# BLEEDING ON ANTITHROMBOTIC TREATMENT IN SECONDARY STROKE PREVENTION

**Nina Hilkens**

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# BLEEDING ON ANTITHROMBOTIC TREATMENT IN SECONDARY STROKE PREVENTION

Bloedingen bij het gebruik van antitrombotica
voor secundaire preventie na cerebrale ischemie
(met een samenvatting in het Nederlands)

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te Vlaardingen

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**CONTENTS**

# CHAPTER 1

## GENERAL INTRODUCTION

Stroke is a major cause of death and adult disability worldwide.[1] Although mortality rates of stroke have decreased over the past years,[1] the burden of stroke is predicted to increase over the years ahead due to the rapid rise in the elderly population in both the developed and developing world.[1-3] In the Netherlands, approximately 41,000 patients experience a stroke each year,[4] of which the majority are ischaemic (about 80%) and a smaller proportion are haemorrhagic (15-20%).[5]

Patients who survive their stroke are at increased risk of a recurrent stroke or vascular event, with a one-year risk of 11%.[6] After five years, one in four stroke survivors will have had a recurrence.[6] Recurrent strokes are more disabling, more likely to cause dementia, and more often fatal than the first stroke.[7,8] Adequate secondary prevention is essential to reduce risk of recurrent stroke and vascular events following a transient ischaemic attack (TIA) or stroke.

**Antithrombotic treatment**

Antithrombotic treatment is a key element in secondary prevention after a TIA or ischaemic stroke.[9] The choice of antithrombotic treatment is dependent on the underlying cause; roughly 20-25% of all ischaemic strokes have a cardiac origin[10-12] - most commonly atrial fibrillation - for which oral anticoagulants are indicated. Oral anticoagulants effectively reduce the risk of recurrent stroke or systemic embolism by about two-thirds.[13]

For noncardioembolic strokes, treatment with antiplatelet drugs is indicated. Current guidelines recommend aspirin, aspirin-dipyridamole or clopidogrel as first line agents.[9,14] Aspirin is modestly effective in long-term secondary prevention and reduces risk of recurrent stroke, myocardial infarction, or vascular death by 13% (95% confidence interval 6 to 19%) compared with placebo.[15] Clopidogrel provides an additional 7% risk reduction compared with aspirin,[16] and the combination of aspirin and extended release dipyridamole reduces recurrent stroke, MI or vascular death by about 18% compared with aspirin.[17] Surprisingly, aspirin-dipyridamole was not more effective than clopidogrel in secondary prevention following ischaemic stroke.[18]

**Bleeding on antithrombotic treatment**

The beneficial effect of antithrombotic treatment is partly counterbalanced by an increased risk of bleeding.[19] Aspirin increases risk of serious bleeding approximately 1.5 to 2-fold compared with placebo, mainly driven by an increase in gastro-intestinal bleeds.[20] The absolute risk of a major bleed on antiplatelet treatment is 1.0-1.5% per year,[21,22] and this risk increases steeply with age, to up to 4% per year in patients over 85 years of age.[21] Risk of major bleeding on oral anticoagulants is even higher, approximately 3-4% per year.[23-25]

Intracranial bleeding is the most catastrophic complication of antithrombotic treatment, with a case fatality of 40-50% and high rates of disability among survivors.[21,26,27] However, also patients who experienced a moderate or severe extracranial bleed have a worse prognosis, with an increased risk of future cardiovascular events and mortality.[22,28]

In search for more effective ways to reduce risk of vascular events, studies have investigated more potent treatment strategies, including combination of antiplatelet drugs.[29-32] Although combination of two antiplatelet drugs with different mechanisms of action may be more effective, increased bleeding risks may result.[33]

**Weighing benefits and risks**

The reduction of ischaemic events with antithrombotic treatment has to be weighed against the increase of major bleedings. For currently recommended treatments, trials have shown that the benefits on average outweigh the risks.[13,19] However, an overall trial result might not be applicable to each individual patient, as there is notable variation in the underlying absolute risk of a recurrent ischaemic event and bleed. The harms of antithrombotic treatment may offset the benefits in patients at high risk of bleeding and low risk of recurrent stroke. Risk stratification according to bleeding risk could potentially inform the decision to treat, and might influence the choice of treatment. Also, identification of patients at high risk of bleeding may target other strategies to prevent bleeding, like prescription of gastro-protective drugs.

**Blood pressure reduction**

Next to antiplatelet treatment, blood pressure control is another pillar of secondary stroke prevention.[9,14] Among patients with a recent ischaemic stroke, approximately 70% have a history of hypertension.[34,35] Blood pressure lowering reduces risk of recurrent strokes by 20-30%, with larger reductions in recurrent stroke if larger blood pressure reductions are achieved.[36,37] However, uncertainty exists regarding the optimal target blood pressure. Some studies have suggested a possible J-shaped association between blood pressure levels and recurrent stroke, with higher risk of recurrent stroke below a certain threshold.[38,39] It is unclear whether this association would hold for intracerebral haemorrhage (ICH), which is more strongly related to blood pressure than ischaemic stroke.[40]

**Diagnostic imaging following intracerebral haemorrhage**

The majority of ICHs are so called 'primary' ICH, caused by damage to small vessels of the brain.[41] About one in five ICHs is a 'secondary' ICH, caused by an underlying macrovascular cause such as an arteriovenous malformation or aneurysm.[42-44] Identification of secondary causes of ICH is important for both therapy and prognosis, as timely intervention may prevent recurrent haemorrhage. However, selection of patients for further diagnostic work-up represents a clinical dilemma. Digital subtraction angiography is the gold standard for detection of a macrovascular cause, but is an invasive procedure associated with some risk of complications.[45] CT angiography and MRI/MR angiography are less invasive, but also have lower diagnostic accuracy.[46] International guidelines offer little or no guidance on selection of patients for diagnostic work-up and as a result there is large variation in

clinical practice.[47] Risk stratification of patients with ICH might help physicians to make well-informed decisions about who to select for further diagnostic work-up.

**Aim and outline of this thesis**

The main aim of this thesis is to predict bleeding risk on antithrombotic treatment, and to assess whether bleeding risk stratification may help to optimise antithrombotic treatment in secondary stroke prevention.

In *chapter 2* an overview of currently available prediction models for major bleeding and intracranial haemorrhage on antiplatelet treatment is presented. *Chapter 3* describes the development of the $S_2$TOP-BLEED score, a prediction model for the risk of major bleeding on antiplatelet treatment after a TIA or ischaemic stroke, based on individual patient data from six randomised clinical trials. Validation of a prediction model in an independent cohort is an essential step before a model may be used in clinical practice. In *chapter 4* the external validity of the $S_2$TOP-BLEED score is investigated in a population-based cohort and its performance is compared with other risk scores for major bleeding. Subsequently, it is investigated whether prediction of major bleeding on antiplatelet drugs can be refined by updating the $S_2$TOP-BLEED score with additional predictors (*chapter 5*). Risk of major bleeding might not be constant over time. In *chapter 6* the early time course of bleeding on single and dual antiplatelet treatment after a TIA or ischaemic stroke is explored. In *chapter 7* the balance between benefits and risks of antiplatelet treatment for individual patients is assessed, and it is investigated whether the choice of antiplatelet treatment can be individualised based on bleeding risk assessment. Among patients with an ischaemic stroke from cardiac origin, treatment with oral anticoagulants is indicated. In *chapter 8* the predictive performance of risk scores for major bleeding in patients with a TIA or stroke on oral anticoagulants is assessed. Furthermore, the balance between benefits and risks of this treatment is studied among such patients with a TIA or stroke.

In *chapter 9* the association between blood pressure and the risk of intracerebral haemorrhage after a TIA or ischaemic stroke is studied. *Chapter 10* describes the development and external validation of a risk score to predict the likelihood of a macrovascular cause in patients with non-traumatic intracerebral haemorrhage.

*Chapter 11* provides a reflection on the findings in this thesis and a discussion of the implications for clinical practice and directions for future studies.

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# CHAPTER 2

## PREDICTION MODELS FOR INTRACRANIAL HAEMORRHAGE OR MAJOR BLEEDING IN PATIENTS ON ANTIPLATELET THERAPY: A SYSTEMATIC REVIEW AND EXTERNAL VALIDATION STUDY

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## ABSTRACT

**Background** Antiplatelet therapy is widely used in secondary prevention after a transient ischaemic attack (TIA) or ischaemic stroke. Bleeding is the main adverse effect of antiplatelet therapy and is potentially life-threatening. Identification of patients at increased risk of bleeding may help target antiplatelet therapy.

**Objective** This study sought to identify existing prediction models for intracranial haemorrhage or major bleeding in patients on antiplatelet therapy and evaluate their performance in patients with cerebral ischaemia.

**Methods** We systematically searched PubMed and Embase for existing prediction models up to December 2014. The methodological quality of the included studies was assessed with the CHARMS checklist. Prediction models were externally validated in the European Stroke Prevention Study 2, comprising 6602 patients with a TIA or ischaemic stroke. We assessed discrimination and calibration of included prediction models.

**Results** Five prediction models were identified, of which two were derived in patients with previous cerebral ischaemia. Three studies assessed major bleeding, one studied intracerebral haemorrhage and one gastro-intestinal bleeding. None of the studies met all criteria of good quality. External validation showed poor discriminative performance with c-statistics ranging from 0.53 to 0.64 and poor calibration.

**Conclusion** A limited number of prediction models is available that predict intracranial haemorrhage or major bleeding in patients on antiplatelet therapy. Methodological quality of the models varied, but was generally low. Predictive performance in patients with cerebral ischaemia was poor. In order to reliably predict the risk of bleeding in patients with cerebral ischaemia, development of a prediction model according to current methodological standards is needed.

## INTRODUCTION

Each year, approximately 800.000 people experience a stroke in the European Union, of which 80% are ischaemic strokes.[1] Roughly 30% of these strokes occur in patients with previous cerebral ischaemia.[2] Given the high risk of recurrent ischaemic events after a transient ischaemic attack (TIA) or minor ischaemic stroke, secondary prevention is of major importance.

Antiplatelet therapy has proven to be beneficial in patients who have had a TIA or minor stroke and significantly reduces the yearly risk of vascular events and vascular mortality.[3] However, use of antiplatelet therapy is associated with an increased risk of haemorrhage, including intracranial haemorrhage.[4] Intracranial haemorrhage can have devastating consequences and may result in major disability or death.[5] A combination of different antithrombotic agents, which is widely applied in patients who experienced a myocardial infarction, further increases the risk of bleeding proportional to the number of drugs used.[6]

Accurate prediction of bleeding risks may help physicians to identify those patients for whom the benefits of antiplatelet therapy outweigh the risks and may target antithrombotic therapy. Our aim was to identify existing prediction models (or rules or scores) from the literature that predict major bleeding or intracranial haemorrhage, either in patients with a TIA or stroke, or in patients who use antiplatelet therapy for secondary prevention. Subsequently, we assessed performance of these prediction models in patients with cerebral ischaemia.

## METHODS

### Search strategy and selection criteria

We systematically searched PubMed and Embase up to 1 December 2014, to retrieve all relevant studies on prediction of bleeding in patients on antiplatelet therapy. We used synonyms of the following terms: "(stroke OR secondary prevention OR antiplatelet agents) AND (prediction models) AND (bleeding OR intracranial haemorrhage)" (for search syntax, see supplementary information). A study was eligible when (1) a prediction model was developed in patients with previous cerebral ischaemia or patients with an indication for secondary prevention with antiplatelet agents, (2) the outcome of the prediction model was major bleeding, intracranial haemorrhage, or other subtypes of major bleeding and (3) a prediction model was presented, not merely a multivariable analysis of predictors for major bleeding. We excluded non-human studies and prediction models that predicted major bleeding in the acute phase of stroke or myocardial infarction or bleeding related to an intervention. One author (NAH) screened titles and abstracts of the identified publications. Full text screening of potentially relevant articles was performed independently by two

authors (NAH, JPG). Discrepancies were discussed and resolved in a consensus meeting. References of retrieved articles were screened until no additional publications were found.

**Data extraction**

Two authors (NAH, JPG) independently extracted data from selected articles and assessed the methodological quality of the included studies. We used a standardized form, based on the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS).[7] The CHARMS checklist addresses 11 domains that potentially induce bias or influence the applicability of the results. The following information was extracted from each study: study design, sample size, number of events, definition and coding of predictors, timing of measurement of predictors, definition of outcome, handling of missing data, model building strategies and evaluation of model performance. We reported strengths and weaknesses of the individual studies with regard to methodological aspects. Results are reported in accordance with TRIPOD and PRISMA guidelines.[8,9]

**Validation cohort**

We externally validated the included prediction models with patients enrolled in the European Stroke Prevention Study 2 (ESPS 2). Design and methods of ESPS 2 have been described previously.[10] Briefly, ESPS 2 is a large clinical trial that investigated the effect of aspirin and dipyridamole on the recurrence of vascular events after a TIA or ischaemic stroke. Patients aged 18 years or older with a TIA or stroke in the preceding three months were included in 59 centres across 13 European countries. A total of 6602 patients were included between 1989 and 1993, of whom 212 experienced a major bleeding event during follow-up (median followup 2.0 years, range 0 to 2.5 years). Major bleeding was defined as bleeding that required blood transfusion or other specific treatment and was assessed at three monthly follow-up visits. Predictors were measured at baseline by means of a questionnaire, physical examination and laboratory measurements.

**Data analysis**

Predictors in the models were matched to variables measured in ESPS 2. If no direct match was available, the variable was replaced by a proxy. We had to approximate the presence of chronic liver disease by the abnormal liver function tests values in ESPS 2. All patients were assigned a value of zero for use of oral anticoagulants and history of major bleeding, since these were exclusion criteria in ESPS 2.

The original regression equation was used to calculate the bleeding risk for each individual. If the regression equation was unavailable and authors were unable to provide additional information, the performance of the score chart was assessed. Time at risk was calculated as time between inclusion in the trial and occurrence of a major bleeding event, date of death, or end of follow-up, whichever came first. Forty-eight patients (0.7%) were lost to follow-up and were excluded from the validation cohort. Most predictors had less than 2% of

data missing, although 10.5% of the values were missing for history of TIA or stroke, 7.3% were missing for glucose and 5.7% were missing for blood urea nitrogen. Missing data on predictors were imputed with single imputation with aregImpute from the Hmisc package in R.[11]

We examined discrimination and calibration of the included models. Discrimination indicates the extent to which a model can distinguish between someone with and without the outcome and was assessed with the c-statistic for time to event data. C-statistics vary from 0.5 (no discrimination) to 1.0 (perfect discrimination), with values of 0.7-0.8 considered acceptable and 0.8-0.9 good.[12] Calibration indicates how well the predicted probability corresponds with the observed probability and was assessed with calibration plots and the Hosmer-Lemeshow chi-square test. Calibration is optimal if observed and predicted probabilities are on the 45° line.[13] All statistical analysis were performed with SPSS version 22 or R version 3.0.3 for Windows (http://cran.r-project.org/).

## RESULTS

### Search strategy

The systematic search in PubMed and Embase yielded 4655 unique articles. After screening titles, 256 remained for abstract screening. The main reasons for exclusion were therapeutic or etiological research and prediction of haemorrhage in the acute phase of stroke or myocardial infarction. Twenty-three articles were retrieved for full text screening, of which five were included in the review (Figure 1, Flowchart). Characteristics of the included studies are presented in Table 1.

### Study characteristics

Four studies were prospective cohort studies,[14-17] one was a retrospective cohort.[18] Two prediction models were developed in patients with a previous TIA or ischaemic stroke.[14,15] Of the remaining three models, two were developed in patients who had had a myocardial infarction.[16,18] The last model was developed in patients with or at high risk of atherothrombosis; the vast majority of these patients was treated with antiplatelet agents.[17] The development study samples ranged from 1050 to 56,616 patients, the proportion of bleeding events ranged from 0.85% to 5.9%. The outcome of interest was major bleeding in three studies.[15-17] One study specifically focused on intracerebral haemorrhage[14] and one study assessed gastrointestinal haemorrhage.[18] The number of included predictors ranged from four to eleven. Definition and categorization of predictors varied among the included studies. Commonly used predictors were age, hypertension, renal failure and use of anticoagulants. Three prediction models have been externally validated previously (supplementary table 1).[15-17]

The quality of the included prediction models varied; all studies had considerable weaknesses in study design and quality assessment was often hindered by poor reporting of

methods. One study was only published as an abstract and provided insufficient information to reliably assess methodological quality.[15] All models were developed in reasonably large cohorts and provided adequate definitions of the outcome of interest. However, some weaknesses in methodology and reporting can be distinguished. One study did not specify the type of statistical model used[16] and two studies did not specify a timeframe for the predicted risks.[16,18] Furthermore, two studies did not specify methods for model development, either with regard to selection of candidate predictors[18] or with regard to selection of predictors during modeling,[16] and only one out of four studies adequately reported about missing data and handling of missing data.[17] Results of the quality assessment are shown in Table 2.

**Figure 1. Flowchart**

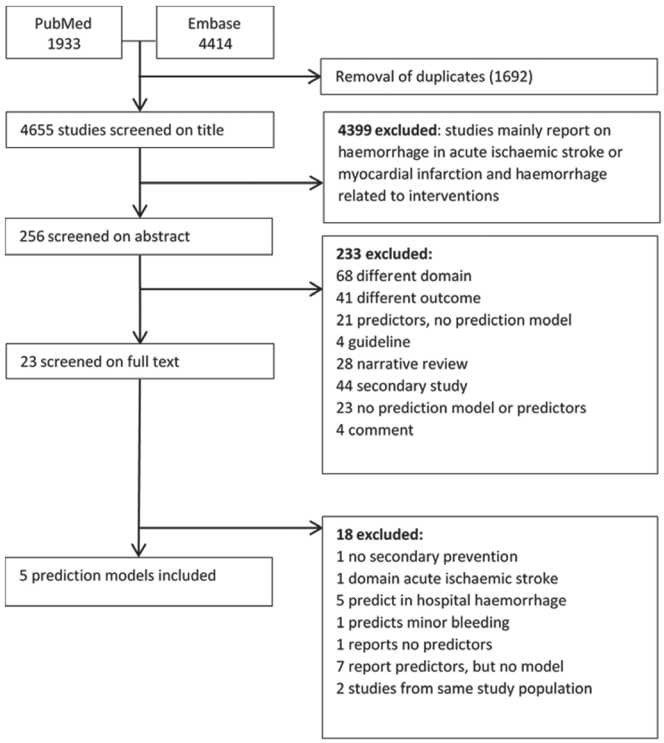

**Table 1. Prediction models for major bleeding in patients on antiplatelet therapy for secondary prevention**

| Author, year | Development population | Outcome | n events/ n total | Type of model | Predicted years | No. of predictors | Apparent discrimination (c-statistic) | Apparent calibration (p value Hosmer –Lemeshow) | Method of internal validation | Presentation of risk model |
|---|---|---|---|---|---|---|---|---|---|---|
| Ariesen, 2006[14] | Patients with a TIA or ischaemic stroke | Sympto-matic ICH | 107/ 12,648 | Cox | 5 | 4 | 0.65 (0.59-0.70) | NR | Bootstrapping | Regression coefficients Score chart |
| Ducrocq, 2010[17] | Patients with established CVD, CAD, PAD or ≥3 atherosclerosis risk factors | Serious bleeding | 804/ 56,616 | Logistic | 2 | 9 | 0.68 | 0.43 | Bootstrapping | Score chart |
| Geraghty, 2012[15] [abstract] | Patients with a TIA or ischaemic stroke | Bleeding events requiring medical attention | -/ 1.257 | NR | 3 | 8 | NR | NR | NR | - |
| Barra, 2013[16] | Patients with myocardial infarction | Clinically significant bleeding | 62/ 1,050 | NR | NR | 11 | 0.75 (0.69-0.82) | 0.37 | NR | Score chart |
| Cuschieri, 2014[18] | Patients with myocardial infarction receiving clopidogrel | Gastro-intestinal bleeding | 107/ 3,218 | Cox | NR | 5 | NR | NR | Bootstrapping | Regression coefficients Score chart |

TIA transient ischaemic attack; ACS acute coronary syndrome; CVD cerebrovascular disease; CAD coronary artery disease; PAD peripheral arterial disease; ICH intracerebral haemorrhage; NR not reported

**Table 2. Quality assessment**

| Reference | Short description | Predictors | Strong points | Weak points |
|---|---|---|---|---|
| Ariesen, 2006[14] | Prediction of intracerebral haemorrhage in patients with a TIA or stroke | Age<br>SBP<br>Antihypertensive agents<br>Blood glucose | Large cohort study,<br>Adequate number of events per candidate predictor.<br>Definition of outcome available.<br>Internal validation with bootstrapping.<br>Shrinkage of regression coefficients.<br>Appropriate handling of continuous variables. | Handling of missing data not reported.<br>Selection of candidate predictors based on univariable analysis.<br>Forward selection.<br>No external validation. |
| Ducrocq, 2011[17] | Prediction of major bleeding in patients with established CVD, CAD, PAD or ≥3 atherosclerotic risk factors | Age<br>Hypertension<br>Hypercholesterol-emia<br>Heart failure<br>DM<br>PAD<br>Smoking<br>Antiplatelets<br>OAC | Large cohort study<br>Adequate number of events per candidate predictor.<br>Definition of predictors and outcome available.<br>Adequate reporting of missing predictors and outcome.<br>Backward elimination.<br>Internal validation with bootstrapping.<br>External validation. | Complete case analysis.<br>Method for handling continuous predictors not reported.<br>Selection of candidate predictors partly based on univariable analysis. |
| Barra, 2013[16] | Prediction of major bleeding in patients with myocardial infarction | Age<br>Hypertension<br>Heart failure<br>DM<br>History of stroke/TIA<br>History of bleeding<br>Smoking<br>Renal failure<br>Hemoglobin<br>Blood urea nitrogen<br>Antiplatelets/ OAC | Cohort study.<br>Definition of predictors and outcome available.<br>External validation. | Number of events per candidate predictor insufficient.<br>Method for handling continuous predictors not reported<br>Handling of missing data not reported.<br>Selection of candidate predictors partly based on univariable analysis.<br>Criteria for selection of predictors during modelling not reported.<br>No internal validation. |

| | | | | |
|---|---|---|---|---|
| Cuschieri, 2014[18] | Prediction of gastro intestinal bleeding in patients with myocardial infarction | Age<br>DM<br>Renal failure<br>Hepatic failure<br>OAC | Cohort study.<br>Definition of outcome available.<br>Backward elimination.<br>Internal validation with bootstrapping. | Number of events per candidate predictor insufficient.<br>Method for handling continuous predictors not reported.<br>Handling of missing data not reported.<br>Criteria for selection of candidate predictors not reported.<br>No external validation. |
| Geraghty, 2012[15] | Prediction of major bleeding in patients with TIA or stroke | Age<br>Male sex<br>History of vascular disease<br>History of GI bleeding<br>Gastroduodenal ulcer<br>Prior cancer<br>Frailty<br>Renal failure | Insufficient information for proper quality assessment. | |

CVD cerebrovascular disease; CAD coronary artery disease; PAD peripheral arterial disease; DM diabetes mellitus; OAC: oral anticoagulants; SBP systolic blood pressure; GI gastro-intestinal bleeding

**External validation**

Supplementary table 2 displays the baseline characteristics of the development and validation cohorts. One prediction model was only published as an abstract and provided insufficient information to perform external validation. Three studies did not report the original regression equation and the authors were unable to provide additional information upon request; therefore we assessed performance of the score charts.[16-18]

Discrimination of all prediction models was poor, with c-statistics ranging from 0.53 (0.49-0.57) to 0.64 (0.61-0.69) (Table 3). The calibration of the models is shown in calibration plots (Figure 2). The Hosmer-Lemeshow chi-squared test was significant ($p<0.05$) for all models, indicating poor calibration.

**Figure 2. Calibration plots depicting the predicted 2 year bleeding risk against the observed 2 year bleeding risk.**

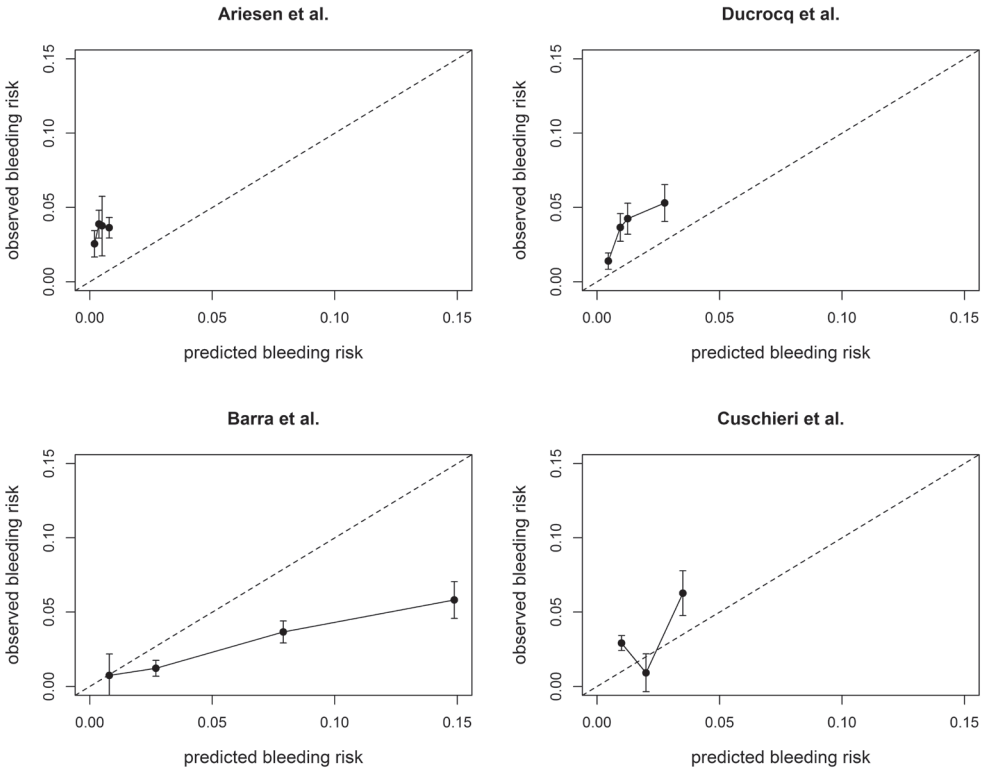


**Table 3. Predictive performance of prediction models**

| | Original publication | | External validation ESPS 2 |
|---|---|---|---|
| | C-statistic (95% CI) development data | C-statistic (95% CI) validation data | C-statistic (95% CI) |
| Ariesen[14] | 0.65 (0.59-0.70) | - | 0.53 (0.49-0.57) |
| Ducrocq[17] | 0.68 | 0.64 | 0.63 (0.60-0.66) |
| Barra[16] | 0.75 (0.69-0.82) | 0.72 (0.65-0.78) | 0.64 (0.61-0.69) |
| Cuschieri[18] | - | - | 0.62 (0.58-0.65) |

CI confidence interval

## DISCUSSION

This systematic review provides an overview of currently available models for prediction of major bleeding in patients on antiplatelet therapy. Only two models were specifically derived in patients with a previous TIA or ischaemic stroke. Methodological quality of the available models varied, but was generally low. The predictive performance of the models in patients with cerebral ischaemia was poor and use of these models in clinical practice would not be recommended.

Over the past years, much research has been done in the field of oral anticoagulants and individualised treatment strategies based on risk of bleeding and ischaemic events. This review shows that less is known about prediction of bleeding in patients on antiplatelet therapy, and more specifically in those with cerebral ischaemia. Although prediction models for bleeding can make physicians aware of patients at increased bleeding risk, they should not serve as an argument to withhold effective antiplatelet therapy, as bleeding risk should be carefully balanced against the risk of recurrent ischaemic events.

A strength of our study is the comprehensive search we performed and the fact that this is the first systematic review that summarizes the available evidence for prediction of bleeding in patients on antiplatelet therapy. We could include most existing models in the validation study.

Nevertheless, several methodological drawbacks of the studies included in our review need to be addressed. First of all, quality of reporting was generally poor, impeding the assessment of bias. Second, the number of outcome events per candidate predictor was insufficient in two studies,[16,18] which may have led to overfitting of the model. Third, the presence of missing data and handling of missing data was not adequately reported in any of the studies but one.[17] Exclusion of those patients with missing data may introduce selection bias if data are missing not at random.[19] Fourth, most studies based the inclusion of candidate predictors partly on associations in univariable analysis,[14,16,17] however, inclusion of candidate predictors based on pathophysiological knowledge may be preferred.[20] Fifth, regression coefficients and model intercepts or baseline hazards were not adequately reported, which severely hampered the possibilities for recalibration and model updating during the external validation process.

Recently, the TRIPOD statement was launched which aims to improve the quality of reporting of prediction model studies.[8] Adherence to this statement would allow for proper risk of bias assessment and may thereby facilitate systematic reviews of prediction models and, subsequently, external validation.

Some limitations of our systematic review and validation study need to be mentioned as well. We included models from a heterogeneous population with varying outcomes, which impedes comparability of the results. Our primary interest was prediction of bleeding in patients with cerebral ischaemia, but to prevent missing relevant prediction models in closely related fields, we kept our scope broad. Furthermore, we only validated models

in patients with cerebral ischaemia, which does not correspond with the original target population of two prediction models. This may in part explain the decreased performance of prediction models in our validation data. Also, models were validated in a population of trial participants, which is likely to be more homogeneous due to stricter inclusion criteria and may subsequently have led to decreased performance. Based on the results from this study we may conclude that models used for prediction of bleeding in patients on antiplatelet therapy are not suitable for prediction of bleeding in patients with cerebral ischaemia.

In conclusion, widespread use of currently available prediction models for prediction of major bleeding in cerebral ischaemia seems premature, given methodological drawbacks and poor performance of models in an independent population. Development of a model according to current standards may help physicians to accurately predict the risk of major bleeding in patients with cerebral ischaemia.

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## SUPPLEMENT

### Search syntax, conducted on December 1st, 2014

**Pubmed**

**#1 Stroke OR secondary prevention OR antiplatelet therapy & synonyms**

stroke[Title/Abstract] OR strokes[Title/Abstract] OR stroke[MeSH] OR cerebrovascular accident[Title/Abstract] OR cerebrovascular accidents[Title/Abstract] OR CVA[Title/Abstract] OR CVAs[Title/Abstract] OR brain ischemia[Title/Abstract] OR brain ischemias[Title/Abstract] OR brain ischemia [MeSH] OR cerebral ischemia[Title/Abstract] OR cerebral ischemias[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR TIA[Title/Abstract] OR TIAs[Title/Abstract] OR transient ischemic attacks[Title/Abstract] OR transient ischemic attacks [MeSH] OR brain infarction[Title/Abstract] OR brain infarctions[Title/Abstract] OR cerebral infarction[Title/Abstract] OR cerebral infarctions[Title/Abstract] OR secondary prevention[Title/Abstract] OR secondary prevention[MeSH] OR antiplatelet drugs[Title/Abstract] OR antiplatelet agent[Title/Abstract] OR antiplatelet agents[Title/Abstract] OR platelet inhibitor[Title/Abstract] OR platelet inhibitors[Title/Abstract] OR platelet aggregation inhibitors[Title/Abstract] OR platelet aggregation inhibitors[MeSH] OR aspirin[Title/Abstract] OR aspirin[MeSH] OR acetylsalicylic acid[Title/Abstract] OR clopidogrel[Title/Abstract] OR dipyridamole[Title/Abstract] OR prasugrel[Title/Abstract] OR ticagrelor[Title/Abstract]

**#2 Prediction models & synonyms**

prognostic score[Title/Abstract] OR prognostic scores[Title/Abstract] OR prognostic model[Title/Abstract] OR prognostic models[Title/Abstract] OR prognostic scheme[Title/Abstract] OR prognostic schemes[Title/Abstract] OR prognostic factor[Title/Abstract] OR prognostic factors[Title/Abstract] OR prognostic index[Title/Abstract] OR prognostic indices[Title/Abstract] OR prediction rule[Title/Abstract] OR prediction rules[Title/Abstract] OR prediction model[Title/Abstract] OR prediction models[Title/Abstract] OR prediction score[Title/Abstract] OR prediction scores[Title/Abstract] OR prediction scheme[Title/Abstract] OR prediction schemes[Title/Abstract] OR prediction index[Title/Abstract] OR prediction indices[Title/Abstract] OR risk score[Title/Abstract] OR risk scores[Title/Abstract] OR risk model[Title/Abstract] OR risk models[Title/Abstract] OR risk scheme[Title/Abstract] OR risk schemes[Title/Abstract] OR risk index[Title/Abstract] OR risk indices[Title/Abstract] OR risk stratification[Title/Abstract] OR risk stratifications[Title/Abstract] OR risk assessment[Title/Abstract] OR risk assessments[Title/Abstract] OR algorithm[Title/Abstract] OR algorithms[Title/Abstract] OR grading scale[Title/Abstract] OR grading scales[Title/Abstract] OR assessing risk[Title/Abstract] OR assessing risks[Title/Abstract] OR predicting risk[Title/Abstract] OR predicting risks[Title/Abstract] OR predictive factor[Title/Abstract] OR predictive factors[Title/Abstract] OR (predictor[Title/Abstract] OR predictors[Title/Abstract]) AND (score[Title/Abstract] OR scores[Title/Abstract] OR model[Title/Abstract] OR models[Title/Abstract] OR scheme[Title/Abstract] OR schemes[Title/Abstract] OR index[Title/Abstract] OR indices[Title/Abstract])

**#3 Bleeding & synonyms:**

hemorrhage[Title/Abstract] OR hemorrhages[Title/Abstract] OR haemorrhage[Title/Abstract] OR haemorrhages[Title/Abstract] OR bleeding[Title/Abstract] OR bleedings[Title/Abstract] OR hemorrhagic stroke[Title/Abstract] OR hemorrhagic strokes[Title/Abstract] OR haemorrhagic stroke[Title/Abstract] OR haemorrhagic strokes[Title/Abstract] OR bleed[Title/Abstract] OR bleeds[Title/Abstract] OR hemorrhage[MeSH Terms]

**#4**: #1 **AND** #2 **AND** #3

**Supplementary table 1. Overview of prediction models that have been externally validated previously**

| Reference | Validation population | Outcome | N events/ n total | Discrimination (C-statistic) | Calibration (p value Hosmer-Lemeshow) |
|---|---|---|---|---|---|
| Ducrocq[1] | CHARISMA trial: patients with cardiovascular disease or multiple risk factors | Moderate and severe bleeding | 487/15,603 | 0.64 | 0.31 |
| Geraghty[2] | Patients with ACS on antiplatelet therapy | Major bleeding | ?/786 | 0.67 (0.58-0.75) | - |
| Barra[3] | Patients with myocardial infarction admitted to same hospital in a different time frame | Clinically significant bleeding | 60/852 | 0.72 (0.65-0.78) | 0.44 |

ACS acute coronary syndrome; ICH intracerebral haemorrhage; AUC area under the curve

**Supplementary table 2. Baseline characteristics of development and validation cohorts**

| | **Validation cohort N=6602** | **Ariesen[4] N= 12,648** | **Ducrocq[1] N=64,589** | **Barra[3] N=1050** | **Cuschieri[5] N=3218** |
|---|---|---|---|---|---|
| Age, mean (SD) | 67 (11) | 64 (10) | 69 | 68 (14) | 63 |
| Female Sex | 2774 (42%) | 4051 (32%) | 23,252 (36%) | 364 (35%) | 111 (3%) |
| Current smoking | 1591 (24%) | 5866 (46%) | 9510 (15%) | 287 (27%) | - |
| Hypertension | 3997 (61%) | - | 52,759 (82%) | 796 (75%) | - |
| Hypercholesterolemia | 1509 (23%) | - | 46,412(72%) | 591 (56%) | - |
| Diabetes mellitus | 1011 (15%) | 1352 (11%) | 28,298 (44%) | 380 (36%) | 1313 (41%) |
| Prior stroke/TIA | 6602 (100%) | 12,648 (100%) | 17,893 (28%) | 94 (9%) | - |
| Prior MI | 563 (9%) | 1601 (13%) | - | 1050 (100%) | 3218 (100%) |
| CAD | - | - | 38,330 (59%) | 283 (27%) | - |
| Angina pectoris | 1344 (20%) | 2128 (17%) | 19,041 (30%) | - | - |
| Congestive heart failure | 555 (9%) | - | 8782 (14%) | - | - |
| Atrial fibrillation | 429 (7%) | - | 6743 (11%) | 144 (14%) | 368 (11%) |
| PAD | 1454 (22%) | 1533 (12%) | 7852 (12%) | - | - |
| Major bleeding | 212 (3.2%) | - | 903 (1.4%) | 62 (6%) | - |
| Intracerebral haemorrhage | - | 107 (1%) | - | - | - |
| Gastro-intestinal bleeding | - | - | - | - | 107 (3%) |

TIA transient ischaemic attack; MI myocardial infarction; CAD coronary artery disease; PAD peripheral arterial disease

## REFERENCES SUPPLEMENT

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# CHAPTER 3

## PREDICTING MAJOR BLEEDING IN PATIENTS WITH NONCARDIOEMBOLIC STROKE ON ANTIPLATELETS: $S_2$TOP-BLEED

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## ABSTRACT

**Objective** To develop and externally validate a prediction model for major bleeding in patients with a TIA or ischaemic stroke on antiplatelet agents.

**Methods** We combined individual patient data from six randomised clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT and PRoFESS) investigating antiplatelet therapy after TIA or ischaemic stroke. Cox regression analyses stratified by trial were performed to study the association between predictors and major bleeding. A risk prediction model was derived and validated in the PERFORM trial. Performance was assessed with the c-statistic and calibration plots.

**Results** Major bleeding occurred in 1530 of the 43,112 patients during 94,833 person-years of follow-up. The observed three-year risk of major bleeding was 4.6% (95% CI 4.4-4.9%). Predictors were male Sex, Smoking, Type of antiplatelet agents (aspirin-clopidogrel), Outcome on modified Rankin Scale ≥3, Prior stroke, high Blood pressure, Lower BMI, Elderly, Asian Ethnicity and Diabetes ($S_2$TOP-BLEED). The $S_2$TOP-BLEED score had a c-statistic of 0.63 (95% CI 0.61-0.64) and showed good calibration in the development data. Major bleeding risk ranged from 2% in patients aged 45-54 years without additional risk factors, to more than 10% in patients aged 75-84 years with multiple risk factors. In external validation, the model had a c-statistic of 0.61 (95% CI 0.59-0.63) and slightly underestimated major bleeding risk.

**Conclusion** The $S_2$TOP-BLEED score can be used to estimate three-year major bleeding risk in patients with TIA or ischaemic stroke who use antiplatelet agents, based on readily available characteristics. The discriminatory performance may be improved by identifying stronger predictors for major bleeding.

## INTRODUCTION

Antithrombotic therapy is a cornerstone in secondary stroke prevention, either with oral anticoagulants in patients with a cardioembolic stroke or with antiplatelet agents in patients with a stroke from arterial origin. Antiplatelet therapy successfully reduces the number of serious vascular events by approximately 25%.[1,2] Despite its proven benefit, antiplatelet therapy increases the risk of bleeding. On average bleeding risks are increased two-fold in patients on aspirin compared with placebo.[3] More potent treatment strategies such as dual antiplatelet therapy increase this risk even further.[4] Bleeding events appear to be associated with future major vascular events and higher mortality rates.[5,6]

Different factors have been proposed that increase bleeding risk, including older age, hypertension, and ethnicity.[6-8] Prediction of bleeding risk based on patient characteristics may help physicians to balance benefits and risks of antiplatelet therapy for individual patients. Also, risk stratification may guide treatment decisions for other preventive strategies, such as gastro-protective agents.

A recent systematic review showed that a limited number of prediction models is available for prediction of bleeding in patients on antiplatelet therapy for secondary prevention.[9] In an external validation study, accurate performance of available models could not be confirmed in patients with a TIA or ischaemic stroke.[9]

The purpose of the current study was to develop and externally validate a prediction model to predict three-year risk of major bleeding in patients with a TIA or ischaemic stroke who use antiplatelet agents.

## METHODS

### Study population

The design of the individual patient data meta-analysis has been described in detail elsewhere.[10] Briefly, we collected individual patient data (IPD) from trials investigating the efficacy of antiplatelet therapy in long-term secondary prevention after a TIA or ischaemic stroke. Trials were eligible if they randomised patients with a TIA or ischaemic stroke to aspirin, or to antiplatelet drugs that are recommended as first-line treatment in secondary prevention of stroke as an alternative to aspirin or in addition, and had a duration of at least one year. Trials had to be published before December 2010 in peer-reviewed journals. Six trials met the inclusion criteria (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS[11-16]), including 48,023 patients with a TIA or ischaemic stroke between 1989 and 2006. Median follow-up ranged from 1.4 to 3.5 years. Details of studies included in the IPD meta-analysis (recruitment period, details of antiplatelet regimens, inclusion criteria, sample size) are presented in supplementary table 1.

Patients with a possible cardioembolic origin of their stroke (those with a history of atrial fibrillation or TOAST classification cardioembolic stroke) were excluded. Also, patients randomised to dipyridamole alone or placebo were excluded, as our interest was in bleeding risk on common antiplatelet regimens after a TIA or ischaemic stroke.

We used trial specific definitions of major bleeding (supplementary table 2). Major bleedings included bleedings that were fatal, intracranial, required hospital admission or led to significant disability. The outcome was assessed at regular follow-up visits, as specified in the trial protocols (supplementary table 3). Information on candidate predictors was available at the time of outcome assessment.

We performed a literature review to identify candidate predictors for major bleeding. Candidate predictors had to be easily available in clinical practice and their inclusion was dependent on availability in the trials. We refrained from the inclusion of interactions in our model because we were not aware of clear evidence in the literature on potentially relevant interactions. Potential predictors included patient characteristics (age, sex, Asian ethnicity, BMI, smoking, heavy alcohol use), characteristics of the index event (modified Rankin Scale (mRS), lacunar stroke subtype), medical history (hypertension, hypercholesterolemia, diabetes mellitus, prior stroke or TIA, history of cardiovascular disease, history of heart failure) and type of antiplatelet agent. Information on candidate predictors was collected at baseline in each trial. Definitions of candidate predictors are presented supplementary table 4.

**Statistical analysis**

Ten outcome events per candidate predictor is generally accepted as a minimum required sample size to develop multivariable prediction models.[17,18] Given the large number of outcome events available in our study, a sufficiently large number of candidate predictors could be studied.

