart failure, left ventricular ejection fraction <30%, unstable angina or myocardial infarction 30 days before surgery). History of peripheral vascular disease was used as proxy for *large artery atherosclerosis*. Presence of contralateral stenosis 70-99% or occlusion was available only as dichotomous variable in the validation population and was used as proxy for *contralateral stenosis  $\geq 50\%$* .

We assigned a value of zero for *malignant disease, valvular heart disease, previous ipsilateral CEA, emergency procedure, and impending major surgery* because these characteristics were exclusion criteria in some or all of the four trials.

### Outcome measures

Disabling stroke was defined as an mRS score  $\geq 3$  30 days or later after stroke onset in the four trials and was used as proxy for *major stroke* (i.e. fatal stroke or stroke lasting longer than 7 days) for the two prediction models that were originally developed to predict this outcome.<sup>19,20</sup>

*Duration of in-hospital stay after the procedure* was not collected in EVA-3S. Therefore, we used a period of 30 days after the procedure as duration of follow-up for all short-term outcome models.

**Table I. Predictors used in prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome**

Predictors	CAS short-term				CEA short-term			
	Hofmann 2006a <sup>21</sup>	Hofmann 2006b <sup>21</sup>	Hawkins 2012 <sup>22</sup>	Wimmer 2012 <sup>23</sup>	McCrorry 1993 <sup>24</sup>	Kucey 1998 <sup>25</sup>	Rothwell 1999 <sup>19</sup>	Kuhan 2001 <sup>20</sup>
Age	X	X	X	X	X	X		
Sex						X	X	
Race								
Smoking								
Diabetes mellitus	X	X						X
High blood pressure					X		X	
History of stroke or TIA								
History of stroke			X	X				
History of stroke with residual symptoms								
History of stroke without residual symptoms								
History of TIA				X				
Cerebral degeneration*								
Myocardial infarction				X				
Angina					X			
Heart failure								
Coronary artery disease								
Valvular heart disease								
Atrial fibrillation			X					
Cardiomyopathy*								
Results of cardiac stress test*								
Heart disease <sup>†</sup>								X
Peripheral vascular disease or surgery							X	
Large artery atherosclerosis								
Prior coronary intervention								
Any prior vascular surgery*								
COPD or dyspnea*								
Renal function or dialysis				X				
Malignant disease								
Prior neck radiation*								
Bleeding disorder*								
Symptomatic ICA stenosis	X		X			X		
Type of preoperative event <sup>‡</sup>					X			X
Dependent functional status								
Contralateral ICA stenosis	X	X						
Contralateral ICA occlusion								
Anatomical characteristics on imaging*		X		X	X			
Laboratory characteristics*								
Antiplatelet use								
Statin use								
Antihypertensives use*								
Previous ipsilateral CEA			X					
Emergency procedure								
Carotid revascularization prior to other surgery*				X	X			
Side of procedure				X		X		
Operator experience*						X		
Physiologic high-risk characteristic								
ASA classification*								
Impending major surgery			X					
Total number of predictors	4	4	6	10	7	6	3	3
Number of predictors unavailable in validation population	0	1	0	4	3	2	0	0

**Table I. Predictors used in prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome (continued)**

Predictors	CEA short-term							Bekelis 2013a <sup>13</sup>	Bekelis 2013b <sup>13</sup>
	Tu 2003 <sup>26</sup>	Matsen 2005 <sup>27</sup>	Goodney 2008 <sup>28</sup>	Calvillo-King 2010a <sup>29</sup>	Calvillo-King 2010b <sup>29</sup>	Calvillo-King 2010c <sup>29</sup>			
Age		X	X				X		
Sex				X	X	X	X		
Race				X	X	X			
Smoking									
Diabetes mellitus	X								
High blood pressure									
History of stroke or TIA	X			X	X	X			
History of stroke									
History of stroke with residual symptoms							X	X	
History of stroke without residual symptoms							X	X	
History of TIA							X	X	
Cerebral degeneration*		X							
Myocardial infarction							X		
Angina							X	X	
Heart failure	X		X	X		X	X		
Coronary artery disease				X	X	X			
Valvular heart disease				X	X	X			
Atrial fibrillation	X								
Cardiomyopathy*		X							
Results of cardiac stress test*									
Heart disease <sup>†</sup>									
Peripheral vascular disease or surgery							X		
Large artery atherosclerosis		X							
Prior coronary intervention									
Any prior vascular surgery*									
COPD or dyspnea*							X		
Renal function or dialysis							X		
Malignant disease									
Prior neck radiation*									
Bleeding disorder*		X							
Symptomatic ICA stenosis									
Type of preoperative event <sup>‡</sup>			X						
Dependent functional status									
Contralateral ICA stenosis				X	X	X			
Contralateral ICA occlusion	X		X						
Anatomical characteristics on imaging*									
Laboratory characteristics*									
Antiplatelet use			X						
Statin use									
Antihypertensives use*									
Previous ipsilateral CEA									
Emergency procedure			X						
Carotid revascularization prior to other surgery*									
Side of procedure									
Operator experience*									
Physiologic high-risk characteristic									
ASA classification*									
Impending major surgery									
Total number of predictors	5	5	6	8	7	7	11	4	
Number of predictors unavailable in validation population	0	3	0	0	0	0	1	0	

**Table I. Predictors used in prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome (continued)**

Predictors	CEA short-term						
	Bekelis 2013c <sup>13</sup>	Gupta 2013 <sup>30</sup>	Wimmer 2014 <sup>31</sup>	Bennett 2015a <sup>3</sup>	Bennett 2015b <sup>3</sup>	Chaudhry 2016 <sup>32</sup>	Eslami 2016 <sup>33</sup>
Age	X	X	X			X	X
Sex							
Race							
Smoking						X	
Diabetes mellitus			X				X
High blood pressure							
History of stroke or TIA							
History of stroke							
History of stroke with residual symptoms	X						
History of stroke without residual symptoms							
History of TIA							
Cerebral degeneration*							
Myocardial infarction	X		X				
Angina		X					
Heart failure	X		X			X	X
Coronary artery disease							
Valvular heart disease							
Atrial fibrillation						X	
Cardiomyopathy*							
Results of cardiac stress test*							
Heart disease <sup>†</sup>							
Peripheral vascular disease or surgery	X	X	X				X
Large artery atherosclerosis							
Prior coronary intervention							
Any prior vascular surgery*							
COPD or dyspnea*	X	X					
Renal function or dialysis	X					X	
Malignant disease							
Prior neck radiation*							
Bleeding disorder*							
Symptomatic ICA stenosis			X			X	X
Type of preoperative event <sup>‡</sup>				X			
Dependent functional status		X					X
Contralateral ICA stenosis				X	X		
Contralateral ICA occlusion			X				X
Anatomical characteristics on imaging*							
Laboratory characteristics*							
Antiplatelet use							
Statin use							
Antihypertensives use*							
Previous ipsilateral CEA							
Emergency procedure				X			X
Carotid revascularization prior to other surgery*							
Side of procedure							
Operator experience*							
Physiologic high-risk characteristic				X			
ASA classification*					X		
Impending major surgery							
Total number of predictors	7	6	7	4	2	6	8
Number of predictors unavailable in validation population	1	2	0	0	1	0	0

**Table I. Predictors used in prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome (continued)**

Predictors	CAS long-term		CEA long-term				CAS and CEA long-term
	Hoke 2012 <sup>34</sup>	Cheng 2016 <sup>35</sup>	Van Lammeren 2012 <sup>36</sup>	Conrad 2013 <sup>37</sup>	Wallaert 2013 <sup>38</sup>	Gates 2015 <sup>39</sup>	Alcocer 2013 <sup>40</sup>
Age	X	X	X	X	X	X	X
Sex							
Race							
Smoking			X		X		
Diabetes mellitus	X	X		X	X	X	X
High blood pressure			X				
History of stroke or TIA						X	
History of stroke							
History of stroke with residual symptoms							
History of stroke without residual symptoms							
History of TIA							
Cerebral degeneration*							
Myocardial infarction							
Angina							
Heart failure	X	X			X	X	
Coronary artery disease			X	X			
Valvular heart disease							
Atrial fibrillation							
Cardiomyopathy*							
Results of cardiac stress test*							
Heart disease†							
Peripheral vascular disease or surgery	X		X				
Large artery atherosclerosis							
Prior coronary intervention							X
Any prior vascular surgery*							
COPD or dyspnea*				X	X	X	X
Renal function or dialysis			X	X	X		X
Malignant disease		X					
Prior neck radiation*				X			
Bleeding disorder*							
Symptomatic ICA stenosis		X	X				
Type of preoperative event‡							
Dependent functional status						X	
Contralateral ICA stenosis			X		X	X	
Contralateral ICA occlusion	X						
Anatomical characteristics on imaging*	X						
Laboratory characteristics*							
Antiplatelet use							
Statin use				X	X		
Antihypertensives use*			X				
Previous ipsilateral CEA							
Emergency procedure							
Carotid revascularization prior to other surgery*							
Side of procedure							
Operator experience*							
Physiologic high-risk characteristic							
ASA classification*							
Impending major surgery							
Total number of predictors	7	5	8	7	8	7	5
Number of predictors unavailable in validation population	2	0	1	2	1	1	1

Some models used multiple predictors of the same type (e.g. for anatomical characteristics on angiogram).

\*Data not available in any of the four trials; therefore, a value of zero was assigned.

†Composite of angina, myocardial infarction, heart failure, or cardiac arrhythmia.

‡Amaurosis fugax, transient ischemic attack, or ischemic stroke.

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ICA, internal carotid artery; ASA, American Society of Anesthesiologists.



**Table II. Description of development cohorts of prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome**

Prediction model	Country of recruitment	Recruitment period	Data source	Number of including centers	Asymptomatic/symptomatic patients	Predicted outcome	Prediction horizon	Model type	Number of events/patients (%)	Symptomatic patients, %	Age, mean (SD)	Male sex, %
CAS short-term models												
Hofmann 2006a <sup>21</sup>	Austria	1997-2005	Secondary care hospital	1	Both	Stroke, MI or death	≤30 days after procedure	Logistic	26/606 (4.3)	36.1	71.5 (NR)*	67.3
Hofmann 2006b <sup>21</sup>	Austria	1997-2005	Secondary care hospital	1	Both	Stroke, MI or death	≤30 days after procedure	Logistic	26/606 (4.3)	36.1	71.5 (NR)*	67.3
Hawkins 2012 <sup>22</sup>	USA	2005-2011	National carotid revascularization registry	173	Both	Stroke or death	Postprocedural in-hospital	Logistic	271/11,122 (2.4) <sup>†</sup>	41.4	70.6 (NR)	61.5
Wimmer 2012 <sup>23</sup>	USA, Canada	2006-2010	Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) worldwide study	364	Both	Stroke or death	≤30 days after procedure	Logistic	366/10,186 (3.6)	29.8	72.3 (±9.7)	61.1
CEA short-term models												
McCrory 1993 <sup>24</sup>	USA	1988-1990	Discharge database of 12 academic hospitals	12	Both	Stroke, MI or death	Postprocedural in-hospital	Other	27/388 (6.9) <sup>‡</sup>	59.0 <sup>‡</sup>	67 (±8.4) <sup>§</sup>	65.0 <sup>§</sup>
Kucey 1998 <sup>25</sup>	Canada	1994-1996	Discharge database of 8 secondary care hospitals	8	Both	Stroke or death	≤30 days after procedure	Logistic	81/1,280 (6.3)	73.3	NR	66.1
Rothwell 1999 <sup>19</sup>	Europe	1981-1994	European Carotid Surgery Trial (ECST)	100	Symptomatic	Major stroke or death	≤30 days after procedure	Logistic	84/1,203 (7.0) <sup>  </sup>	100	62.5 (±8.1) <sup>#</sup>	71.9 <sup>#</sup>
Kuhan 2001 <sup>20</sup>	UK	1992-1999	Two vascular surgery units from one academic hospital	2	Both	Major stroke or death	≤30 days after procedure	Logistic	29/741 (3.9)	87.2	68 (NR)*	60.4
Tu 2003 <sup>26</sup>	Canada	1994-1997	Regional hospital discharge database	34	Both	Stroke or death	≤30 days after procedure	Logistic	362/6,038 (6.0)	69.4	68.3 (NR)	65.3
Matsen 2005 <sup>27</sup>	USA	1994-2003	Secondary care hospital	1	NR	Mortality	Postprocedural in-hospital	Logistic	125/23,237 (0.5)	NR	70.6 (NR)	54.7
Goodney 2008 <sup>28</sup>	USA	2003-2007	Regional vascular surgery quality improvement database	11	Both	Stroke or death	≤30 days after procedure	Logistic	57/3,092 (1.8)	44.0	69.0 (NR)	59.0