The proportion of missing data within each trial was low, the percentage (sporadically) missing values across all candidate predictors and all trials was below 1%. Some candidate predictors were not measured in all trials and were therefore missing systematically (supplementary table 5). Only variables that were available in at least five out of six trials were considered for inclusion in the prediction model. Missing data were imputed multiple times with the MICE package in R, creating 20 imputed sets.

Restricted cubic splines were used to assess whether continuous predictors (age, BMI) could be analysed as linear terms or needed transformations. A squared term for age was found to be significant, BMI under 30 kg/m2 showed a linear association with the outcome. We studied predictors for major bleeding with Cox regression analyses stratified by trial, thereby estimating common predictor effects and separate baseline survival functions per trial. The full model containing all candidate predictors was simplified by performing backward selection based on Akaike's Information Criterion (AIC). The proportional hazards assumption was checked by studying log-minus-log plots. The final baseline survival function was estimated based on a Cox regression model in all data pooled, with the linear predictor as sole variable.

We assessed both discrimination and calibration. Calibration reflects the correspondence between the observed and predicted probabilities of the outcome and was assessed with the Gronnesby and Borgan test and graphically with calibration plots.[19] Discrimination reflects the ability of the model to distinguish between someone with and without the outcome and was evaluated with the concordance statistic.[20]

We performed internal-external cross-validation, a method which allows us to study the consistency and performance of a model across different datasets.[21] A model was developed in all studies but one, repeating all steps as described previously, and this model was subsequently validated in the remaining study. This process was repeated for all combinations of trials.



We performed bootstrapping to correct for overfitting of the final model. In each bootstrap sample the entire modelling process was repeated. A shrinkage factor was estimated from the bootstrap procedure and regression coefficients were shrunk to provide improved predictions for future patients. We translated the regression model into a score chart by dividing all regression coefficients by the smallest coefficient and subsequently rounded them to the nearest integer. The score chart is accompanied by a table displaying estimated three-year major bleeding risks. Patients were divided in low, medium and high risk according to their score. We assessed both risk of bleeding and risk of recurrent ischaemic events across the risk groups. We subsequently assessed the performance of the developed model for prediction of intracranial haemorrhages, in terms of discrimination and calibration. Methods are described in more detail in the supplementary methods.

We performed three sensitivity analyses: one including only patients with an ischaemic stroke as index event, one in which we excluded patients who were randomised more than three months after their qualifying event and one in which we excluded patients with missing data.

**External validation**

We externally validated the developed prediction model in the PERFORM trial, a randomised clinical trial including 18,417 patients with a recent TIA or ischaemic stroke from arterial origin, who were randomised to terutroban or aspirin.[22] Seven hundred seventy-three patients experienced a major or life-threatening bleeding event during follow-up (mean follow-up 28.3 months (SD 7.7)). Major or life-threatening bleeding was defined as bleeding that was fatal, symptomatic intracranial, significantly disabling, required hospital admission, transfusion or surgery. We applied the original regression equation and baseline survival function to the data and calculated three-year major bleeding probabilities for each patient. Again, discrimination and calibration were assessed by means of the c-statistic, calibration plots and the D'Agostino and Nam test. Results are reported in accordance with the TRIPOD statement.[23] All statistical analyses were performed with R version 3.2.0 and SAS.

**Standard protocol approvals, registrations and patients consents.**

The trials were approved by the ethics committee or institutional review board at each participating centre and all patients gave written informed consent.

**Table 1. Baseline characteristics of 43,112 patients included in 6 trials**

| | No major bleeding (n=41,582) | Major bleeding (n=1530) |
|---|---|---|
| Age, mean (SD), years | 65.4 (9.7) | 68.8 (9.7) |
| Male sex | 26375 (63) | 1028 (67) |
| Ethnic group | | |
| Caucasian | 31,616 (76) | 1140 (75) |
| Black | 1398 (3) | 44 (3) |
| Asian | 7298 (18) | 305 (20) |
| Other | 1270 (3) | 41 (3) |
| BMI, mean (SD), kg/m$^2$ | 26.9 (4.8) | 26.2 (4.7) |
| Qualifying event | | |
| Stroke | 37,399 (90) | 1418 (93) |
| TIA | 4183 (10) | 112 (7) |
| Index stroke severity | | |
| mRS 0-2 | 32,842 (79) | 1113 (73) |
| mRS 3-5 | 8740 (21) | 417 (27) |
| Lacunar stroke subtype | 20,136 (48) | 747 (49) |
| Current smoker | 9233 (22) | 345 (23) |
| Heavy alcohol use | 3454 (8) | 123 (8) |
| Hypertension | 31,564 (76) | 1197 (78) |
| Hypercholesterolemia | 22,439 (54) | 780 (51) |
| Diabetes | 13,835 (33) | 538 (35) |
| Prior stroke | 7099 (17) | 320 (21) |
| Prior TIA | 5204 (13) | 213 (14) |
| History of cardiovascular disease | 8486 (20) | 330 (22) |
| Congestive heart failure | 1529 (4) | 48 (3) |
| Antiplatelet regimen | | |
| Aspirin | 7850 (19) | 277 (18) |
| Clopidogrel | 16,014 (39) | 505 (33) |
| Aspirin+Dipyridamole | 12,210 (29) | 502 (33) |
| Aspirin+Clopidogrel | 5508 (13) | 246 (16) |

Data are numbers (percentages), unless otherwise indicated. mRS modified Rankin Scale

## RESULTS

After exclusion of patients with a possible cardioembolic origin of their stroke (n=1829) and patients randomised to placebo or dipyridamole alone (n=3082), 43,112 patients remained for the analyses (supplementary figure 1). Major bleeding occurred in 1530 patients during 94,833 person-years of follow-up. Of these, 155 (10%) were fatal and 273 (18%) were intracranial (non-fatal) (supplementary table 6). The mean observed 1-year risk of major bleeding was 1.9% (95% CI 1.7-2.0) and the observed 3-year risk was 4.6% (95% CI 4.4-4.9). Table 1 shows the baseline characteristics of patients included in the development population.



The results of the multivariable Cox regression analyses are presented in Table 2. The following predictors for major bleeding were identified: male sex, smoking, type of antiplatelet agents, outcome on modified Rankin Scale, prior stroke, high blood pressure (hypertension), lower BMI, elderly Asian ethnicity and diabetes ($S_2$TOP-BLEED, i.e. male Sex, Smoking, Type of antiplatelet agents, Outcome on modified Rankin Scale ≥3, Prior stroke, high Blood pressure (hypertension), Lower BMI, Elderly, Asian Ethnicity, and Diabetes). History of heart failure was not included in the final model due to varying definitions across trials and conflicting results. We visually inspected log-minus-log plots and detected no deviations from the assumption of proportional hazards. Internal-external cross validation showed that model performance was comparable across all trials, indicating little heterogeneity in predictor outcome associations and baseline risk (supplementary table 7, 8, supplementary figure 2). We therefore considered it appropriate to use all data, although applying stratified Cox regression analysis to account for the hierarchical nature of the data.

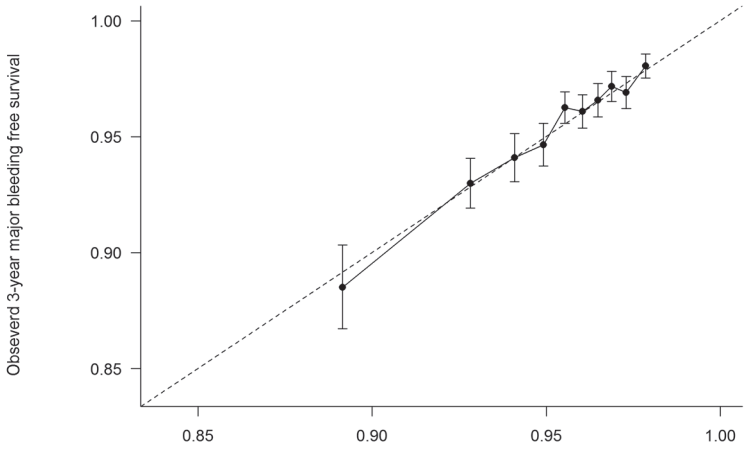
**Table 2. Multivariable hazard ratios for risk of major bleeding from final model after shrinkage**

| | Multivariable Hazard Ratio (95%CI) |
|---|---|
| Age | 0.95 (0.90-1.00) |
| $Age^2$ | 1.00 (1.00-1.00) |
| Male sex | 1.29 (1.16-1.44) |
| Asian ethnicity | 1.15 (0.99-1.33) |
| Current smoking | 1.19 (1.05-1.36) |
| Hypertension | 1.16 (1.01-1.32) |
| Diabetes mellitus | 1.22 (1.09-1.37) |
| Prior stroke | 1.23 (1.08-1.39) |
| Modified Rankin Scale ≥3 | 1.29 (1.15-1.46) |
| BMI | 0.97 (0.96-0.99) |
| Antiplatelet agents | |
| Aspirin (+/- Dipyridamole) | 1 [Reference] |
| Clopidogrel | 0.85 (0.75-0.96) |
| Aspirin-Clopidogrel | 1.73 (1.38-2.18) |

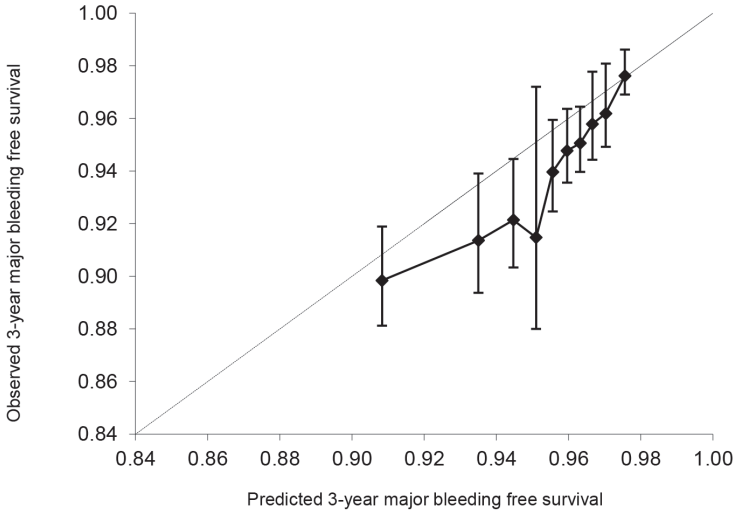
We combined all identified predictors in one model. After shrinkage, the model had a c-statistic of 0.63 (95% CI 0.61-0.64). The calibration plot showed good correspondence between predicted and observed risks (Figure 1A) and the Gronnesby and Borgan tests was not statistically significant (p=0.74), indicating good overall fit.

**Figure 1. Calibration of the $S_2$TOP-BLEED model in the development data (A) and external validation data (B)**

**A**




**B**



We translated regression coefficients into score charts presented in Table 3. The $S_2$TOP-BLEED score chart can be used in combination with Figure 2, to obtain approximate predictions for individual patients. Major bleeding risk ranged from 2% in patients aged 45-54 years without additional risk factors, to more than 10% in patients aged 75-84 years with multiple risk factors. 23,678 patients were categorized as low risk (0-11 points; 55%), 16,621 as medium risk (11-15 points; 38.5%) and 2813 patients as high risk (≥16 points, 6.5%). Observed risk of major bleeding increased across risk groups, as did the risk of recurrent ischaemic events (supplementary table 9). The original regression equation and baseline survival function are shown in supplementary table 10. All sensitivity analyses showed largely similar results (supplementary table 11). The $S_2$TOP-BLEED model showed a c-statistic of 0.61 (0.58-0.64) when used to predict intracranial haemorrhage risk. Calibration was adequate after re-estimation of the baseline hazard (supplementary figure 3). Estimated three-year risks of intracranial haemorrhage based on the $S_2$TOP-BLEED score are presented in supplementary table 12.



**Table 3. $S_2$TOP-BLEED score for major bleeding derived from multivariable Cox regression model**

| Factor | Points |
|---|---|
| Male **S**ex | 2 |
| **S**moking | 1 |
| **T**ype of antiplatelet agent | |
| Clopidogrel | 0 |
| Aspirin (+/- Dipyridamole) | 1 |
| Aspirin-Clopidogrel | 5 |
| **O**utcome on mRS ≥3 | 2 |
| **P**rior stroke | 1 |
| **B**lood pressure (hypertension) | 1 |
| **L**ow BMI | |
| <20 | 2 |
| 20-25 | 1 |
| >25 | 0 |
| **E**lderly | |
| 45-54 | 2 |
| 55-64 | 4 |
| 65-74 | 6 |
| 75-84 | 9 |
| ≥85 | 12 |
| Asian **E**thnicity | 1 |
| **D**iabetes | 1 |

mRS modified Rankin Scale

To calculate the $S_2$TOP-BLEED score for an individual, the number of points associated with each indicator, apart from age, should be added up. The corresponding three-year risk of major bleeding can be read from Figure 2 for the appropriate age group.

**External validation**

The baseline characteristics of the validation population are presented in supplementary table 13. Patients in the validation cohort were slightly older (mean age 67 years (SD 8)) and less often had a lacunar stroke. The mean observed three-year risk of major bleeding was somewhat higher in the validation population (5.5% versus 4.6% in the development population). The prediction model for major bleeding had a c-statistic of 0.61 (0.59-0.63) and slightly underestimated major bleeding risk in the validation data, as represented in the calibration plot (Figure 1B) and by a significant D'Agostino and Nam test (p<0.001).

**Figure 2. Estimated 3-year risk of major bleeding (%) in development data based on the $S_2$TOP-BLEED score**

| Points | Age group 45-54 | 55-64 | 65-74 | 75-84 | ≥85 |
|---|---|---|---|---|---|
| 0 | 2 | 2 | 2 | 4 | |
| 1 | 2 | 2 | 3 | 4 | 6 |
| 2 | 2 | 2 | 3 | 5 | 7 |
| 3 | 2 | 3 | 4 | 6 | 8 |
| 4 | 2 | 3 | 4 | 6 | 10 |
| 5 | 3 | 4 | 5 | 7 | 11 |
| 6 | 3 | 4 | 6 | 8 | 13 |
| 7 | 4 | 5 | 6 | 10 | 14 |
| 8 | 4 | 6 | 7 | 11 | 17 |
| 9 | 5 | 6 | 8 | 13 | 18 |
| 10 | 6 | 7 | 10 | 14 | >20 |
| 11 | 6 | 8 | 11 | 17 | >20 |
| 12 | 7 | 10 | 13 | 18 | >20 |
| 13 | 8 | 11 | 14 | >20 | |

Points: number of points on $S_2$TOP-BLEED score, without the score for age. The predicted probability per age group can be read from the appropriate column. Cells containing less than 5 patients were removed

## DISCUSSION

We developed the $S_2$TOP-BLEED score to predict an individualised risk of major bleeding after a TIA or ischaemic stroke, based on readily available characteristics. Age was identified as the strongest predictor for major bleeding. Calibration was accurate in the development data, but bleeding risk was slightly underestimated in the external validation data. Discriminatory performance of the model may be improved by identifying stronger predictors for major bleeding.



Previously, two models have been developed to predict intracranial haemorrhage in patients with a TIA or ischaemic stroke,[24,25] and one additional model was developed to predict major bleeding in patients with or at risk of atherothrombosis[26] (supplementary table 14). Considerable overlap exists between predictors in these models and those identified in our study, including age, hypertension, diabetes, smoking and antiplatelet agents. Age contained most prognostic information in our model, followed by type of antiplatelet agent and BMI. The increasing risk of bleeding with higher age seems particularly important given the rising number of elderly patients with a TIA or ischaemic stroke, with around 30% of strokes occurring in patients over 80 years of age.[27]

Clear discrimination between patients with and without a bleeding event based on patient characteristics appears to be difficult, as is shown by the low c-statistic of our model and other bleeding models in stroke patients. Similar results are also seen for major bleeding scores in other domains, such as the HASBLED and HEMORR$_2$HAGES scores for patients with atrial fibrillation.[30,31] In most validation studies, c-statistics of these models did not exceed 0.65.[32-34] Prediction of bleeding might be difficult because major bleeding consists of various types of bleedings with different underlying pathophysiological mechanisms and risk factors profiles. The discriminatory performance of the $S_2$TOP-BLEED score slightly dropped when applied to predict intracranial haemorrhage, possibly due to differences in risk factors for major and intracranial bleeding, or differences in the strength of the associations between predictors and outcome. Lacunar stroke subtype is reported to be a risk factor for intracerebral haemorrhage,[24,35] but was not identified in the current study, possibly because the majority of major bleedings were gastro-intestinal, which may have masked the association. Alternatively, prediction of major bleeding might be difficult because occurrence of bleeding may be a more random process without clear precursors. Discrimination of the current model might be improved by incorporating other, potentially stronger predictors, such as renal failure, history of bleeding (major and minor), ibuprofen or paracetamol use and results from neuroimaging (e.g. microbleeds).

Although calibration of our model was excellent in the development data, major bleeding risk was slightly underestimated in the external validation. The discrepancy between the observed and predicted risk is likely due to difference in overall observed risk between the development and validation population (three-year risk 4.6 vs 5.5%), leading to a systematic underestimation. Given the large number of patients included in

our development data and consistent performance in the internal-external cross-validation procedure we chose not to adjust our model.

Although the current model may help to identify patients at high risk of major bleeding events, it does not aim to guide treatment choices for antiplatelet agents, as the risk of bleeding should always be balanced against the risk of recurrent ischaemic events. However, the current analyses show considerable overlap in risk factors for bleeding and recurrent ischaemic events, as well as increasing risks of ischaemic events along with rising bleeding risks. The correlation between the two risks suggests that it may be difficult to individualise treatment decisions based on this balance. However, decision analytical studies are needed to assess whether the bleeding risk may outweigh the risk of recurrent ischaemic events in a specific subgroup of patients.

An important strength of our study is the large sample size, which enabled us to study a broad range of prognostic factors without the risk of overfitting. Second, quality of the trial data was high, with accurate follow-up and little missing data. Third, patients were included from all continents and had varying ethnic backgrounds, which enhances generalizability of the results. Fourth, even though inclusion criteria varied across trials, internal-external cross validation showed adequate performance in all trials and sensitivity analyses showed comparable results, which endorses the robustness of the model. Fifth, we externally validated our model in an independent population and found similar discriminatory power and slight underestimation that could be explained by differences in the incidence of major bleeding.

Several limitations of our study need to be addressed. First, we developed our prediction model in a population of trial participants. Due to application of strict in- and exclusion criteria, trial participants may not be representative for the entire stroke population. Since patients at highest risk of bleeding have been excluded (e.g. those with a history of bleeding), our model may underestimate bleeding risk. Validation of the current model in observational data would therefore be valuable. Second, the trials included in our IPD meta-analysis are relatively old and diagnosis and treatment of stroke patients has improved ever since. The lack of MR imaging in the older trials will likely have led to some misclassification of stroke subtypes, but may not have had a large influence on the classification of strokes as either cardioembolic or noncardioembolic, which was an important distinction for our study population. Third, we could only study candidate predictors that were measured in the majority of trials. As a result, we were unable to study some potentially relevant predictors, such as renal failure and blood pressure. However, we were able to include hypertension as predictor in our model. Fourth, the definition of major bleeding varied slightly across trials. Unfortunately, we were unable to reclassify major bleeding events according to a standardized definition with the available data. Also, we could not assign weights to different types of bleedings, while the severity and impact of included major bleedings clearly differs. Fifth, some candidate predictors were missing systematically and were imputed with multiple imputation. Although imputation is increasingly recognized as

a valid approach for handling of missing data, imputation of systematically missing data is relatively new and methods for dealing with systematically missing data are topic of further study. Nevertheless, the hazard ratios remained comparable after exclusion of those patients with missing data.

We developed and externally validated a practical score that can generate individualised risk predictions of major bleeding after a TIA or ischaemic stroke. Whether this model can guide treatment decisions needs to be investigated in a decision analytical study in which the risk of major bleeding is balanced against the risk of recurrent ischaemic events.

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## SUPPLEMENT

**Supplementary table 1. Details of six trials included in the IPD meta-analysis**

| Trial by year | Country | Recruitment period | No. of patients | Interventions | Inclusion criteria | Primary endpoint | Study period median (range; years) |
|---|---|---|---|---|---|---|---|
| CAPRIE -stroke subgroup 1996 | Australia, Canada, Europe (10) and USA. | 1992-95 | 6431 | CLO 75 mg *vs* ASA 325 mg | IS within six months | composite of IS, MI, or vascular death (excluding haemorrhage) | 2.0 (0-3.3) |
| ESPS-2 1996 | Europe (13) | 1989-93 | 3299 | ASA 50mg +DIP 400mg *vs* ASA 50mg | TIA/IS within three months | stroke; death; stroke or death. | 2.0 (0-2.5) |
| MATCH 2004 | Asia (4), Australia, Canada, Europe (21) and USA. | 2000-02 | 7599 | ASA 75mg +CLO 75mg *vs* CLO 75mg | TIA/IS within three months and one additional vascular risk factor within three years. | composite of IS, MI, vascular death or rehospitalisation for an acute ischaemic event | 1.4 (0-1.5) |
| CHARISMA -stroke subgroup 2006 | Asia (6), Australia, Canada, Europe (17), Mexico, South Africa, South America (3) and USA. | 2002-03 | 4320 | ASA 75-162mg +CLO 75mg *vs* ASA 75-162mg | TIA/IS within five years; age ≥45. | composite of stroke, MI, or vascular death | 2.1 (0-2.9) |
| ESPRIT 2006 | Asia (1), Australia, Europe (11) and USA. | 1997-2005 | 2739 | ASA 30-325mg +DIP 400mg *vs* ASA 30-325mg | TIA/minor IS within six months | composite of stroke, MI, vascular death, or major bleeding | 3.5 (0-8.1) |
| PRoFESS 2008 | Asia (12), Australia, Canada, Europe (16), Mexico, South Africa, South America (2) and USA. | 2003-06 | 20332 | ASA 50mg +DIP 400mg *vs* CLO 75mg | IS within three months; clinical and neurologic stable; age ≥55. | recurrent stroke; composite of stroke, MI, or vascular death | 2.4 (0-4.4) |

CLO clopidogrel; ASA aspirin; DIP dipyridamole; IS ischaemic stroke; TIA transient ischaemic attack; MI myocardial infarction

**Supplementary table 2. Criteria for the definitions of safety outcomes used in the included trials**

| Trial | Site of bleeding | Haemoglobin decrease (g/dL) | Transfusion requirements | Death | Other criteria |
|---|---|---|---|---|---|
| **CAPRIE, 1996** | | | | | |
| No outcome pre-defined<br>*major bleeding | intracranial or intraocular | - | - | Fatal bleeding | Significant disabling or requiring hospital admission |
| **ESPS-2, 1996** | | | | | |
| *severe or fatal bleeding | - | - | - | Fatal bleeding | Bleeding requiring blood transfusion |
| *moderate bleeding | - | - | - | - | Bleeding requiring specific treatment, but no blood transfusion |
| **MATCH, 2004** | | | | | |
| *life-threatening bleeding | symptomatic intracranial haemorrhage | ≥5.0 | ≥4 units | Fatal bleeding | Significant hypotension requiring inotropes |
| *major bleeding | intraocular bleeding leading to significant loss of vision | - | ≤3 units | - | Significantly disabling |
| **CHARISMA, 2006** | | | | | |
| *severe bleeding | intracranial | - | - | Fatal bleeding | Bleeding causing hemodynamic compromise that required blood or fluid replacement, inotropic support or surgical intervention. |
| *moderate bleeding | - | - | - | - | Bleeding that led to transfusion but did not meet the criteria for severe bleeding |
| **ESPRIT, 2006** | | | | | |
| *major bleeding | intracranial | - | - | Fatal bleeding | Bleeding requiring hospital admission |
| **PRoFESS, 2008** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| *life-threatening bleeding | symptomatic intracranial haemorrhage, intraocular bleeding causing loss of vision | - | ≥4 units | Fatal bleeding | Bleeding requiring surgical intervention, hypotension requiring inotropes |
| *major haemorrhagic event, comprising life-threatening as subset | symptomatic intracranial haemorrhage, intraocular bleeding causing loss of vision | - | ≥2 units | | Clinically significant disabling. Bleeding requiring hospitalization |

**Supplementary table 3. Assessment of major bleeding per trial**

| | Scheduled follow-up visits (months after randomisation) | Method of outcome assessment |
|---|---|---|
| **CAPRIE** | 1/2/3/4/every 4 mo. thereafter | Recorded as adverse event by investigator |
| **ESPS-2** | 1/3/every 3 mo. thereafter | Recorded as adverse event by investigator |
| **MATCH** | 1/3/6/every 6 mo. thereafter | An adjudication committee blindly validated all major bleeding outcome events reported by investigators |
| **CHARISMA** | 1/3/6/every 6 mo. thereafter | Major bleeding events were validated by the independent Cleveland Clinic Foundation Clinical Events Adjudication Committee. |
| **ESPRIT** | 1/6/every 6 mo. thereafter | Major bleedings were audited by the Auditing Committee for Outcome Events |
| **PRoFESS** | 1wk/1/3/6/every 6 mo. thereafter | Major bleeding events were adjudicated by a central committee |

Mo months

**Supplementary table 4. Definitions of candidate predictors**

| Variable | Definition |
|---|---|
| Age | - |
| Sex | - |
| Asian ethnicity | Self-reported ethnicity |
| Smoking | Current smoking |
| Heavy alcohol use | Alcohol abuse or >5 drinks/day at least once a week |
| Modified Rankin Scale | 0 - No symptoms.<br>1 - No significant disability. Able to carry out all usual activities, despite some symptoms.<br>2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.<br>3 - Moderate disability. Requires some help, but able to walk unassisted.<br>4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.<br>5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.<br>6 - Dead. |
| Lacunar stroke subtype | TOAST classification small vessel disease or lacunar stroke subtype in CAPRIE |
| Hypertension | Documented history of hypertension or use of antihypertensive agents |
| Hypercholesterolemia | Documented history of hypercholesterolemia or use of statins |
| Diabetes | - |
| Prior stroke | Stroke prior to index event |
| Prior TIA | TIA prior to index event |
| History of cardiovascular disease | History of myocardial infarction, angina pectoris or peripheral arterial disease |
| History of heart failure | - |

**Supplementary table 5. Overview of systematically missing candidate predictors**

| | CAPRIE 6431 | ESPS-2 3299 | MATCH 7599 | CHARISMA 4320 | ESPRIT 2739 | PRoFESS 20332 | Sporadically missing |
|---|---|---|---|---|---|---|---|
| Age | √ | √ | √ | √ | √ | √ | 0 |
| Sex | √ | √ | √ | √ | √ | √ | 0 |
| Ethnic group | √ | √ | √ | √ | √ | √ | 0 |
| Smoking | √ | √ | √ | √ | √ | √ | <1% |
| Heavy alcohol use | √ | √ | √ | - | 0 | √ | <1% |
| Modified Rankin Scale | √ | √ | √ | - | √ | √ | <1% |
| Lacunar subtype | √ | √ | √ | - | √ | √ | 4% |
| Hypertension | √ | √ | √ | √ | √ | √ | <1% |
| Diabetes | √ | √ | √ | √ | √ | √ | 0 |
| Hypercholesterolemia | √ | √ | √ | √ | √ | √ | <1% |
| Prior stroke | √ | √ | √ | √ | √ | √ | <1% |
| Prior TIA | √ | √ | √ | √ | - | √ | <1% |
| Prior MI | √ | √ | √ | √ | √ | √ | <1% |
| Peripheral arterial disease | √ | √ | √ | √ | √ | √ | <1% |
| Angina pectoris | √ | √ | √ | - | √ | √ | <1% |
| Heart failure | √ | √ | √ | √ | - | √ | <1% |
| Use of antihypertensive agents | - | √ | √ | √ | √ | √ | <1% |
| Use of statins | 0 | 0 | √ | √ | - | √ | <1% |
| Height | √ | √ | √ | √ | - | √ | <1% |
| Weight | √ | √ | √ | √ | - | √ | <1% |

√ variable measured in trial; - variable not measured in trial; 0 exclusion criterion or assumed to be absent given timeframe in which trial took place.

**Supplementary table 6. Types of major bleeding**

| | Fatal (n=155) | Intracranial, non-fatal (n=273) | Other (n=1102) | Total (n=1530) |
|---|---|---|---|---|
| Intracranial | 119 (77) | 273 (100) | - | **392 (26)** |
| Gastro-intestinal | 20 (13) | - | 677 (61) | **697 (46)** |
| Internal/retroperitoneal | 5 (3) | - | 13 (1) | **18 (1)** |
| Ocular | - | - | 75 (7) | **75 (5)** |
| Urogenital | - | - | 110 (10) | **110 (7)** |
| Haemoptysis | - | - | 6 (0.5) | **6 (0.5)** |
| Epistaxis | - | - | 64 (6) | **64 (4)** |
| Surgical/Operative wound/ puncture site | - | - | 22 (2) | **22 (1)** |
| Hematoma/purpura | - | - | 19 (2) | **19 (1)** |
| Other | 9 (6) | - | 109 (10) | **118 (8)** |
| Missing | 2 (1) | - | 7 (0.5) | **9 (0.5)** |

Values are numbers (%)

**Supplementary table 7. Variables selected in Internal-External Cross Validation**

| **Validated in trial:** **Selected variables:** | **CAPRIE** | **ESPS-2** | **MATCH** | **CHARISMA** | **ESPRIT** | **PRoFESS** |
|---|---|---|---|---|---|---|
| Age | √ | √ | √ | √ | √ | √ |
| Sex | √ | √ | √ | √ | √ | √ |
| Asian ethnicity | √ | √ | - | √ | √ | √ |
| BMI | √ | √ | √ | √ | √ | √ |
| Smoking | √ | √ | √ | √ | √ | √ |
| Heavy alcohol use | - | - | - | - | - | - |
| Modified Rankin Scale | √ | √ | √ | √ | √ | √ |
| Lacunar stroke subtype | - | - | - | - | - | - |
| Hypertension | √ | √ | √ | √ | √ | √ |
| Hypercholesterolemia | - | - | - | - | - | - |
| Diabetes | √ | √ | √ | √ | √ | √ |
| Prior stroke | √ | √ | √ | √ | √ | √ |
| Prior TIA | - | √ | - | - | - | - |
| History of cardiovascular disease | - | - | - | - | - | - |
| Antiplatelet agents | √ | √ | √ | √ | √ | √ |

**Supplementary table 8. Performance in Internal-External Cross Validation**

| Validated in trial: | Calibration slope (SD) | C-statistic (95% CI) |
|---|---|---|
| **CAPRIE** | 1.02 (0.15) | 0.63 (0.59-0.68) |
| **ESPS-2** | 0.96 (0.17) | 0.63 (0.58-0.68) |
| **MATCH** | 0.89 (0.11) | 0.65 (0.62-0.69) |
| **CHARISMA** | 1.15 (0.16) | 0.66 (0.61-0.67) |
| **ESPRIT** | 1.21 (0.23) | 0.66 (0.60-0.72) |
| **PRoFESS** | 0.78 (0.07) | 0.61 (0.59-0.63) |

CI confidence interval



**Supplementary table 9. Observed three-year risk of bleeding and recurrent ischaemic events across risk groups in development cohort**

| | | Major bleeding | Ischaemic events |
|---|---|---|---|
| **Risk group** | | **Event/N (KM estimate)** | **Event/N (KM estimate)** |
| Low | 0-10 points | 602/23,678 (3%) | 2,165/23,678 (11%) |
| Medium | 11-15 points | 716/16,621 (6%) | 1875/16,621 (18%) |
| High | ≥16 points | 212/2,813 (12%) | 323/2,813 (25%) |

KM Kaplan-Meier

**Supplementary table 10. Original regression equation and baseline survival**

| |
|---|
| **Linear predictor (LP)** |
| -0.05493*age + 0.00069*age$^2$ + 0.25718*Male + 0.13878*Asian ethnicity + 0.17781*current smoking + 0.25723*modified Rankin Scale ≥3 + 0.14618*Hypertension + 0.19888*Diabetes + 0.20467*Prior stroke - 0.02767*BMI † -0.16016*clopidogrel + 0.54980*aspirin+clopidogrel |
| **Baseline survival** |
| 3 year: 0.9562434 |
| **Mean linear predictor** |
| -0.7849 |

†if BMI>30, use BMI 30.

The absolute 3 year risk of major bleeding (%) is calculated as:

'1- $S(t_3)^{\exp(\text{LP-mean LP})}$'

The beta coefficients of the final Cox regression model are used to calculate the linear predictor (LP), as described in the table. The latter is corrected for the averages of the patients risk factors (mean LP). $S(t_3)$ is the baseline survival at 3 years, which is 0.9562434.

As an example how to use this formula: consider a 75-year-old Caucasian male, non-smoker, with hypertension, no diabetes or prior stroke. He had a mRS of 2 after his qualifying stroke and has a BMI of 26. He uses aspirin-dipyridamole.

In this instance the LP is:

-0.05493*75 (for age 75) + 0.00069*75$^2$ (age 75 squared) + 0.25718 (for being male) + 0 (non-Asian) + 0 (non-smoker) + 0 (mRS below 3) + 0.14618 (for hypertension) + 0 (no Diabetes) + 0 (no prior stroke) - 0.02767*26 (for BMI 26) - 0 (no clopidogrel) + 0 (no aspirin-clopidogrel) = -0.55456

LP-mean LP = -0.55456--0.7849= 0.23034

$1 - 0.9562434^{\exp(0.23034)} = 5.45$

He will have a 3-year major bleeding risk of 5.5%.

**Supplementary table 11. Sensitivity analyses**

| | Sens. analysis 1 HR (95%CI) (n=38,816) | Sens. analysis 2 HR (95% CI) (n=38,000) | Sens. analysis 3 HR (95% CI) (n=32,922) |
|---|---|---|---|
| Age | 0.94 (0.89-1.00) | 0.94 (0.89-1.00) | 0.94 (0.88-1.00) |
| $Age^2$ | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| Male sex | 1.33 (1.19-1.49) | 1.35 (1.20-1.51) | 1.31 (1.16-1.48) |
| Asian ethnicity | 1.15 (1.00-1.33) | 1.16 (0.99-1.34) | 1.15 (0.98-1.34) |
| Current smoking | 1.24 (1.09-1.41) | 1.22 (1.06-1.39) | 1.20 (1.04-1.38) |
| Hypertension | 1.22 (1.06-1.39) | 1.23 (1.08-1.41) | - |
| Diabetes mellitus | 1.20 (1.06-1.35) | 1.24 (1.10-1.39) | 1.25 (1.10-1.42) |
| Prior stroke | 1.25 (1.10-1.42) | 1.24 (1.08-1.41) | 1.27 (1.11-1.45) |
| Modified Rankin Scale ≥3 | 1.34 (1.19-1.51) | 1.32 (1.17-1.49) | 1.30 (1.15-1.47) |
| BMI <30 | 0.97 (0.96-0.99) | 0.97 (0.95-0.99) | 0.97 (0.96-0.99) |
| Antiplatelet agents | | | |
| Aspirin | Reference | Reference | Reference |
| Aspirin-Dipyridamole | 0.89 (0.72-1.10) | 0.82 (0.66-1.01) | 0.96 (0.73-1.23) |
| Clopidogrel | 0.77 (0.63-0.94) | 0.71 (0.58-0.89) | 0.83 (0.66-1.06) |
| Aspirin-Clopidogrel | 1.71 (1.31-2.22) | 1.50 (1.12-2.01) | 1.90 (1.32-2.74) |

HR hazard ratio; CI confidence interval

Sensitivity analysis 1: exclusion of patients with TIA as index event;
Sensitivity analysis 2: exclusion of patients randomised more than 3 months after the index event;
Sensitivity analysis 3: exclusion of patients with missing data (all patients from CHARISMA and ESPRIT were excluded, as mRS was not available in CHARISMA and BMI was not measured in ESPRIT).

**Supplementary table 12. Predicted three-year probability (%) of intracranial haemorrhage based on the $S_2$TOP-BLEED score**

| Points | Age group 45-54 | 55-64 | 65-74 | 75-84 |
|---|---|---|---|---|
| 0 | 0.5 | 0.5 | 0.7 | 1.0 |
| 1 | 0.5 | 0.6 | 0.7 | 1.1 |
| 2 | 0.5 | 0.7 | 0.9 | 1.3 |
| 3 | 0.6 | 0.7 | 1.0 | 1.5 |
| 4 | 0.7 | 0.9 | 1.1 | 1.8 |
| 5 | 0.7 | 1.0 | 1.3 | 2.0 |
| 6 | 0.9 | 1.1 | 1.5 | 2.4 |
| 7 | 1.0 | 1.3 | 1.8 | 2.7 |
| 8 | 1.1 | 1.5 | 2.0 | 3.2 |
| 9 | 1.3 | 1.8 | 2.4 | 3.6 |
| 10 | 1.5 | 2.0 | 2.7 | 4.2 |
| 11 | 1.8 | 2.4 | 3.2 | 4.9 |
| 12 | 2.0 | 2.7 | 3.6 | 5.4 |
| 13 | 2.4 | 3.2 | 4.2 | 6.5 |
| 14 | 2.7 | | 4.9 | |

* cells containing less than 5 patients were removed

**Supplementary table 13. Baseline characteristics of validation population**

| | No major bleeding (n=17,644) | Major bleeding (n=773) |
|---|---|---|
| Age, mean (SD), years | 67 (7.8) | 69 (8.0) |
| Male sex | 11035 (62.5) | 517 (66.9) |
| Ethnic group | | |
| Caucasian | 14775 (83.7) | 630 (81.5) |
| Black | 293 (1.7) | 21 (2.7) |
| Asian | 2092 (11.9) | 104 (13.4) |
| Other | 484 (2.7) | 18 (2.3) |
| BMI (mean, SD), kg/m$^2$ | 27.1 (4.3) | 26.6 (4.5) |
| Qualifying event | | |
| Stroke | 15848 (89.8) | 704 (91.1) |
| TIA | 1791 (10.1) | 69 (8.9) |
| Index stroke severity | | |
| mRS 0-2 | 14683 (83.3) | 603 (78.0) |
| mRS 3-5 | 2953(16.7) | 170 (22.0) |
| Lacunar stroke subtype | 3705 (21.0) | 169 (21.9) |
| Current smoker | 4734 (26.8) | 216 (27.9) |
| Heavy alcohol use | - | - |
| Hypertension | 15073 (85.4) | 688 (89.0) |
| Hyperlipidaemia | 12734 (72.2) | 550 (71.1) |
| Diabetes | 4920 (27.9) | 226 (29.2) |
| Prior stroke | 2594 (14.7) | 153 (19.8) |
| Prior TIA | 1327 (7.5) | 59 (7.6) |
| History of cardiovascular disease | 2188 (12.4) | 107 (13.8) |
| Congestive heart failure | 689 (3.9) | 42 (5.4) |
| Antiplatelet regimen | | |
| Aspirin | 8913 (50.5) | 394 (51.0) |
| Terutroban | 8731 (49.5) | 379 (49.0) |

mRS modified Rankin Scale

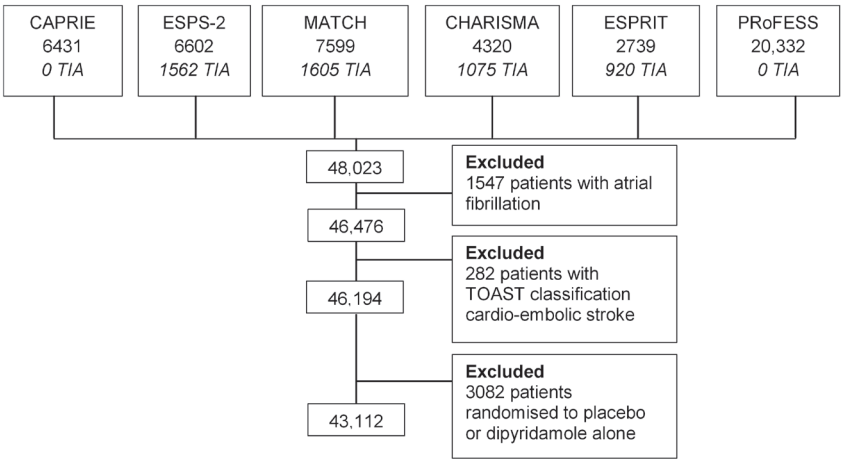
**Supplementary table 14. Overview of existing prediction models for major and intracranial bleeding in patients with a TIA or ischaemic stroke**

| Risk score | Study population | Development cohort | Validation cohort | Follow-up; years (median, IQR) | Outcome | Included items | Performance development cohort | Performance validation cohort |
|---|---|---|---|---|---|---|---|---|
| **Ariesen**[1] | Patients with TIA or stroke | Cerebrovascular cohort studies collaboration | ESPS 2 trial | Mean 4.3 | Intracranial bleeding | Age<br>Blood glucose<br>SBP<br>Antihypertensive drug use | 0.65 (0.59-0.74) | 0.53 (49-0.57)*[2] |
| **REACH**[3] | Patients with or at risk of atherothrombosis | REACH registry | 1) CHARISMA trial<br>2) ESPS 2 trial | - | Major bleeding | Age<br>PAD<br>CHF<br>Diabetes<br>Hypercholesterolemia<br>Hypertension<br>Smoking<br>Antiplatelet agents<br>Oral anticoagulants | 0.68 | 1) 0.64<br>2) 0.63<br>(0.60-0.66)[2] |
| **Intracranial $B_2LEED_3S$**[4] | Patients with TIA or non cardioembolic ischaemic stroke | PERFORM trial | PRoFESS trial | 2.3 (2.0-2.8) | Intracranial bleeding | Age<br>Sex<br>BMI<br>Asian ethnicity<br>Hypertension<br>Cardiovascular disease<br>Cerebrovascular disease<br>Lacune/small vessel disease<br>Dual antiplatelet or oral anticoagulants | 0.64 (0.61-0.67) | 0.59 (0.55-0.62) |

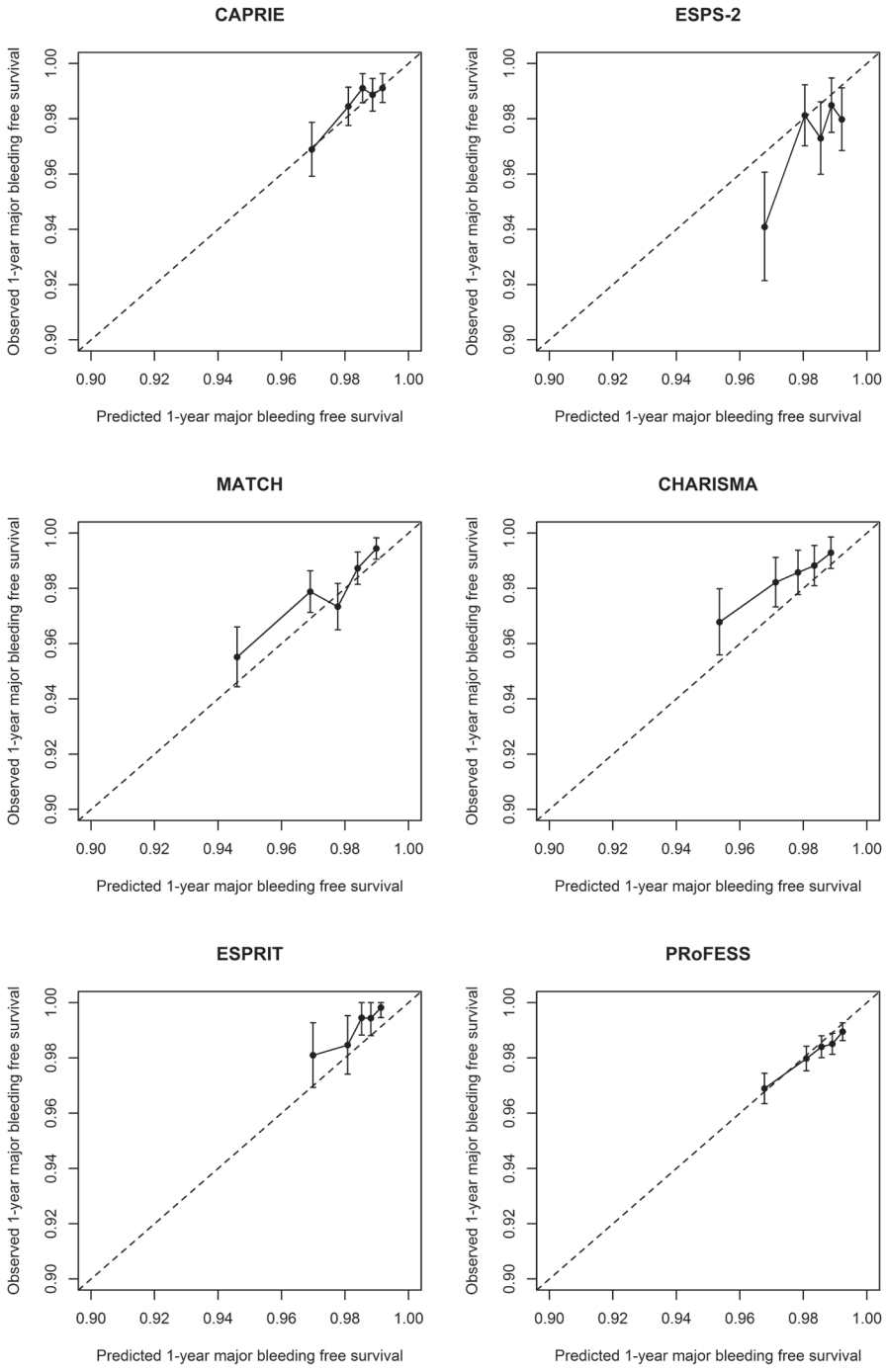
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **$S_2$TOP-BLEED** | Patients with TIA or non cardioembolic ischaemic stroke | CAPRIE, ESPS 2, MATCH, CHARISMA, ESPRIT, PRoFESS trials | PERFORM trial | 2.0 (1.5-2.7) | Major bleeding | Age<br>Sex<br>BMI<br>Asian ethnicity<br>Smoking<br>Hypertension<br>Diabetes<br>Stroke<br>mRS score<br>Antiplatelet agents | 0.63 (0.61-0.64) | 0.61 (0.59-0.63) |

*validated for major bleeding

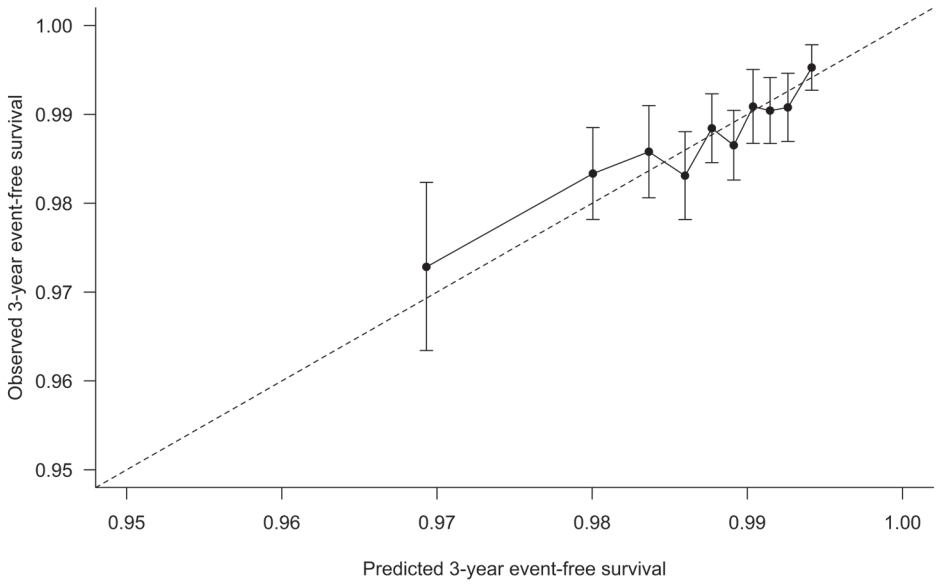
**Supplementary figure 1. Flowchart**



**Supplementary figure 2. Calibration plots Internal-External Cross validation**



**Supplementary figure 3. Calibration plot of S2TOP-BLEED for prediction of intracranial haemorrhage after adjustment of baseline hazard**




Estimated baseline survival at 3 years for intracranial haemorrhage: 0.98794

## SUPPLEMENTARY METHODS. PERFORMANCE OF $S_2$TOP-BLEED SCORE FOR PREDICTION OF INTRACRANIAL HAEMORRHAGE.

Intracranial haemorrhages included intracerebral haemorrhages, subarachnoid haemorrhages, subdural and epidural haematomas. Haemorrhagic transformations of ischaemic strokes were not counted as intracranial haemorrhages.

We calculated the linear predictor for each patient by multiplying the original regression coefficients by covariate values. Predicted risks based on the $S_2$TOP-BLEED model overestimate the risk of intracranial haemorrhage, as the incidence of intracranial haemorrhage is lower than the incidence of major bleeding. To correct for this discrepancy we re-estimated the baseline hazard function. This was done by performing Cox regression analysis with intracranial haemorrhage as outcome and the linear predictor as offset in the model. The resulting baseline hazard was combined with the original linear predictor. The figure below shows the calibration plot after adjustment of the baseline hazard. The accompanying table presents the predicted three-year risk of intracranial haemorrhage based on the $S_2$TOP-BLEED score.

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# CHAPTER 4

## EXTERNAL VALIDATION OF RISK SCORES FOR MAJOR BLEEDING IN A POPULATION-BASED COHORT OF TRANSIENT ISCHAEMIC ATTACK AND ISCHAEMIC STROKE PATIENTS

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## ABSTRACT

**Background and purpose** The $S_2$TOP-BLEED score may help to identify patients at high risk of bleeding on antiplatelet drugs after a transient ischaemic attack (TIA) or ischaemic stroke. The score was derived on trial populations and its performance in a real world setting is unknown. We aimed to externally validate the $S_2$TOP-BLEED score for major bleeding in a population-based cohort and to compare its performance with other risk scores for bleeding.

**Methods** We studied risk of bleeding in 2,072 patients with a TIA or ischaemic stroke on antiplatelet agents in the population-based Oxford Vascular Study (OXVASC) according to three scores: $S_2$TOP-BLEED, REACH and Intracranial-$B_2$LEED$_3$S. Performance was assessed with c-statistics and calibration plots.

**Results** During 8,302 patient years of follow-up, 117 patients had a major bleed. The $S_2$TOP-BLEED score showed a c-statistic of 0.69 (95% CI 0.64-0.73) and accurate calibration for three-year risk of major bleeding. The $S_2$TOP-BLEED score was much more predictive of fatal bleeding than non-major bleeding (c-statistics 0.77; 0.69-0.85 and 0.50; 0.44-0.58). The REACH score had a c-statistic of 0.63 (0.58-0.69) for major bleeding and the Intracranial-$B_2$LEED$_3$S score a c-statistic of 0.60 (0.51-0.70) for intracranial bleeding. The ratio of ischaemic events versus bleeds decreased across risk groups of bleeding from 7.5: 1in the low risk group, to 1.8:1 in the high risk group.

**Conclusion** The $S_2$TOP-BLEED score shows modest performance in a population-based cohort of patients with a TIA or ischaemic stroke. Although bleeding risks were associated with risks of ischaemic events, risk stratification may still be useful to identify a subgroup of patients at particularly high risk of bleeding, in whom preventive measures are indicated.

## INTRODUCTION

Lifelong secondary prevention with antiplatelet agents is recommended in patients who experienced a transient ischaemic attack (TIA) or ischaemic stroke.[1] Bleeding is a clinically important and potentially life-threatening side effect of antiplatelet drugs.[2] Risk of bleeding increases steadily with age, and the gastro-intestinal (GI) tract is shown to be the most common source of bleeding.[3-5] Individualised prediction of bleeding risk may help physicians to identify patients at highest risk and may guide treatment decisions regarding initiation of gastro-protective agents.

Recently, the $S_2$TOP-BLEED score was developed to predict risk of major bleeding in patients with a TIA or ischaemic stroke on antiplatelet agents.[6] The model was derived from individual patient data from six randomised clinical trials (supplementary table 1),[7-12] including over 43,000 patients with a TIA or ischaemic stroke and was subsequently validated in the PERFORM trial,[13] including another 19,000 patients with a recent TIA or ischaemic stroke.



A potential drawback of using trial data for development of a risk score is that participants may represent a selective subset of the population of interest, as frail and elderly patients are often excluded from trials. As a consequence, absolute risks may be underestimated in a real world setting and associations between predictors and outcome may differ.[14,15] External validation of a risk score in observational data could, therefore, provide valuable insight into the accuracy of the predicted risks and the generalizability to a wider range of patients.

We aimed to externally validate the $S_2$TOP-BLEED score in a population-based cohort and to assess its performance according to site and severity of bleeding. Subsequently, we compared its performance to other risk scores for bleeding in patients with a TIA or ischaemic stroke.

## METHODS

### Study population

The Oxford Vascular Study (OXVASC) is an ongoing population-based study on the incidence and outcome of all acute vascular events in Oxfordshire, UK. Methods and definition of events have been described previously.[16] Briefly, the study population comprises 92,728 individuals, registered with 100 general practitioners in nine general practices in Oxfordshire. Multiple overlapping methods of hot and cold pursuit are used for ascertainment of all acute vascular events in the study population, which has been shown to be near complete.[17] For the current analysis, we studied patients with a TIA or ischaemic stroke between 2002 and 2012, who were on antiplatelet drugs after their event. These included both patients who were on premorbid antiplatelet drugs, as well as patients who started antiplatelet drugs after the

index event. Patients who switched to oral anticoagulants during follow-up were censored at the time of starting (supplementary table 1).

Information on patient demographics and vascular risk factors was collected during the initial assessment. Patients were followed-up face to face by a study nurse or physician at 1 month, 6 months, 1 year, 5 and 10 years after the index event. Recurrent ischaemic events, bleeding events that required medical attention, and disability (modified Rankin Scale, mRS) were recorded at each follow-up. Bleeding events were also identified by daily searches of all hospital admissions, by review of administrative diagnostic codes from hospital and primary care records, and by searches of blood transfusion records. Only bleeds that required medical attention or were fatal prior to medical attention could be sought were included. Bleeds secondary to trauma, surgery, or haematological malignancy were excluded.

Bleeds were classified according to site of haemorrhage as either intracranial (intracerebral, subarachnoid and subdural), upper GI, lower GI, epistaxis, genitourinary or other. The severity of bleeds was recorded according to the CURE criteria.[18] Major bleeds were bleeds that were substantially disabling with persistent sequelae, intraocular bleeds leading to significant loss of vision, or bleeds requiring transfusion of 2 or more units of blood. Major bleeds were classified as life-threatening if the bleeding episode was fatal, symptomatic intracranial, led to a reduction in haemoglobin level of at least 5 g/dl (3.1 mmol/L), led to substantial hypotension requiring use of intravenous inotropic agents, necessitated a surgical intervention, or necessitated transfusion of four or more units of blood. Bleeding events that required medical attention but did not fulfil the criteria of major bleeding were recorded as significant non-major bleeds. OXVASC has been approved by the local ethics committee and all participants gave written informed consent. Requests for anonymised data will be considered by Professor Rothwell (peter.rothwell@clneuro.ox.ac.uk).

**Statistical analysis**

Data were missing on BMI in 79 patients (4%) and on smoking in 3 patients (<1%). These patients were excluded from the analysis. Variables of the $S_2$TOP-BLEED score (supplementary table 2) were matched to variables in OXVASC. A proxy was used if no direct match was available. The National Institute of Health Stroke Scale (NIHSS) was used to assess severity of the index event and was used as a proxy for the mRS score, where a NIHSS score ≤3 was considered a minor stroke and a score >3 a severe stroke. All patients who received a short course of aspirin plus clopidogrel (for the first 30-90 days) and were treated with aspirin (plus dipyridamole) thereafter, were analysed as if they were on aspirin (plus dipyridamole), as our interest was in long term risk of bleeding.

The original regression equation was applied to the validation data to calculate three-year risk of major bleeding. We assessed discriminatory performance of the model with the c-statistic and calibration with the calibration slope and plots. Calibration at three years was examined by dividing patients in quintiles according to their predicted risk. The

mean predicted risk per quintile group was subsequently plotted against the observed risk per quintile group. Calibration over time was assessed across risk groups that were pre-defined as low risk (0-10 points on the $S_2$TOP-BLEED score), medium risk (11-15 points) and high risk (>15 points).[19] Model performance was also assessed separately by severity of bleeding (non-major, major and life-threatening, or fatal) and by site of bleeding (intracranial, upper GI, lower GI, epistaxis, genitourinary, or other). We performed a sensitivity analysis excluding patients with an established high risk of bleeding or reduced life expectancy (patients with renal failure, liver failure, cancer or a prior peptic ulcer), who are generally not included in trials.

We compared performance of the $S_2$TOP-BLEED score with performance of the REACH score for major bleeding,[20] and the Intracranial-$B_2$LEED$_3$S score for intracranial haemorrhage after TIA or ischaemic stroke (supplementary table 3), [21] by means of the c-statistic, integrated discrimination improvement (IDI) and net reclassification improvement (NRI).[22,23] Another risk score for intracranial haemorrhage after TIA or stroke could not be validated as it required post-acute blood glucose levels, which were not available in the validation cohort. To study the influence of the different age categories used in the different risk scores for major bleeding on the performance, we assessed the c-statistic of the models containing age only and compared it to the c-statistic of the remainder of the model.

As risk factors for bleeding events are also known to be risk factors for recurrent ischaemic events, we assessed the discriminatory ability of the $S_2$TOP-BLEED score for recurrent ischaemic events at three years (defined as recurrent ischaemic stroke, myocardial infarction or sudden cardiac death). Next, we assessed the cumulative incidence of bleeding events and recurrent ischaemic events at three years and their ratio across risk groups of the $S_2$TOP-BLEED score. Results are reported in accordance with the TRIPOD statement.[24] All analyses were performed with R version 3.3.2.

## RESULTS

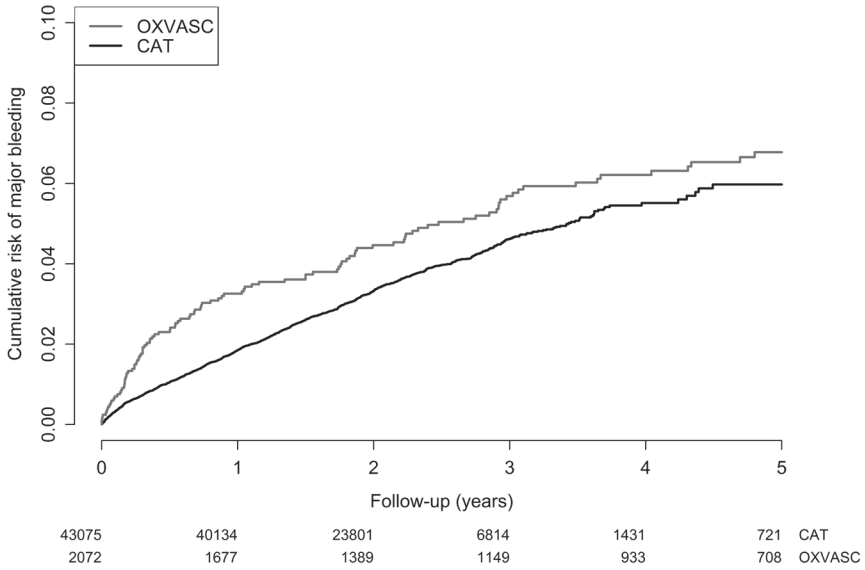
Between 2002 and 2012, 2,072 patients with a TIA or ischaemic stroke on antiplatelet drugs were included in OXVASC. Median follow-up was 3.5 years (IQR 1.5 to 6.3). Baseline characteristics of patients in the development and validation cohort are shown in Table 1. Patients in OXVASC were older than patients in the Cerebrovascular Antiplatelet Trialists' (CAT) trials (mean age 73 years (SD 13.4) versus 66 years (SD 9.7)). 254 bleeds occurred during follow-up, of which 117 (46%) were major bleeds. Upper gastro-intestinal bleeds were the most common type of bleeding (32%, supplementary table 4). 461 patients (22%) were classified as having an established high risk of bleeding, 39% of all major bleeds occurred within this group. Risk of major bleeding was higher in the validation cohort than in the development cohort (Figure 1).

**Table 1. Baseline characteristics of patients in development (CAT) and validation cohort (OXVASC)**

| | OXVASC N=2,072 | CAT N=43,112 |
|---|---|---|
| Age, mean (SD), years | 73 (13.4) | 66 (9.7) |
| Female sex | 1,071 (52) | 15,709 (36) |
| Caucasian | 2,000 (97) | 32,756 (76) |
| BMI, mean (SD), kg/m$^2$ | 26.1 (5.5) | 26.9 (4.8) |
| Qualifying event: | | |
| Stroke | 1,177 (57) | 38,817 (90) |
| TIA | 895 (43) | 4,295 (10) |
| Severity of index stroke: | | |
| mRS 0-2/NIHSS ≤3 | 739 (36) | 29,826 (69) |
| mRS 3-5/NIHSS >3 | 438 (21) | 8,991 (21) |
| Risk factors and medical history: | | |
| Current smoker | 307 (15) | 9,578 (22) |
| Heavy alcohol use | 304 (15) | 3,577 (8) |
| Hypertension | 1,173 (57) | 30,406 (71) |
| Hyperlipidaemia | 557 (28) | 23,219 (54) |
| Diabetes | 282 (14) | 14,373 (33) |
| Prior stroke | 227 (11) | 7,419 (17) |
| Prior TIA | 189 (9) | 5,417 (13) |
| Prior MI | 174 (8) | 3,087 (7) |
| PAD | 138 (7) | 2,392 (6) |
| Congestive heart failure | 162 (8) | 1,577 (4) |

Values are numbers (percentages) unless otherwise stated. mRS modified Rankin Scale; NIHSS national institute of health stroke scale; MI myocardial infarction; PAD peripheral arterial disease

**Figure 1. Cumulative risk of major bleeding in development cohort (CAT) and validation cohort (OXVASC)**






The c-statistic of the $S_2$TOP-BLEED score for major bleeding was 0.69 (95% CI 0.64 to 0.73) and calibration at three years was accurate (calibration slope 1.13, p=0.48; Figure 2A). Early risk of bleeding was underestimated by the model, but calibration across risk groups was accurate for long term risk of bleeding (Figure 2B). The $S_2$TOP-BLEED score was much more predictive for fatal and major bleeding (c-statistic 0.77 and 0.69), than for non-major bleeds (c-statistic 0.50; Table 2). Discriminatory ability was higher for intracranial and upper GI bleeds, than for lower GI bleeds, genitourinary bleeds and epistaxis (Table 2). A sensitivity analysis excluding patients with an established high risk of bleeding or reduced life expectancy showed comparable discriminatory performance of the $S_2$TOP-BLEED score (0.70; 0.64-0.77).

The REACH score showed a c-statistic of 0.63 (95% CI 0.58-0.69) for major bleeding at two years and systematically underestimated risk of bleeding (supplementary figure 1A). The Intracranial-$B_2LEED_3S$ score had a c-statistic of 0.60 (95% CI 0.51-0.70) for intracranial bleeding at two years and showed accurate calibration (supplementary figure 1B). The $S_2$TOP-BLEED score showed improved reclassification and integrated discrimination as compared with the REACH and Intrancranial-$B_2LEED_3S$ scores (supplementary table 5).

A model with five age categories only as defined in the $S_2$TOP-BLEED score (45-54,55-64,65-74,75-85,85+) showed a c-statistic of 0.66 (0.62-0.71), a model containing four age categories as defined in the REACH score (45-54, 55-64, 65-74, 75+) had a c-statistic of 0.64 (0.60-0.69) (supplementary table 6). The predictive performance of the models without age was 0.57 (0.51-0.64) for $S_2$TOP-BLEED and 0.52 (0.45-0.58) for REACH.

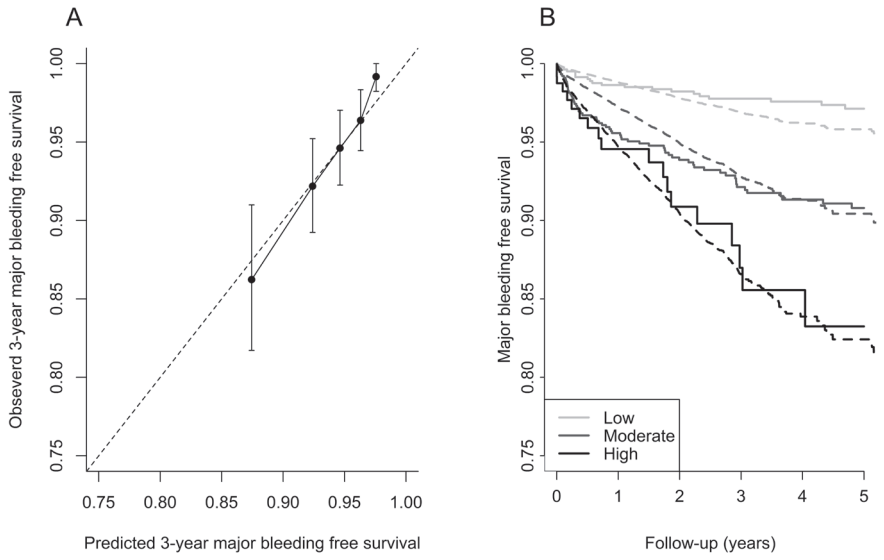
438 patients experienced a recurrent ischaemic event during follow-up, the overall observed three-year risk was 19% (95% CI 17-21%). The c-statistic of the $S_2$TOP-BLEED score for predicting recurrent ischaemic events was 0.58 (95% CI 0.55-0.61). Three-year risk of recurrent ischaemic events was 15% (95% CI 12-17%) in the low bleeding risk group and 23% (95% CI 16-30%) in both the medium and high risk group (Figure 3; p for trend 0.22). The ratio of ischaemic events versus bleeds decreased from 7.5:1 in the low risk group, to 2.9:1 in the intermediate risk group and 1.8:1 in the high risk group (p for trend <0.001).

**Table 2. C-statistic (95% confidence interval) of $S_2$TOP-BLEED score in validation cohort**

| | **C-statistic (95% CI)** |
|---|---|
| Severity of bleeding | |
| Fatal | 0.77 (0.69-0.85) |
| Major (fatal+non-fatal) | 0.69 (0.64-0.73) |
| Non-major | 0.50 (0.44-0.56) |
| | |
| Site of bleeding* | |
| Intracranial | 0.65 (0.58-0.72) |
| Upper GI | 0.70 (0.64-0.75) |
| Lower GI | 0.51 (0.40-0.62) |
| Epistaxis | 0.43 (0.30-0.55) |
| Genitourinary | 0.53 (0.40-0.67) |
| Other | 0.53 (0.38-0.67) |

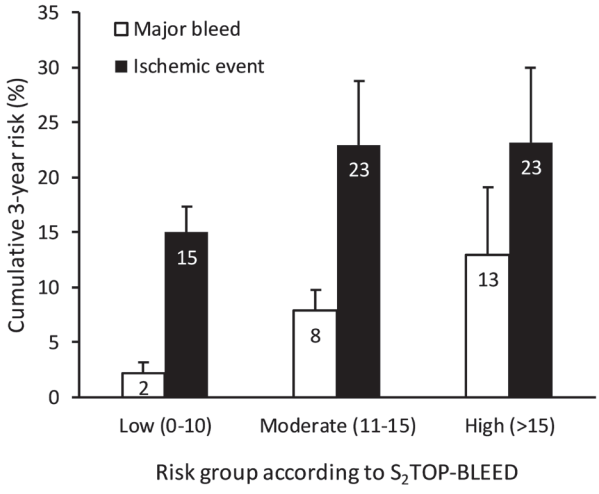
CI confidence interval; GI gastro-intestinal
* Analyses according to site of bleeding include both non-major and major bleeds. Regression equation included as continuous variable.

**Figure 2. Calibration plots: three year major bleeding free survival (A) and calibration across risk groups (B)**




Correspondence between observed and predicted three-year major bleeding free survival across quintile groups (A). Observed risk (solid line) and predicted risk (dotted line) across pre-defined risk groups of the $S_2$TOP-BLEED score (B).

**Figure 3. Cumulative 3-year risk of recurrent ischaemic events and major bleeding events across risk groups of the S2TOP-BLEED score**




Observed three-year risk of major bleeds and recurrent ischaemic events across pre-defined risk groups of the S2TOP-BLEED score

## DISCUSSION

We externally validated the $S_2$TOP-BLEED score for major bleeding in patients with a TIA or ischaemic stroke in a population-based cohort and found modest discriminatory performance and calibration. Compared with the REACH and Intracranial-$B_2$LEED$_3$S scores, the $S_2$TOP-BLEED score showed best performance, both for prediction of intracranial and major bleeds. Although high bleeding risks were also associated with high risks of recurrent ischaemic events, risk stratification may still be useful to identify a group of patients at particularly high risk of bleeding, in whom preventive measures are indicated.

Discriminatory performance of the $S_2$TOP-BLEED score slightly improved compared with the original development study (c-statistic 0.69; 95% CI 0.64-0.73 versus 0.63; 95% CI 0.61-0.64). This is likely explained by the fact that the validation cohort is more heterogeneous than the development cohort, as patients were not selected on the basis of strict in- and exclusion criteria. In general, external validation studies tend to show a drop in performance of models, often due to overfitting of risk scores in the development data.[15,25] The observation that performance is maintained in a broader setting underlines the robustness of the model and confirms its generalisability to a wide range of stroke patients. Also, performance of the model is maintained after excluding patients with an established high bleeding risk or reduced life expectancy, showing that the model can help to stratify patients in the group with most uncertainty about the risk of bleeding. Of note, the $S_2$TOP-BLEED score performed particularly well for prediction of major and fatal bleeds, which are of clinical importance and may substantially offset the benefit of antiplatelet drugs.

The REACH score systematically underestimated risk of bleeding, which is likely due to the fact that the model was derived from patients with or at risk of atherothrombosis. It has been shown previously that patients with symptomatic vascular disease have higher risks of bleeding than patients with risk factors only.[26] The slightly lower discriminatory performance of REACH compared with $S_2$TOP-BLEED can partly be explained by differences in the representation of age in both models, as shown by differences in c-statistics for models containing age only. In the REACH score, the weights assigned to age groups imply a linear association between age and bleeding, while the risk of bleeding tends to increase more rapidly at older ages.[5] Also, the very elderly patients were not represented separately in the REACH score (the highest category was >75 years), while nearly half of all patients with a TIA or stroke are over 75 years of age.[5] Although age was the most important factor in predicting risk of bleeding, other variables in the $S_2$TOP-BLEED score do have a relevant contribution to risk prediction, as is shown in supplementary figure 2; younger patients with multiple risk factors may have higher predicted risk of bleeding than patients in older age groups without additional risk factors.

Although the c-statistic improved slightly compared with the development cohort, values below 0.7 are still considered moderately discriminative. However, similar c-statistics are seen for bleeding risk scores in other domains, such as for the HAS-BLED and ORBIT scores in atrial fibrillation.[27,28] Furthermore, calibration of a risk score is as important as its

discrimination, or may be considered even more important in the current setting, where risk of bleeding has to be weighed against the risk of recurrent ischaemic events. We showed that long-term predicted risks accurately corresponded with observed risks. The fact that the model showed good calibration in the validation cohort despite differences in baseline risk and case-mix indicates that variables in the model accounted for most of the differences between the two cohorts.

As shown previously, high bleeding risks are associated with high risks of recurrent ischaemic events.[29] As such, high estimated bleeding risks cannot easily guide treatment decisions of antiplatelet therapy and should always be accompanied by the assessment of ischaemic event risk. However, our results do show that risk of ischaemic events stabilizes while risk of bleeding increases in patients in medium and high risk groups of the $S_2$TOP-BLEED score. Risk stratification may therefore be useful to identify patients in the high risk group, in whom caution seems warranted before starting aggressive dual antiplatelet therapy. Also, estimation of bleeding risk may help to identify patients in whom gastro-protective agents might be indicated. Trials have shown that proton pomp inhibitors (PPI) effectively reduce the risk of upper GI bleeding by 70-90%,[30] but in clinical practice PPIs are not routinely prescribed, possibly due to concerns over side effects associated with long term use.[31,32] A recent study has shown that the numbers needed to treat (NNT) to prevent one upper-GI bleed in patients on aspirin are reasonable, particularly in elderly patients (NNT 23 to prevent one upper GI bleed over 5 years in patients aged 75 years and older).[5] Co-prescription of PPIs may be an effective intervention to lower the risk of GI bleeds, but safety of long-term PPI treatment has not been established in a randomised trial yet. Furthermore, high predicted bleeding risks may trigger physicians to treat and monitor hypertension more closely, aiming to reduce risk of intracerebral haemorrhages.[33]

Strengths of our study include the population-based nature of the study, the thorough ascertainment of bleeding events through multiple overlapping sources and the long-term follow-up. However, there are also some limitations. Not all variables included in the risk scores were available in the validation cohort, but suitable proxies could be found for most variables. Furthermore, the number of bleeds in the validation cohort was moderate, particularly for the assessment of performance according to site and severity. Last, a small proportion of patients were excluded as they were not prescribed antiplatelet drugs due to recent bleeding or intolerance. However, this reflects clinical practice.

In conclusion, the current study shows that the $S_2$TOP-BLEED score can be used to estimate the risk of major bleeding in patients with a TIA or ischaemic stroke on antiplatelet drugs. Although the risk of recurrent ischaemic events will outweigh the risk of bleeding in the majority of patients, the risk score identifies patients at particularly high risk of bleeding in whom preventive measures should be taken. Future studies may focus on refinement of the $S_2$TOP-BLEED score for major bleeding by including results from laboratory tests, such as renal failure and anaemia, or radiological characteristics such as microbleeds. Also, a more thorough assessment of the balance between benefits and risks of long-term antiplatelet drugs is required, incorporating risk estimates on risk of recurrent ischaemic events as well as risk of bleeding.

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## SUPPLEMENT

**Supplementary table 1. Characteristics of development cohort (CAT) and validation cohort (OXVASC)**

| | CAT | OXVASC |
|---|---|---|
| **Source** | Trials: CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, PRoFESS | Population-based cohort |
| **Inclusion criteria** | TIA or noncardioembolic ischaemic stroke | TIA or ischaemic stroke |
| **Inclusion period** | 1989-2006 | 2002-2012 |
| **Sample size** | 43,112 | 2,072 |
| **Region** | North-America, South-America, Europe, Asia, Australia, South-Africa | Oxfordshire, UK |
| **Outcome** | Trial specific definitions of major bleeding | CURE criteria for bleeding |
| **Follow-up, years (median, range)** | 2.0 (0-8.1) | 3.5 (0-10.9) |
| **No of major bleeds** | 1,530 | 117 |

**Supplementary table 2. Score chart of $S_2$TOP-BLEED score for major bleeding[1]**

| Factor | Points |
|---|---|
| Male **S**ex | 2 |
| **S**moking | 1 |
| **T**ype of antiplatelet agent | |
| Clopidogrel | 0 |
| Aspirin (+/- Dipyridamole) | 1 |
| Aspirin-Clopidogrel | 5 |
| **O**utcome on mRS ≥3 | 2 |
| **P**rior stroke | 1 |
| **B**lood pressure (hypertension) | 1 |
| **L**ow BMI | |
| <20 | 2 |
| 20-25 | 1 |
| >25 | 0 |
| **E**lderly | |
| 45-54 | 2 |
| 55-64 | 4 |
| 65-74 | 6 |
| 75-84 | 9 |
| ≥85 | 12 |
| Asian **E**thnicity | 1 |
| **D**iabetes | 1 |

mRS, modified Rankin Scale

**Supplementary table 3. Overview of REACH, Intracranial-$B_2LEED_3S$ and $S_2TOP$-BLEED scores**

| Risk score | Study population | Development cohort | Number of bleeds /N | Outcome | Prediction horizon | Included items | Performance in development cohort |
|---|---|---|---|---|---|---|---|
| **REACH**[2] | Patients with or at risk of atherothrombosis | REACH registry | 804/ 56,616 | Major bleeding | 2 year | Age<br>Smoking<br>Hypertension<br>Diabetes<br>Hypercholesterolemia<br>Peripheral arterial disease<br>Heart failure<br>Antiplatelet agents<br>Oral anticoagulants | 0.68 |
| **Intracranial $B_2LEED_3S$**[3] | Patients with TIA or noncardioembolic ischaemic stroke | PERFORM trial | 263/ 19,100 | Intracranial bleeding | 2 year | Age<br>Sex<br>BMI<br>Asian ethnicity<br>Hypertension<br>Cardiovascular disease<br>Cerebrovascular disease<br>Lacune/small vessel disease<br>Dual antiplatelet or oral anticoagulants | 0.64 (0.61-0.67) |
| **$S_2TOP$-BLEED**[1] | Patients with TIA or noncardioembolic ischaemic stroke | CAPRIE, ESPS 2, MATCH, CHARISMA, ESPRIT, PRoFESS trials | 1530/ 43,112 | Major bleeding | 3 year | Age<br>Sex<br>BMI<br>Asian ethnicity<br>Smoking<br>Hypertension<br>Diabetes<br>Stroke<br>mRS score<br>Antiplatelet agents | 0.63 (0.61-0.64) |

mRS modified Rankin Scale

**Supplementary table 4. Site and severity of bleeding in OXVASC**

| | Severity of bleeding | | | | |
|---|---|---|---|---|---|
| | **Non-major, N** | **Major, N** | **Life-threatening, N** | **Fatal, N** | **Total, N (%)** |
| Intracranial | 0 | 0 | 17 | 19 | **36 (14%)** |
| Upper GI | 35 | 16 | 20 | 10 | **81 (32%)** |
| Lower GI | 26 | 6 | 4 | 1 | **37 (15%)** |
| Unknown GI | 5 | 3 | 4 | 1 | **13 (5%)** |
| Epistaxis | 29 | 1 | 1 | 0 | **31 (12%)** |
| Genitourinary | 29 | 4 | 2 | 0 | **35 (14%)** |
| Other | 13 | 4 | 4 | 0 | **21 (8%)** |
| **Total** | **137 (54)** | **34 (13)** | **52 (20)** | **31 (12)** | **254 (100%)** |

GI gastro-intestinal

**Supplementary table 5. Comparison of $S_2$TOP-BLEED, REACH and Intracranial-$B_2$LEED$_3$S scores**

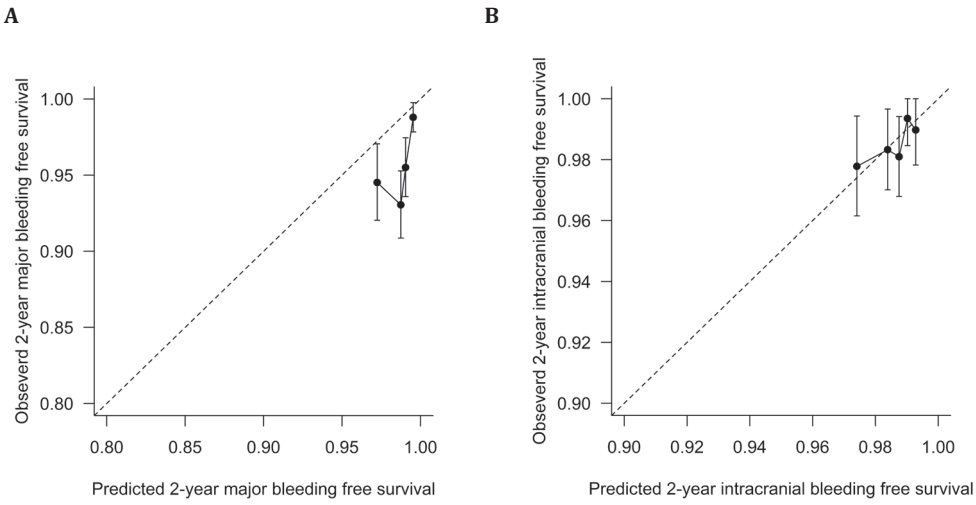
| | Major bleeding | | | Intracranial bleeding | | |
|---|---|---|---|---|---|---|
| | **C-statistic (95% CI)** | **NRI** | **IDI** | **C-statistic (95% CI)** | **NRI** | **IDI** |
| $S_2$TOP-BLEED | 0.69 (0.64-0.73) | 0.27 | 0.006 | 0.65 (0.58-0.72) | 0.39 | 0.0004 |
| REACH | 0.63 (0.58-0.69) | Ref | Ref | - | - | - |
| Intracranial $B_2$LEED$_2$S | - | - | - | 0.60 (0.51-0.70) | Ref | Ref |

CI: confidence interval; NRI: net reclassification improvement; IDI: integrated discrimination improvement; Ref: reference

**Supplementary table 6. Representation of age in $S_2$TOP-BLEED and REACH scores and their performance**

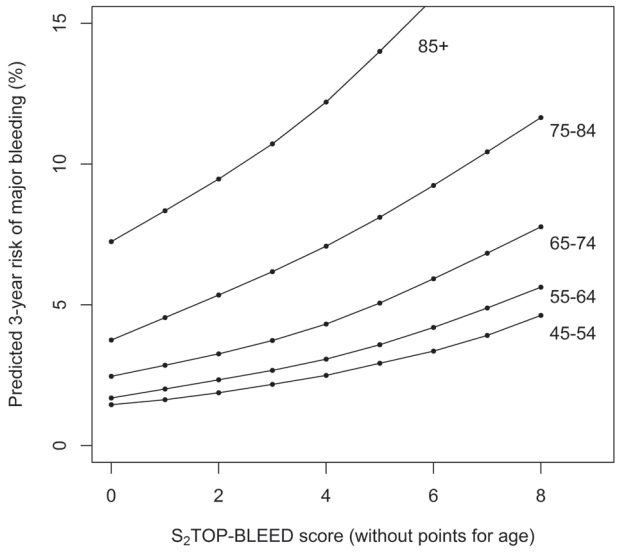
| **Risk score** | **Age groups** | **Points** | **C-statistic – age only** | **C-statistic – overall** |
|---|---|---|---|---|
| **$S_2$TOP-BLEED** | | | 0.66 (0.62-0.71) | 0.69 (0.64-0.73) |
| | 45-54 | 2 | | |
| | 55-64 | 4 | | |
| | 65-74 | 6 | | |
| | 75-84 | 9 | | |
| | ≥85 | 12 | | |
| **REACH** | | | 0.64 (0.60-0.69) | 0.63 (0.58-0.69) |
| | 45-54 | 0 | | |
| | 55-64 | 2 | | |
| | 65-74 | 4 | | |
| | ≥75 | 6 | | |

**Supplementary figure 1. Calibration of REACH score and Intracranial $B_2LEED_3S$ score**




Calibration of REACH score for two-year risk of major bleeding in OXVASC (A) and calibration of Intracranial-$B_2LEED_3S$ score for two-year risk of intracranial haemorrhage in OXVASC (B)

**Supplementary figure 2. Predicted three-year risk of major bleeding according to the S2TOP-BLEED score per age group**



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# CHAPTER 5

## REFINING PREDICTION OF MAJOR BLEEDING ON ANTIPLATELET TREATMENT AFTER NONCARDIOEMBOLIC STROKE OR TIA IN A POPULATION-BASED STUDY

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*Submitted*

## ABSTRACT

**Objective** To refine prediction of major bleeding on antiplatelet treatment after a TIA or stroke by assessing the added value of new predictors to the existing $S_2$TOP-BLEED score.

**Methods** We used Cox regression analysis to study the association between candidate predictors and major bleeding among 2,072 patients with a TIA or ischaemic stroke included in a population-based study (Oxford Vascular Study - OXVASC). An updated model was proposed and validated in 1,094 patients with a myocardial infarction included in OXVASC. Models were compared with c-statistics, calibration plots, net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

**Results** Independent predictors for major bleeding on top of $S_2$TOP-BLEED variables were peptic ulcer (HR 1.72; 95% CI 1.04-2.86), cancer (HR 2.40; 1.57-3.68), anaemia (HR 1.55; 0.99-2.44) and renal failure (HR 2.20; 1.13-4.28). Addition of those variables to the $S_2$TOP-BLEED score improved discriminatory performance from 0.69 (0.64-0.73) to 0.73 (0.69-0.78) in the TIA/stroke cohort (p=0.01). Performance improved particularly for upper gastro-intestinal bleeds (0.70; 0.64-0.75 to 0.77; 0.72-0.82). Three-year risk of major bleeding ranged from 0.6 to 14% across quartiles of predicted risk with the new model, compared with 0.8 to 11.6% according to the original score. Net reclassification improved over the entire range of the score (NRI 0.56; 0.36-0.76). In the validation cohort, discriminatory performance improved from 0.68 (0.62-0.74) to 0.70 (0.64-0.76).