**Table II. Description of development cohorts of prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome (continued)**

Prediction model	Country of recruitment	Recruitment period	Data source	Number of including centers	Asymptomatic/ symptomatic patients	Predicted outcome	Prediction horizon	Model type	Number of events/ patients (%)	Symptomatic patients, %	Age, mean (SD)	Male sex, %
CEA short-term models												
Calvillo-King 2010a <sup>29</sup>	USA	1998-1999	New York Carotid Artery Surgery (NYCAS) study	157	Asymptomatic	Stroke or death	≤30 days after procedure	Logistic	200/6,553 (3.1)	0	74.5 (±6.6)	54.9
Calvillo-King 2010b <sup>29</sup>	USA	1998-1999	New York Carotid Artery Surgery (NYCAS) study	157	Asymptomatic	Stroke	≤30 days after procedure	Logistic	165/6,553 (2.5)	0	74.5 (±6.6)	54.9
Calvillo-King 2010c <sup>29</sup>	USA	1998-1999	New York Carotid Artery Surgery (NYCAS) study	157	Asymptomatic	Stroke or death	≤30 days after procedure	Logistic	200/6,553 (3.1)	0	74.5 (±6.6)	54.9
Bekelis 2013a <sup>13</sup>	USA	2005-2010	National database	>180	Both	Stroke, MI or death	≤30 days after procedure	Logistic	994/35,698 (2.8)	43.9	71.1 (NR)	59.1
Bekelis 2013b <sup>13</sup>	USA	2005-2010	National database	>180	Both	Stroke	≤30 days after procedure	Logistic	585/35,698 (1.6)	43.9	71.1 (NR)	59.1
Bekelis 2013c <sup>13</sup>	USA	2005-2010	National database	>180	Both	Mortality	≤30 days after procedure	Logistic	267/35,698 (0.8)	43.9	71.1 (NR)	59.1
Gupta 2013 <sup>30</sup>	USA	2005-2010	National database	>250	Asymptomatic	Stroke, MI or death	≤30 days after procedure	Logistic	324/17,692 (1.8)	0	72.0 (NR)	57.9
Wimmer 2014 <sup>31</sup>	USA	2005-2013	National carotid revascularization registry	60	Both	Stroke or death	Postprocedural in-hospital	Logistic	213/12,889 (1.7) <sup>†</sup>	35.0	70.8 (±10.6)	59.0
Bennett 2015a <sup>3</sup>	USA	2012	National disease-specific database	78	Symptomatic	Stroke or death	≤30 days after procedure	Logistic	74/1,609 (4.6)	100	NR	63.0
Bennett 2015b <sup>3</sup>	USA	2012	National disease-specific database	78	Asymptomatic	Stroke or death	≤30 days after procedure	Logistic	43/2,236 (1.9)	0	NR	59.6
Chaudhry 2016 <sup>32</sup>	USA	2005-2006	All-payer inpatient care database	ca. 1,000	Both	Stroke, cardiac complications or death	Postprocedural in-hospital	Logistic	1,494/49,411 (3.0) <sup>*</sup>	NR	71.1 (±9.5) <sup>§</sup>	57.6 <sup>§</sup>
Eslami 2016 <sup>33</sup>	USA	2003-2013	Regional vascular surgery database	>35	Both	Stroke, MI, death or discharge to rehabilitation facility	Postprocedural in-hospital	Logistic	389/8,661 (4.5)	24.6	69.6 (±9.4)	59.9

**Table II. Description of development cohorts of prediction models for short-term outcome after CAS, short-term outcome after CEA, and long-term outcome (continued)**

Prediction model	Country of recruitment	Recruitment period	Data source	Number of including centers	Asymptomatic/symptomatic patients	Predicted outcome	Prediction horizon	Model type	Number of events/patients (%)	Symptomatic patients, %	Age, mean (SD)	Male sex, %
CAS long-term models												
Hoke 2012 <sup>34</sup>	Austria	1997-2005	Secondary care hospital	1	Both	Mortality	Median follow-up 6.5 years	Cox	211/602 (35.0)	NR	71.0 (NR)	67.6
Cheng 2016 <sup>35</sup>	Taiwan	2004-2009	Random selection from national health insurance claim database	NR	Both	Stroke, MI or death	1 year after procedure	Cox	44/317 (13.9)	40.4	70.5 (±9.7)	77.9
CEA long-term models												
Van Lammeren 2012 <sup>36</sup>	The Netherlands	2002-2009	Secondary care hospital and academic hospital	2	Both	Stroke, MI or death from cardiovascular causes	3 years after procedure	Cox	148/1,138 (13.0)	83.3	67.3 (±8.9)	69.9
Conrad 2013 <sup>37</sup>	USA	1989-2005	Secondary care hospital	1	Asymptomatic	Mortality	5 years after procedure	Logistic	536/2,001 (26.8) <sup>†</sup>	0	71 (±8.6)	60.7
Wallaert 2013 <sup>38</sup>	USA	2003-2011	Regional vascular surgery database	24	Asymptomatic	Mortality	5 years after procedure	Cox	741/4,114 (18.0)	0	70.0 (NR)	58.0
Gates 2015 <sup>39</sup>	USA	2003-2011	Regional vascular surgery database	20	Both	Short-term stroke, MI or death, long-term ipsilateral stroke or death from neurological causes	1 year after procedure	Logistic	440/3,098 (14.2)	54.3	69.9 (±9.5)	60.3
CAS and CEA long-term model												
Alcocer 2013 <sup>40</sup>	USA	1999-2008	Academic hospital	1	Asymptomatic	Mortality	3 years after procedure	Cox	70/506 (13.8)	0	69.0 (±9.0)	62.3

\*Median (range).

†Number of events out of total number of procedures.

‡In development cohort.

§In development and validation cohort.

||Number of patients with 0-69% stenosis who underwent surgery within ECST.

#Numbers are based on total group of patients with 0-100% ICA stenosis who underwent surgery within ECST.<sup>41</sup>

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction; SD, standard deviation; NR, not reported.

**Table III. Baseline characteristics and missings in validation population**

Characteristic	All trials				Per trial					
	All (n=4,445)		EVA-3S (n=503)		SPACE (n=1,136)		ICSS (n=1,581)		CREST (n=1,225)	
	Patients	Missings	Patients	Missings	Patients	Missings	Patients	Missings	Patients	Missings
<b>Demographics</b>										
Age, mean (SD)	69.2 (±9.2)	0	70.1 (±10.4)	0	68.3 (±8.4)	0	70.0 (±9.1)	0	68.7 (±9.5)	0
Male sex	3,102 (69.8)	0	379 (75.3)	0	817 (71.9)	0	1,110 (70.2)	0	796 (65.0)	0
<b>History of</b>										
Hypertension	3,338 (75.4)	16 (0.4)	368 (73.2)	0	859 (75.6)	0	1,091 (69.7)	15 (0.9)	1,020 (83.3)	1 (0.1)
Current smoking	1,160 (26.3)	34 (0.8)	120 (23.9)	0	316 (27.8)	0	376 (24.0)	15 (0.9)	348 (28.9)	19 (1.6)
Diabetes	1,112 (25.0)	2 (0.0)	120 (23.9)	0	313 (27.6)	0	342 (21.6)	0	337 (27.6)	2 (0.2)
Angina	146 (9.3)	2,879 (64.8)	0	503 (100)	0	1,136 (100)	146 (9.3)	15 (0.9)	0	1,225 (100)
Atrial fibrillation	100 (6.4)	2,879 (64.8)	0	503 (100)	0	1,136 (100)	100 (6.4)	15 (0.9)	0	1,225 (100)
Myocardial infarction	344 (16.6)	2,376 (53.5)	62 (12.3)	0	0	1,136 (100)	282 (18.0)	15 (0.9)	0	1,225 (100)
Heart failure	79 (3.8)	2,069 (46.5)	14 (2.8)	0	0	1,136 (100)	65 (4.2)	15 (0.9)	0	1,225 (100)
Coronary revascularization	69 (13.7)	3,942 (88.7)	69 (13.7)	0	0	1,136 (100)	0	1,581 (100)	0	1,225 (100)
Peripheral vascular disease	324 (15.7)	2,376 (53.5)	65 (12.9)	0	0	1,136 (100)	259 (16.5)	15 (0.9)	0	1,225 (100)
Stroke or TIA*	713 (34.2)	2,361 (53.1)	186 (37.0)	0	0	1,136 (100)	527 (33.3)	0	0	1,225 (100)
<b>Medication use</b>										
Antiplatelets	1512 (91.4)	2,790 (62.8)	213 (83.2)	247 (49.1)	0	1,136 (100)	725 (93.3)	804 (50.9)	574 (92.3)	603 (49.2)
Lipidlowering	806 (49.2)	2,806 (63.1)	248 (49.3)	0	558 (49.1)	0	0	1,581 (100)	0	1,225 (100)
<b>Laboratory measures</b>										
Creatinine level in mg/dL, mean (SD)	1.1 (±0.3)	3,220 (72.0)	0	503 (100)	0	1,136 (100)	0	1,581 (100)	1.1 (±0.3)	16 (1.3)
<b>Anatomical characteristics</b>										
Contralateral ICA occlusion	164 (4.1)	454 (10.2)	14 (2.8)	0	35 (4.0)	253 (22.3)	79 (5.0)	10 (0.6)	36 (3.5)	191 (15.6)

Results are presented as numbers (%), unless stated otherwise.

\*Before the qualifying event.

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; TIA, transient ischemic attack; ICA, internal carotid artery; SD, standard deviation.