**Conclusion** Peptic ulcer, cancer, anaemia and renal failure improve predictive performance of the $S_2$TOP-BLEED score for major bleeding after stroke. Future external validation studies will be required to confirm the value of the $S_2$TOP-BLEED+ score in TIA/stroke patients.

## INTRODUCTION

Treatment with antiplatelet drugs is indicated following a TIA or noncardioembolic ischaemic stroke.[1] Bleeding is the main safety concern of treatment with antiplatelet drugs, with an average one year risk of 1.0-1.5%.[2,3] This risk is not uniform and influenced by patient characteristics, including age, presence of comorbidities and type of treatment.[3]

Clinical prediction scores, such as the $S_2$TOP-BLEED score, have been developed to improve risk stratification for major bleeding and are mainly based on patient characteristics.[4] Performance of currently available scores is modest, with c-statistics generally below 0.70.[4-6] Discriminatory ability might be improved by extending models with other known risk factors for bleeding. Presence of a peptic ulcer is a frequent cause of upper gastro-intestinal (GI) bleeding and increases risk approximately three-fold.[7,8] Also, cancer has been associated with risk of bleeding, which is further enhanced by antithrombotic treatment.[9,10] Furthermore, several laboratory characteristics have been associated with an increased risk of major bleeding, including renal failure, liver failure and anaemia.[11-13]

The $S_2$TOP-BLEED score was derived from individual patient data from trials studying antiplatelet treatment after a TIA or stroke.[4] As patients with the highest risk of bleeding are often excluded from trials studying antiplatelet therapy, the predictive value of factors that served as exclusion criteria could not be assessed in the development of the score. We aimed to investigate whether we can refine prediction of major bleeding on antiplatelet treatment after a TIA or ischaemic stroke by extending the previously developed $S_2$TOP-BLEED score ($S_2$TOP-BLEED+) in a population-based cohort of patients without exclusions.



## METHODS

### Study population

We studied patients with a TIA, ischaemic stroke or myocardial infarction (MI) on antiplatelet treatment, included in the Oxford Vascular Study (OXVASC) between 2002 and 2012. OXVASC is an ongoing population based cohort study of all acute vascular events in a population of 92,728 individuals registered with 100 general practitioners in 9 general practices in Oxfordshire, UK.[14] Overlapping methods of hot and cold pursuit are used to identify all vascular events in the study population. During an initial visit information on baseline characteristics and risk factors was collected. Patients were followed-up at 30 days, 6 months, 1 year, 5 and 10 years by a study nurse or physician.

At each follow-up visit recurrent ischaemic events and bleeding events that required medical attention were recorded. Bleeding events were also identified by daily searches of all hospital admissions, by review of administrative diagnostic codes from hospital and primary care records, and by searches of blood transfusion records. Only bleeds that

required medical attention or were fatal prior to medical attention were included. Bleeds secondary to trauma, surgery, or haematological malignancy were excluded. The severity of bleeds was classified according to the CURE criteria.[15] Major bleeds were bleeds that were substantially disabling with persistent sequelae, intraocular bleeds leading to significant loss of vision, or bleeds requiring transfusion of two or more units of blood. Bleeding events that required medical attention but did not fulfil the criteria of major bleeding were recorded as significant non-major bleeds.

Candidate predictors that could potentially improve prediction of bleeding were selected based on the literature. Their inclusion was dependent on availability in OXVASC. Predictors of interest that could be studied were history of peptic ulcer, history of cancer, renal failure (defined as eGFR <30ml/min/1.73m2 according to the MDRD equation), liver failure and anaemia (haemoglobin <12g/dL (7.5 mmol/L) for women and <13g/dL (8.1 mmol/L) for men).

**Standard protocol approvals, registrations, and patient consents**

OXVASC has been approved by the local ethics committee. Patients gave written informed consent or assent was obtained from relatives for patients who were unable to provide consent.

**Statistical analysis**

Data on BMI were missing for 403 patients (13%) in both cohorts combined, for these patients the mean BMI was imputed. Twenty-two patients (0.7%) had missing values on variables other than BMI, these patients were excluded from the analyses. We performed Cox regression analysis to study the association between candidate predictors and major bleeding, while including the linear predictor of the original $S_2$TOP-BLEED score as variable in the model. This method for model updating is referred to as recalibration plus extension.[16] It has shown to provide well calibrated results for new patients and is recommended when the dataset for updating is relatively small compared with the development cohort[16] (for the current study: 2,072 patients in the update cohort versus 43,112 patients in the derivation cohort), as it limits the number of coefficients that is re-estimated. We constructed a Cox regression model containing all candidate predictors and applied least absolute shrinkage and selection operator (lasso) regression with repeated cross validation to select the optimal model.[17,18] Compared with traditional stepwise selection, lasso is less likely to produce over-fitted models, particularly when the number of events per variable is small.[19] The baseline hazard and mean linear predictor were re-estimated after addition of new predictors.

We calculated three-year risk of major bleeding according to both the original and the updated model and classified patients into risk categories of low (<5%), intermediate (5-10%) and high risk (>10%). We assigned weights to the additional variables by dividing the regression coefficients by the smallest coefficient of the original model and rounded them to the nearest integer.

Performance of the proposed updated model was assessed with discrimination, calibration and reclassification measures. Discrimination reflects the ability of the model to distinguish between someone with and without a major bleed and was assessed with the c-statistic. The c-statistic was calculated separately for upper GI bleeding, the most frequent type of antiplatelet related bleeding, which may partly be prevented by treatment with gastro-protective drugs. Calibration addresses the correspondence between the observed and predicted risk of major bleeding and was investigated with calibration plots. We calculated the net reclassification improvement (NRI) to assess change in risk stratification with the updated model.[20] The NRI quantifies the percentage of correct movement across risk categories for patients with and without a major bleed. Correct movement is defined as upward classification for patients with an event, and downward classification for patients without an event. Net reclassification was assessed while taking survival time into account.[21] Last, we assessed the improvement without applying risk categories, by means of the continuous NRI and the integrated discrimination improvement (IDI).[20] Confidence intervals were obtained with bootstrapping.

We examined the robustness of the updated model by validating the model in MI patients included in OXVASC. We applied the coefficients of the model as determined in the TIA/stroke cohort and calculated the three-year risk of major bleeding for each patient. All patients were assigned zero points for the modified Rankin Scale variable. Again, discrimination, calibration and reclassification were assessed. All analyses were performed with R version 3.3.2. Results are reported in accordance with the TRIPOD statement.[22]



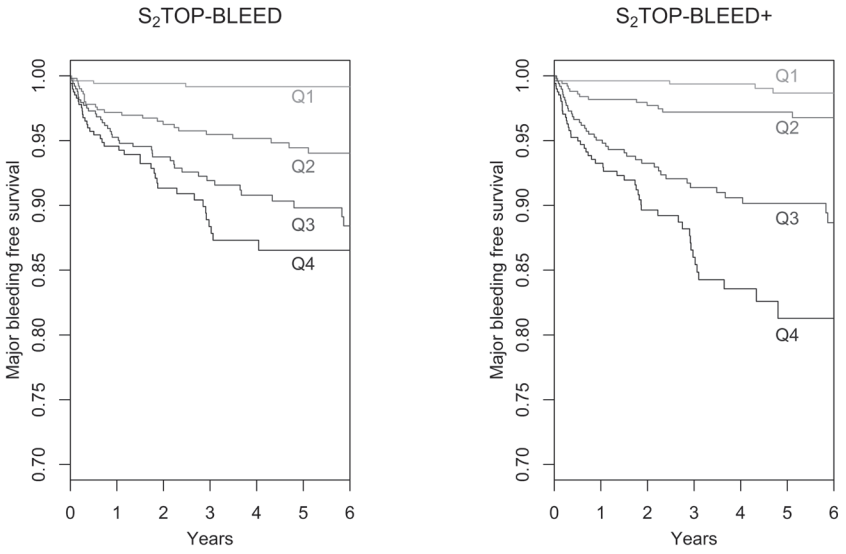
## RESULTS

Between 2002 and 2012, 2,072 patients with a TIA or ischaemic stroke on antiplatelet treatment were included in OXVASC. During 8,302 person-years of follow-up, 117 patients experienced a major bleed. Three-year risk of major bleeding was 5.7%. The validation cohort consisted of 1,094 patients with an MI included in OXVASC during the same period, of whom 70 had had a major bleed (three-year risk 7.1%; supplementary figure 1). Baseline characteristics of patients are presented in supplementary table 1.

Among patients with a TIA or ischaemic stroke we identified history of cancer, peptic ulcer, anaemia and renal failure as independent predictors for major bleeding on top of the $S_2$TOP-BLEED risk factors (Table 1). Addition of those variables to the original $S_2$TOP-BLEED score led to an increment in c-statistic from 0.69 (0.64-0.73) to 0.73 (0.69-0.78), p=0.01 (Table 2, for regression equation see supplementary table 2). Liver failure was initially selected as predictor in the model, but we decided to exclude it given the very low prevalence (1%) and wide confidence intervals. Three-year predicted risk of major bleeding based on the updated score was in close agreement with the observed risk of major bleeding as estimated with Kaplan-Meier (supplementary figure 2). The discriminatory performance

for upper GI bleeds improved from 0.70 (0.64-0.75) to 0.77 (0.72-0.82) with $S_2$TOP-BLEED+. Table 3 shows the distribution of patients with and without events among risk categories based on the original and updated $S_2$TOP-BLEED scores. 66% of patients remained in the same risk category. With the updated model 4.1% of patients with a major bleed (event NRI) and 4.7% of patients without a major bleed (non-event NRI) were correctly reclassified, leading to an overall NRI of 0.088 (-0.04 to 0.22) (Table 2, Table 3). Over the entire range of predicted risks the $S_2$TOP-BLEED+ score improved reclassification (continuous NRI 0.56; 0.36-0.76, Table 2), mainly driven by correct downward classification of non-events (38%) and a smaller improvement in classification of events (18%) (supplementary table 3). When patients were divided in quartiles according to their predicted risk, the observed 3-year risk of major bleeding ranged from 0.6 to 14.0%, as compared with 0.8 to 11.6% according to the original model (Figure 1).

**Figure 1. Observed risk of major bleeding across quartiles of predicted risk according to $S_2$TOP-BLEED and $S_2$TOP-BLEED+ scores**




Q quartile

**Table 1. Hazard ratios of candidate predictors for major bleeding, in presence of original $S_2$TOP-BLEED variables**

| | Multivariable HR (95% CI)* | Beta coefficients estimated with lasso |
|---|---|---|
| Cancer | 2.40 (1.57-3.68) | 0.847 |
| Peptic ulcer | 1.72 (1.04-2.86) | 0.511 |
| Anaemia | 1.55 (0.99-2.44) | 0.429 |
| Renal failure | 2.20 (1.13-4.28) | 0.766 |
| Liver failure | 1.62 (0.40-6.61) | - |

HR hazard ratio; CI confidence interval
*Adjusted for original $S_2$TOP-BLEED variables (age, male sex, Asian ethnicity, body mass index, smoking, modified Rankin Scale score ≥3, hypertension, diabetes, prior stroke, type of antiplatelet treatment)



**Table 2. Performance of $S_2$TOP-BLEED and $S_2$TOP-BLEED+ scores in TIA/stroke and MI cohorts**

| | C-statistic (95% CI) | Continuous NRI (95% CI) | Categorical NRI (95% CI) | IDI (95% CI) |
|---|---|---|---|---|
| **TIA/Stroke cohort** | | | | |
| $S_2$TOP-BLEED | 0.69 (0.64-0.73) | Ref | Ref | Ref |
| $S_2$TOP-BLEED+ | 0.73 (0.69-0.78) | 0.56 (0.36-0.76) | 0.088 (-0.04-0.22) | 0.019 (0.007-0.03) |
| **MI cohort** | | | | |
| $S_2$TOP-BLEED | 0.68 (0.62-0.74) | Ref | Ref | Ref |
| $S_2$TOP-BLEED+ | 0.70 (0.64-0.76) | 0.49 (0.21-0.78) | 0.139 (-0.03-0.31) | 0.011 (-0.005-0.028) |

MI myocardial infarction; CI confidence interval; NRI net reclassification index; IDI integrated discrimination index; Ref reference

Based on the regression coefficients we assigned points to anaemia (3 points), peptic ulcer (4 points), cancer (6 points) and renal failure (6 points). An updated score chart is presented in Table 4, with predicted risks displayed in Figure 2.

The $S_2$TOP-BLEED+ score as proposed in the TIA/stroke cohort had a c-statistic of 0.70 (0.64-0.76) in the MI cohort, compared with 0.68 (0.62-0.74) for the original $S_2$TOP-BLEED score (p=0.39), Table 2. Calibration was slightly better for the updated model than for the original $S_2$TOP-BLEED score, although both models underestimated risk of major bleeding (supplementary figure 3).

**Table 3: Reclassification tables in TIA/stroke cohort**

**A. Events**

| | | $S_2$TOP-BLEED+ | | | |
|---|---|---|---|---|---|
| | | <5% | 5-10% | ≥10% | |
| $S_2$TOP-BLEED | <5% | 14.6 | 4.4 | 5.2 | |
| | 5-10% | 8.9 | 29.1 | 20.8 | |
| | ≥10% | 0 | 16.3 | 37.6 | |
| | | 23.3 | 48.3 | 58.9 | 130.5 |

**B. Non events**

| | | $S_2$TOP-BLEED+ | | | |
|---|---|---|---|---|---|
| | | <5% | 5-10% | ≥10% | |
| $S_2$TOP-BLEED | <5% | 809.4 | 54.6 | 43.8 | |
| | 5-10% | 265.1 | 282.9 | 182.2 | |
| | ≥10% | 0 | 106.7 | 185.4 | |
| | | 1074.7 | 445.7 | 416.1 | 1936.5 |

**C. KM estimate at 3 y**

| | | $S_2$TOP-BLEED+ | | |
|---|---|---|---|---|
| | | <5% | 5-10% | ≥10% |
| $S_2$TOP-BLEED | <5% | 1.8 | 7.5 | 10.6 |
| | 5-10% | 3.2 | 9.3 | 10.3 |
| | ≥10% | - | 13.2 | 16.9 |
| | | 2.1 | 9.8 | 12.4 |

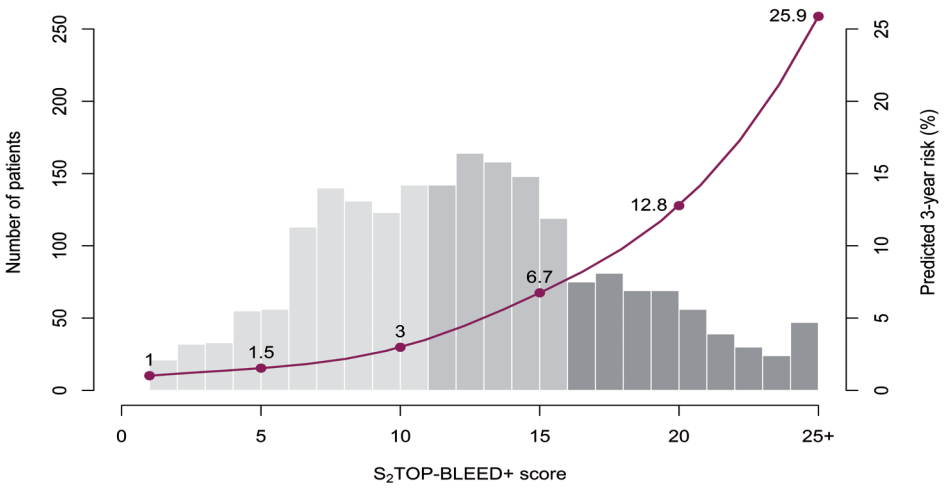
KM Kaplan-Meier
Same risk category: (14.6+29.1+37.6+809.4+282.9+185.4)/2067=66%
Event NRI: ((4.4+5.2+20.8)-(8.9+16.3))/130.5 = 0.041;
Non-event NRI: ((265.1+106.7)-(54.6+43.8+182.2))/1936.5=0.047;
Overall NRI: 0.041+0.047=0.088

**Table 4. $S_2$TOP-BLEED and $S_2$TOP-BLEED+ score**

| Risk factor | | $S_2$TOP-BLEED Points | $S_2$TOP-BLEED+ Points |
|---|---|---|---|
| **Age** | 45-54 | 2 | 2 |
| | 55-64 | 4 | 4 |
| | 65-74 | 6 | 6 |
| | 75-84 | 9 | 9 |
| | ≥85 | 12 | 12 |
| **Male sex** | | 2 | 2 |
| **Asian ethnicity** | | 1 | 1 |
| **Current smoking** | | 1 | 1 |
| **Hypertension** | | 1 | 1 |
| **Diabetes** | | 1 | 1 |
| **Prior stroke** | | 1 | 1 |
| **mRS ≥3** | | 2 | 2 |
| **BMI** | <20 | 2 | 2 |
| | 20-25 | 1 | 1 |
| **Antiplatelet treatment** | A, A+D | 1 | 1 |
| | A+C | 5 | 5 |
| **Peptic ulcer** | | NA | 4 |
| **Cancer** | | NA | 6 |
| **Anaemia** | | NA | 3 |
| **Renal failure** | | NA | 6 |

mRS modified Rankin Scale; A aspirin; A+D aspirin+dipyridamole;
A+C aspirin+clopidogrel; NA not applicable

**Figure 2. Predicted three-year risk of major bleeding (%) according to the S2TOP-BLEED+ score**




## DISCUSSION

Prediction of major bleeding can be refined by incorporating cancer, peptic ulcer, anaemia and renal failure in the existing $S_2$TOP-BLEED score for major bleeding in patients with a TIA or ischaemic stroke on antiplatelet therapy. Compared with the original score, the $S_2$TOP-BLEED+ score showed higher discriminatory ability and a larger range of predicted probabilities. A slight improvement in discrimination and calibration was also observed when the model was applied to patients with an MI on antiplatelet drugs, supporting the robustness of the model extension.

Although the associations between anaemia, renal failure, peptic ulcer, cancer and major bleeding have been established previously,[8,9,23] the $S_2$TOP-BLEED+ score is the first to incorporate these characteristics in a model for bleeding among stroke patients. Other scores like REACH[5] and Intracranial-$B_2$LEED$_3$S[6] could not investigate these factors, due to a lack of measurement in the derivation cohorts, and the likelihood that many patients with these characteristics would be excluded from trial populations and selective registries. However, studies in other areas have shown the importance of these variables in prediction of major bleeding, both in patients with atrial fibrillation[24-26] and in patients with acute coronary syndrome.[27,28] The importance of the new variables is also reflected by their relatively large weights in the $S_2$TOP-BLEED+ score.

The primary goal of updating $S_2$TOP-BLEED was to improve the discriminatory ability of the model, aiming to better separate patients with and without a major bleed.

Although the increment in c-statistic is small, previous studies have shown that the c-statistic is not very sensitive to addition of new predictors, and possible improvements are highly dependent on the strength of the baseline model.[29] Relying solely on the c-statistic for the assessment of added value of predictors is therefore not recommended, as it may lead to exclusion of risk factors that do have a relevant impact on risk stratification in clinical practice.[30] Reclassification measures such as the NRI have been proposed as alternatives to assess the incremental value of new predictors and aim to assess whether addition of new predictors actually leads to a change in clinical practice. Calculation of both traditional performance measures (c-statistic, calibration plots) and newer reclassification measures is currently recommended to assess added value of new predictors, as these measures provide complementary information.[29] Ultimately, the best way to assess robustness of a model extension is by external validation in an independent population.[31]

The absolute risk of major bleeding was higher among patients with an MI in OXVASC, particularly in the early phase. This is likely explained by a higher incidence of procedure related bleedings and more frequent prescription of dual antiplatelet treatment. As a consequence there was some underestimation of bleeding risk in the MI cohort by both models, which was more pronounced for the original score. Although validation in patients with an MI provides some insight in the robustness of the model extension, future validation studies among patients with a TIA or ischaemic stroke will be required.

Although prediction of bleeding may be slightly improved with the updated score, a trade off should be made between increasing complexity and improved performance. The updated score may be less suitable for use at the bedside, due to the larger number of predictors and complexity of the weights assigned to each factor. However, given the increasing use of electronic patient records calculations could be integrated in health records and performed automatically. Moreover, the new variables are likely to be easily available in all patients with a TIA or stroke and do not require additional imaging or biomarker assessment. An important advantage of the updated model is that it will likely provide better predictions for patients who do not fit in a clinical trial profile, but for whom decisions need to be made in clinical practice. A further advantage is the improved prediction of upper GI bleeding, which is substantially preventable by co-prescription of proton-pump inhibitor (PPI) drugs, such that the score might be used to target the use of PPI drugs or other similar interventions in high-risk patients.

Strengths of our study include the population-based nature of the cohort, thereby representing the entire range of patients with TIA or stroke on antiplatelet drugs and the validation of the updated model in a separate cohort. A limitation of our study is the relatively small number of bleeding events for model updating and subsequent validation. However, we tried to account for this by using state-of-the-art statistical methods. Another limitation is the fact that we could not validate the model in patients with a TIA or ischaemic stroke, for which the model is intended to be used.

In conclusion, we propose the $S_2$TOP-BLEED+ score as a refinement to the original $S_2$TOP-BLEED score, aiming to predict bleeding after a TIA or noncardioembolic ischaemic stroke. Addition of cancer, peptic ulcer, anaemia and renal failure improves discriminatory performance and increases the range of predicted risks. A further external validation study will be required to confirm the value of the $S_2$TOP-BLEED+ score in TIA/ischaemic stroke patients.

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## SUPPLEMENT

**Supplementary table 1. Baseline characteristics of patients with TIA/ischaemic stroke and myocardial infarction on antiplatelet treatment included in OXVASC between 2002 and 2012**

| | TIA/ischaemic stroke | MI |
|---|---|---|
| | N=2,072 | N=1,094 |
| Mean age (SD), years | 73 (13.4) | 71 (13.4) |
| Male | 1001 (48) | 716 (65) |
| Current smoking | 307 (15) | 269 (25) |
| Hypertension | 1,173 (57) | 559 (51) |
| Diabetes | 282 (14) | 191 (18) |
| Prior stroke | 227 (11) | 50 (5) |
| Prior MI | 174 (8) | 195 (18) |
| Cancer | 278 (13) | 105 (10) |
| Peptic ulcer | 173 (8) | 89 (8) |
| Anaemia | 286 (14) | 377 (34) |
| Renal failure | 90 (4) | 130 (12) |

Data are numbers (percentages), unless otherwise indicated.
MI: myocardial infarction, SD: standard deviation

**Supplementary table 2. Regression equation $S_2$TOP-BLEED and $S_2$TOP-BLEED+ scores**

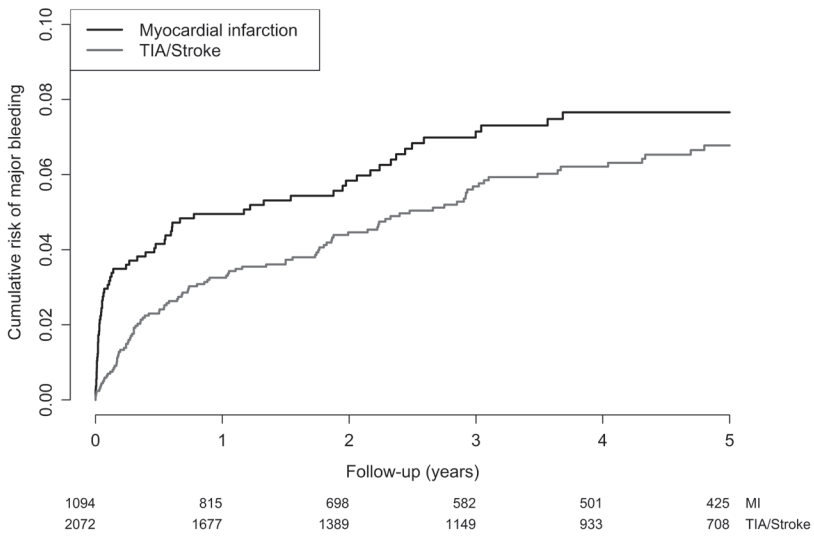
| |
|---|
| **Linear predictor $S_2$TOP-BLEED** |
| -0.05493*age + 0.00069*age$^2$ + 0.25718*Male + 0.13878*Asian ethnicity + 0.17781*current smoking + 0.25723*modified Rankin Scale ≥3 + 0.14618*Hypertension + 0.19888*Diabetes + 0.20467*Prior stroke - 0.02767*BMI † -0.16016*clopidogrel + 0.54980*aspirin+clopidogrel |
| **Regression equation $S_2$TOP-BLEED (three-year major bleeding free survival)** |
| 0.9562434 ^ exp(linear predictor $S_2$TOP-BLEED + 0.7849) |
| **Linear predictor $S_2$TOP-BLEED+** |
| 1.0*linear predictor $S_2$TOP-BLEED + 0.8469*cancer + 0.5113*peptic ulcer + 0.4290*anaemia + 0.7662 * renal failure |
| **Regression equation $S_2$TOP-BLEED+ (three-year major bleeding free survival)** |
| 0.9522705^ exp(linear predictor $S_2$TOP-BLEED+ + 0.3090 ) |

†if BMI>30, use BMI 30.

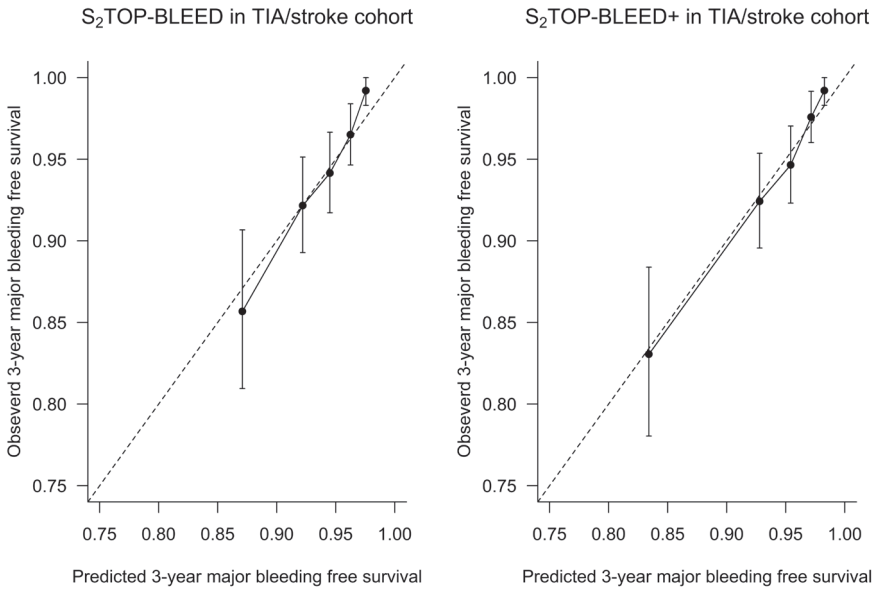
**Supplementary table 3. Continuous net reclassification index (NRI)**

| | All patients | Classified up | Classified down | | |
|---|---|---|---|---|---|
| **N** | 2067 | 671 | 1396 | | |
| **KM estimate at 3-years** | 5.70 | 10.72 | 3.64 | | |
| **Expected number of events** | 117.7 | 71.9 | 50.8 | **Event NRI** | 0.180 |
| **Expected number of non-events** | 1949.3 | 599.1 | 1345.2 | **Non-event NRI** | 0.383 |
| | | | | **NRI** | 0.56 (0.36-0.76) |

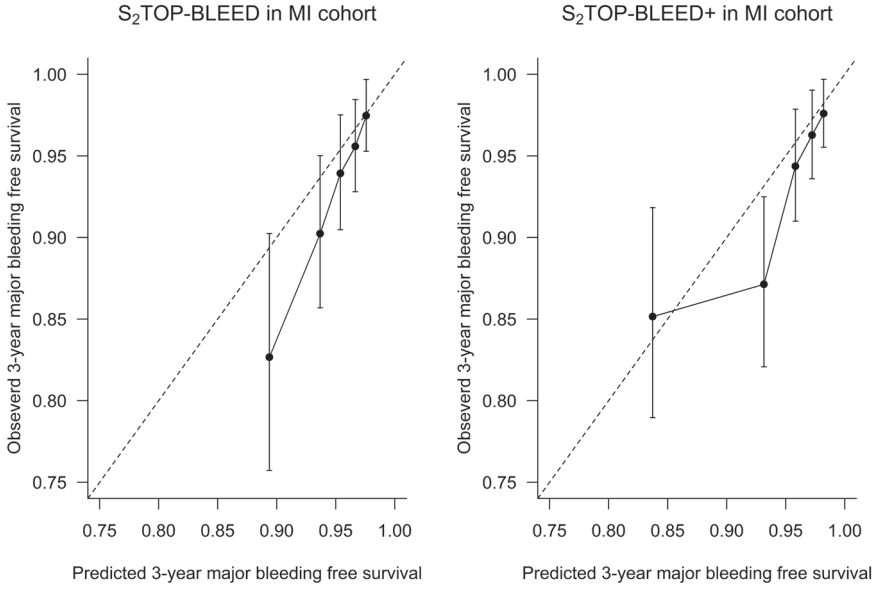
**Supplementary figure 1. Cumulative incidence of major bleeding in TIA/Stroke and myocardial infarction cohorts**



**Supplementary figure 2. Calibration plots of S2TOP-BLEED and S2TOP-BLEED+ scores in TIA/ stroke cohort**




**Supplementary figure 3. Calibration plots of S2TOP-BLEED and S2TOP-BLEED+ score in myocardial infarction (MI) cohort**



# CHAPTER 6

## EARLY TIME COURSE OF MAJOR BLEEDING ON ANTIPLATELET THERAPY AFTER A TIA OR ISCHAEMIC STROKE

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## ABSTRACT

**Objective** To study the early time course of major bleeding and its subtypes in patients with cerebral ischaemia on dual and single antiplatelet therapy.

**Methods.** We performed a post hoc analysis on individual patient data from six randomised clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT and PRoFESS), including 45,195 patients with a TIA or non-cardioembolic ischaemic stroke. We studied incidence rates of bleeding per antiplatelet regimen stratified by time from randomisation (≤30, 31-90, 91-180, 181-365, >365 days). We calculated incidence rates per trial and pooled estimates with random-effects meta-analysis. We performed Poisson regression to assess differences between time periods with adjustment for age and sex.

**Results.** The incidence of major bleeding on aspirin-clopidogrel and aspirin-dipyridamole was highest in the first 30 days: 5.8 and 4.9 per 100 person-years respectively, and was significantly higher than at 31-90 days (rate ratio (RR) 1.98; 95% confidence interval (CI) 1.16-3.40 for aspirin-clopidogrel and 1.94; 1.24-3.03 for aspirin-dipyridamole). Incidence rates on aspirin and clopidogrel monotherapy were 2.8 and 2.5 per 100 person-years respectively in the first 30 days, with no significant change over time. The time course was similar for gastro-intestinal bleeds. There was no early excess of intracranial haemorrhage in patients on either dual or single antiplatelet therapy.

**Conclusion.** Dual antiplatelet therapy is associated with high early risks of major and gastro-intestinal bleeding that decline after the first month in trial cohorts.

## INTRODUCTION

Antiplatelet drugs are widely applied in secondary prevention of cardiovascular disease. Although they successfully reduce the risk of recurrent ischaemic events,[1] antiplatelet drugs are associated with a small but relevant risk of serious bleeding,[1] which is reported to vary between 1% and 1.5% per year.[2,3] The prognosis of patients who have experienced a bleeding event is worse, with higher all-cause and cardiovascular mortality.[4] Given the wide application of antiplatelet therapy and consequences of bleeding events it is important to gain more insight in safety of antiplatelet agents.

It has been shown previously that the excess risk of major bleeding on aspirin compared with placebo falls with time in primary prevention trials, driven mainly by an excess early risk of bleeding on aspirin.[5] It is uncertain whether the time course would be the same in secondary prevention of cerebral ischaemia. In addition, it is unknown whether the time course differs for dual antiplatelet therapy, which is known to be associated with higher risks of bleeding than monotherapy.[6,7] Indeed, there is some preliminary evidence of a high early risk of bleeding on dual antiplatelet treatment after TIA and minor stroke, particularly among aspirin-naïve patients,[8] but larger studies are required. We aimed to study the time course of major bleeding events and their subtypes in patients with cerebral ischaemia on dual and single antiplatelet therapy.



## METHODS

### Study population

We analysed individual patient data from six randomised clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT and PRoFESS[6,7,9-12]) investigating the efficacy of antiplatelet agents in patients with a TIA or ischaemic stroke. Details of the individual patient data meta-analysis have been described previously.[13] In total, 48,023 patients with cerebral ischaemia were included in the trials between 1989 and 2006. Details of the included trials are presented in Table 1. Aspirin was studied in four trials (CAPRIE, ESPS-2, CHARISMA and ESPRIT), clopidogrel was studied in three (CAPRIE, MATCH and PRoFESS), aspirin in combination with (extended-release) dipyridamole was examined in three (ESPS-2, ESPRIT, PRoFESS) and aspirin in combination with clopidogrel was assessed in two (MATCH and CHARISMA). The ESPS-2 trial had four arms and randomised patients to either aspirin, aspirin plus extended-release dipyridamole, extended-release dipyridamole only or placebo. Median follow-up ranged from 1.4 to 3.5 years.

**Table 1. Overview of included trials**

| Trial, year | Recruitment period | N | Intervention | Time to randomisation, median (IQR; days) | Inclusion criteria | Mean age (SD) | Follow-up, median (range; years) |
|---|---|---|---|---|---|---|---|
| CAPRIE – stroke subgroup, 1996 | 1992-1995 | 6431 | C vs A | 34 (16-80) | IS within six months | 65 (11.1) | 2.0 (0-3.3) |
| ESPS-2, 1996 | 1989-1993 | 6602 | A+D vs A vs D vs Placebo | 22 (9-48) | TIA/IS within three months | 67 (11.1) | 2.0 (0-5.7) |
| MATCH, 2004 | 2000-2002 | 7599 | A+C vs C | 15 (8-39) | TIA/IS within three months and one additional vascular risk factor within three years. | 66 (9.9) | 1.5 (0-1.5) |
| CHARISMA – stroke subgroup, 2006 | 2002-2003 | 4320 | A+C vs A | 126 (19-510) | TIA/IS within five years; age ≥45. | 65 (9.8) | 2.1 (0-2.9) |
| ESPRIT, 2006 | 1997-2005 | 2739 | A+D vs A | 50 (21-84) | TIA/minor IS within six months | 63 (10.9) | 3.4 (0-8.1) |
| PRoFESS, 2008 | 2003-2006 | 20,332 | A+D vs C | 15 (7-39) | IS within three months; clinical and neurologic stable; age ≥55. | 66 (8.6) | 2.4 (0-4.4) |

C Clopidogrel; A Aspirin; A+D aspirin+dipyridamole; D Dipyridamole; A+C aspirin+clopidogrel; IS ischaemic stroke

We excluded patients with a possible cardioembolic origin of their stroke (those with a history of atrial fibrillation or TOAST classification cardioembolic stroke). We used trial specific definitions for major bleeding. Major bleeding events included bleedings that were fatal, intracranial, significantly disabling or required hospital admission. Intracranial bleeding events included intracerebral haemorrhages, subarachnoid haemorrhages, subdural and epidural hematomas. Haemorrhagic transformations of ischaemic strokes were not counted as intracranial haemorrhages. Gastrointestinal (GI) bleeding events included upper and lower GI bleeds that were fatal or required hospital admission.

**Statistical analysis**

We restricted our analyses to patients who were on treatment. For patients who permanently discontinued trial medication, on-treatment time was defined as time until last intake of study drugs plus 28 days. For patients who completed the trial, on-treatment time was the same as intention-to-treat time. We calculated incidence rates of bleeding per antiplatelet regimen stratified by time from randomisation (≤30 days, 31-90 days, 91-180 days, 181-365 days and >365 days). Incidence rates were calculated for each trial separately and were subsequently pooled per antiplatelet regimen with random-effects meta-analysis. We performed Poisson regression analysis to quantify the difference between time periods with adjustment for age and sex. Rate ratios were calculated per trial and subsequently pooled per antiplatelet regimen with random-effects meta-analysis. Time period 31-90 days was chosen as the reference category in all analyses. We examined the influence of age and prior antiplatelet drug use on the time course of bleeding by performing stratified analyses. Definitions of prior antiplatelet drug use varied considerably across trials; therefore, we used prior vascular disease as a proxy for long-term prior antiplatelet drug use, which we defined as a past medical history of stroke, TIA, myocardial infarction, angina or peripheral artery disease. All analyses were performed with R version 3.2.2.

**Standard protocol approvals, registrations and patients consents.**

The trials were approved by the ethics committee or institutional review board at each participating center and all patients gave written informed consent.

## RESULTS

After exclusion of patients with a possible cardioembolic stroke (n=1,829) and patients who permanently discontinued treatment but in whom date of last intake was unknown (n=999; rate of major bleeding 0.8 per 100 person-years), 45,195 patients remained for the analysis. During 82,199 person-years of follow-up, 1,338 major bleedings, 324 intracranial bleedings and 618 gastro-intestinal bleedings occurred. Baseline characteristics of patients are presented in Table 2.

**Table 2. Baseline characteristics of 45,195 patients included in the analyses**

| | n (%) |
|---|---|
| Mean age (SD), years | 65.5 (9.8) |
| Male sex | 28,595 (63) |
| Qualifying event | |
| TIA | 5013 (11) |
| Ischaemic stroke | 40,179 (89) |
| Current smoking | 10,116 (22) |
| Hypertension | 33,325 (74) |
| Diabetes | 14,579 (32) |
| Prior stroke | 7,375 (17) |
| Prior myocardial infarction | 3,341 (7) |
| Prior vascular disease | 17,909 (40) |
| Type of antiplatelet | |
| Aspirin | 8,103 (18) |
| Clopidogrel | 16,084 (36) |
| Aspirin + Dipyridamole | 12,218 (27) |
| Aspirin + Clopidogrel | 5,754 (13) |
| Dipyridamole | 1,521 (3) |
| Placebo | 1,515 (3) |

Data are numbers (percentages), unless otherwise indicated

The time course of major bleeding per antiplatelet regimen is displayed in Figure 1. The risk of major bleeding was highest during the first 30 days for all antiplatelet regimens except for dipyridamole only. The incidence rate was 2.8 per 100 person-years for aspirin, 2.5 per 100 person-years for clopidogrel, 4.9 per 100 person-years for aspirin-dipyridamole and 5.8 per 100 person-years for aspirin- clopidogrel (supplementary figure 1). Results per trial are shown in supplementary figures 2-6. In patients on dual antiplatelet therapy, the risk of major bleeding was significantly higher in the first 30 days compared with 31-90 days (rate ratio (RR) 1.98; 95% CI 1.16 to 3.40 for aspirin-clopidogrel and 1.94; 95% CI 1.24 to 3.03 for aspirin-dipyridamole, Table 3). No significant change over time was seen for single antiplatelet regimens (RR 1.27; 0.69 to 2.37 for aspirin, 1.28; 0.66 to 2.48 for clopidogrel and 0.87; 0.12 to 4.44 for dipyridamole, Table 3). The same patterns were seen for GI bleeds (Figure 2A). Risk of intracranial haemorrhage was stable over time (Figure 2B, supplementary table 1). Pooled incidence rates of gastro-intestinal and intracranial bleeding per antiplatelet regimen are presented in supplementary figures 7 and 8.

Among elderly patients (age ≥ 65 years), absolute risks of major bleeding were higher. The time course of the risk of bleeding was comparable for younger and older patients

(supplementary figure 9). 17,909 patients (40%) had a diagnosis of vascular disease prior to their presenting event. Patterns of bleeding risk over time were essentially similar for patients with and without prior vascular disease (supplementary figure 10).