**Table IV. Discrimination (c-statistic) of each prediction model in complete cases**

Prediction model	External validation		C-statistic (95% CI)*
	Number of events/patients (%)	Number of patients excluded from complete case analysis (%)	
<b>CAS short-term models</b>			
Hofmann 2006a	139/1,961 (7.1)	223 (10.2)	0.54 (0.47-0.60)
Hofmann 2006b	139/1,961 (7.1)	223 (10.2)	0.54 (0.47-0.60)
Hawkins 2012	55/750 (7.3)	1,434 (65.7)	0.65 (0.58-0.72)
Wimmer 2012	55/750 (7.3)	1,434 (65.7)	0.62 (0.55-0.68)
<b>CEA short-term models</b>			
McCrorry 1993	25/772 (3.2)	1,489 (65.9)	0.56 (0.45-0.67)
Kucey 1998	84/2,261 (3.7)	0 (0)	0.53 (0.47-0.59)
Rothwell 1999	35/1,035 (3.4)	1,226 (54.2)	0.57 (0.48-0.65)
Kuhan 2001	83/2,197 (3.8)	64 (2.8)	0.55 (0.47-0.62)
Tu 2003	26/796 (3.3)	1,465 (64.8)	0.51 (0.42-0.61)
Matsen 2005	37/1,069 (3.5)	1,192 (52.7)	0.46 (0.38-0.55)
Goodney 2008	33/1,012 (3.3)	1,249 (55.2)	0.53 (0.43-0.63)
Calvillo-King 2010a	35/1,051 (3.3)	1,210 (53.5)	0.61 (0.53-0.69)
Calvillo-King 2010b	35/1,051 (3.3)	1,210 (53.5)	0.62 (0.54-0.69)
Calvillo-King 2010c	36/1,058 (3.4)	1,203 (53.2)	0.63 (0.56-0.68)
Bekelis 2013a	27/797 (3.4)	1,464 (64.8)	0.61 (0.50-0.71)
Bekelis 2013b	27/797 (3.4)	1,464 (64.8)	0.62 (0.51-0.72)
Bekelis 2013c	37/1,057 (3.5)	1,204 (53.3)	0.59 (0.51-0.67)
Gupta 2013	26/801 (3.2)	1,460 (64.6)	0.51 (0.39-0.64)
Wimmer 2014	36/1,062 (3.4)	1,199 (53.0)	0.54 (0.45-0.63)
Bennett 2015a	66/2,002 (3.3)	259 (11.5)	0.56 (0.44-0.67)
Bennett 2015b	66/2,029 (3.3)	232 (10.3)	0.53 (0.47-0.58)
Chaudhry 2016	27/812 (3.3)	1,449 (64.1)	0.47 (0.37-0.57)
Eslami 2016	35/1,051 (3.3)	1,210 (53.5)	0.50 (0.40-0.59)
<b>CAS long-term models</b>			
Hoke 2012 <sup>†</sup>	152/997 (15.2)	12 (1.2)	0.67 (0.63-0.71)
Cheng 2016	118/1,000 (11.8)	1,184 (54.2)	0.60 (0.55-0.64)
<b>CEA long-term models</b>			
Van Lammeren 2012 <sup>‡</sup>	0/0	2,261 (100)	NA
Conrad 2013 <sup>‡</sup>	0/0	2,261 (100)	NA
Wallaert 2013 <sup>‡</sup>	0/0	2,261 (100)	NA
Gates 2015	68/1,051 (6.5)	1,210 (53.5)	0.63 (0.56-0.70)
<b>CAS and CEA long-term model</b>			
Alcocer 2013 <sup>‡</sup>	0/0	4,445 (100)	NA

\*Risk of stroke or death within 30 days after the procedure was used as outcome for all short-term outcome models; the original outcome measure was used for all long-term outcome models.

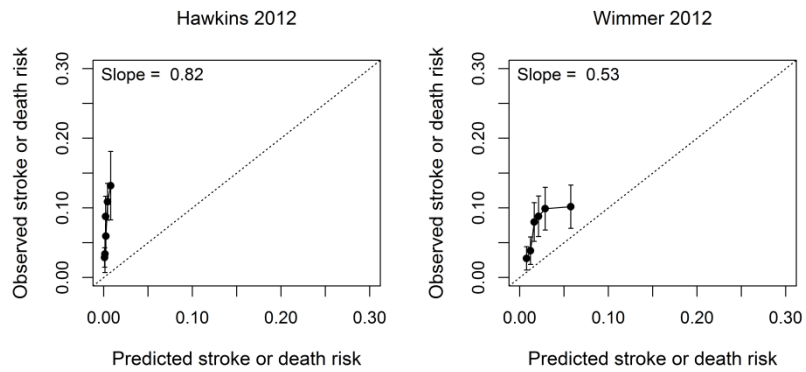
<sup>†</sup>Externally validated with data from EVA-3S and ICSS only.

<sup>‡</sup>No patients had data on all variables available.

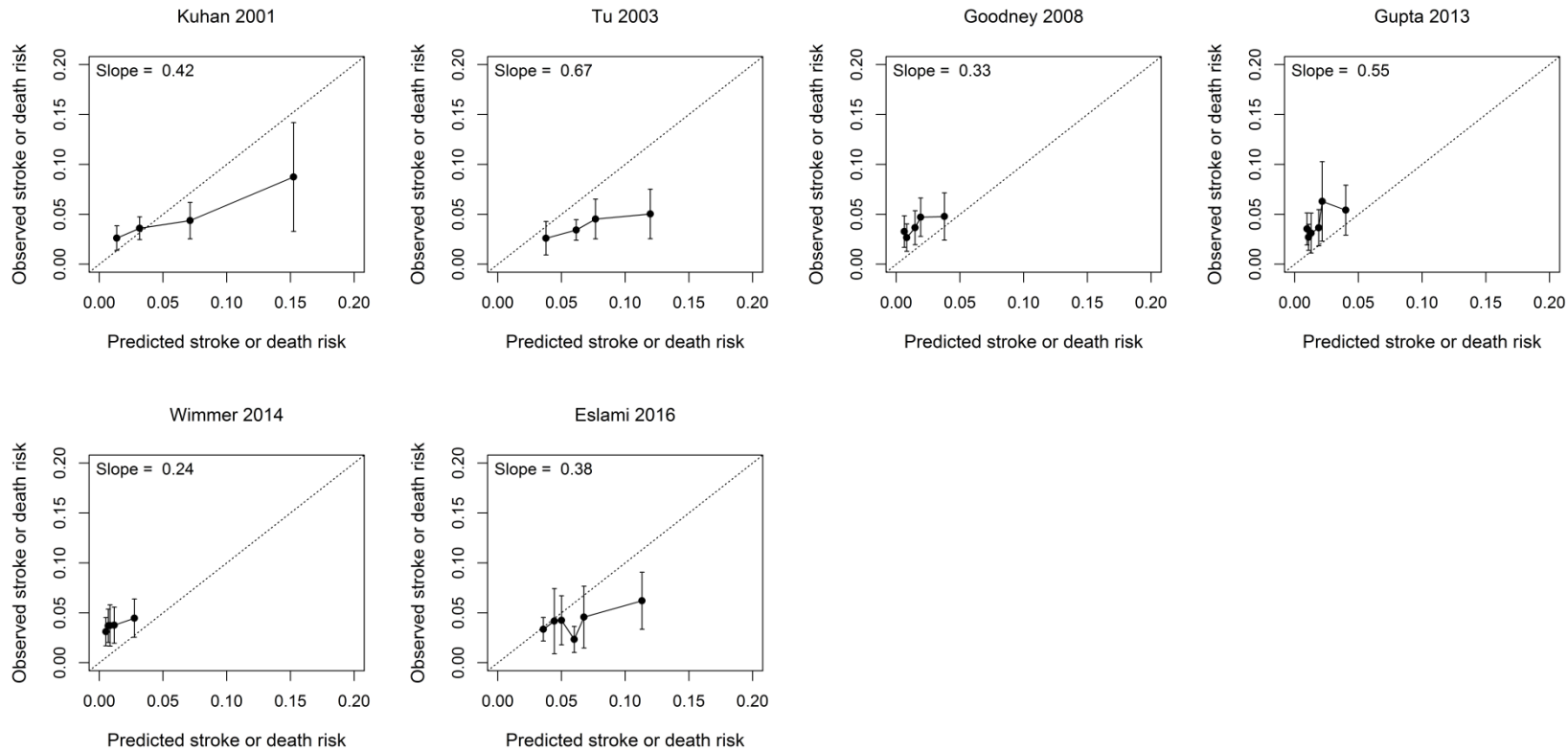
Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; NA, not applicable.

**Figure I. Calibration plots before recalibration for the nine prediction models with known intercept or baseline hazard\***

**A. CAS short-term models**

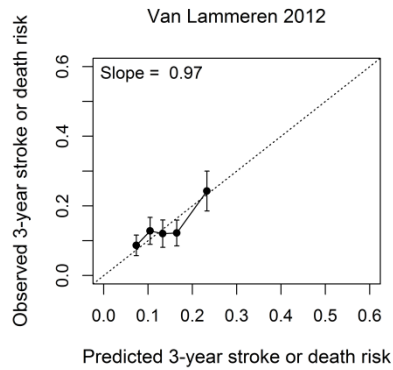


**B. CEA short-term models**



**Figure I. Calibration plots before recalibration for the nine prediction models with known intercept or baseline hazard (continued)\***

**C. Long-term model**



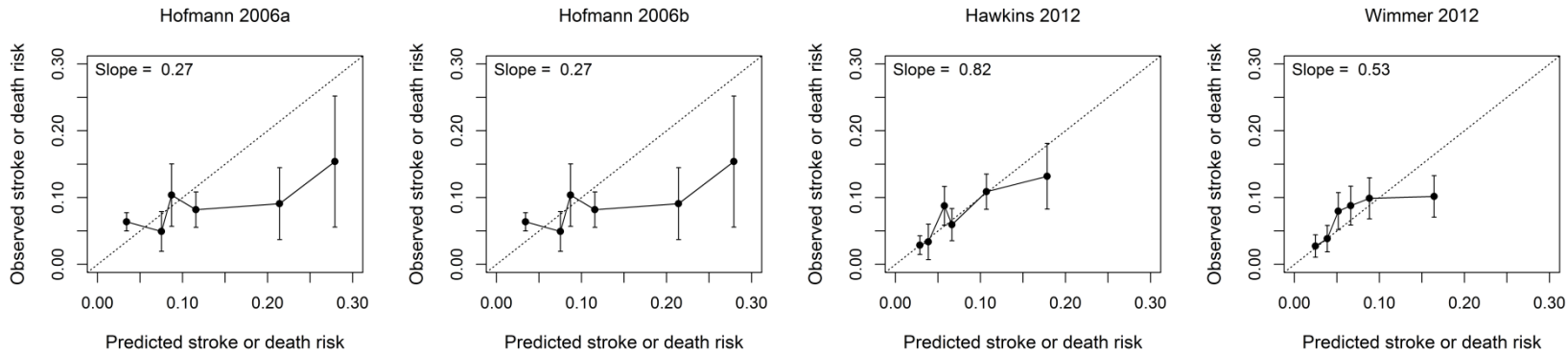
Risk of stroke or death within 30 days after the procedure was used as primary outcome for all short-term outcome models; the original outcome measure was used for the long-term outcome model. Calibration plots display the calibration curve in the first imputed dataset; calibration curves in the other multiple imputed datasets were comparable.

\*The original intercept or baseline hazard was reported for 9 out of the 22 models for which we applied the original regression formula.