**Table 3. Adjusted rate ratios with 95% CI for major bleeding**

| | 0-30 days | 31-90 days | 91-180 days | 181-365 days | >365 days |
|---|---|---|---|---|---|
| **Aspirin** | 1.27 (0.69-2.37) | 1 [ref] | 0.74 (0.40-1.34) | 0.84 (0.44-1.61) | 0.82 (0.54-1.27) |
| **Clopidogrel** | 1.28 (0.66-2.48) | 1 [ref] | 0.82 (0.55-1.21) | 0.77 (0.44-1.36) | 0.74 (0.42-1.29) |
| **Aspirin + Dipyridamole** | 1.94 (1.24-3.03) | 1 [ref] | 0.66 (0.42-1.03) | 0.62 (0.42-0.91) | 0.62 (0.44-0.87) |
| **Aspirin + Clopidogrel** | 1.98 (1.16-3.40) | 1 [ref] | 0.92 (0.39-2.18) | 0.84 (0.53-1.34) | 0.84 (0.53-1.33) |
| **Dipyridamole** | 0.87 (0.12-4.44) | 1 [ref] | 0.93 (0.25-3.76) | 0.52 (0.14-2.08) | 0.28 (0.07-1.14) |
| **Placebo** | 4.59 (0.99-32.1) | 1 [ref] | 2.16 (0.50-14.8) | 1.19 (0.27-8.10) | 0.66 (0.15-4.50) |

Ref reference. Adjusted for age and sex



**Figure 1. Time course of major bleeding per antiplatelet regimen (pooled estimates)**

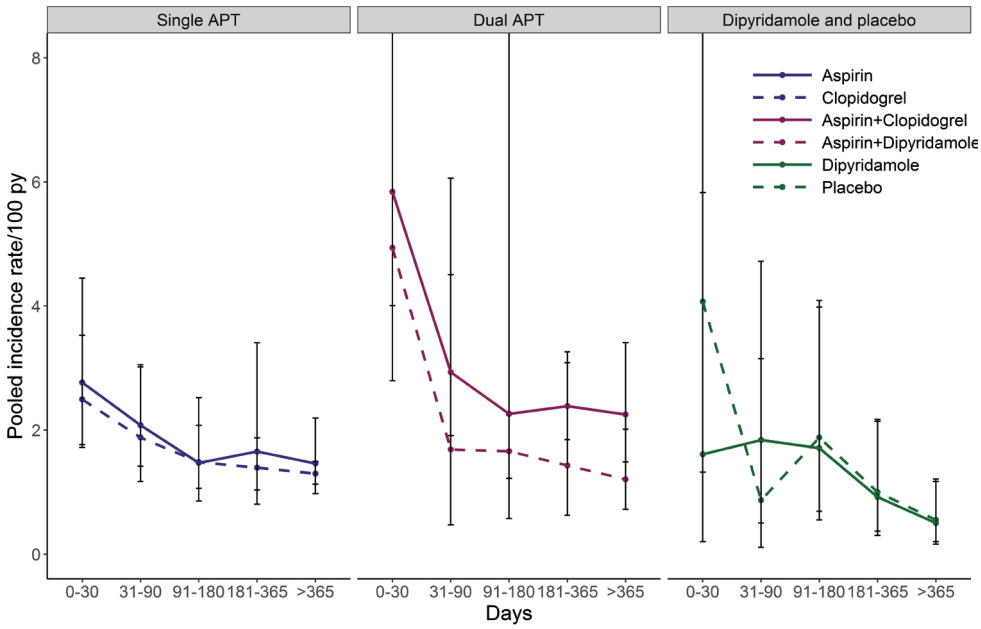
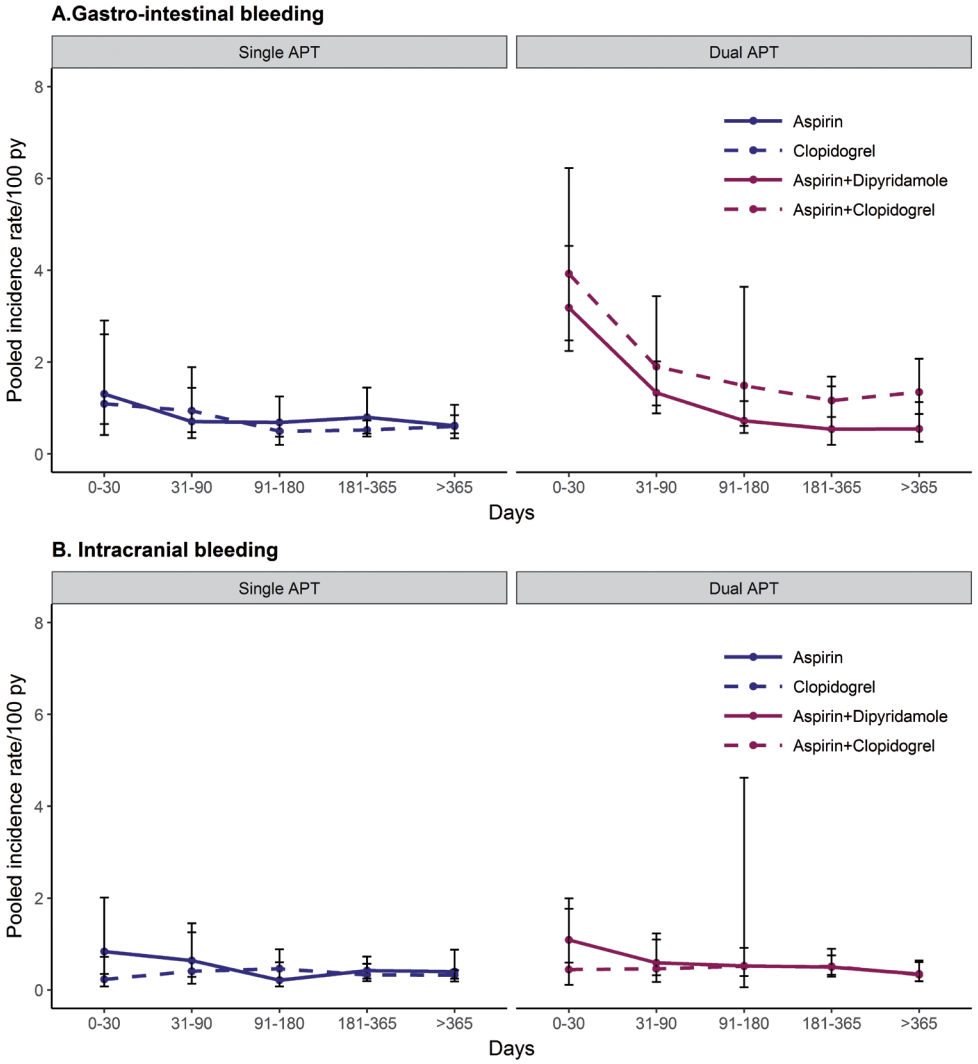


**Figure 2. Time course of gastro-intestinal bleeding (A) and intracranial bleeding (B) per antiplatelet regimen (pooled estimates)**




## DISCUSSION

Our study showed high early risks of major bleeding and more specifically gastro-intestinal bleeding on dual antiplatelet therapy, that decline over time. There was no early excess risk of intracranial haemorrhages among patients on either dual antiplatelet therapy or monotherapy.

Multiple trials have shown the increased risk of major bleeding associated with long-term dual antiplatelet therapy after stroke: MATCH, CHARISMA and SPS3 demonstrated that aspirin plus clopidogrel is associated with statistically significant higher bleeding risks than each of the regimens separately.[6,7,14] Furthermore, the PRoFESS trial showed that aspirin plus dipyridamole led to more major and intracranial bleedings than clopidogrel monotherapy.[12] Recent trials have investigated the benefit of a short course of aspirin plus clopidogrel, aiming to reduce the risk of early recurrent strokes, without exposing patients to long-term dual antiplatelet treatment. Combination therapy was shown to be more protective against ischaemic events than monotherapy, but results regarding risk of bleeding in the early phase were conflicting.[15,16] While the CHANCE trial showed similar risks of bleeding among both groups,[15] the FASTER trial showed a significantly higher risk of symptomatic and asymptomatic bleeds among patients treated with dual antiplatelet therapy.[16] The recent TARDIS trial compared short-term triple therapy (aspirin plus dipyridamole plus clopidogrel) with guideline-based therapy and found no net clinical benefit due to an excess of bleeding complications with triple antiplatelet therapy.[17]

Evidence for a time course of bleeding risk is scarce. Post hoc analyses on data from CHARISMA showed that the excess risk of bleeding on aspirin plus clopidogrel was greatest in the first year and similar to aspirin thereafter.[18,19] This is in line with our results, indicating high early risks on dual antiplatelet therapy that decline over time. Results from this study and ours suggest that some form of resistance to antiplatelet drugs occurs over time. Previous studies investigating platelet response over time have shown conflicting results. Some reported stable platelet reactivity,[20] while others showed decreased platelet inhibition after the first months of exposure to both aspirin and clopidogrel.[21-23] The mechanisms by which this reduced sensitivity over time may be caused remain unclear. Possibly, upregulation of other pathways that mediate platelet aggregation may play a role. Our findings may also suggest that patients who are prone to bleeding experience a bleed shortly after start of treatment, leaving a cohort that is at relatively lower risk. Alternatively, the high early risk may partly be explained by the natural history of bleeds as suggested by the time course in placebo treated patients. However, the number of bleeds in the placebo group was small and analyses of other data sources are required to better understand the natural history of bleeding after stroke.

High bleeding risks on aspirin plus clopidogrel have been reported previously and are a cause for concern. A post hoc analysis on data from the EXPRESS study and FASTER pilot trial showed excessive risks during the first 90 days, particularly among aspirin naïve patients.[8] Whether the risk decreased over time was not investigated. The high observed risks were partly attributed to the fact that patients were vulnerable shortly after their TIA or ischaemic stroke. However, our data show that also after the acute phase of TIA or stroke, initiation of dual antiplatelet therapy is accompanied with a doubling of risk in the first 30 days.

Our study addresses time course of gastrointestinal and intracranial bleeding separately. The finding that aggressive antiplatelet therapy has a more pronounced effect

on gastro-intestinal bleeding is plausible, as patients with inherited and acquired platelet disorders often present with mucocutaneous bleeding patterns.[24]

A strength of our study is the large sample size, with a large number of bleeding events. Also, the quality of the data was high, with regular follow-up and adjudication of events by an independent committee. Furthermore, we were able to restrict our analysis to patients who were on treatment, thereby reducing the possibility that our findings reflect poor compliance. Our study also has limitations. First, we did not have data on other antiplatelet agents such as cilostazol, terutroban or triflusal. However, the antiplatelet drugs investigated in our study are those recommended as first line agents in current guidelines.[25,26] Second, absolute risks of bleeding may have been underestimated, as patients at highest bleeding risk were excluded from the trials. It is also possible that the time course of bleeding risk might differ in older or frailer populations. Third, control of medication intake was not performed in all trials and therefore we cannot exclude that patients that were included in the on-treatment analyses in reality did not take their medication anymore. Last, we performed a post hoc analysis on trial data, and although adjustment for age and sex did not change the results, the possibility of residual confounding remains.

The risk of major bleeding and more specifically gastrointestinal bleeding is increased two-fold in the first month on dual antiplatelet treatment. The risk of intracranial haemorrhage is stable over time. Although the risk of early recurrent ischaemic events will likely outweigh the risk of bleeding, our findings draw attention to the high early risks of bleeding associated with dual antiplatelet therapy, which may have previously been underestimated. The high early risks may warrant initiation of gastro-protective agents in patients on dual antiplatelet therapy, as well as close monitoring of patients in the early phase.

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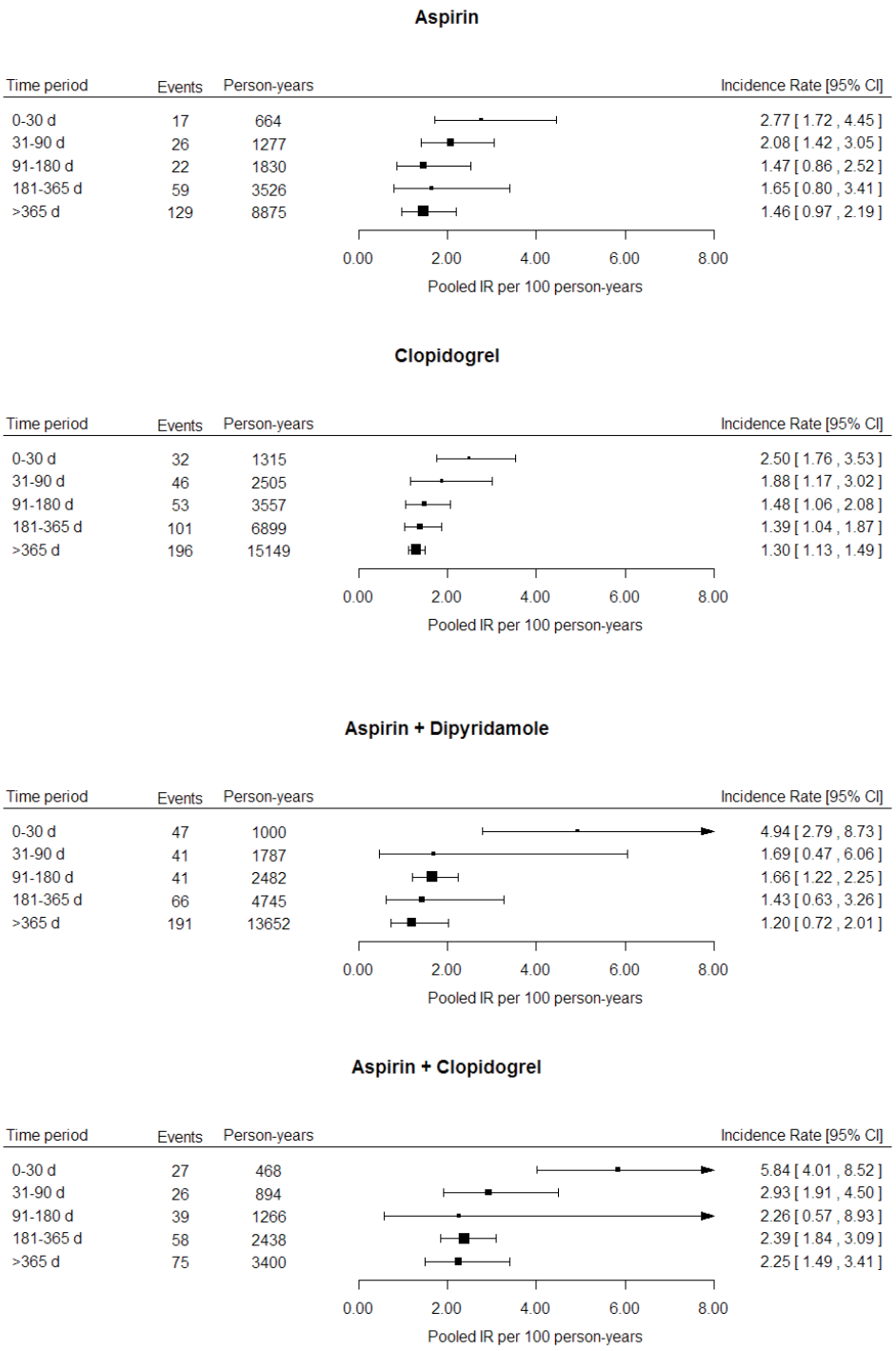
## SUPPLEMENT

**Supplementary table 1. Rate ratio with 95% confidence interval for intracranial bleeding**

| | 0-30 days | 31-90 days | 91-180 days | 181-365 days | >365 days |
|---|---|---|---|---|---|
| **Aspirin** | 1.27 (0.33-4.47) | 1 [ref] | 0.35 (0.07-1.33) | 0.75 (0.29-2.16) | 1.05 (0.46-2.65) |
| **Clopidogrel** | 0.47 (0.71-1.89) | 1 [ref] | 1.33 (0.58-3.29) | 1.03 (0.48-2.47) | 1.02 (0.51-2.34) |
| **Aspirin-dipyridamole** | 2.00 (0.80-5.02) | 1 [ref] | 0.96 (0.41-2.35) | 0.90 (0.43-2.06) | 0.88 (0.46-1.89) |
| **Aspirin-clopidogrel** | 0.96 (0.18-5.22) | 1 [ref] | 1.59 (0.52-5.85) | 1.13 (0.39-4.05) | 0.81 (0.28-2.96) |

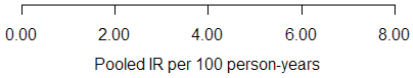
Ref reference. Adjusted for age and sex

**Supplementary figure 1. Incidence rates of major bleeding per antiplatelet regimen (pooled estimates)**



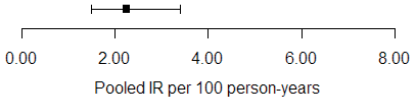
**Aspirin + Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 47 | 1000 | 4.94 [ 2.79 , 8.73 ] |
| 31-90 d | 41 | 1787 | 1.69 [ 0.47 , 6.06 ] |
| 91-180 d | 41 | 2482 | 1.66 [ 1.22 , 2.25 ] |
| 181-365 d | 66 | 4745 | 1.43 [ 0.63 , 3.26 ] |
| >365 d | 191 | 13652 | 1.20 [ 0.72 , 2.01 ] |



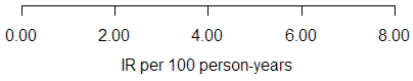

**Aspirin + Clopidogrel**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 27 | 468 | 5.84 [ 4.01 , 8.52 ] |
| 31-90 d | 26 | 894 | 2.93 [ 1.91 , 4.50 ] |
| 91-180 d | 39 | 1266 | 2.26 [ 0.57 , 8.93 ] |
| 181-365 d | 58 | 2438 | 2.39 [ 1.84 , 3.09 ] |
| >365 d | 75 | 3400 | 2.25 [ 1.49 , 3.41 ] |



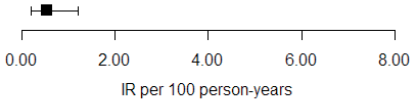

**Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 2 | 124 | 1.61 [ 0.20 , 5.83 ] |
| 31-90 d | 4 | 217 | 1.84 [ 0.50 , 4.72 ] |
| 91-180 d | 5 | 293 | 1.71 [ 0.55 , 3.98 ] |
| 181-365 d | 5 | 546 | 0.92 [ 0.30 , 2.14 ] |
| >365 d | 5 | 994 | 0.50 [ 0.16 , 1.17 ] |

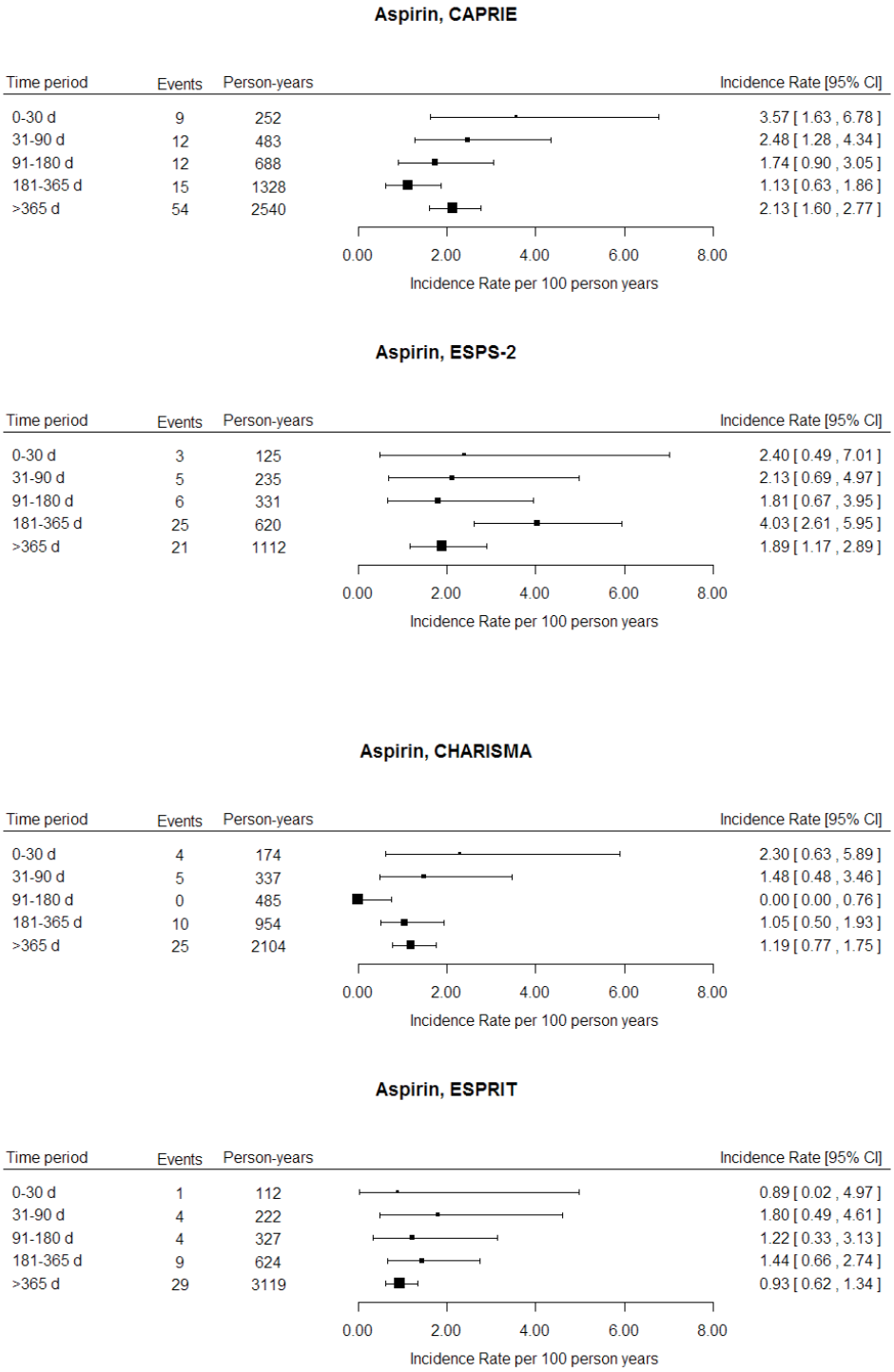



**Placebo**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 5 | 123 | 4.07 [ 1.32 , 9.49 ] |
| 31-90 d | 2 | 229 | 0.87 [ 0.11 , 3.15 ] |
| 91-180 d | 6 | 319 | 1.88 [ 0.69 , 4.09 ] |
| 181-365 d | 6 | 603 | 1.00 [ 0.37 , 2.17 ] |
| >365 d | 6 | 1082 | 0.55 [ 0.20 , 1.21 ] |

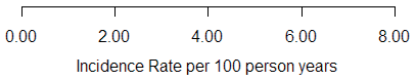


**Supplementary figure 2. Incidence rates of major bleeding on aspirin, per trial**



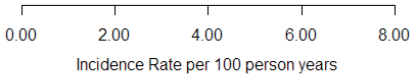
**Aspirin, CHARISMA**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 4 | 174 | 2.30 [ 0.63 , 5.89 ] |
| 31-90 d | 5 | 337 | 1.48 [ 0.48 , 3.46 ] |
| 91-180 d | 0 | 485 | 0.00 [ 0.00 , 0.76 ] |
| 181-365 d | 10 | 954 | 1.05 [ 0.50 , 1.93 ] |
| >365 d | 25 | 2104 | 1.19 [ 0.77 , 1.75 ] |

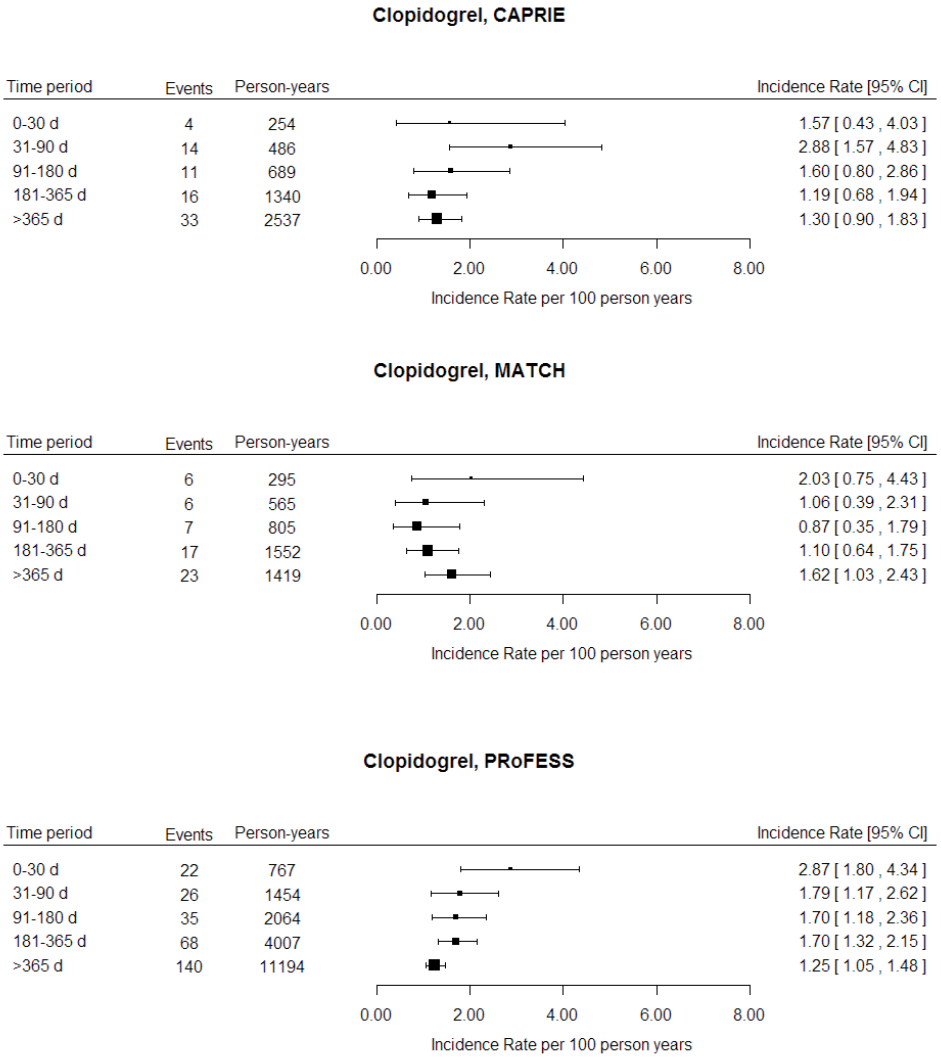



**Aspirin, ESPRIT**

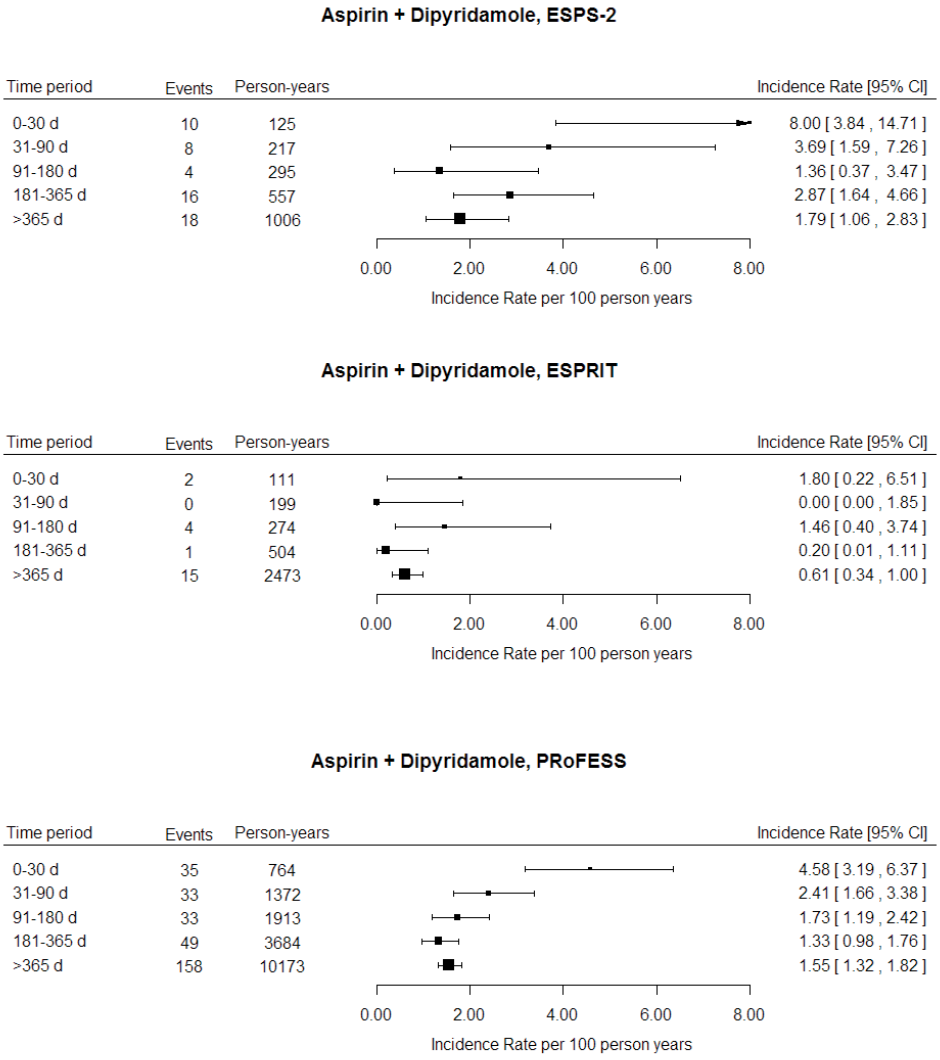
| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 1 | 112 | 0.89 [ 0.02 , 4.97 ] |
| 31-90 d | 4 | 222 | 1.80 [ 0.49 , 4.61 ] |
| 91-180 d | 4 | 327 | 1.22 [ 0.33 , 3.13 ] |
| 181-365 d | 9 | 624 | 1.44 [ 0.66 , 2.74 ] |
| >365 d | 29 | 3119 | 0.93 [ 0.62 , 1.34 ] |



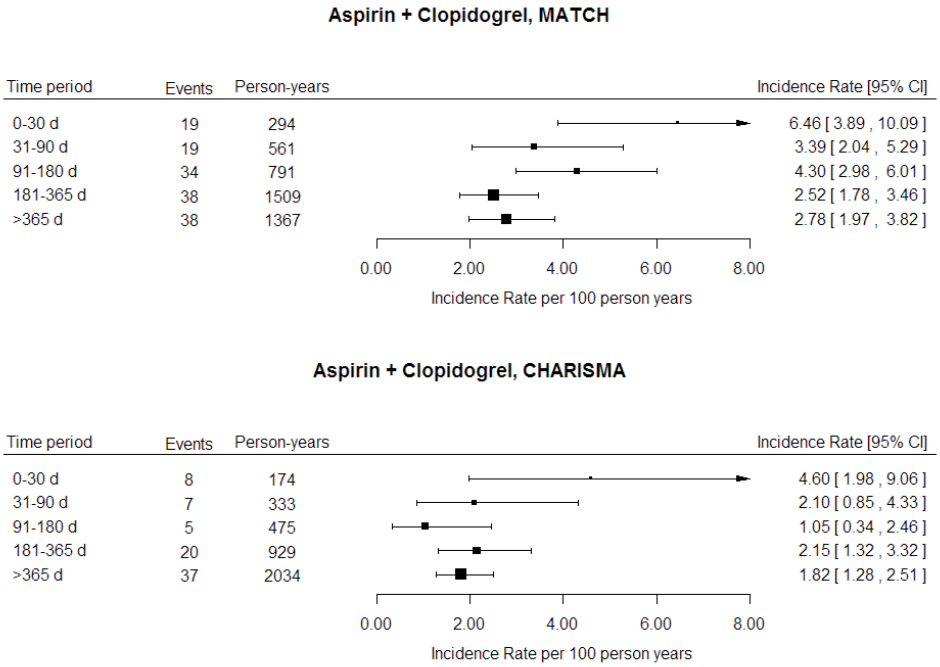
**Supplementary figure 3. Incidence rates of major bleeding on clopidogrel, per trial**



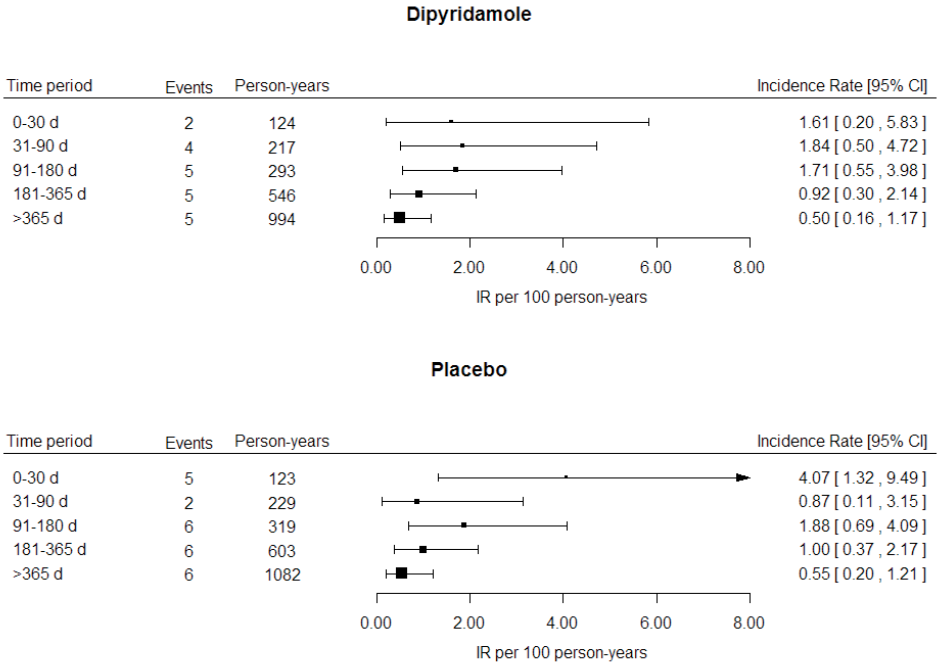
**Supplementary figure 4. Incidence rates of major bleeding on aspirin + dipyridamole, per trial**



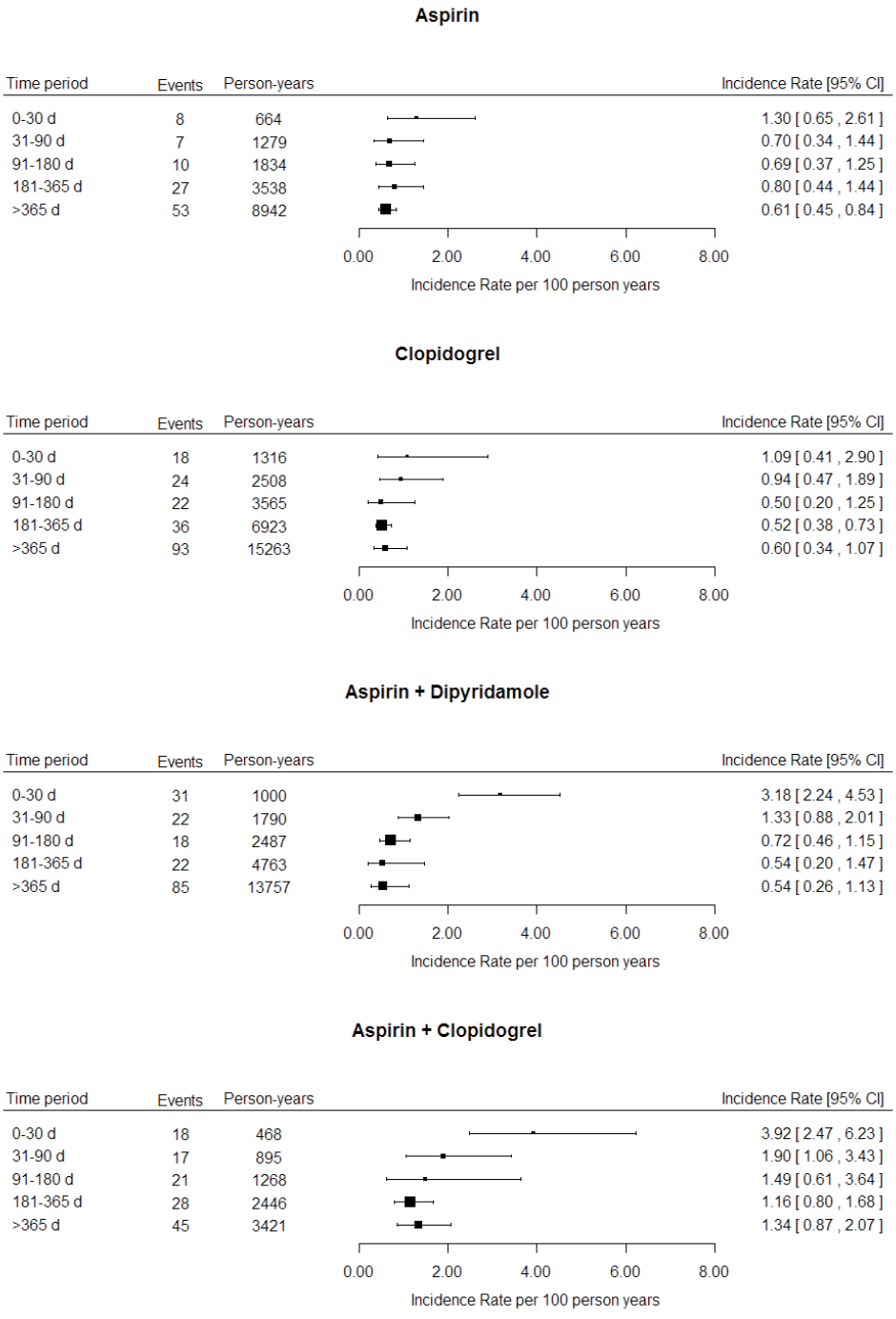
**Supplementary figure 5. Incidence rates of major bleeding on aspirin + clopidogrel, per trial**



**Supplementary figure 6. Incidence rates of major bleeding on dipyridamole and placebo**

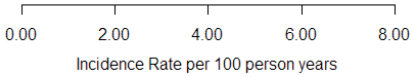


**Supplementary figure 7. Incidence rates of gastro-intestinal bleeding per antiplatelet regimen (pooled)**



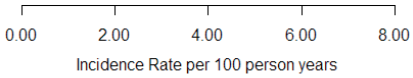
**Aspirin + Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 31 | 1000 | 3.18 [ 2.24 , 4.53 ] |
| 31-90 d | 22 | 1790 | 1.33 [ 0.88 , 2.01 ] |
| 91-180 d | 18 | 2487 | 0.72 [ 0.46 , 1.15 ] |
| 181-365 d | 22 | 4763 | 0.54 [ 0.20 , 1.47 ] |
| >365 d | 85 | 13757 | 0.54 [ 0.26 , 1.13 ] |



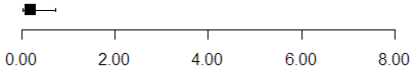

**Aspirin + Clopidogrel**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 18 | 468 | 3.92 [ 2.47 , 6.23 ] |
| 31-90 d | 17 | 895 | 1.90 [ 1.06 , 3.43 ] |
| 91-180 d | 21 | 1268 | 1.49 [ 0.61 , 3.64 ] |
| 181-365 d | 28 | 2446 | 1.16 [ 0.80 , 1.68 ] |
| >365 d | 45 | 3421 | 1.34 [ 0.87 , 2.07 ] |



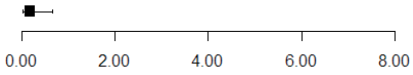

**Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 0 | 124 | 0.00 [ 0.00 , 2.97 ] |
| 31-90 d | 2 | 217 | 0.92 [ 0.11 , 3.33 ] |
| 91-180 d | 1 | 294 | 0.34 [ 0.01 , 1.90 ] |
| 181-365 d | 1 | 549 | 0.18 [ 0.00 , 1.01 ] |
| >365 d | 2 | 1000 | 0.20 [ 0.02 , 0.72 ] |




**Placebo**

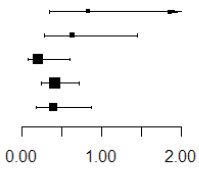
| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 1 | 123 | 0.81 [ 0.02 , 4.53 ] |
| 31-90 d | 0 | 229 | 0.00 [ 0.00 , 1.61 ] |
| 91-180 d | 2 | 320 | 0.62 [ 0.08 , 2.26 ] |
| 181-365 d | 2 | 606 | 0.33 [ 0.04 , 1.19 ] |
| >365 d | 2 | 1089 | 0.18 [ 0.02 , 0.66 ] |



**Supplementary figure 8. Incidence rates of intracranial bleeding per antiplatelet regimen (pooled)**

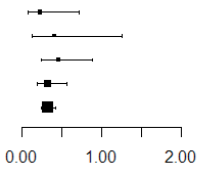
**Aspirin**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 4 | 664 | 0.84 [ 0.35 , 2.01 ] |
| 31-90 d | 6 | 1279 | 0.64 [ 0.28 , 1.45 ] |
| 91-180 d | 3 | 1835 | 0.21 [ 0.07 , 0.60 ] |
| 181-365 d | 13 | 3542 | 0.42 [ 0.24 , 0.72 ] |
| >365 d | 39 | 8954 | 0.40 [ 0.18 , 0.88 ] |



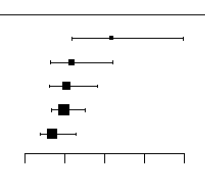

**Clopidogrel**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 2 | 1316 | 0.23 [ 0.07 , 0.72 ] |
| 31-90 d | 8 | 2511 | 0.41 [ 0.13 , 1.26 ] |
| 91-180 d | 15 | 3570 | 0.46 [ 0.24 , 0.89 ] |
| 181-365 d | 23 | 6937 | 0.33 [ 0.19 , 0.57 ] |
| >365 d | 49 | 15303 | 0.32 [ 0.25 , 0.43 ] |



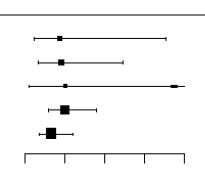

**Aspirin + Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 10 | 1001 | 1.09 [ 0.59 , 1.99 ] |
| 31-90 d | 9 | 1792 | 0.59 [ 0.32 , 1.10 ] |
| 91-180 d | 12 | 2491 | 0.53 [ 0.30 , 0.92 ] |
| 181-365 d | 22 | 4772 | 0.50 [ 0.33 , 0.75 ] |
| >365 d | 59 | 13818 | 0.35 [ 0.19 , 0.64 ] |



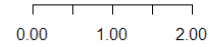

**Aspirin + Clopidogrel**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 2 | 468 | 0.44 [ 0.11 , 1.77 ] |
| 31-90 d | 4 | 897 | 0.46 [ 0.17 , 1.23 ] |
| 91-180 d | 9 | 1270 | 0.51 [ 0.06 , 4.62 ] |
| 181-365 d | 12 | 2451 | 0.51 [ 0.29 , 0.90 ] |
| >365 d | 11 | 3440 | 0.33 [ 0.18 , 0.60 ] |



**Aspirin + Dipyridamole**

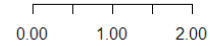
| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 10 | 1001 | 1.09 [ 0.59 , 1.99 ] |
| 31-90 d | 9 | 1792 | 0.59 [ 0.32 , 1.10 ] |
| 91-180 d | 12 | 2491 | 0.53 [ 0.30 , 0.92 ] |
| 181-365 d | 22 | 4772 | 0.50 [ 0.33 , 0.75 ] |
| >365 d | 59 | 13818 | 0.35 [ 0.19 , 0.64 ] |




Incidence Rate per 100 person years

**Aspirin + Clopidogrel**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 2 | 468 | 0.44 [ 0.11 , 1.77 ] |
| 31-90 d | 4 | 897 | 0.46 [ 0.17 , 1.23 ] |
| 91-180 d | 9 | 1270 | 0.51 [ 0.06 , 4.62 ] |
| 181-365 d | 12 | 2451 | 0.51 [ 0.29 , 0.90 ] |
| >365 d | 11 | 3440 | 0.33 [ 0.18 , 0.60 ] |




Incidence Rate per 100 person years

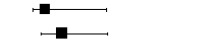
**Dipyridamole**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 0 | 124 | 0.00 [ 0.00 , 2.97 ] |
| 31-90 d | 1 | 217 | 0.46 [ 0.01 , 2.57 ] |
| 91-180 d | 1 | 293 | 0.34 [ 0.01 , 1.90 ] |
| 181-365 d | 2 | 549 | 0.36 [ 0.04 , 1.32 ] |
| >365 d | 0 | 998 | 0.00 [ 0.00 , 0.37 ] |


Incidence Rate per 100 person years

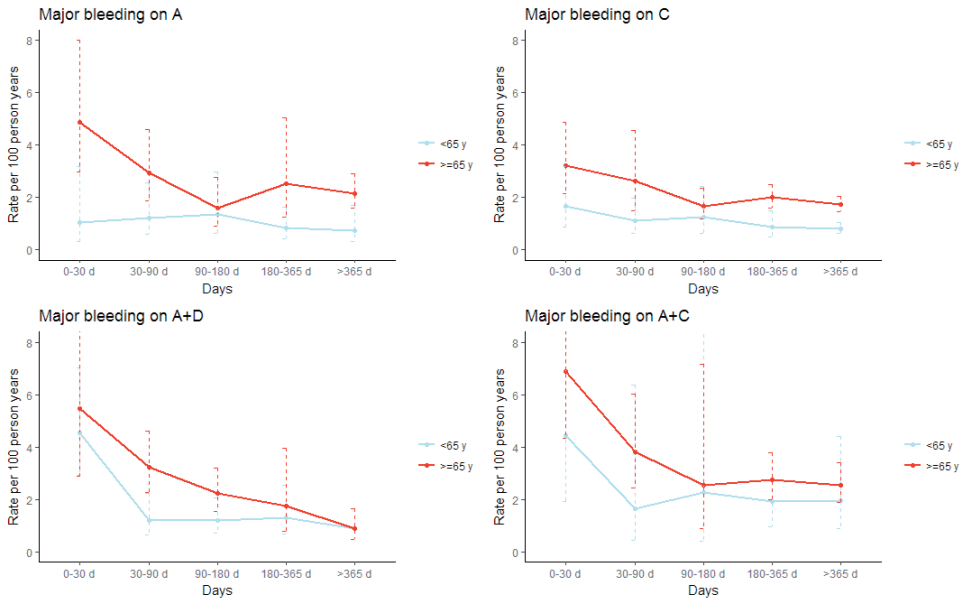
**Placebo**

| Time period | Events | Person-years | Incidence Rate [95% CI] |
|---|---|---|---|
| 0-30 d | 2 | 123 | 1.63 [ 0.20 , 5.87 ] |
| 31-90 d | 0 | 229 | 0.00 [ 0.00 , 1.61 ] |
| 91-180 d | 1 | 321 | 0.31 [ 0.01 , 1.74 ] |
| 181-365 d | 1 | 607 | 0.16 [ 0.00 , 0.92 ] |
| >365 d | 4 | 1088 | 0.37 [ 0.10 , 0.94 ] |



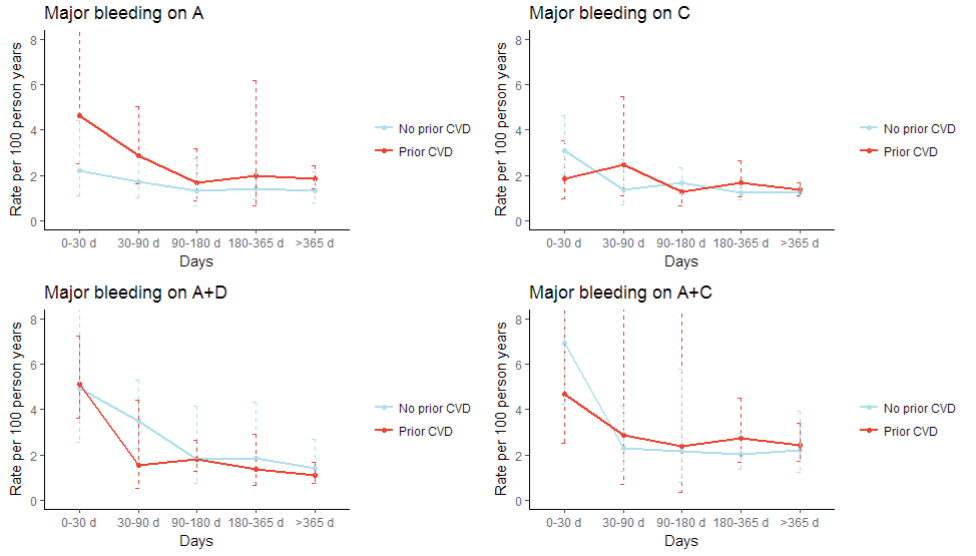

Incidence Rate per 100 person years

**Supplementary figure 9. Time course of major bleeding by age group**




A aspirin; C clopidogrel; A+D aspirin+dipyridamole; A+C aspirin+clopidogrel

**Supplementary figure 10. Time course of major bleeding by prior cardiovascular disease status**




CVD cardiovascular disease; A aspirin; C clopidogrel; A+D aspirin+dipyridamole; A+C aspirin+clopidogrel

# CHAPTER 7

## BALANCING BENEFITS AND RISKS OF LONG-TERM ANTIPLATELET THERAPY IN PATIENTS WITH NON-CARDIOEMBOLIC TIA OR ISCHAEMIC STROKE: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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*In preparation*

## ABSTRACT

**Background** Lifelong treatment with antiplatelet drugs is recommended following a TIA or ischaemic stroke. Bleeding complications may offset the benefit of antiplatelet drugs in patients at increased risk of bleeding and low risk of recurrent ischaemic events. We aimed to investigate the net benefit of antiplatelet treatment according to an individuals' bleeding risk.