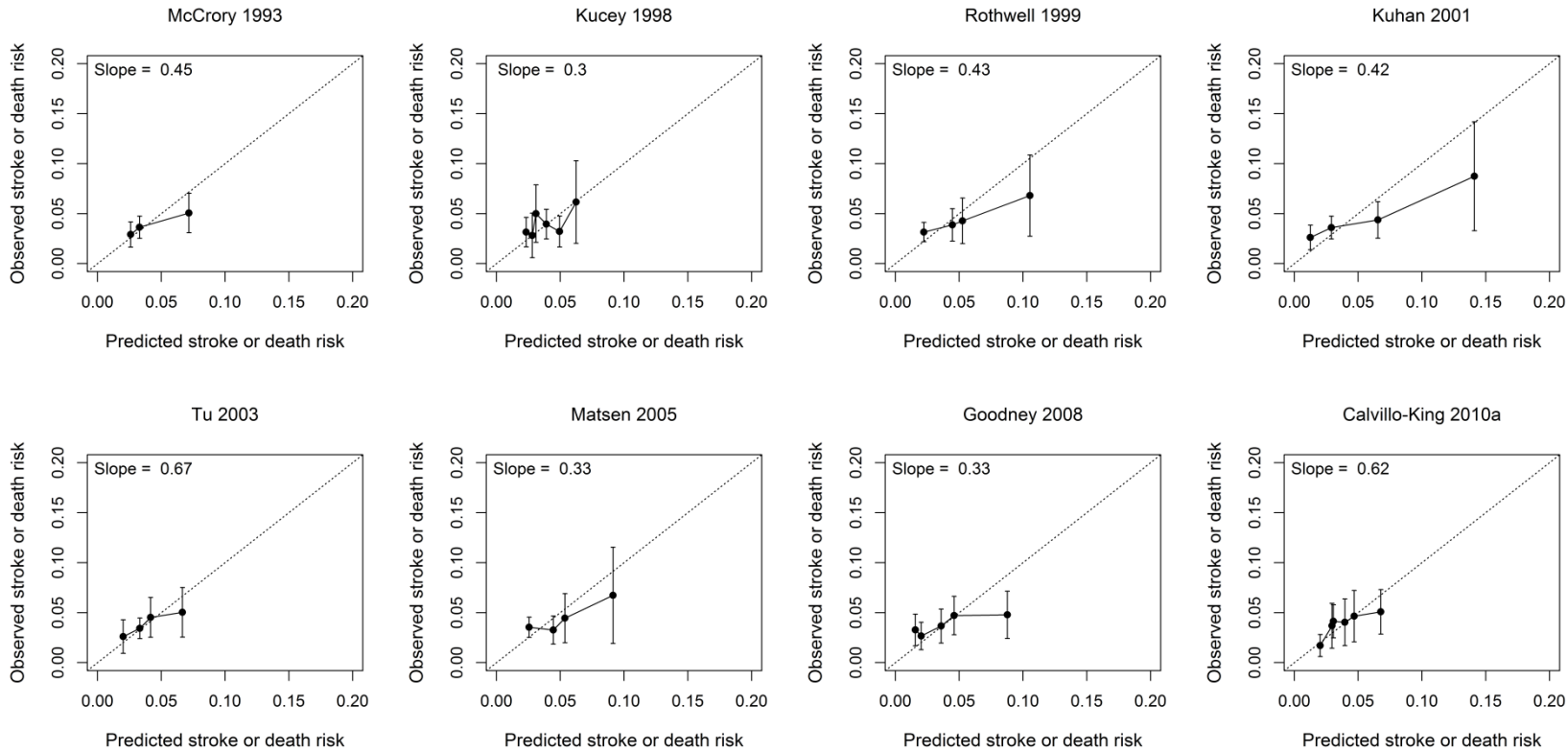
Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy.

## Figure II. Calibration plots after recalibration

### A. CAS short-term models



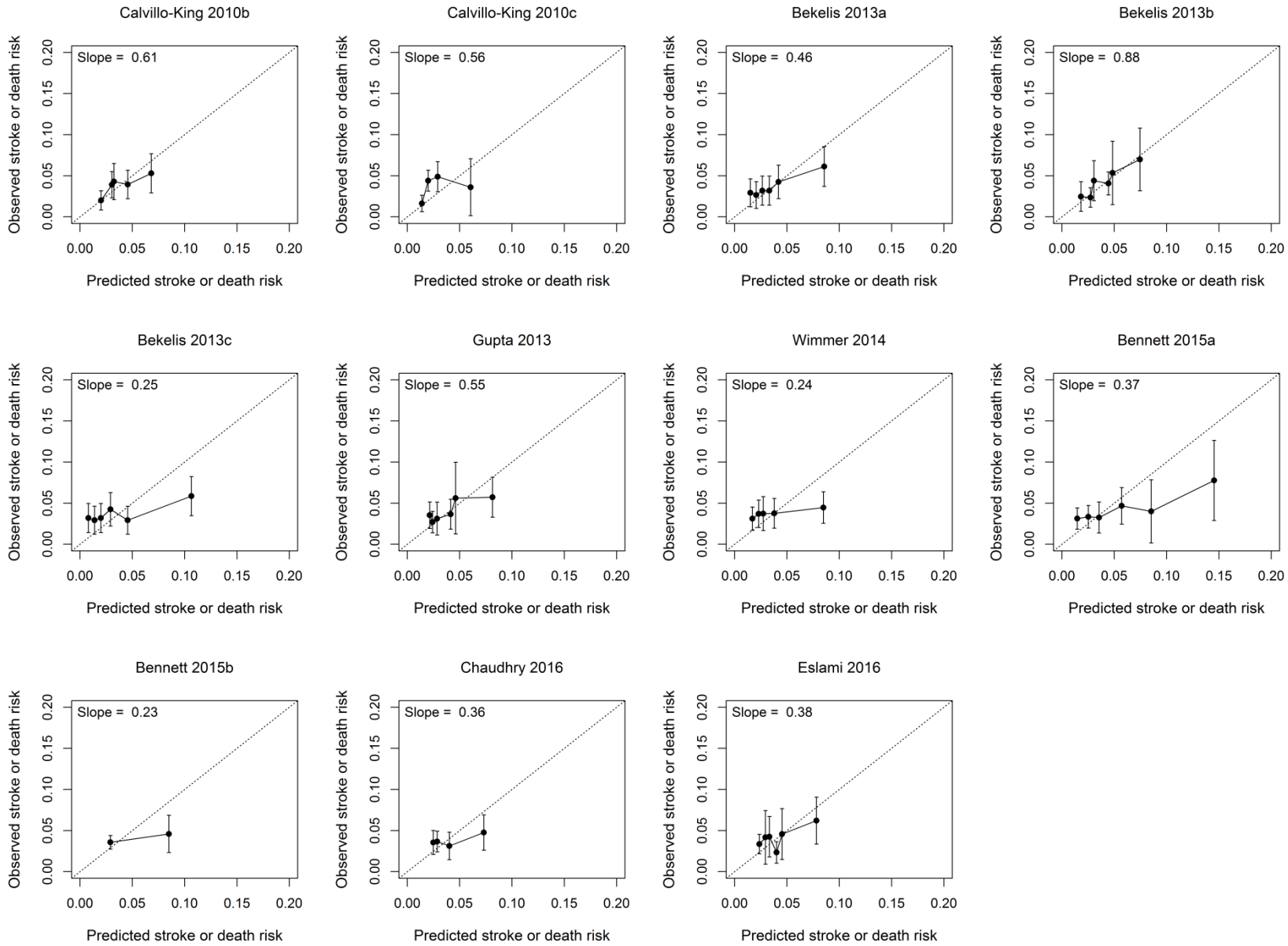
### B. CEA short-term models





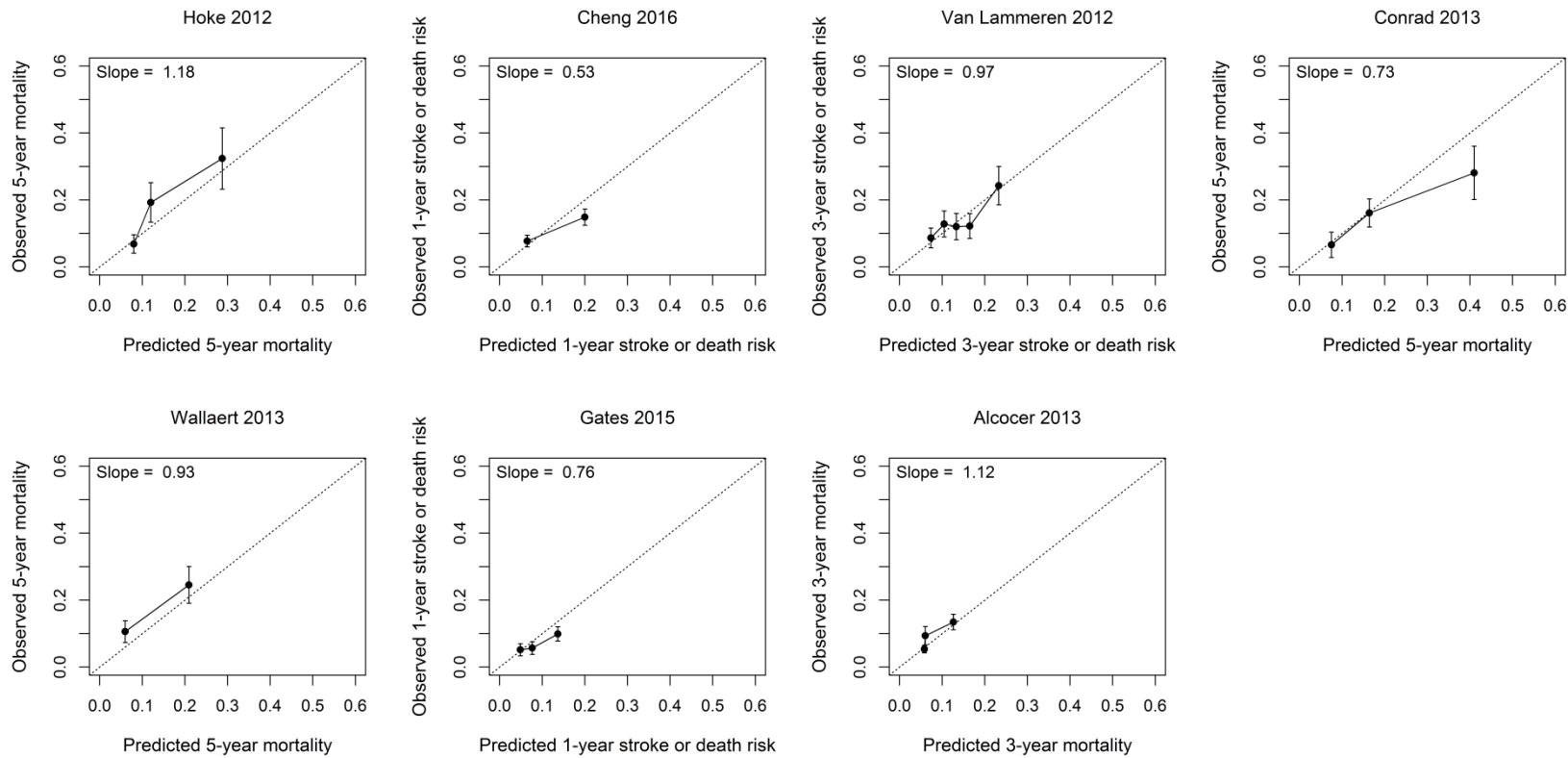
## Figure II. Calibration plots after recalibration (continued)

### B. CEA short-term models



## Figure II. Calibration plots after recalibration (continued)

### C. Long-term models



Risk of stroke or death within 30 days after the procedure was used as primary outcome for all short-term outcome models; the original outcome measure was used for all long-term outcome models. Calibration plots display the calibration curve in the first imputed dataset; calibration curves in the other multiple imputed datasets were comparable. Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy.

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