**Methods** We pooled individual patient data from six randomised clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT and PRoFESS) investigating antiplatelet therapy in secondary stroke prevention. Patients were stratified into quintiles according to their predicted risk of major bleeding with the $S_2$TOP-BLEED score. The annual risk of major bleeding and recurrent ischaemic events was assessed per quintile and the net benefit was compared for three scenarios: 1) aspirin versus no antiplatelet treatment, 2) aspirin-clopidogrel versus aspirin or clopidogrel monotherapy and 3) aspirin-dipyridamole versus clopidogrel.

**Results** 37,087 patients were included in the analyses. Both risk of major bleeding and recurrent ischaemic events increased over quintiles of predicted bleeding risk, but risk of ischaemic events was consistently higher. The net benefit was positive for aspirin versus no antiplatelet treatment irrespective of baseline bleeding risk. Treatment with aspirin-clopidogrel led to more major bleeding than reduction in ischaemic events. There was no clear preference for either aspirin-dipyridamole or clopidogrel according to baseline bleeding risk.
**Conclusion** Risk of recurrent ischaemic events and of major bleeding increase in parallel. Bleeding risk assessment is not a reliable element for individualised antiplatelet treatment.

## INTRODUCTION

Life-long treatment with antiplatelet drugs is recommended following a TIA or non-cardioembolic ischaemic stroke.[1] Aspirin, aspirin in combination with dipyridamole, and clopidogrel alone are currently recommended as first-line agents in secondary prevention of stroke[1,2] and reduce the risk of recurrent ischaemic events by about a 20-25% compared with placebo or no therapy.[3,4] Despite treatment, the residual risk of a recurrent ischaemic event is substantial, approximately 5% per year.[5,6] To further reduce the risk of vascular events the benefits of adding an extra antiplatelet drug have been investigated; some trials observed a small reduction in risk of recurrent ischaemic events during the use of aspirin-clopidogrel, but at the cost of a significantly increased bleeding risk.[7-10]

For currently recommended antiplatelet regimens the reduction in ischaemic events is, on average, larger than the increase in major bleeds. However, for an individual patient the balance between benefits and risks may differ, due to variations in the underlying absolute risk of a major bleed or recurrent ischaemic event. Bleeding complications may offset the benefit of antiplatelet drugs in patients at increased risk of bleeding and low risk of recurrent ischaemic events.

Prognostic models may be used to stratify trial populations and explore the effect of variation in absolute risk on the benefit and risk from treatment.[11,12] In the current study, we aimed to investigate the balance between benefits and risks of long-term antiplatelet treatment according to an individual's bleeding risk.



## METHODS

### Study population

We pooled individual patient data from six randomised clinical trials that investigated efficacy and safety of antiplatelet treatment in long-term secondary prevention after a TIA or minor ischaemic stroke.[7,8,13-16] The design of the individual patient data meta-analysis has been described in detail elsewhere.[17] Briefly, we performed a literature search to identify trials on long-term antiplatelet therapy after a TIA or stroke. Trials were eligible if they randomised patients with a TIA or ischaemic stroke to aspirin, or to antiplatelet drugs that are recommended as first-line treatment in secondary prevention of stroke as an alternative or in addition to aspirin, and had a duration of at least one year. Trials had to be published before December 2010 in peer-reviewed journals. Six trials met the inclusion criteria (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS), including 48,023 patients with a TIA or ischaemic stroke between 1989 and 2006. Details of studies included in the IPD meta-analysis (recruitment period, details of antiplatelet regimens, inclusion criteria, sample size) are presented in Table 1. For the current analysis we excluded patients with a possible cardioembolic origin of their stroke (patients with a history of atrial fibrillation or

TOAST classification of cardioembolic stroke) and patients randomised to dipyridamole only or placebo. Patients were followed-up at regular intervals according to the trial protocols. Median follow-up ranged from 1.4 to 3.5 years.

The outcome of interest for benefit of antiplatelet treatment was a recurrent ischaemic event, defined as a recurrent ischaemic stroke, myocardial infarction, or vascular death from non-haemorrhagic cause. For evaluating harms of antiplatelet treatment we focused on major bleeding. Trial specific definitions for major bleeding were used. Major bleeds included bleeds that were fatal, intracranial, significantly disabling or requiring hospital admission. Haemorrhagic strokes were counted as major bleedings, not as recurrent strokes. Haemorrhagic transformations of ischaemic strokes were counted as ischaemic strokes.

**Statistical analysis**

We calculated predicted risk of major bleeding for each patient with the $S_2$TOP-BLEED score.[18] This score comprises ten variables (age, sex, smoking, modified Rankin scale score, hypertension, diabetes, prior stroke, Asian ethnicity, BMI and type of antiplatelet treatment, supplementary table 1) and was derived from the same individual patient data. External validation of the score in a trial cohort and population based cohort confirmed the robustness of the model.[18,19] For the current analysis we did not assign points for type of antiplatelet treatment as we were interested in the effect of this treatment. 7,931 patients (18%) had missing values on one of the items of the $S_2$TOP-BLEED score, almost entirely due to the fact that two variables were not measured in the original trials. For the development of the score multiple imputation was performed. For the current analysis we used a single imputed dataset.

We investigated benefits and risks of antiplatelet treatment for three different scenarios: 1) aspirin versus no antiplatelet treatment, to assess the net benefit of antiplatelet treatment per se over a range of absolute bleeding risks, 2) enhanced dual antiplatelet therapy (aspirin-clopidogrel) versus monotherapy to assess if a specific subgroup might benefit from long-term dual therapy, and 3) aspirin-dipyridamole versus clopidogrel to assess whether there is a preference for one of these guideline recommended treatments depending on the absolute bleeding risk.

For the first scenario we pooled data from patients randomised to aspirin (aspirin arm from CAPRIE, ESPS-2, CHARISMA and ESPRIT trials, n=8,127). For the second scenario we combined data from MATCH and CHARISMA trials (n=11,492). Patients randomised to either aspirin or clopidogrel were pooled in a 'monotherapy' group, and compared with the dual therapy group comprising those randomised to aspirin-clopidogrel. For the last scenario we used data from the PRoFESS trial (n=19,589), comparing aspirin-dipyridamole with clopidogrel. All analyses were performed according to the intention-to-treat principle. Patients were censored at the time of a major bleed or recurrent ischaemic event (depending on the outcome of interest), death or end of follow-up.

Patients were divided into quintiles according to their predicted risk of major bleeding. For each quintile the annual rate of major bleeding and recurrent ischaemic events was calculated (number of events / person-years at risk * 100) per trial and subsequently pooled with random effects meta-analysis. The absolute rate difference was calculated for each treatment contrast. Next, we calculated the net benefit with the following formula: (Risk of ischaemic event [without treatment] – Risk of ischaemic event [with treatment]) – (Risk of major bleeding [with treatment] – Risk of major bleeding [without treatment]). A positive net benefit indicates that the benefits of treatment outweigh the risks.

In order to compare aspirin with no antiplatelet treatment we had to estimate the annual rate of both outcomes in absence of aspirin by applying the relative risks as determined in previous meta-analyses of aspirin versus placebo (RR 0.87 for recurrent ischaemic events and RR 1.71 for major bleedings).[20,21] In this scenario, we assumed that treatment effect was independent of baseline risk.

A major bleed may be deemed less severe than a recurrent stroke, therefore we performed a sensitivity analysis including only intracranial haemorrhages instead of all major bleedings. Intracranial haemorrhages were assigned a weight of 1.5 to account for their generally worse outcome.[22]

The same analyses were performed stratified for risk of a recurrent ischaemic event, for which we used the Essen Stroke Risk Score (ESRS), originally derived from the CAPRIE data.[23] The score consists of nine variables (age, hypertension, diabetes, previous myocardial infarction, other cardiovascular disease, peripheral arterial disease, smoking, prior TIA or ischaemic stroke in addition to qualifying event) and ranges from 0 to 9 points (supplementary table 2). This score was chosen among other scores predicting recurrent vascular events because all predictors required to calculate the score were available and it showed reasonable performance (supplementary figure 1). Instead of dividing patients into quintiles we performed the analyses per ESRS score, combining all patients with a score of five or higher. All analyses were performed with R version 3.3.2. Results are reported in accordance with the STROBE statement.

**Table 1. Details of six trials included in the IPD meta-analysis**

| Trial by year | Country | Recruitment period | No. of patients | Interventions | Inclusion criteria | Primary endpoint | Study period median (range; years) |
|---|---|---|---|---|---|---|---|
| CAPRIE -stroke subgroup 1996 | Australia, Canada, Europe (10) and USA. | 1992-95 | 6431 | CLO 75 mg *vs* ASA 325 mg | IS within six months | composite of IS, MI, or vascular death (excluding haemorrhage) | 2.0 (0-3.3) |
| ESPS-2 1996 | Europe (13) | 1989-93 | 3299 | ASA 50mg +DIP 400mg *vs* ASA 50mg | TIA/IS within three months | stroke; death; stroke or death. | 2.0 (0-2.5) |
| MATCH 2004 | Asia (4), Australia, Canada, Europe (21) and USA. | 2000-02 | 7599 | ASA 75mg +CLO 75mg *vs* CLO 75mg | TIA/IS within three months and one additional vascular risk factor within three years. | composite of IS, MI, vascular death or rehospitalization for an acute ischaemic event | 1.4 (0-1.5) |
| CHARISMA -stroke subgroup 2006 | Asia (6), Australia, Canada, Europe (17), Mexico, South Africa, South America (3) and USA. | 2002-03 | 4320 | ASA 75-162mg +CLO 75mg *vs* ASA 75-162mg | TIA/IS within five years; age ≥45. | composite of stroke, MI, or vascular death | 2.1 (0-2.9) |
| ESPRIT 2006 | Asia (1), Australia, Europe (11) and USA. | 1997-2005 | 2739 | ASA 30-325mg +DIP 400mg *vs* ASA 30-325mg | TIA/minor IS within six months | composite of stroke, MI, vascular death, or major bleeding | 3.5 (0-8.1) |
| PRoFESS 2008 | Asia (12), Australia, Canada, Europe (16), Mexico, South Africa, South America (2) and USA. | 2003-06 | 20332 | ASA 50mg +DIP 400mg *vs* CLO 75mg | IS within three months; clinical and neurologic stable; age ≥55. | recurrent stroke; composite of stroke, MI, or vascular death | 2.4 (0-4.4) |

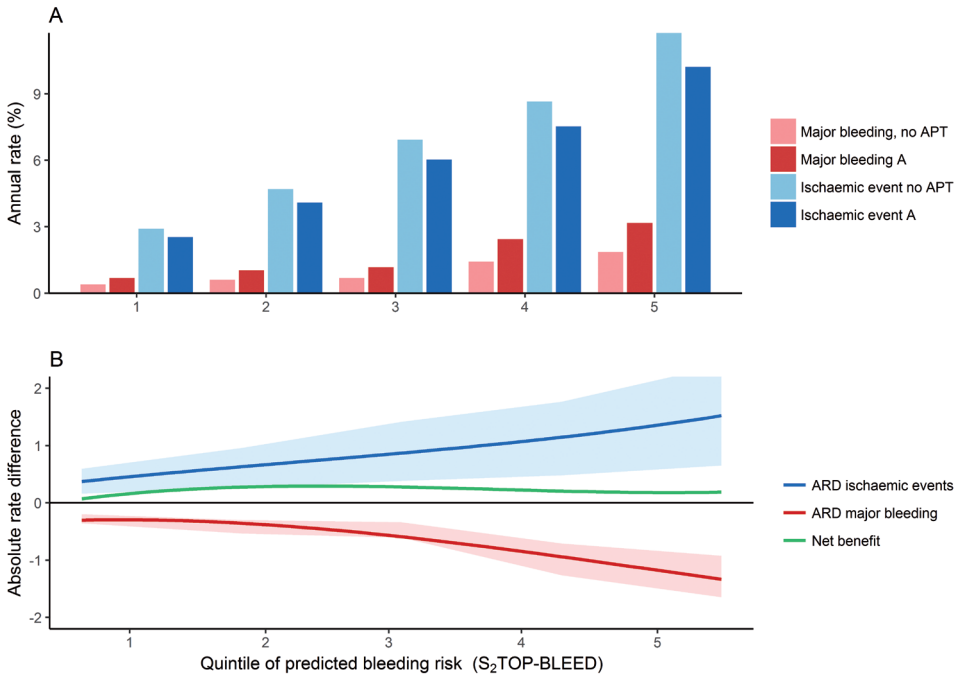
CLO clopidogrel; ASA aspirin; DIP dipyridamole; IS ischaemic stroke; TIA transient ischaemic attack; MI myocardial infarction

## RESULTS

### Aspirin

We studied 8,127 patients randomised to aspirin in order to investigate the net benefit of aspirin compared with no antiplatelet treatment. During 17,538 person-years of follow-up, 1,001 patients had a recurrent ischaemic event and 277 patients had a major bleed. The annual rate of recurrent ischaemic events increased across bleeding risk quintiles from 2.5 to 10.2%, as did the annual rate of major bleeding (0.7 to 3.2%; Figure 1A). Aspirin reduced the absolute risk of ischaemic events and this benefit continued to accrue over the quintiles with the largest benefit seen in the highest quintile. A similar pattern was observed for the harms (supplementary table 3). The risk reduction of recurrent ischaemic events attributable to aspirin was slightly larger than the risk increase of major bleeding, resulting in a positive net benefit for each quintile (Figure 1B). In the lowest quintile, 38 (95% CI 16 to 59) ischaemic events were prevented per 10.000 person-years treated with aspirin, at a cost of 28 (95% CI 20 to 35) major bleeds. In the highest quintile this number increased to 153 (95% CI 65 to 240) ischaemic events prevented per 10.000 person-years, and to 132 (95% CI 92 to 165) major bleeds caused (supplementary table 4). The benefit of aspirin was more pronounced when only intracranial haemorrhages were taken into account instead of all major bleeds (supplementary figure 2).

**Figure 1. Net benefit of aspirin versus no antiplatelet treatment according to bleeding risk groups**

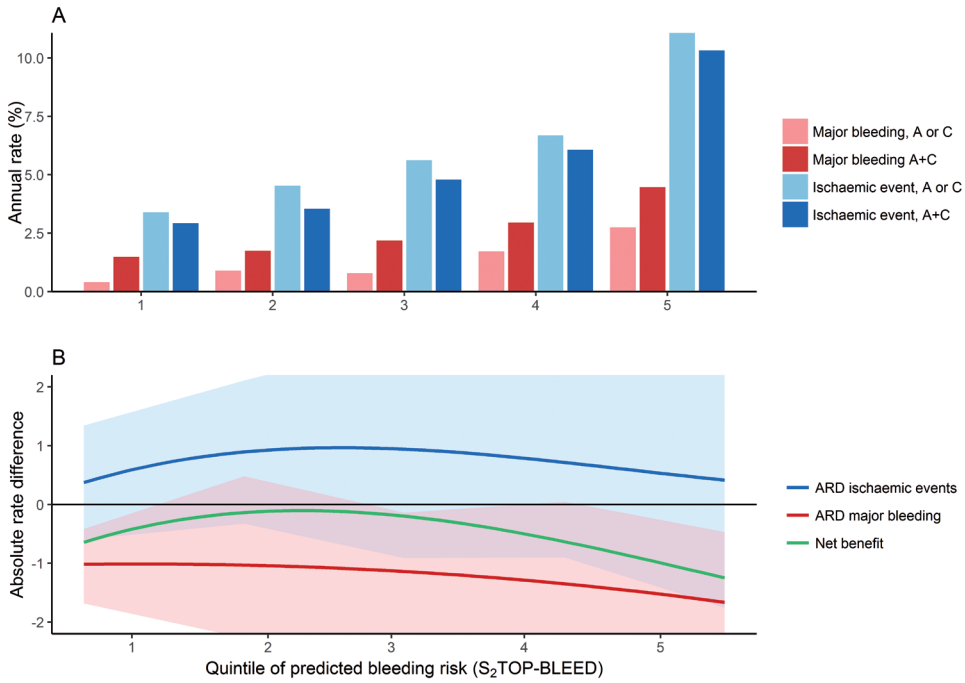



APT antiplatelet therapy; A aspirin; ARD absolute rate difference. Shaded areas indicates 95% confidence intervals. Mean predicted 1-year risk of major bleeding on aspirin per quintile: Q1=1.0%, Q2=1.3%, Q3=1.6%, Q4=2.0%, Q5=3.2%.

### Aspirin-clopidogrel

11,492 patients contributed to the analysis comparing aspirin-clopidogrel with aspirin or clopidogrel monotherapy. A recurrent ischaemic event occurred in 613 patients randomised to monotherapy and in 548 randomised to aspirin-clopidogrel. A major bleed occurred in 126 patients on monotherapy and in 246 patients on aspirin-clopidogrel. The risk of major bleeding and recurrent ischaemic events increased simultaneously across the quintiles (Figure 2A). The risk reduction of ischaemic events with aspirin-clopidogrel did not outweigh the risk increase of major bleedings in any of the quintiles (Figure 2B, supplementary table 3). The net benefit of aspirin-clopidogrel was positive in the lowest three quintiles when only intracranial haemorrhages were taken into account (supplementary figure 3).

**Figure 2. Net benefit of aspirin-clopidogrel versus aspirin or clopidogrel monotherapy according to bleeding risk group**



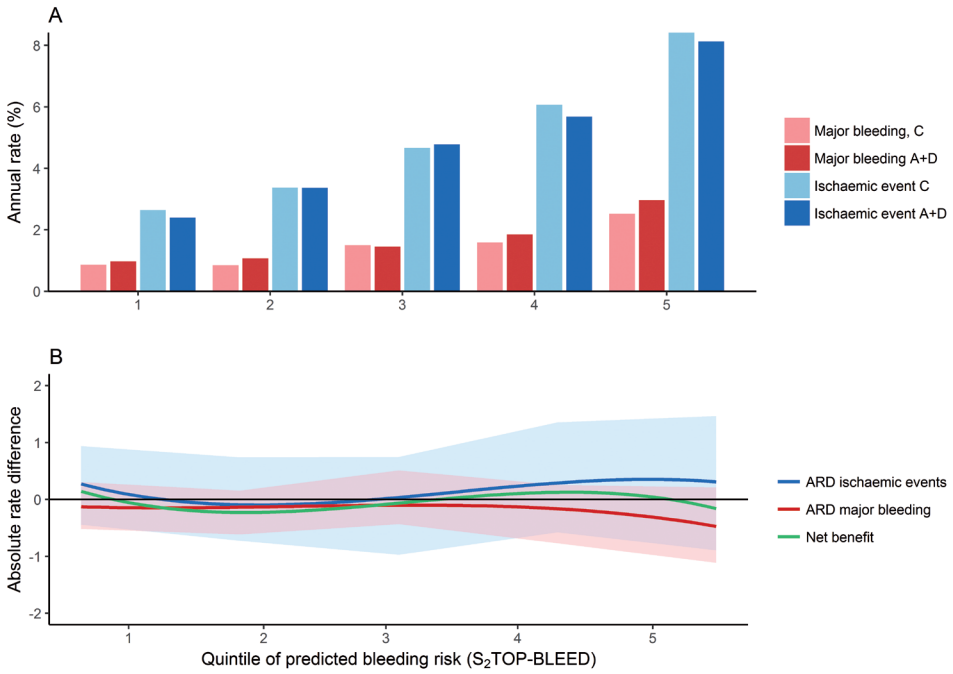

A aspirin; C clopidogrel; A+C aspirin-clopidogrel; ARD absolute rate difference. Shaded areas indicated 95% confidence interval. Mean predicted 1-year risk of major bleeding on aspirin per quintile: Q1=1.0%, Q2=1.3%, Q3=1.6%, Q4=2.0%, Q5=3.2%.



### Aspirin-dipyridamole vs. clopidogrel

For the analysis comparing aspirin-dipyridamole with clopidogrel we analysed data from 19,589 patients included in the PRoFESS trial. Among patients randomised to aspirin-dipyridamole, 1,146 had a recurrent ischaemic event and 403 had a major bleed. Among patients randomised to clopidogrel, 1,173 patients had a recurrent ischaemic event and 354 had a major bleed. There was no clear preference for either of the two treatments according to bleeding risk group when all major bleeds were taken into account (Figure 3, supplementary table 3), or when only intracranial haemorrhages were taken into account (supplementary figure 4).

**Figure 3. Net benefit of aspirin-dipyridamole compared with clopidogrel according to bleeding risk group**




C clopidogrel; A+D aspirin-dipyridamole; ARD absolute rate difference. Shaded areas indicate 95% confidence intervals. Mean predicted 1-year risk of major bleeding on aspirin per quintile (Q): Q1=1.0%, Q2=1.3%, Q3=1.6%, Q4=2.0%, Q5=3.2%.

Results for all three scenarios were largely similar when patients were stratified with the ESRS score according to their risk of a recurrent ischaemic event (supplementary figures 5-7).

## DISCUSSION

We observed that the risk of major bleeding and the risk of recurrent ischaemic events increased in parallel across bleeding risk groups in long-term secondary prevention after a TIA or minor ischaemic stroke. The benefits of aspirin monotherapy outweighed the risks when compared to no treatment, irrespective of baseline bleeding risk. We demonstrated that the risk of major bleeding associated with aggressive long-term dual antiplatelet therapy was larger than the benefit for all risk groups. No preference was observed for either aspirin-dipyridamole or clopidogrel according to baseline bleeding risk.

Early trials that compared aspirin with placebo suggested that the risk of bleeding on low-dose aspirin was relatively small and that the case fatality was low.[24-26] However, a recent population-based study has drawn attention to the substantial risks associated with long-term aspirin use in elderly patients.[27] The incidence of major bleeds (mostly gastro-intestinal bleeds) increased steeply with age, reaching an annualized rate of 4% in patients over 85 years. Also, the case fatality and disability associated with bleeds increased in elderly patients.[27] These findings raised concern about the net benefit of long-term aspirin when the risk of adverse events is substantial. Indeed, in the very elderly patients (>85 years) it was observed that the risk reduction in ischaemic events was approximately similar to the increase in major bleeds attributable to aspirin.[27] In our study we did not observe a clear change in net benefit with increasing risk of bleeding. Although in absolute terms the harms increased, the benefits also increased due to simultaneously rising risk of ischaemic events. A possible explanation for the discrepancy with the previously mentioned study is that patients at highest risk of bleeding were excluded from the trial cohorts, and the very elderly (>85 years) and frail patients in whom the net benefit might change were relatively underrepresented.

The net benefit of aspirin observed in our study was relatively small. However, it should be noted that aspirin has the least favourable risk-benefit ratio compared with the other two guideline recommended antiplatelet regimens; both aspirin-dipyridamole and clopidogrel reduce risk of vascular events more successfully than aspirin,[14,15] and clopidogrel also causes less haemorrhages than aspirin.[13] Also, one may argue that a major bleed should not be given equal weight to a recurrent ischaemic event. We addressed this in a sensitivity analysis including only intracranial haemorrhages, which showed a more pronounced benefit of aspirin.



Among patients with coronary artery disease, trials found benefit of adding clopidogrel to standard treatment (mainly aspirin), with an acceptable increase in risk of major bleedings.[28,29] A similar approach was investigated in stroke patients, but did not yield a comparable benefit without significantly increasing harm.[7-9] In the present study we could not identify a subgroup according to risk of bleeding in whom the benefits of long-term aspirin-clopidogrel would outweigh the risks. The results of the CHANCE trial suggest that aspirin-clopidogrel is beneficial when initiated early after stroke and continued for the first 90 days. However, the CHANCE trial took place almost exclusively among Chinese patients and results from a similar trial in Western countries have to be awaited.[30] In the current study we could not address the balance between benefits and risks in the very early phase, as patients were generally randomised after the acute phase of TIA or stroke (median time from qualifying event to randomisation 21 days (interquartile range 9-57 days)).

The American Stroke Association guideline states that the choice of antiplatelet treatment should be based on individual characteristics, next to considerations on efficacy, safety and costs.[1] Aspirin-dipyridamole and clopidogrel have comparable efficacy and safety profiles, but our results suggest that it is unlikely that patient characteristics will further

guide the choice for either of these two treatments. It is difficult to distinguish patients based on their risk of recurrent ischaemic events and major bleedings, because the risk factors underlying both major bleedings and recurrent ischaemic events are very similar.[31,32]A predicted high bleeding risk should therefore not serve as criterion to withhold antiplatelet treatment. Nevertheless, bleeding risk assessment may still be useful to identify modifiable risk factors for bleeding (e.g. hypertension) and to identify patients in whom preventive strategies should be implemented. Co-prescription of a proton pump inhibitor (PPI) may be considered in patients with a high estimated bleeding risk as it substantially reduces risk of upper gastro-intestinal bleeding.[27,33,34] Age above 75 years has recently been suggested as criterion to start PPIs, with a number needed to treat of 23 to prevent 1 major bleeding at 5 years follow-up.[27] Age above 75 years would correspond with an annual risk of major bleeding of >2%.

Strengths of our study include the large sample size and the high quality of the data, with thorough follow-up. Also, the outcome events were adjudicated centrally by an independent committee. Some limitations need to be addressed. First, our study population may not be representative of all patients with a TIA or ischaemic stroke, as patients with the highest bleeding risk and advanced age have been excluded from the trials. The balance between benefits and risks may differ for frail and very elderly patients, as was suggested in a recent population-based cohort study.[27] Second, the $S_2$TOP-BLEED score that was used to stratify patients in risk groups was derived from the same individual patient data. However, previous external validation studies have shown that the score is robust.[18,19] Third, for the analysis comparing aspirin with placebo we had to estimate the number of events prevented or caused and could not directly derive this from the data. We retrieved risk ratios for efficacy and safety from previous meta-analyses, but our results do not reflect the uncertainty surrounding these estimates. Also, the relative risk of 0.87 pertains to all serious vascular events, including haemorrhagic strokes and death from haemorrhagic causes, while our interest was in pure ischaemic events. Fourth, we could not assign weights to the different types of major bleeding based on the available data, while the severity and consequences of bleeds differ. Fifth, we did not have data on the very early phase following a TIA or stroke and could therefore not address the benefit and risk of short term aspirin-clopidogrel. Sixth, we could not investigate the influence of stroke subtype (e.g. large artery atherosclerosis versus small vessel disease) on the balance between benefits and risks of antiplatelet treatment, as these data were not routinely collected in all trials.

In conclusion, we showed that the risk of recurrent ischaemic events and major bleedings increase in parallel in patients with a TIA or ischaemic stroke on antiplatelet treatment. Bleeding risk assessment based on patient characteristics cannot be used to guide decision on long-term antiplatelet treatment for individual patients. In order to meaningfully inform treatment decisions for antiplatelet treatment, stronger predictors for major bleeding and ischaemia need to be identified.

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## SUPPLEMENT

**Supplementary table 1. Score chart of the $S_2$TOP-BLEED score for major bleeding[1]**

| Factor | Points |
|---|---|
| Male **S**ex | **2** |
| **S**moking | **1** |
| **T**ype of antiplatelet agent | |
| Clopidogrel | **0** |
| Aspirin (+/- dipyridamole) | **1** |
| Aspirin-clopidogrel | **5** |
| **O**utcome on mRS ≥3 | **2** |
| **P**rior stroke | **1** |
| **B**lood pressure (hypertension) | **1** |
| **L**ow BMI | |
| <20 | **2** |
| 20-25 | **1** |
| >25 | **0** |
| **E**lderly (age, years) | |
| 45-54 | **2** |
| 55-64 | **4** |
| 65-74 | **6** |
| 75-84 | **9** |
| ≥85 | **12** |
| **E**thnicity – Asian | **1** |
| **D**iabetes | **1** |

mRS modified Rankin Scale

**Supplementary table 2. Essen Stroke Risk Score (ESRS) for risk of recurrent ischaemic events after a TIA or ischaemic stroke[2]**

| Factor | Points |
|---|---|
| Age (years) | |
| <65 | **0** |
| 65-75 | **1** |
| >75 | **2** |
| Hypertension | **1** |
| Diabetes | **1** |
| Previous myocardial infarction | **1** |
| Other cardiovascular disease* | **1** |
| Peripheral artery disease | **1** |
| Smoker | **1** |
| Prior TIA or ischaemic stroke | **1** |

*except myocardial infarction and atrial fibrillation.

**Supplementary table 3: Absolute annual risks and risk differences for 3 scenarios**

**Scenario 1. Aspirin versus no antiplatelet treatment**

**Major bleeding**

| | Aspirin | | No antiplatelet treatment | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk* (%/year)** | **Absolute rate increase (%)** |
| 1 | 35 | 0.68 | . | 0.40 | 0.28 |
| 2 | 40 | 1.03 | . | 0.60 | 0.43 |
| 3 | 40 | 1.17 | . | 0.68 | 0.49 |
| 4 | 77 | 2.43 | . | 1.42 | 1.01 |
| 5 | 85 | 3.17 | . | 1.85 | 1.32 |
| Overall | 277 | 1.51 | . | 0.88 | 0.63 |

***** Estimated by dividing number the annual risk by 1.71

**Ischaemic events**

| | Aspirin | | No antiplatelet treatment | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk (%/year)*** | **Absolute rate reduction (%)** |
| 1 | 136 | 2.53 | . | 2.91 | 0.38 |
| 2 | 164 | 4.09 | . | 4.70 | 0.61 |
| 3 | 202 | 6.03 | . | 6.93 | 0.90 |
| 4 | 228 | 7.53 | . | 8.66 | 1.13 |
| 5 | 271 | 10.22 | . | 11.75 | 1.53 |
| Overall | 1001 | 5.49 | . | 6.31 | 0.82 |

* Estimated by dividing the annual risk by 0.87

**Scenario 2. Aspirin-clopidogrel versus aspirin or clopidogrel monotherapy**

**Major bleeding**

| | Aspirin-clopidogrel | | Aspirin or clopidogrel | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk (%/year)** | **Absolute rate increase (%)** |
| 1 | 30 | 1.49 | 8 | 0.4 | 1.05 (0.42;1.68) |
| 2 | 35 | 1.74 | 18 | 0.9 | 0.90 (-0.48;2.27) |
| 3 | 43 | 2.19 | 15 | 0.79 | 1.34 (0.14;2.54) |
| 4 | 57 | 2.95 | 33 | 1.72 | 1.21 (-0.04;2.48) |
| 5 | 81 | 4.47 | 52 | 2.75 | 1.70 (0.47;2.92) |
| Overall | 246 | 2.47 | 126 | 1.30 | 1.26 (0.87;1.66) |

**Ischaemic events**

| | Aspirin-clopidogrel | | Aspirin or clopidogrel | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk (%/year)** | **Absolute rate reduction (%)** |
| 1 | 58 | 2.93 | 67 | 3.39 | 0.37 (-0.59;1.34) |
| 2 | 74 | 3.54 | 94 | 4.54 | 0.89 (-0.33;2.11) |
| 3 | 97 | 4.79 | 114 | 5.62 | 0.95 (-0.91;2.80) |
| 4 | 118 | 6.07 | 132 | 6.68 | 0.71 (-0.90;2.32) |
| 5 | 201 | 10.32 | 206 | 11.07 | 0.42 (-1.75;2.59) |
| Overall | 548 | 5.24 | 613 | 6.01 | 0.72 (0.01;1.44) |

**Scenario 3. Aspirin-dipyridamole versus clopidogrel monotherapy**

**Major bleeding**

| | Aspirin-dipyridamole | | Clopidogrel | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk (%/year)** | **Absolute rate increase (%)** |
| 1 | 40 | 0.97 | 36 | 0.86 | 0.11 (-0.31;0.52) |
| 2 | 53 | 1.07 | 42 | 0.84 | 0.23 (-0.16;0.61) |
| 3 | 75 | 1.45 | 75 | 1.49 | -0.04 (-0.51;0.43) |
| 4 | 92 | 1.84 | 81 | 1.59 | 0.26 (-0.25;0.77) |
| 5 | 143 | 2.97 | 120 | 2.52 | 0.45 (-0.21;1.11) |
| Overall | 403 | 1.67 | 354 | 1.47 | 0.20 (0.02;0.43) |

**Ischaemic events**

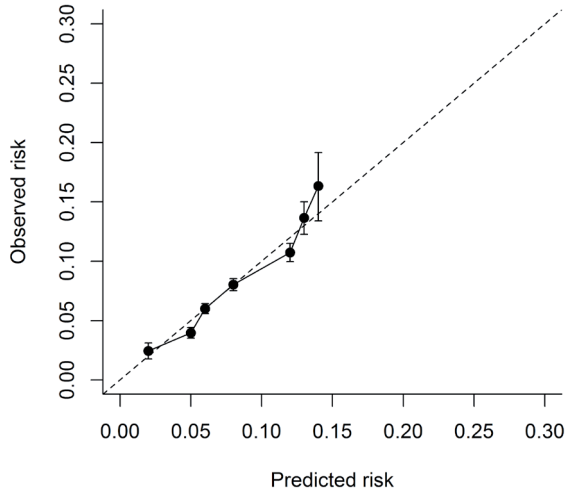
| | Aspirin-dipyridamole | | Clopidogrel | | |
|---|---|---|---|---|---|
| **Quintile of predicted bleeding risk** | **Events** | **Annual risk (%/year)** | **Events** | **Annual risk (%/year)** | **Absolute rate reduction (%)** |
| 1 | 97 | 2.40 | 108 | 2.64 | 0.25 (-0.44;0.94) |
| 2 | 162 | 3.36 | 163 | 3.37 | 0.01 (-0.73;0.74) |
| 3 | 239 | 4.78 | 227 | 4.67 | -0.11 (-0.97;0.75) |
| 4 | 273 | 5.68 | 295 | 6.07 | 0.39 (-0.58;1.36) |
| 5 | 375 | 8.13 | 380 | 8.41 | 0.29 (-0.89;1.47) |
| Overall | 1146 | 4.92 | 1173 | 5.06 | 0.14 (-0.26;0.56) |

**Supplementary table 4. Events prevented and caused with aspirin per 10.000 person-years**

| Quintile | Ischaemic events prevented (95% CI)* | Major bleeds caused (95% CI)* |
|---|---|---|
| 1 | 38 (16-59) | 28 (20-35) |
| 2 | 61 (26-96) | 43 (30-53) |
| 3 | 90 (38-141) | 49 (34-61) |
| 4 | 113 (48-177) | 101 (71-126) |
| 5 | 153 (65-240) | 132 (92-165) |
| Overall | 82 (35-129) | 63 (44-78) |

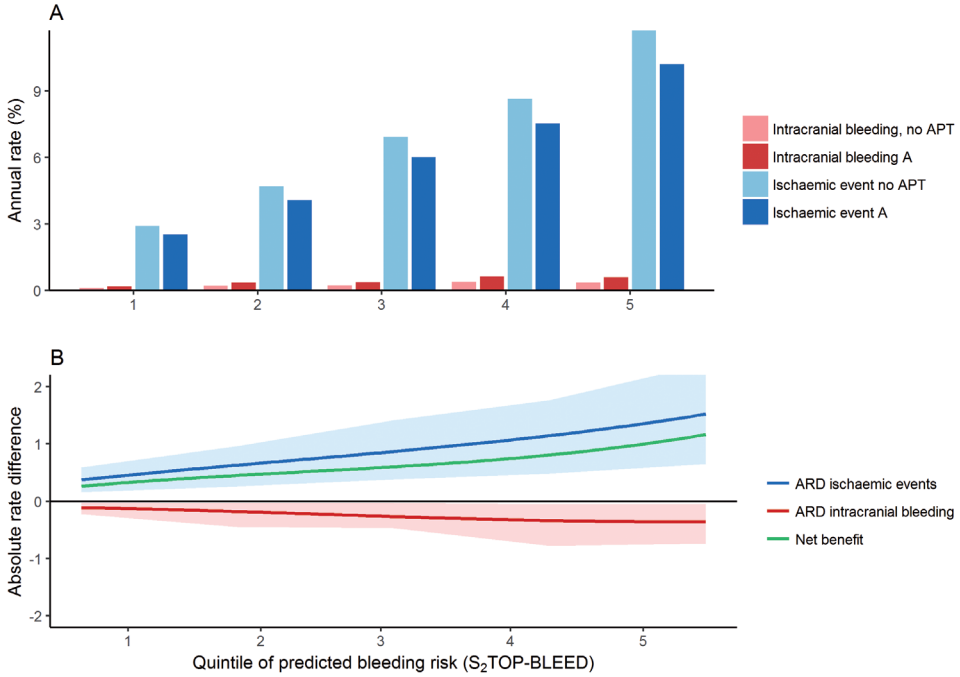
*95% confidence intervals based on the upper and lower bound of the relative risk for aspirin versus placebo.

**Supplementary figure 1. Performance of the Essen Stroke Risk Score (ESRS) in individual patient data from six randomised clinical trials**



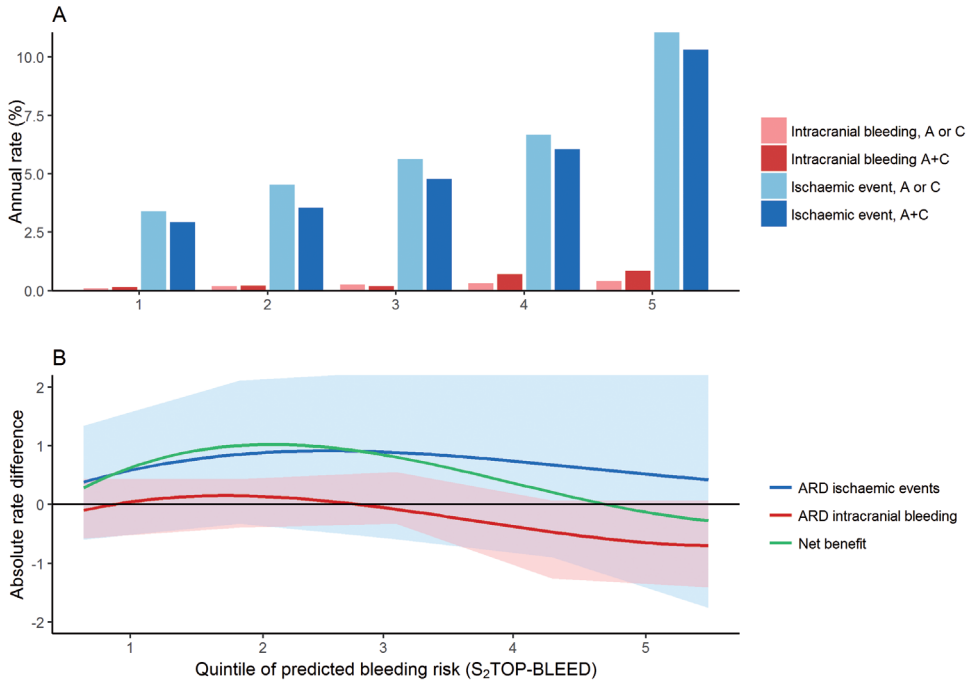

C-statistic 0.62 (0.61-0.63)

**Supplementary figure 2. Net benefit of aspirin compared with no antiplatelet therapy according to baseline bleeding risk, only intracranial bleeds taken into account**



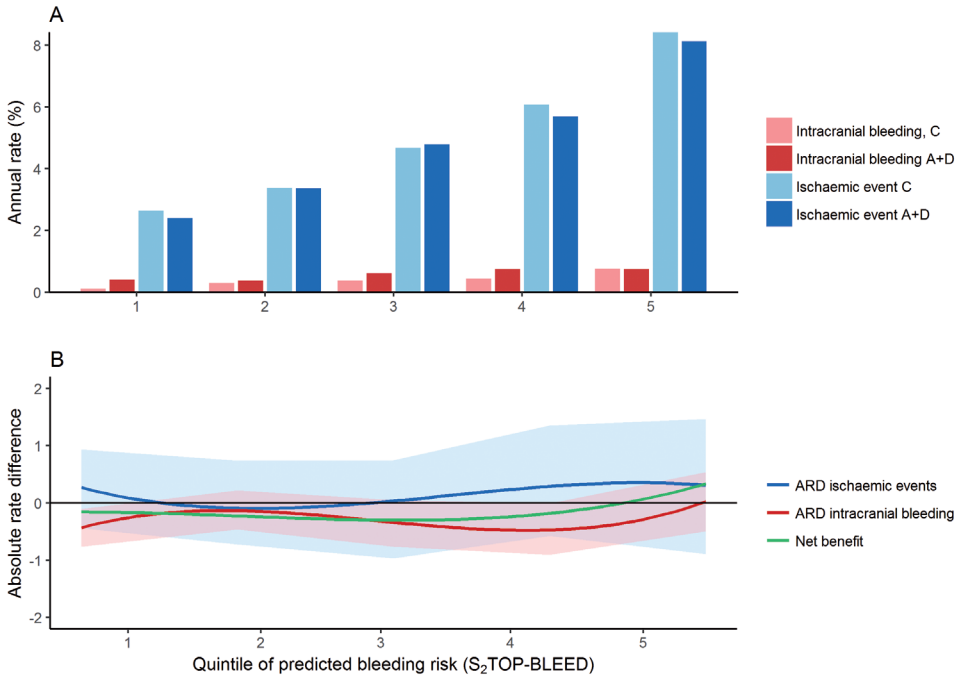

APT antiplatelet therapy; A aspirin; ARD absolute rate difference. Shaded areas indicates 95% confidence intervals.
Intracranial bleeds were given a weight of 1.5. (Formula net benefit: Absolute risk reduction ischaemic events – 1.5* Absolute risk increase intracranial bleeding).

**Supplementary figure 3. Net benefit of aspirin+clopidogrel compared with monotherapy according to baseline bleeding risk, only intracranial bleeds taken into account**



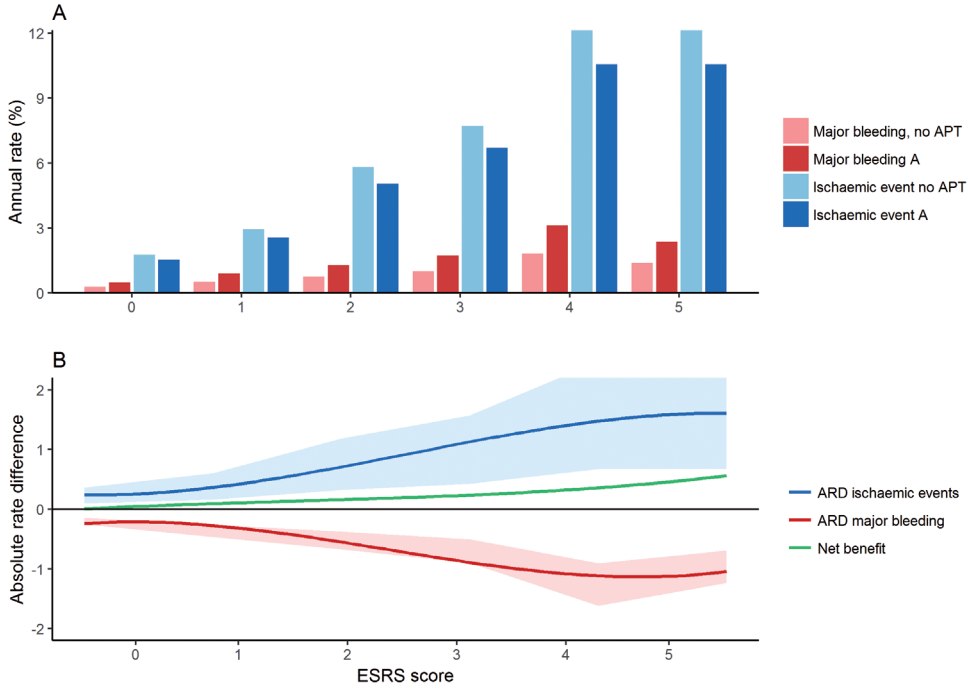

A aspirin; C clopidogrel; A+C aspirin-clopidogrel; ARD absolute rate difference. Shaded areas indicated 95% confidence interval.
Intracranial bleeds were given a weight of 1.5. (Formula net benefit: Absolute risk reduction ischaemic events – 1.5* Absolute risk increase intracranial bleeding).

**Supplementary figure 4. Net benefit of aspirin+dipyridamole compared with clopidogrel according to baseline bleeding risk, only intracranial bleeds taken into account**



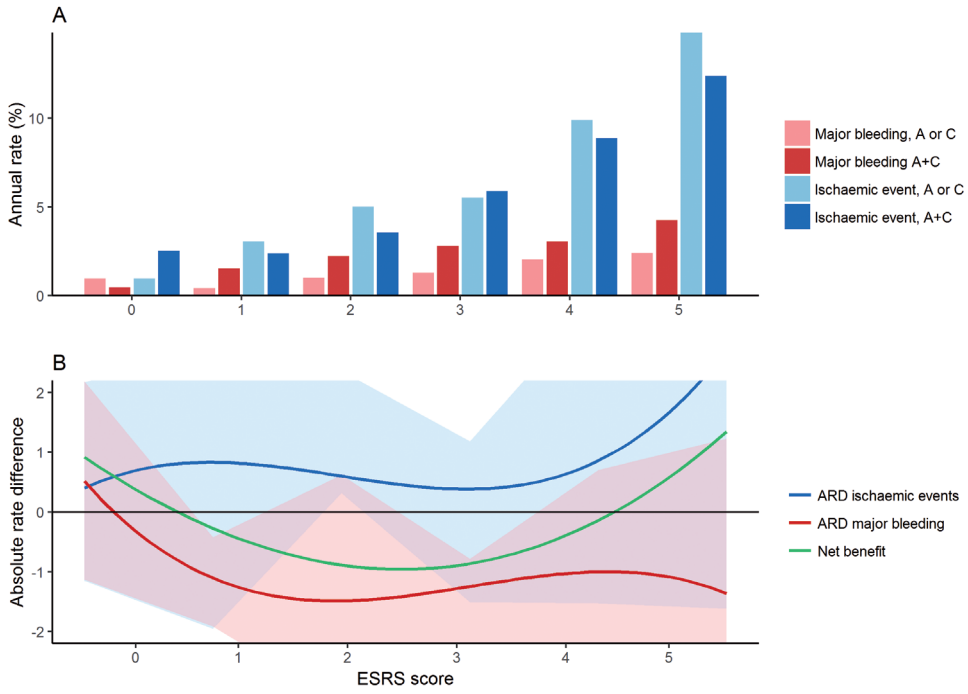

C clopidogrel; A+D aspirin-dipyridamole; ARD absolute rate difference. Shaded areas indicate 95% confidence intervals.
Intracranial bleeds were given a weight of 1.5. (Formula net benefit: Absolute risk reduction ischaemic events – 1.5* Absolute risk increase intracranial bleeding).

**Supplementary figure 5. Net benefit of aspirin compared with no antiplatelet therapy according to baseline risk of ischaemic events**



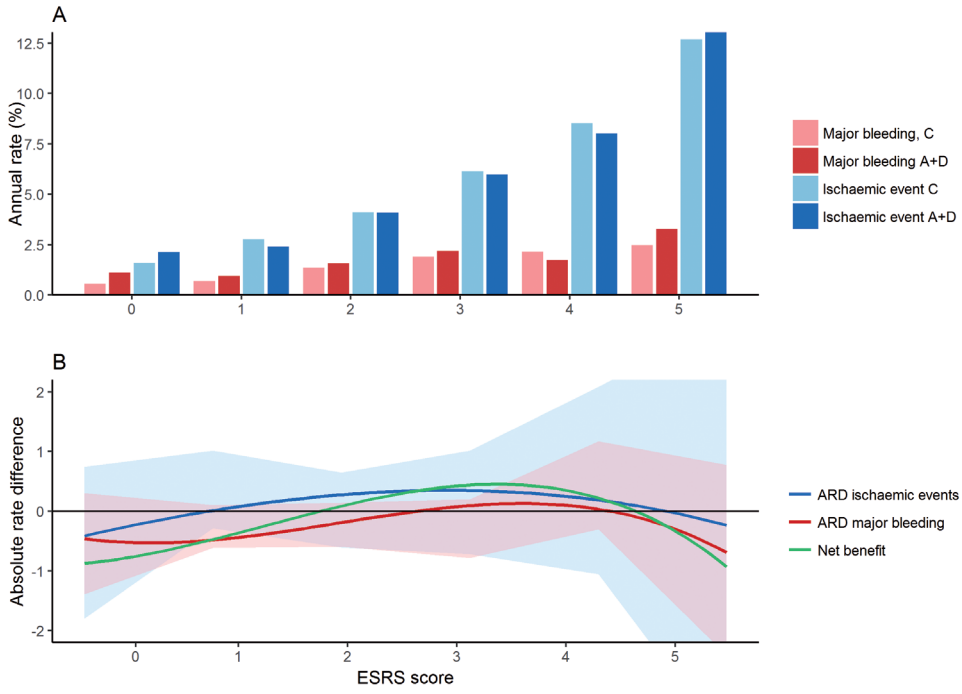

APT antiplatelet therapy; A aspirin; ARD absolute rate difference. Shaded areas indicates 95% confidence intervals.

**Supplementary figure 6. Net benefit of aspirin plus clopidogrel compared with monotherapy according to baseline risk of ischaemic events**




A aspirin; C clopidogrel; A+C aspirin-clopidogrel; ARD absolute rate difference. Shaded areas indicated 95% confidence interval.

**Supplementary figure 7. Net benefit of aspirin plus dipyridamole compared with clopidogrel according to baseline risk of ischaemic events**




C clopidogrel; A+D aspirin-dipyridamole; ARD absolute rate difference. Shaded areas indicate 95% confidence intervals.



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# CHAPTER 8

## PREDICTING MAJOR BLEEDING IN ISCHAEMIC STROKE PATIENTS WITH ATRIAL FIBRILLATION

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## ABSTRACT

**Background and purpose** Performance of risk scores for major bleeding in patients with atrial fibrillation (AF) and a previous TIA or ischaemic stroke is not well established. We aimed to validate risk scores for major bleeding in patients with AF treated with oral anticoagulants (OAC) after cerebral ischaemia, and explore the net benefit of OAC among bleeding risk categories.

**Methods** We analysed 3,623 patients with a history of TIA or stroke included in the RE-LY trial. We assessed performance of HEMORR$_2$HAGES, Shireman, HASBLED, ATRIA and ORBIT scores with c-statistics and calibration plots. Net benefit of OAC was explored by comparing risk reduction in ischaemic stroke with risk increase in major bleedings on warfarin.

**Results** During 6,922 person-years of follow-up, 266 patients experienced a major bleed (3.8 per 100 person-years). C-statistics ranged from 0.62 (Shireman) to 0.67 (ATRIA). Calibration was poor for ATRIA and moderate for other models. The reduction in recurrent ischaemic strokes on warfarin was larger than the increase in major bleeding risk, irrespective of bleeding risk category.

**Conclusion** Performance of prediction models for major bleeding in patients with cerebral ischaemia and AF is modest, but comparable with performance in patients with only AF. Bleeding risk scores cannot guide treatment decisions for OAC, but may still be useful to identify modifiable risk factors for bleeding. Clinical usefulness may be best for ORBIT, which is based on a limited number of easily obtainable variables and showed reasonable performance.

## INTRODUCTION

The benefit of prevention with oral anticoagulants (OAC) is partially offset by an increased risk of bleeding.[1] Risk scores have been developed to assess stroke and bleeding risk for individual patients with atrial fibrillation (AF),[2,3] helping physicians to weigh benefits and risks of oral anticoagulation.

Patients with AF and a previous TIA or ischaemic stroke form a distinct group, as they have a high risk of recurrent stroke[4] as well as a high risk of bleeding, including intracranial haemorrhage.[5] Performance of risk scores for major bleeding in patients with a previous stroke is not well established. We aimed to externally validate existing risk scores for major bleeding in patients with a TIA or ischaemic stroke on OAC, and explore the net benefit of OAC among bleeding risk categories.

## METHODS

We used a previously published literature review to identify existing prediction models for major bleeding in patients with AF[6] and performed an additional search in PubMed to identify models published after 2012 (see supplementary material). We validated available models in patients with a previous TIA or stroke included in the RE-LY trial (Randomised Evaluation of Long-Term Anticoagulation Therapy).[7] RE-LY included patients with documented AF in the preceding six months and one additional risk factor, and randomised patients to dabigatran (110/150 mg twice daily) or warfarin. Between 2005 and 2007, 18,113 patients were included of whom 3,623 had a history of TIA or stroke. The median follow-up duration was two years. The primary safety outcome was major bleeding, defined as reduction in haemoglobin level ≥20g/l, transfusion of ≥2 units of blood or symptomatic bleeding in a critical area or organ. RE-LY was approved by the institutional review board of each participating centre.

### Statistical analysis

Predictors included in the models were matched to variables in RE-LY. Data on genetic factors were not available in RE-LY and were discarded. We applied the original regression equations to the validation data to calculate the predicted one- and two-year probability of major bleeding for each patient. If the regression equation was unavailable, we validated the score chart. Model performance was assessed with the c-statistic and calibration plots. If predicted risks were not reported, rates per 100 person-years were used. Performance of models was also assessed separately for patients on dabigatran and warfarin. We explored whether the net benefit of treatment with warfarin differed among bleeding risk categories, by comparing the reduction in ischaemic strokes and increase in major bleedings attributable to warfarin (see supplementary methods). Analyses were performed with R version 3.3.0.

Results are reported in accordance with the TRIPOD statement (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis).

## RESULTS

We identified six risk scores for major bleeding in patients with AF: four from a previously published literature review[3,8-10] and two from our additional search[11,12] (supplementary table 1). Frequently included predictors were age, prior bleeding, anaemia and renal failure (supplementary table 2). Five models could be validated; one required information on biomarkers,[11] which was not available in RE-LY.

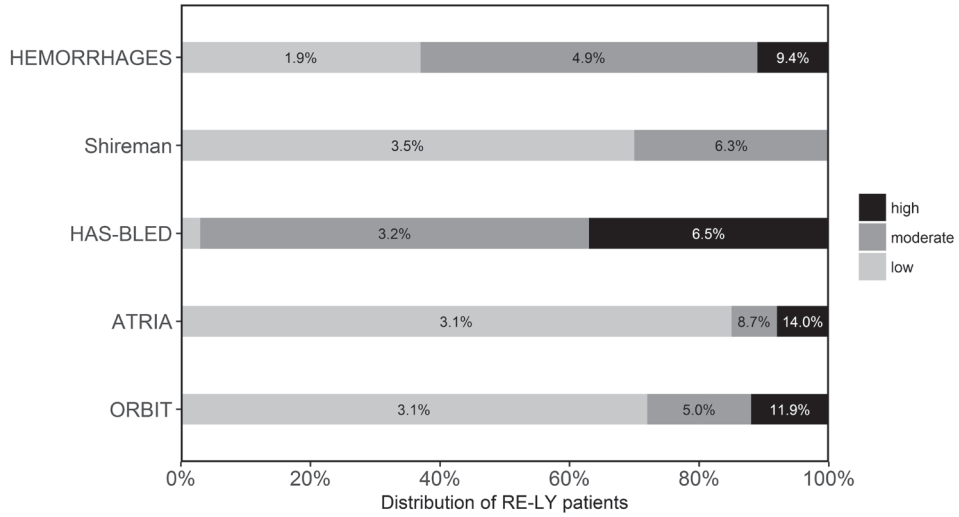
Baseline characteristics of the development and validation cohorts are presented in supplementary table 3. During 6,922 person-years of follow-up, 266 major bleedings occurred (rate 3.8, 95% CI 3.4-4.3 per 100 person-years). C-statistics ranged from 0.62 to 0.67 at one year (Table 1), and were comparable at two years (supplementary table 4). Discriminatory performance of all models was better among patients randomised to dabigatran than warfarin (Table 1). At one year, calibration was reasonable for most scores, apart from ATRIA which underestimated major bleeding risk (supplementary figure 1). ORBIT showed best calibration at two years (supplementary figure 2). Risk stratification capacity of each score across risk groups is shown in Figure 1. Figure 2 shows that the reduction in recurrent ischaemic strokes with warfarin treatment is larger than the increase in major bleeds, irrespective of bleeding risk category (supplementary figure 3 shows additional results).

**Table 1. C-statistic (95% confidence interval) of risk scores in patients with a previous TIA or ischaemic stroke on oral anticoagulants at one year**

| | All patients (n=3623) | Warfarin (n=1195) | Dabigatran (n=2428) |
|---|---|---|---|
| HEMORR$_2$HAGES | 0.65 (0.61-0.69) | 0.58 (0.51-0.65) | 0.69 (0.64-0.75) |
| Shireman | 0.62 (0.58-0.66) | 0.57 (0.50-0.63) | 0.66 (0.61-0.71) |
| HASBLED | 0.64 (0.60-0.68) | 0.57 (0.51-0.64) | 0.68 (0.63-0.73) |
| ATRIA | 0.67 (0.62-0.71) | 0.56 (0.49-0.63) | 0.74 (0.68-0.79) |
| ORBIT (score) | 0.66 (0.62-0.71) | 0.56 (0.48-0.64) | 0.73 (0.68-0.78) |
| ORBIT (equation) | 0.66 (0.62-0.71) | 0.56 (0.48-0.64) | 0.73 (0.68-0.78) |

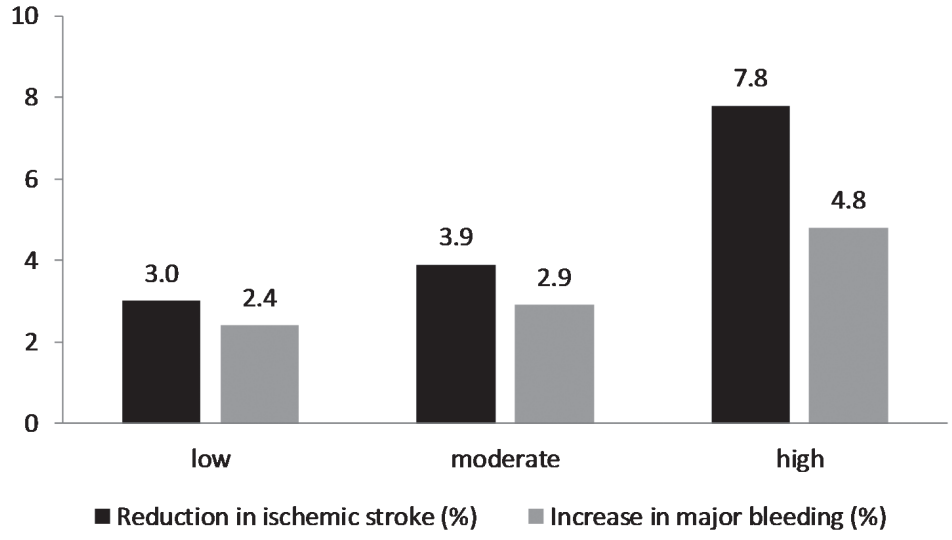
HEMORRHAGES hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, hypertension (uncontrolled) anaemia, genetic factors, excessive fall risk and stroke; HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly; ATRIA anticoagulation and risk factors in atrial fibrillation; ORBIT older age, reduced haemoglobin/haematocrit/history of anaemia, bleeding history, insufficient kidney function, and treatment with antiplatelets.

**Figure 1. Distribution of RE-LY patients in low, moderate and high bleeding risk categories per risk score**




Percentages in bar charts represent the observed 1-year risk of major bleeding in RE-LY by each risk category

**Figure 2. Risk reduction in ischaemic stroke by warfarin treatment and risk increase in major bleeding, per bleeding risk category**



## DISCUSSION

Predictive performance of risk scores for major bleeding in patients with AF is modest in patients with a previous TIA or ischaemic stroke. Irrespective of bleeding risk, the benefits of OAC seem to outweigh the risks.

The moderate performance of models in our study is in line with results from previous studies among patients with AF. C-statistics ranged from 0.63 to 0.72 in the original development cohorts of included models, and did not exceed 0.65 in most external validation studies.[6,13] The comparable discriminatory performance indicates that predictor-outcome associations are largely similar for patients with and without a previous stroke or TIA. The lower c-statistic found in warfarin treated patients may partly be explained by quality of INR control, an important determinant for bleeding. Further refinement of risk scores for patients with cerebral ischaemia might be achieved by incorporating radiological characteristics, including presence of microbleeds or leukoairaiosis, which are known to be strongly associated with intracranial bleeding.[14,15] However, the uptake of a risk score in clinical practice may, next to its performance, also be influenced by its ease of use. This may be best for ATRIA and ORBIT, which are based on a small number of readily available variables.

The benefits of OAC outweighed harms in all bleeding risk groups and risk scores should therefore not be used to guide treatment decisions for OAC. This is in keeping with recommendations in current guidelines, stating that all patients with previous stroke qualify for such treatment. However, assessment of bleeding risk may still be useful to identify modifiable risk factors for bleeding, as well as to identify high risk patients who qualify for treatment with gastro-protective agents.

Our study benefits from high quality data, with detailed follow-up and independent adjudication of bleeds. A limitation is that we used trial data for external validation. Patients at highest risk of bleeding have been excluded from RE-LY and absolute risks may have been underestimated. Furthermore, patients with a stroke in the previous two weeks were excluded, therefore generalisability to patients with acute stroke is unknown.

In conclusion, prediction models for major bleeding in patients with AF show modest performance in patients with cerebral ischaemia and AF, but performance is comparable with that in patients with AF in general. Clinical usefulness may be best for ORBIT, which is based on a limited number of variables and showed reasonable discrimination and calibration.

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## SUPPLEMENT

### Supplemental Methods - Search strategy

We searched on synonyms of the following search terms: "atrial fibrillation", "prediction model" and "major bleeding", and extracted articles that described development of a new risk score for major bleeding.

### Search syntax, conducted on February 1st, 2017

**Pubmed**

**#1 Atrial fibrillation & synonyms**

Atrial fibrillation [Title/Abstract] OR AF [Title/Abstract] OR Atrial Fibrillation [MeSH]

**#2 Prediction models & synonyms**

prognostic score[Title/Abstract] OR prognostic scores[Title/Abstract] OR prognostic model[Title/Abstract] OR prognostic models[Title/Abstract] OR prognostic scheme[Title/Abstract] OR prognostic schemes[Title/Abstract] OR prognostic factor[Title/Abstract] OR prognostic factors[Title/Abstract] OR prognostic index[Title/Abstract] OR prognostic indices[Title/Abstract] OR prediction rule[Title/Abstract] OR prediction rules[Title/Abstract] OR prediction model[Title/Abstract] OR prediction models[Title/Abstract] OR prediction score[Title/Abstract] OR prediction scores[Title/Abstract] OR prediction scheme[Title/Abstract] OR prediction schemes[Title/Abstract] OR prediction index[Title/Abstract] OR prediction indices[Title/Abstract] OR risk score[Title/Abstract] OR risk scores[Title/Abstract] OR risk model[Title/Abstract] OR risk models[Title/Abstract] OR risk scheme[Title/Abstract] OR risk schemes[Title/Abstract] OR risk index[Title/Abstract] OR risk indices[Title/Abstract] OR risk stratification[Title/Abstract] OR risk stratifications[Title/Abstract] OR risk assessment[Title/Abstract] OR risk assessments[Title/Abstract] OR algorithm[Title/Abstract] OR algorithms[Title/Abstract] OR grading scale[Title/Abstract] OR grading scales[Title/Abstract] OR assessing risk[Title/Abstract] OR assessing risks[Title/Abstract] OR predicting risk[Title/Abstract] OR predicting risks[Title/Abstract] OR predictive factor[Title/Abstract] OR predictive factors[Title/Abstract] OR (predictor[Title/Abstract] OR predictors[Title/Abstract]) AND (score[Title/Abstract] OR scores[Title/Abstract] OR model[Title/Abstract] OR models[Title/Abstract] OR scheme[Title/Abstract] OR schemes[Title/Abstract] OR index[Title/Abstract] OR indices[Title/Abstract])

**#3 Bleeding & synonyms:**

hemorrhage[Title/Abstract] OR hemorrhages[Title/Abstract] OR haemorrhage[Title/Abstract] OR haemorrhages[Title/Abstract] OR bleeding[Title/Abstract] OR bleedings[Title/Abstract] OR hemorrhagic stroke[Title/Abstract] OR hemorrhagic strokes[Title/Abstract] OR haemorrhagic stroke[Title/Abstract] OR haemorrhagic strokes[Title/Abstract] OR bleed[Title/Abstract] OR bleeds[Title/Abstract] OR hemorrhage[MeSH Terms]

**#4**: #1 **AND** #2 **AND** #3

**Supplemental Methods - Assessment of net benefit of treatment with oral anticoagulants**

We stratified patients into low, moderate and high bleeding risk according to the ORBIT score. For each risk group, we assessed the observed 1-year risk of recurrent ischaemic stroke and the 1-year risk of major bleeding (1-Kaplan Meier estimate) on warfarin treatment. We chose the ORBIT score to stratify patients because it showed best performance in our external validation study.

Subsequently, we estimated the 1-year risk of a recurrent ischaemic stroke and a major bleed in the absence of warfarin treatment. This estimate was obtained by dividing the observed risk of an event by the relative risk associated with treatment (for recurrent ischaemic stroke RR 0.33 and for major bleeding approximately 2.0).[1] The difference in risks in the presence and absence of warfarin reflects the 1-year risk reduction/increase that is attributable to warfarin. The net benefit was calculated by subtracting the harms (increase in major bleeding) from the benefits (reduction in ischaemic strokes).

## REFERENCES SUPPLEMENT

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857-867.

**Supplementary table 1. Study characteristics of model development studies**

| | HEMORR$_2$HAGES, 2006 | Shireman, 2006 | HASBLED, 2010 | ATRIA, 2011 | ORBIT, 2015 | ABC, 2016 |
|---|---|---|---|---|---|---|
| **Study population** | Patients with AF | Patients with AF, aged >65 years on warfarin | Patients with AF | Patients with AF on warfarin | Patients with AF on OAC at baseline | Patients with AF at increased risk of stroke |
| **Source** | National Registry of Atrial Fibrillation | National Registry of Atrial Fibrillation | Euro Heart Survey | Kaiser Permanente | ORBIT-AF registry | ARISTOTLE trial |
| **Year of inclusion** | 1993-1998 | 1998-1999 and 2000-2001 | 2003-2004 | 1996-1997 | 2010-2012 | 2006-2010 |
| **Treatment** | 42% warfarin | 100% warfarin | 65% warfarin | 100% warfarin | 93.5% warfarin; 6.5% dabigatran | 50% warfarin; 50% apixaban |
| **Outcome definition** | Hospitalization for haemorrhage | Hospitalization for major acute bleeding event (GI or intracranial haemorrhage) | Intracranial bleeding or any bleeding requiring hospitalization, or causing a decrease in hemoglobin of ≥20 g/L and/ or requiring transfusion. | Bleeding that led to a transfusion of ≥2 units of blood, or bleeding that was fatal or occurred in a critical area or organ. | ISTH definition: Clinically overt bleeding with a decrease in haemoglobin of ≥20 g/L, a transfusion of ≥2 units of blood, or bleeding that was fatal or occurred in a critical area or organ. | ISTH definition: Clinically overt bleeding with a decrease in haemoglobin of ≥20 g/L, a transfusion of ≥2 units of blood, or bleeding that was fatal or occurred in a critical area or organ. |
| **Follow-up** | Mean 0.8 years | 90 days | 1 year | Median 3.5 years, (range 1.2-6.0) | Median 2 years, (IQR 1.6-2.5) | Median 1.7 years |
| **Type of model** | NR | Cox regression | Logistic regression | Cox regression | Cox regression | Cox regression |
| **Prediction horizon** | NR | 90 days | 1 year | NR | 1 and 2 years | 1 and 3 years |
| **Variable selection** | Based on the literature | Based on the literature and univariable analysis | Based on literature and univariable analysis | Based on literature and univariable analysis | Based on literature and clinical relevance | Motivation for selection of candidate predictors not reported |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Variable selection multivariable model** | No further variable selection was performed | Stepwise selection | Stepwise selection | Backward selection on 1000 bootstrap samples | Backward elimination | Backward elimination |
| **Number of events/N** | 162/3791 | 318/19,875 | 53/3456 | 307/6,123 | 581/7411 | 662/14,537 |
| **Apparent Discrimination** | 0.67 in patients on warfarin | 0.63 | 0.72 | 0.74 (0.70-0.78)* | 0.67 (0.64-0.69) | 0.68 (0.66–0.70) |

*in validaton cohort (split sample of development cohort) NR not reported

**Supplementary table 2. Predictors included in risk scores**

| | HEMORR$_2$HAGES | Shireman | HAS-BLED | ATRIA | ORBIT | ABC |
|---|---|---|---|---|---|---|
| Age | √ | √ | √ | √ | √ | √ |
| Female sex | | √ | | | | |
| Hypertension | √ | | √ | √ | | |
| Diabetes | | √ | | | | |
| Prior bleed | √ | √[†] | √[‡] | √ | √ | √ |
| Prior stroke | √ | | √ | | | |
| Malignancy | √ | | | | | |
| Drugs/alcohol | √ | √ | √[§] | | | |
| Antiplatelet agents/ reduced platelet count or function | √ | √ | √[§] | | √ | |
| Excessive fall risk | √ | | | | | |
| Anemia/Hemoglobin/ Hematocrit | √ | √ | √[‡] | √ | √ | √ |
| Renal failure | √[*] | | √[*] | √ | √ | |
| Liver failure | √[*] | | √[*] | | | |
| Troponin T | | | | | | √ |
| GDF-15 | | | | | | √ |
| Labile INR | | | √ | | | |
| Genetic factors | √ | | | | | |
| Total number of predictors | **11** | **8** | **7** | **5** | **5** | **5** |

[†] Remote bleed and recent bleed two different predictors; [*, ‡, §] Variables combined into one predictor; GDF growth differentiation factor-15

**Supplementary table 3. Baseline characteristics of development and validation cohorts**

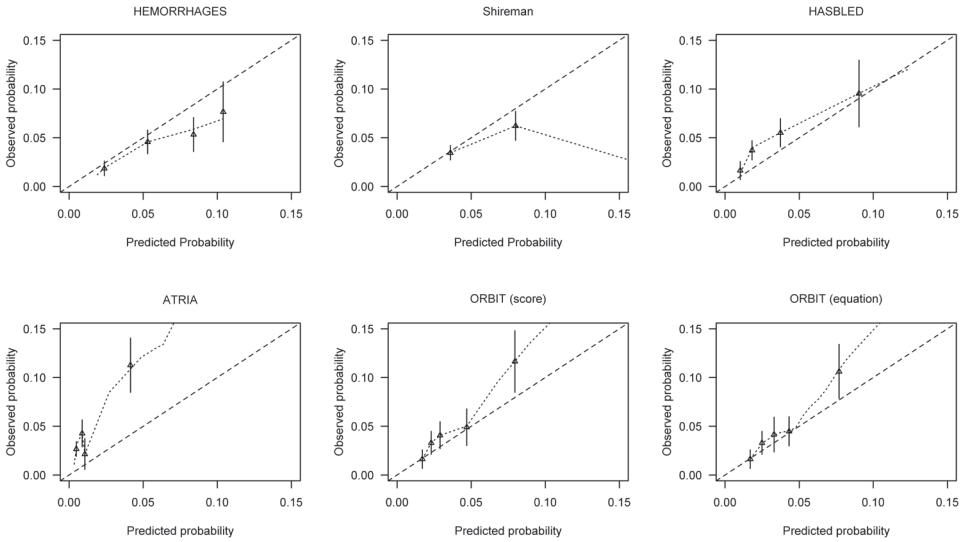
| | HEMORR$_2$HAGES | Shireman | HASBLED | ATRIA | ORBIT | ABC | RE-LY |
|---|---|---|---|---|---|---|---|
| Age, years | Mean 80 | 88% ≥70 | Mean 67 (SD 12.8) | 72% ≥70 | Median 75 (IQR 68-82) | Median 70 (range 19-97) | Median 72 (range 22-90) |
| Female sex (%) | 57 | 53 | 39 | 42 | 42 | 36 | 38 |
| Current smoking (%) | - | - | 13 | - | 5 | 8 | 8 |
| Heavy alcohol use (%) | 0.7 | 2 | - | - | - | 3 | 14 |
| Hypertension (%) | 0.5[a] | 72 | 66 | 62 | 85 | 87 | 77 |
| Diabetes (%) | - | 30 | 18 | 21 | 31 | 25 | 23 |
| Prior stroke (%) | 30 | 32 | 10[b] | 13 | 9 | 19[b] | 63 |
| Coronary artery disease (%) | - | 69 | 35 | - | 16[c] | 13[c] | 26 |
| Heart failure (%) | - | 60 | 29 | - | 35 | 31 | 24 |
| Prior bleed (%) | 19 | 12 | 2[d] | 15 | 8[e] | 16 | 9 |
| Anaemia (%) | 11 | 8 | - | 12 | 37 | - | 14 |
| Renal failure (%) | 10[f] | 0.6[f] | 5 | 3 | 35[g] | - | 0.2 |
| *Treatment* | | | | | | | |
| APT in addition to OAC (%) | 3 | 22 | 13 | 1 | 38 | 39[h] | 46 |
| APT alone (%) | 17 | 0 | 24 | 0 | 0 | 0 | 0 |
| Warfarin (%) | 42 | 100 | 65 | 100 | 93.5 | 50 | 33 |
| DOAC (%) | 0 | 0 | 0 | 0 | 6.5 | 50 | 67 |

[a] uncontrolled hypertension; [b] prior stroke or TIA; [c] prior MI; [d] prior major bleed; [e] prior gastro-intestinal bleed; [f] renal or liver disease; [g] GFR<60; [h] antiplatelet agents or NSAIDs. APT antiplatelet drugs; OAC oral anticoagulation; DOAC direct oral anticoagulation

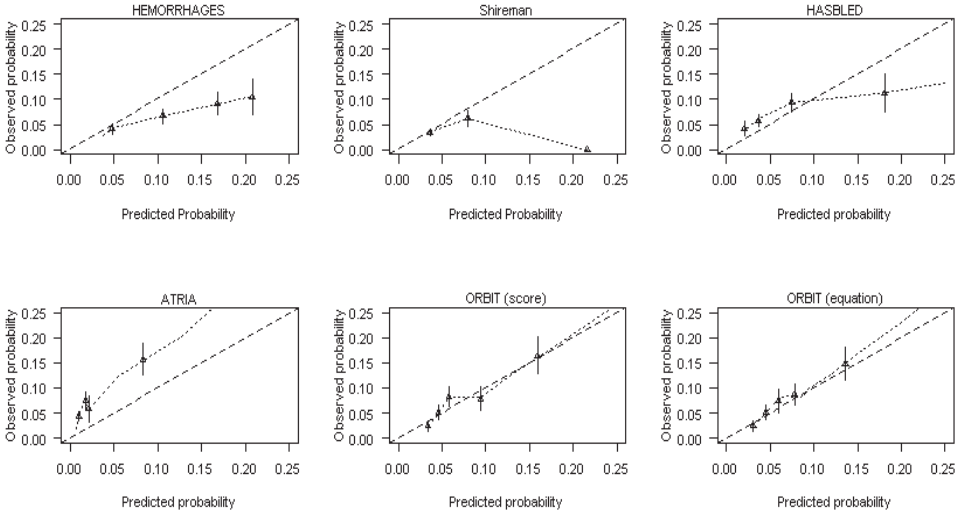
**Supplementary table 4. C-statistic (95% confidence interval) of risk scores for major bleeding in patients with a TIA or stroke on oral anticoagulants at two years**

| | All patients (n=3,623) |
|---|---|
| HEMORR$_2$HAGES | 0.63 (0.59-0.66) |
| Shireman | 0.61 (0.57-0.64) |
| HAS-BLED | 0.62 (0.58-0.65) |
| ATRIA | 0.66 (0.62-0.69) |
| ORBIT (score) | 0.66 (0.62-0.69) |
| ORBIT (equation) | 0.66 (0.62-0.69) |

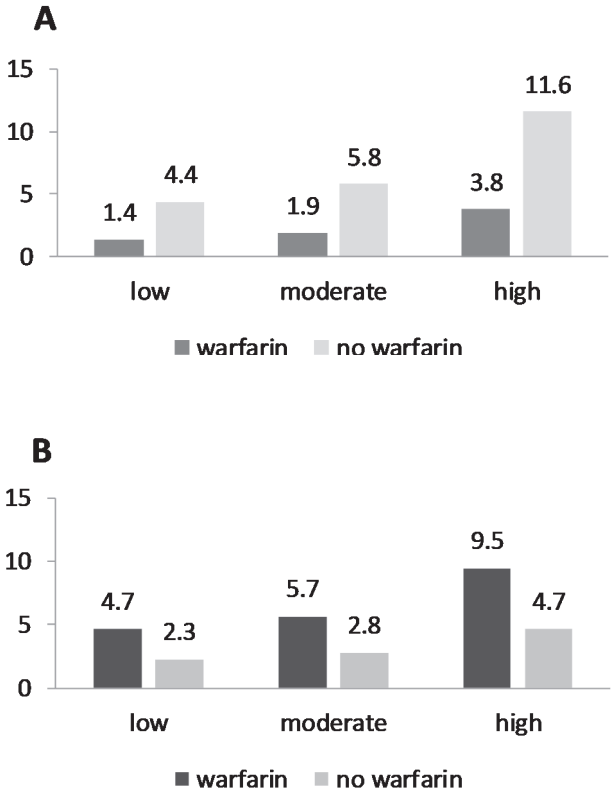
**Supplementary figure 1. Calibration of risk scores for major bleeding in patients with a TIA or stroke on oral anticoagulants at one year**



**Supplementary figure 2. Calibration of risk scores for major bleeding in patients with a TIA or stroke on oral anticoagulants at two years**



**Supplementary figure 3. Absolute 1-year risk of recurrent ischaemic stroke (A) and major bleeding (B) in the presence and absence of warfarin treatment, per bleeding risk category**



# CHAPTER 9

## BLOOD PRESSURE LEVELS AND THE RISK OF INTRACEREBRAL HAEMORRHAGE AFTER ISCHAEMIC STROKE

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## ABSTRACT

**Objective** To investigate the association between blood pressure (BP) levels and risk of intracerebral haemorrhage (ICH) after ischaemic stroke.

**Methods** We performed a post hoc analysis on data from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, a randomised clinical trial including 20,332 patients with recent noncardioembolic ischaemic stroke. BP measurements were divided into predefined categories. We calculated incidence rates per BP category and performed multivariable Cox regression analysis with systolic blood pressure (SBP) and diastolic blood pressure (DBP) categories as time-dependent covariables.

**Results** One hundred thirty-three ICHs occurred during 50,778 person-years of follow-up, resulting in an incidence rate of 2.6 per 1,000 person-years. The incidence rate of ICH increased with increasing SBP and DBP categories. Risk of ICH was significantly higher in patients with SBP ≥160 mmHg (hazard ratio (HR) 2.27; 95% confidence interval (CI) 1.34 to 3.86) compared with SBP of 130-<140 mmHg, and in patients with DBP ≥100mmHg (HR 3.08; 95% CI 1.78 to 5.34) compared with those with DBP of 80-<90 mmHg. The association between SBP or DBP and ICH did not differ by ischaemic stroke subtype (p-value 0.55 and 0.93).

**Conclusion** Among patients with recent noncardioembolic ischaemic stroke, the risk of ICH is high. High SBP and DBP are associated with an increased risk of ICH. The association between BP and ICH is not dependent on ischaemic stroke subtype.

## INTRODUCTION

Hypertension is an important risk factor for ischaemic stroke and intracerebral haemorrhage (ICH).[1] Among patients with a recent ischaemic stroke, approximately 70% have a history of hypertension.[2,3] Adequate treatment of hypertension successfully reduces the risk of recurrent strokes,[4,5] but uncertainty exists regarding the optimal blood pressure (BP) target. Current guidelines for prevention of stroke recommend a target BP of <140 mmHg for systolic BP (SBP) and <90 mmHg for diastolic BP (DBP), and a target of <130 mmHg for SBP in patients with lacunar stroke.[6] Older guidelines used to recommend stricter BP targets.[7] Recent guidelines have been revised based on results from trials in patients with diabetes mellitus showing no beneficial effect of BP-lowering below 120 mmHg,[8] and observational studies among ischaemic stroke patients suggesting that low BP may cause harm.[9,10]

However, stricter BP targets might be beneficial for prevention of ICH. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial comparing two BP targets in patients with a lacunar stroke showed that more intensive BP control (<130mmHg) significantly reduced the risk of ICH.[11] In addition, a post hoc analysis on data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial suggested that patients with the lowest achieved BP levels had the lowest risk of ICH.[12] Moreover, in an observational study among patients with ICH prehypertensive BP levels (SBP 120-139 or DBP 80-89 mmHg) were associated with increased risk of recurrent ICH.[13]

We aimed to study the association between BP levels and the risk of ICH in patients with a recent noncardioembolic ischaemic stroke and to study whether this association differs for patients with lacunar stroke versus other stroke subtypes.

## METHODS

We performed a post hoc analysis on data from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial.[14,15] The design of the trial has been described in detail elsewhere.[16] Briefly, the PRoFESS trial included 20,332 patients with a noncardioembolic ischaemic stroke between 2003 and 2008. The trial took place in 35 countries from various regions including North and South America, Europe, Asia, Australia and South Africa. Patients were included within 120 days of their index event and were randomised to one of two antiplatelet regimes (acetylsalicylic acid in combination with extended release dipyridamole or clopidogrel) and to telmisartan or placebo in a 2x2 factorial design. All patients received additional medication for BP control at the discretion of the treating physician. Follow-up took place one, three and six months after randomisation and every six months thereafter. Patients were followed-up for a median of 2.4 years (range 0 to 4.4 years).

BP was measured at each follow-up visit with a standard and validated Omron sphygmomanometer provided by the sponsor. The average of three consecutive BP

measurements was taken, measured approximately two minutes apart in sitting position. The outcome of interest for the current study was ICH, which was diagnosed on the basis of clinical symptoms and brain imaging if available. Subarachnoid and subdural haemorrhages were excluded. Outcome events were adjudicated by centrally.

**Standard protocol approvals, registrations and patients consents**

The PRoFESS trial was approved by the ethics committee or institutional review board at each participating center and all patients gave written informed consent. The trial is registered on www.clinicaltrials.gov, identifier: NCT00153062.

**Statistical analysis**

We analysed BP measurements in two ways: (1) mean SBP and DBP, to study the association between BP regulation during follow-up and risk of ICH and (2) SBP and DBP as time-dependent covariables, to study the direct association between BP levels and risk of ICH. We calculated mean SBP and DBP by averaging all post baseline measurements prior to occurrence of ICH. In 423 patients post baseline BP measurements were not available; for these patients baseline BP values were used instead of mean BP of all BP measurements. For the time dependent analysis we divided follow-up time of individual patients in intervals, based on dates of follow-up visits. Each follow-up visit initiated a new interval. The follow-up time of this interval was attributed to the BP level that was measured at the start of the interval. If an ICH occurred it was attributed to the most recently measured BP. All BP measurements and mean BP levels were divided in predefined categories: SBP <120, 120-<130, 130-<140, 140-<150, 150-<160 and ≥160 mmHg and DBP <70, 70-<80, 80-<90, 90-<100, and ≥100 mmHg. In the time-dependent analysis patients could contribute follow-up time to multiple categories. Patients were censored at the time of ICH, death or end of follow-up. Two patients without any BP measurements were excluded from the analyses. Among 139,980 follow-up visits, 173 (<1%) BP measurements were missing.

We calculated incidence rates by dividing the number of events per BP category by the number of person-years, both for time-dependent and mean BP categories. Next, we performed univariable and multivariable Cox regression analyses to study the association between SBP or DBP categories as time-dependent covariables and ICH. Separate models were made for SBP and DBP categories. In the first model we adjusted for age and sex, in the second model we additionally adjusted for Asian ethnicity, prior stroke, hyperlipidaemia, lacunar stroke subtype and type of antiplatelet agent. Last, we performed Cox regression analysis with a linear and quadratic term for mean BP, adjusted for variables included in model 2. The association between BP and ICH was visualized by plotting the adjusted hazard ratios from the Cox regression model, with a restricted cubic spline transformation of SBP and DBP. The proportional hazards assumption was assessed by studying log-log plots.

To study whether the association between BP and ICH is different for patients with lacunar stroke versus other stroke subtypes, we performed Cox regression analysis with an

interaction term for BP and ischaemic stroke subtype. All statistical analyses were performed with R version 3.0.2.

## RESULTS

Table 1 shows the baseline characteristics of patients included in our study. Patients who experienced an ICH more often were male, had Asian ethnicity, had a history of stroke (before the index event) and had a lacunar stroke as index event. One hundred thirty three ICHs occurred during 50,778 person-years of follow-up, resulting in an incidence rate of 2.6 (95% confidence interval (CI) 2.2-3.1) per 1,000 person-years. A median of 7 (range 1 to 11) BP measurements were available per patient.

In the time dependent analysis, the incidence rate of ICH increased over SBP categories, from 1.6 (95% CI 0.8-2.9) per 1,000 person-years for SBP <120mmHg to 4.5 (95% CI 3.0-6.4) per 1,000 person-years for SBP ≥160mmHg (Figure 1A). A similar result was seen across mean SBP categories: 1.5 (95% CI 0.6-3.1) per 1,000 person-years for mean SBP <120 mmHg up to 5.7 (95% CI 3.6-8.8) per 1,000 person-years for mean SBP ≥160mmHg (Figure 1B). The incidence rate of ICH was lowest among patients with DBP of 70-<80 mmHg (1.7 per 1,000 person-years; 95% CI 1.1-2.5) and increased across categories >80mmHg. Results were comparable for mean DBP.

In univariable and multivariable analysis, the hazard ratio of ICH increased over BP categories. The risk of ICH was significantly higher among patients with SBP ≥160mmHg, compared with SBP of 130-<140 mmHg (HR 2.07; 95% CI 1.22 to 3.51) and among patients with DBP ≥100 mmHg, compared with DBP of 80-<90 mmHg (HR 2.58; 95% CI 1.50-4.45). The effects remained largely similar after adjustment for confounders (Table 2). A quadratic term for DBP was found significant (p-value 0.006), indicating a non-linear association between DBP and ICH. For SBP, the quadratic term was not significant (p-value 0.94). Graphs displaying the association between BP and ICH are presented in supplementary figure 1.

The interactions between BP and stroke subtype were not statistically significant (p-value 0.55 and 0.93), indicating no difference in the association between SBP or DBP and ICH for patients with lacunar stroke versus other stroke subtypes.

**Table 1. Baseline characteristics**

| | No ICH (n=20,199) | ICH (n=133) |
|---|---|---|
| Age, mean (SD), years | 66 (8.6) | 67 (9.0) |
| Male sex | 12,925 (64) | 97 (73) |
| Ethnicity | | |
| Caucasian | 11,640 (58) | 57 (43) |
| Black | 813 (4) | 3 (2) |
| Asian | 6597 (33) | 63 (47) |
| Current smoking | 4275 (21) | 33 (23) |
| BMI, mean (SD), kg/m$^2$ | 27 (5.0) | 25 (4.2) |
| Baseline SBP, mean (SD), mmHg | 144 (16.6) | 149 (15.5) |
| Baseline DBP, mean (SD), mmHg | 84 (10.5) | 86 (11.6) |
| Follow-up SBP, mean (SD), mmHg | 138 (14.5) | 143 (15.8) |
| Follow-up DBP, mean (SD), mmHg | 80 (8.5) | 84 (11.0) |
| Medical history | | |
| Stroke | 3669 (18) | 37 (28) |
| Hypertension | 14,942 (74) | 106 (80) |
| Diabetes | 5714 (28) | 29 (22) |
| Hyperlipidaemia | 9439 (47) | 54 (41) |
| Myocardial infarction | 1356 (7) | 10 (8) |
| Medication | | |
| Clopidogrel | 10,099 (50) | 52 (39) |
| Any antihypertensive agent | 13,670 (68) | 91 (68) |
| Beta blockers | 4199 (21) | 32 (24) |
| ACE-inhibitor/ARB[a] | 14,280 (71) | 84 (63) |
| Calcium channel blockers | 4923 (24) | 37 (28) |
| Diuretics | 4237 (21) | 24 (18) |
| Other antihypertensives | 1050 (5) | 9 (7) |
| Lipid modifiers | 9811 (49) | 55 (41) |
| TOAST classification index event | | |
| Large vessel atherosclerosis | 5774 (29) | 31 (23) |
| Small artery occlusion | 10,492 (52) | 86 (65) |
| Cardioembolic | 368 (2) | 1 (1) |
| Other | 414 (2) | 2 (2) |
| Unknown | 3136 (16) | 12 (9) |

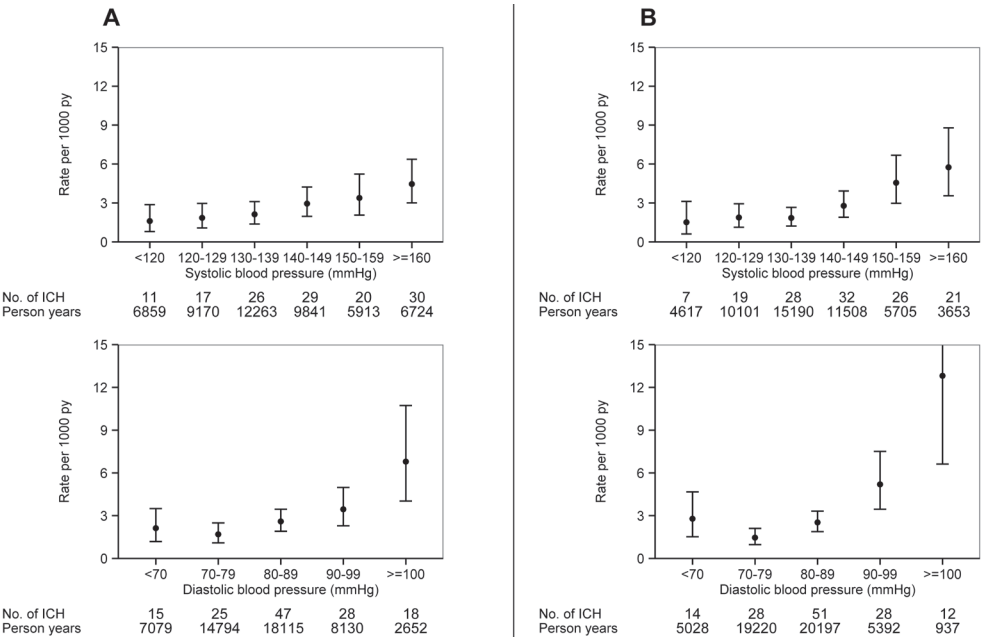
Data are numbers (percentages), unless otherwise indicated. ACE angiotensin-converting enzyme; ARB angiotensin receptor blocker; DBP diastolic blood pressure; SBP systolic blood pressure; a including patients randomised to telmisartan.

**Table 2. Time-dependent analysis of BP levels and risk of ICH**

| | Crude HR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|---|---|---|---|
| **SBP (mmHg)** | | | |
| **<120** | 0.77 (0.38-1.57) | 0.79 (0.39-1.59) | 0.82 (0.41-1.67) |
| **120-<130** | 0.88 (0.48-1.62) | 0.89 (0.48-1.64) | 0.86 (0.46-1.61) |
| **130-<140** | 1 [Ref.] | 1 [Ref.] | 1 [Ref.] |
| **140-<150** | 1.38 (0.82-2.34) | 1.37 (0.81-2.33) | 1.42 (0.84-2.42) |
| **150-<160** | 1.58 (0.88-2.83) | 1.56 (0.87-2.80) | 1.65 (0.92-2.96) |
| **≥160** | 2.07 (1.22-3.51) | 2.09 (1.23-3.54) | 2.27 (1.34-3.86) |
| **DBP (mmHg)** | | | |
| **<70** | 0.84 (0.47-1.50) | 0.77 (0.43-1.38) | 0.80 (0.44-1.45) |
| **70-<80** | 0.66 (0.41-1.08) | 0.64 (0.39-1.04) | 0.65 (0.40-1.06) |
| **80-<90** | 1 [Ref.] | 1 [Ref.] | 1 [Ref.] |
| **90-<100** | 1.31 (0.82-2.09) | 1.34 (0.84-2.17) | 1.40 (0.87-2.24) |
| **≥100** | 2.58 (1.50-4.45) | 2.76 (1.60-4.76) | 3.08 (1.78-5.34) |

HR hazard ratio; CI confidence interval; SBP systolic blood pressure; DBP diastolic blood pressure; Ref reference. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, Asian ethnicity, prior stroke, hypercholesterolemia, lacunar stroke subtype and type of antiplatelet agent.

**Figure 1. Incidence rates of intracerebral haemorrhage per 1,000 person years with 95% confidence intervals for six blood pressure categories**




Blood pressure (BP) analysed as a time-dependent covariable (A), and as mean BP (B).

## DISCUSSION

We demonstrated an association between SBP and DBP and risk of ICH after ischaemic stroke. The risk of ICH increased with increasing BP levels. The association between BP and ICH was similar for patients with lacunar stroke and other stroke subtypes.

The benefit of BP lowering in secondary stroke prevention has been proven in multiple large clinical trials. One of the first was PROGRESS, a multicentre, international study including 6,105 patients with a transient ischaemic attack or stroke (ischaemic or haemorrhagic), who were randomised to active treatment with perindopril +/- indapamide or placebo.[5] Active treatment was associated with a significant reduction in ICH (relative risk reduction 50%; 95% CI 26-67). A similar result was observed in the SPS3 trial, including 3,020 patients with a lacunar stroke, who were randomised to a SBP target of 130-149 mmHg or less than 130 mmHg. This study showed a significantly reduced risk of ICH in the lower target group (HR 0.37; 95% CI 0.15-0.95).[11] The PRoFESS trial randomised 20,332 patients with an ischaemic stroke to telmisartan or placebo, but found no significant difference between treatment groups in occurrence of ICH (HR 0.87; 95% CI 0.63-1.21).[14] The absence of a statistically significant effect in PRoFESS might be explained by the small difference in achieved BP between the treatment and placebo group (SBP 3.8; DBP 2.0 mmHg).

Evidence for an optimal target BP in secondary stroke prevention is scarce. Two post hoc analyses of trial data have shown a J-shaped association between BP and any recurrent stroke (including both ischaemic stroke and ICH), with high risk of recurrence at both high and low BP levels.[10,17] None of these studies has specifically addressed ICH and results are mainly driven by the risk of recurrent ischaemic events. In our study, increasing SBP and DBP were associated with increased risk of ICH. This is in line with results from a recent large retrospective study among patients with ICH.[13] This study showed a linear association between BP and ICH, with lowest risk among normotensive patients (defined as SBP <120 mmHg and DBP <80 mmHg) and a significant increase across all higher BP categories. We also observed the lowest risk of ICH among patients with SBP<120 mmHg, but the risk was not significantly different from those with SBP 130-140 mmHg. Based on current results it remains unclear whether BP lowering below <140 mmHg has additional benefit in prevention of ICH. Although a quadratic term was found significant for DBP, a harmful effect of low DBP could not be confirmed in Cox regression analyses with DBP categories.

Several studies suggested that risk of ICH is higher among patients with a previous lacunar stroke compared with other ischaemic stroke subtypes.[18,19] Patients with previous lacunar stroke may have more fragile deep cerebral arteries and may therefore be more vulnerable to the effect of high BP. However, in our study we did not observe a difference in the association between BP and ICH for patients with lacunar stroke versus non-lacunar stroke, suggesting similar effect of BP on ICH risk regardless of stroke subtype.

Our study benefits from the large sample size with a large number of outcome events. Also, patients were included from a wide range of countries, which supports the

generalisability of the results. Another strength is the prospective and accurate collection of data, with standardised methods for measurement of BP. Some limitations of our study need to be considered as well. We performed a post hoc analysis on trial data and although we adjusted for a large number of potential confounders, the possibility of residual and unmeasured confounding remains. Furthermore, we were unable to differentiate between lobar and non-lobar ICH. This may not have had a large effect on our results, as a large study recently showed that the effect of BP control on ICH recurrence was comparable for patients with lobar and non-lobar ICH.[13]

In patients with noncardioembolic ischaemic stroke, high SBP and DBP are associated with increased risk of ICH. The risk of ICH increases with increasing BP levels. Our data emphasize the need for stringent BP control for prevention of ICH. However, questions regarding the optimal target BP and the best medication regimen remain, in particular for patients with ICH. The Triple therapy prevention of Recurrent Intracerebral Disease EvenNts Trial (TRIDENT) will investigate whether in patients with ICH with high-normal BP more intensive long term BP control with a fixed low-dose combination of BP lowering treatment (Triple pill) is more effective than standard care in preventing recurrent stroke.[20]

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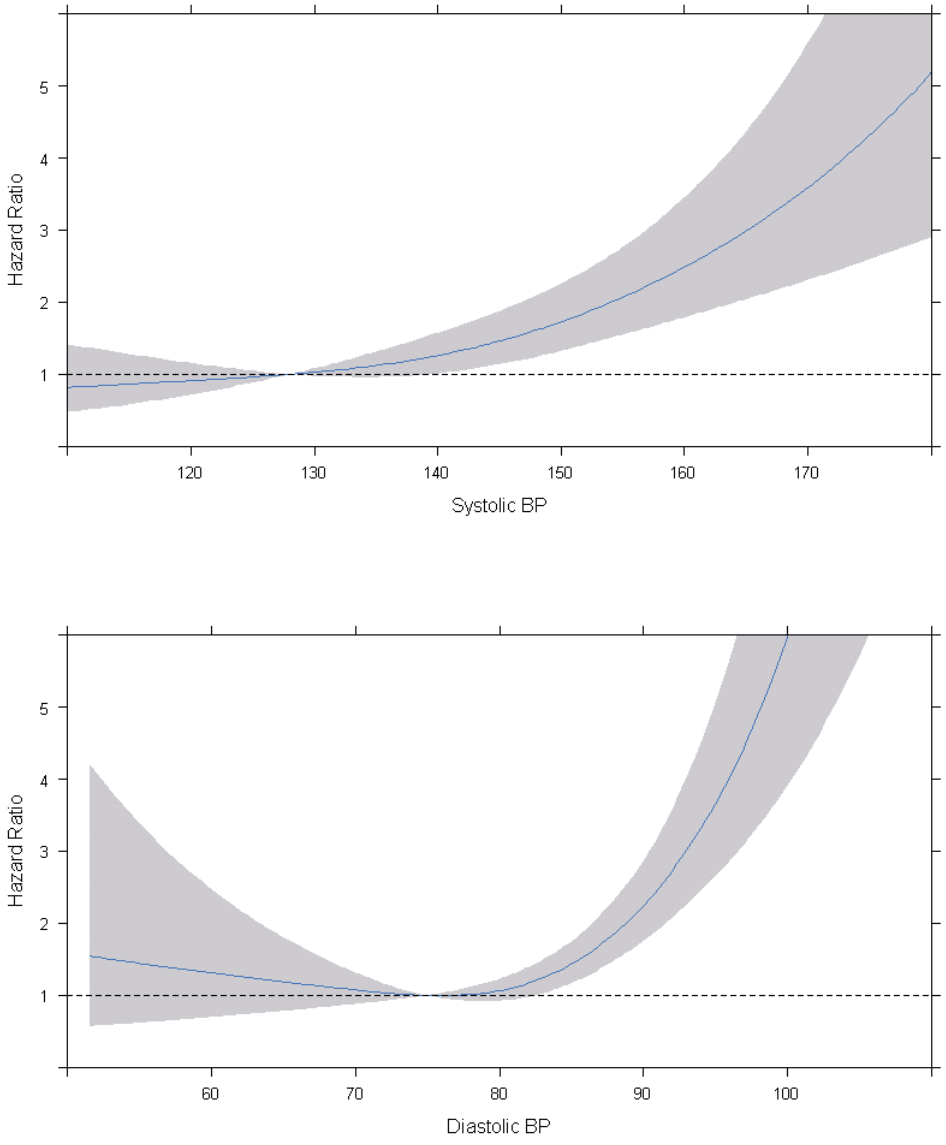
## SUPPLEMENT

**Supplementary figure 1. Hazard ratios and 95% confidence intervals of mean systolic and diastolic blood pressure**




Figures are based on Cox proportional hazards models, adjusted for age, sex, Asian ethnicity, prior stroke, hyperlipidemia, lacunar stroke subtype and type of antiplatelet agents.

BP: blood pressure

# CHAPTER 10

## PREDICTING THE PRESENCE OF MACROVASCULAR CAUSES IN NON-TRAUMATIC INTRACEREBRAL HAEMORRHAGE: THE DIAGRAM PREDICTION SCORE

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* These authors contributed equally to the manuscript

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## ABSTRACT

**Objective** A substantial part of non-traumatic intracerebral haemorrhages (ICH) arises from a macrovascular cause, but there is little guidance on selection of patients for additional diagnostic work-up. We aimed to develop and externally validate a model for predicting the probability of a macrovascular cause in patients with non-traumatic ICH.

**Methods** The DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study (N=298; 69 macrovascular cause; 23%) is a prospective, multicentre study, assessing yield and accuracy of CT angiography (CTA), MRI/MRA and intra-arterial catheter angiography in diagnosing macrovascular causes in patients with non-traumatic ICH. We considered pre-specified patient and ICH characteristics in multivariable logistic regression analyses as predictors for a macrovascular cause. We combined independent predictors in a model, which we validated in an external cohort of 173 ICH patients (78 macrovascular cause; 45%).

**Results** Independent predictors were younger age, lobar or posterior fossa (versus deep) location of ICH and absence of small vessel disease (SVD). A model that combined these predictors showed good performance in the development data (c-statistic 0.83; 95% CI 0.78-0.88) and moderate performance in external validation (c-statistic 0.66; 0.58-0.74). When CTA results were added, the c-statistic was excellent (0.91; 0.88-0.94), and good after external validation (0.88; 0.83-0.94). Predicted probabilities varied from 1% in patients aged 51-70 years with deep ICH and SVD, to more than 50% in patients aged 18-50 years with lobar or posterior fossa ICH without SVD.

**Conclusion** The DIAGRAM scores help to predict the probability of a macrovascular cause in patients with non-traumatic ICH based on age, ICH location, SVD and CTA.

## INTRODUCTION

Intracerebral haemorrhage (ICH) accounts for 15-20% of all strokes and is the most devastating stroke subtype.[1,2] Around 15-25% of ICHs are caused by an underlying macrovascular cause, such as an arteriovenous malformation (AVM), aneurysm, dural arteriovenous fistula (dAVF), cavernoma, and cerebral venous sinus thrombosis.[3-5] Among young adults, macrovascular causes are the leading cause of ICH.[6]

Early diagnosis of underlying macrovascular lesions can influence clinical management and prognosis, as timely intervention might prevent recurrent haemorrhage.[7,8] Intra-arterial digital subtraction angiography (IADSA) is the gold standard for detection of macrovascular abnormalities, but is an invasive procedure associated with some risk of complications.[9] MRI/MRA is less invasive, but has lower diagnostic accuracy for macrovascular causes than IADSA.

Currently, there is little guidance on which patients to select for (invasive) angiographic imaging and clinical practice thus varies widely.[10] Several factors have been associated with a higher likelihood of finding a macrovascular cause, including younger age, lobar location and absence of hypertension.[11] Early risk stratification of patients with ICH might help physicians to make swift, well-informed decisions about who to select for further angiographic imaging.

We aimed to develop and externally validate a prediction model to estimate the probability of finding a macrovascular cause in patients with non-traumatic ICH, based on patient characteristics, haemorrhage characteristics and, optionally, CTA.

## METHODS

### Development cohort

We used data from the DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study, a prospective, multicentre cohort study that assessed yield and diagnostic accuracy of angiographic imaging (CTA, MRA, IADSA) in patients with non-traumatic ICH.[12] Between 2008 and 2014, 298 patients aged 18-70 years were included in 22 participating centres across the Netherlands. Patients over 45 years of age with hypertension and ICH in the basal ganglia, thalamus or posterior fossa were excluded, because of the low probability of finding an underlying macrovascular cause.[13] Also, patients with a known macrovascular abnormality, brain tumour or patients who used oral anticoagulants and had an international normalised ratio of >2.5 at the time of ICH were excluded. All patients underwent CTA within seven days of the ICH, followed by MRI/MRA within four to eight weeks if the CTA was negative. Patients underwent subsequent IADSA if the results of CTA or MRI/MRA were inconclusive or negative. CTA or MRI/MRA were considered inconclusive if a macrovascular cause was suspected but a definite diagnosis could not yet be established. Scans were read

both locally and centrally. In case of a new diagnosis, local centres were informed. One additional arteriovenous fistula was detected at central reading.

Two hundred ninety-one patients had a CTA of sufficient quality for assessment (98%). MRI/MRA was performed in 255 patients (86%), of whom 214 patients with a negative or inconclusive CTA and IADSA in 154 patients (52%), of whom 106 patients with a negative or inconclusive CTA (supplementary figure 1). Quality of IADSA was insufficient for assessment in three patients. One hundred twenty-six patients had a negative or inconclusive CTA, but did not undergo subsequent IADSA. The main reason for not performing IADSA in patients with a negative CTA was an alternative diagnosis on MRI/MRA, or reluctance of either patients or their treating physicians. Four patients with a negative CTA died before MRI/MRA could be performed. The outcome was presence of a macrovascular cause (AVM, aneurysm, dAVF, cavernoma, cerebral venous sinus thrombosis and developmental venous anomaly (DVA)) as cause of the haemorrhage, and was based on best available evidence from all findings (CTA, MRA, DSA) during one year follow-up. The DIAGRAM study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands, and local approval was obtained from all participating hospitals. All participants gave written informed consent.

**Model development**

Candidate predictors were preselected based on the literature and included age, hypertension (defined as a history of hypertension, use of antihypertensive drugs before ICH or evidence of left ventricular hypertrophy on admission ECG), smoking, high alcohol intake (defined as four or more units per day), location of ICH (lobar, deep or posterior fossa), presence of small vessel disease (SVD) on non-contrast CT (NCCT) (defined as presence of white matter lesions, or a lacunar infarct in basal ganglia, thalamus or posterior fossa, irrespective of whether it had been symptomatic or was an asymptomatic finding (see supplementary methods for a detailed description of SVD assessment and supplementary figure 2)) and CTA. We developed two models; one model based on patient characteristics and NCCT (DIAGRAM score) and another model based on patient characteristics, NCCT and results from CTA imaging for use in higher resource settings (DIAGRAM+ score), which may help to estimate the probability of a macrovascular cause given that CTA is negative. For the current analysis, inconclusive CTAs were joined with positive results, because a CTA suggesting a macrovascular cause, yet inconclusive, will always trigger further diagnostic tests. Given the one in ten rule with one predictive variable for every ten outcome events, we could study a maximum of seven predictors.[14,15]

**Statistical Analysis**

Missing values for alcohol consumption (1%), smoking (1%) and CTA (2%) in the development cohort were imputed with single imputation. We used restricted cubic spline functions and graphs to assess whether age could be analysed as linear term or needed transformation. We performed multivariable logistic regression analysis to study the association between

candidate predictors and the presence of a macrovascular cause. The full model containing all candidate predictors was simplified by performing backward selection based on Akaike's Information Criterion (AIC). We internally validated the model by performing bootstrapping. A shrinkage factor was estimated from the bootstrap procedure and regression coefficients were multiplied by this shrinkage factor to correct for overfitting. Model performance was assessed with discrimination and calibration. Discrimination refers to the ability of the model to distinguish between someone with and without a macrovascular cause and was assessed with the c-statistic. Calibration assesses the correspondence between observed and predicted risk and was studied with a calibration plot. As a sensitivity analysis, we examined the performance of the models in a subset of patients (n=171), excluding those who did not undergo IADSA following a negative or inconclusive CTA. We generated prediction charts with predicted probabilities of finding a macrovascular abnormality for each combination of risk factors. Additionally, we created two prediction scores based on regression coefficients of the final multivariable regression models. For the prediction charts and scores, age was dichotomized at a value close to the mean.

**External validation**

For external validation, we used a cohort of 173 patients with non-traumatic ICH.[16] Consecutive patients who underwent IADSA at the National Hospital for Neurology and Neurosurgery in London between 2010 and 2014 were retrospectively reviewed. Patients with non-traumatic ICH with available NCCT and CTA were included. NCCT and CTA were routinely performed in all patients with acute ICH presenting to the hyperacute stroke unit, unless there were contra-indications. The necessity of IADSA performance was judged in a weekly neuroradiological meeting, and was based on age, ICH location and medical history. MRI was performed according to clinical care, but was not systematically undertaken in all patients. The reference standard in the validation cohort was IADSA. All CTAs were reviewed blinded to IADSA result. The study was approved by the Clinical Governance Committee of the National Hospital and the UCL Institute of Neurology and National Hospital Joint Research Ethics Committee.

We applied the original regression equation to the validation data and calculated the predicted probability of finding a macrovascular cause for each patient. We assessed model performance with the c-statistic and calibration plots. As calibration is known to be strongly influenced by the incidence of the outcome in the validation population, we recalibrated the prediction models. Recalibration was performed by logistic regression analysis in the validation data with the linear predictor (the combination of regression coefficients with covariate values) as offset in the model. The resulting intercept was combined with the original regression coefficients to obtain predicted probabilities for the validation population. We present calibration of the models after recalibration, as in practice it is also advised to recalibrate a model before putting it to use. Calibration results before recalibration are provided in the online supplement. Analyses were performed with R version 3.3.2. Results are reported in accordance with the TRIPOD statement.[17]

## RESULTS

Table 1 shows the baseline characteristics of the development and validation cohorts. Among 298 patients included in the development cohort, 69 (23%) had an underlying macrovascular cause (for listing of all causes, see supplementary table 1). In the validation cohort a macrovascular cause was found in 78 of 173 patients (45%). Patients in the development cohort were slightly older (mean age 53 years, SD 11.5 versus 50 years, SD 15.0 in the validation cohort). The frequency of underlying vascular aetiologies in each cohort is presented in Table 2.

**Table 1. Baseline characteristics of development and external validation cohort**

| | Development cohort | | Validation cohort | |
|---|---|---|---|---|
| | **Macrovascular cause (n=69)** | **No macrovascular cause (n=229)** | **Macrovascular cause (n=78)** | **No macrovascular cause (n=95)** |
| Age, mean (SD), years | 47 (12.7) | 55 (10.5) | 49 (17) | 50 (13) |
| Male sex | 45 (65) | 140 (61) | 39 (50) | 54 (57) |
| Smoking (current) | 20 (29) | 52 (23) | - | - |
| High alcohol intake | 4 (6) | 32 (14) | - | - |
| Hypertension | 16 (23) | 79 (34) | 16 (21) | 37 (39) |
| Location of ICH | | | | |
| Deep | 5 (7) | 80 (35) | 13 (17) | 40 (42) |
| Lobar | 49 (71) | 129 (56) | 46 (59) | 37 (39) |
| Posterior fossa | 15 (22) | 20 (9) | 13 (17) | 15 (16) |
| IVH | - | - | 6 (8) | 3 (3) |
| Signs of small vessel disease | 4 (6) | 116 (51) | 12 (15) | 35 (37) |
| CTA | | | | |
| Positive | 47 (68) | 12 (5) | 53 (68) | 0 (0) |
| Inconclusive | 4 (6) | 8 (4) | 11 (14) | 7 (7) |

Values are numbers (percentage), unless otherwise stated. ICH intracerebral haemorrhage; IVH intraventricular haemorrhage; SVD small vessel disease; CTA computed tomography angiography

**Table 2. Macrovascular causes underlying ICH in development and validation cohort**

| | Development cohort n (%) | Validation cohort n (%) |
|---|---|---|
| Arteriovenous malformation | 34 (49) | 68 (87) |
| Dural arteriovenous fistula | 13 (19) | 7 (9) |
| Cavernoma | 10 (14) | - |
| Cerebral venous sinus thrombosis | 4 (6) | - |
| Aneurysm | 7 (10) | 2 (3) |
| Developmental venous anomaly* | 1 (1) | - |
| Carotid cavernous fistula | - | 1 (1) |
| **Total** | **69** | **78** |

ICH intracerebral haemorrhage; *this patient had a large developmental venous anomaly with partial thrombosis, which was clearly the cause of the ICH.

**Table 3. Odds ratios for presence of a macrovascular cause from multivariable models in the development cohort**

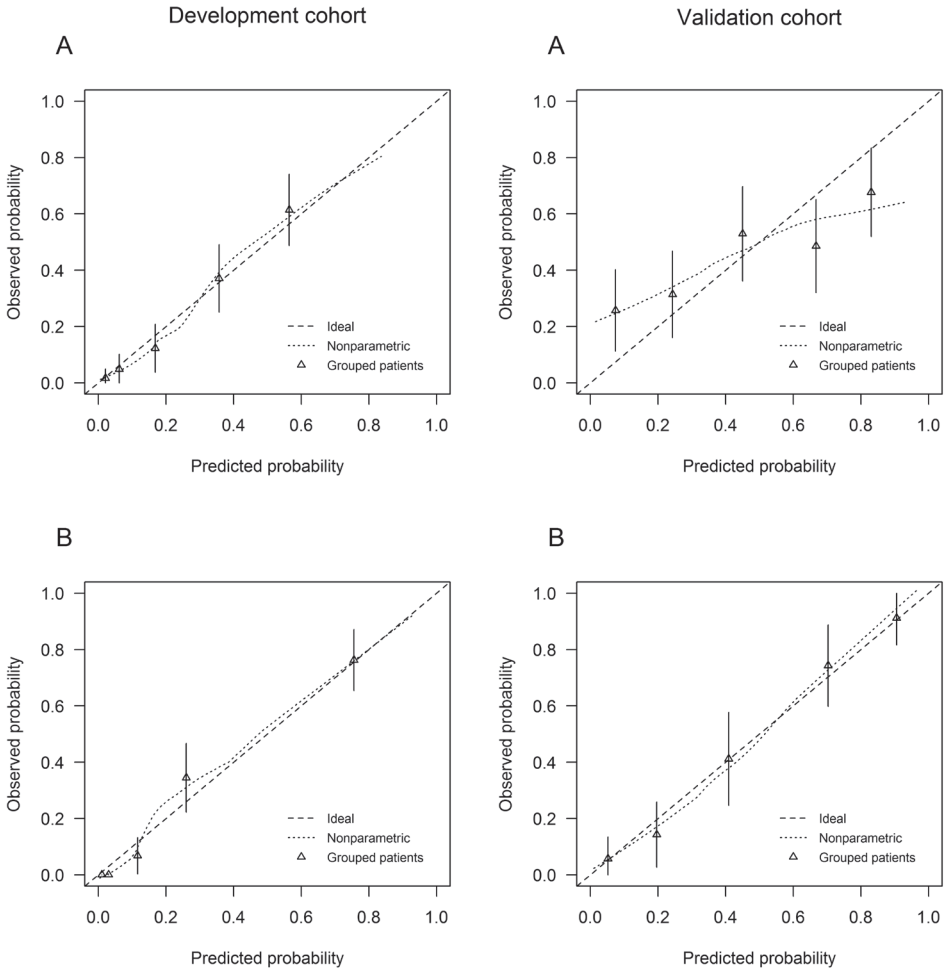
| | Patient characteristics and NCCT OR (95% CI) | Patient characteristics, NCCT and CTA OR (95% CI) |
|---|---|---|
| Age | 0.95 (0.93-0.98) | 0.97 (0.94-1.00) |
| Location | | |
| Deep | 1 [Ref] | 1 [Ref] |
| Lobar | 7.2 (2.8-22.4) | 4.0 (1.3-14.2) |
| Posterior fossa | 19.3 (5.8-75.4) | 9.9 (2.5-44.9) |
| Absence of SVD | 11.8 (4.4-41.2) | 11.8 (3.7-48.6) |
| Positive or inconclusive CTA | - | 15.9 (7.5-35.5) |

NCCT non-contrast CT; CTA computed tomography angiography; SVD small vessel disease; CI confidence interval; OR odds ratio; Ref reference.

In multivariable analysis younger age, location of ICH, absence of signs of SVD and a positive or inconclusive CTA were independent predictors for presence of an underlying macrovascular cause (Table 3).

A simple model based on age, location of ICH and signs of SVD had a c-statistic of 0.83 (95% CI 0.78 to 0.88) in the development cohort after shrinkage. The predictive performance of the model increased if CTA was included as predictor (c-statistic 0.91; 95% CI 0.88 to 0.94). Calibration of both models was accurate, as shown by the calibration plots (Figure 1). The original regression equations are provided in supplementary table 2. When we excluded patients in whom IADSA was not performed following a negative or inconclusive CTA, c-statistics were similar to those of the full cohort analysis. Calibration plots and c-statistics are presented in supplementary figure 3.

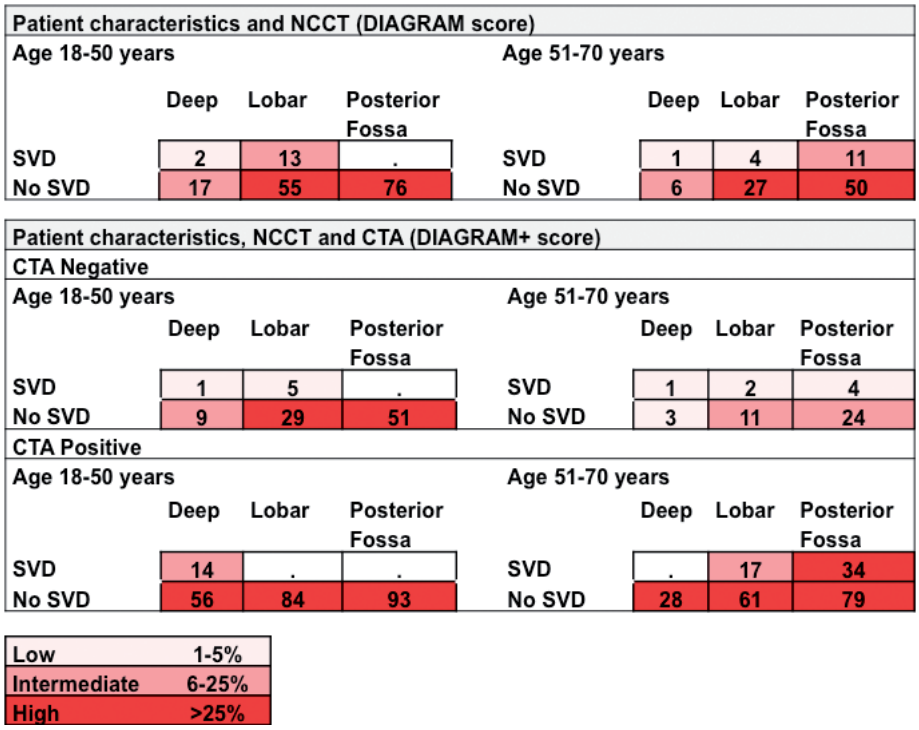
**Figure 1. Calibration plots of DIAGRAM prediction models in the development and validation cohort**




Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B). The triangles indicate the observed frequencies with 95% confidence intervals by quintiles of predicted probability

Figure 2 shows risk charts with estimated probabilities of finding a macrovascular cause according to age, ICH location, presence of SVD, and for the same predictors combined with CTA. The probability of finding a macrovascular cause ranged from 1% in patients aged 51 to 70 years with deep ICH and signs of SVD, up to more than 50% in patients aged 18 to 50 years with lobar or posterior fossa ICH and no signs of SVD. Two simple risk scores are presented in supplementary table 3, which can be used in combination with supplementary figure 4 to obtain predicted probabilities for individual patients.

**Figure 2. Prediction charts with absolute probabilities (%) of an underlying macrovascular cause in individual patients with ICH**




ICH intracerebral haemorrhage; NCCT non contrast CT; SVD small vessel disease; CTA computed tomography angiography.

### External validation

External validation of the models showed a c-statistic of 0.66 (95% CI 0.58 to 0.74) for the model based on patient characteristics and NCCT, and a c-statistic of 0.88 (95% CI 0.83 to 0.94) for the model with additional CTA. The calibration plots show that the likelihood of finding a macrovascular cause increased along the range of predicted probabilities, with moderate calibration for the model with patient characteristics and NCCT (Figure 1A) and good calibration for the model with additional CTA (Figure 1B). Before recalibration, both models systematically underestimated the probability of finding a macrovascular cause (supplementary figure 5).

## DISCUSSION

Our study shows that younger age, lobar or posterior fossa location of ICH, absence of signs of SVD, and a positive or inconclusive CTA are independent predictors for presence of a macrovascular cause in patients with non-traumatic ICH. We combined predictors in two practical prediction charts, which we externally validated. Estimated risks vary from 1% in patient aged 51 to 70 with deep ICH and signs of SVD, to more than 50% in patients aged 18 to 50 with lobar or posterior fossa ICH and no signs of SVD. Both models showed good discriminatory ability and calibration in the development cohort, whereas performance in external validation was moderate for the model with NCCT and good for the model including CTA.

Previously, two other prediction models have been described to predict the probability of a macrovascular cause in patients with non-traumatic ICH (supplementary table 4). The simple ICH score was developed in a retrospective cohort of 160 patients with non-traumatic ICH in which presence of a macrovascular cause was determined with IADSA.[18] Performance of the risk score was moderate in both the development and external validation cohort. This model was derived from a high-risk population, as represented by the relatively young age (mean age 41 years) and high proportion of patients with a macrovascular cause (51%). The results may therefore not be generalizable to all patients with ICH suspected of having a vascular malformation, and the prediction model will likely overestimate the probability of finding a macrovascular cause. The secondary intracerebral haemorrhage score (SICH) was developed in a retrospective cohort of 623 patients with ICH in the US.[11] Presence of a macrovascular cause was determined with CTA. The model was based on patient characteristics and NCCT characteristics, which included enlarged vessels or calcifications along ICH margins and hyperattenuation within a dural venous sinus or cortical vein. Independent validation in the US showed good performance of the model,[19] performance was moderate in an external validation study in the Netherlands.[3] NCCT categorization was a strong predictor for macrovascular causes, but characteristics were not always easy to recognize on NCCT,[3] which may limit easy application of the model in clinical practice. The DIAGRAM prediction score is the first model developed in a prospective cohort, excluding patients in whom yield of angiographic imaging has been shown to be very low (patients older than 45 years with a history of hypertension and a deep or posterior fossa bleed).[13] Next to known predictors for a vascular malformation, we were able to add signs of SVD as important predictor of absence of a macrovascular cause. To our knowledge, this is the first prediction model that also incorporated results from CTA imaging. This can be useful in healthcare settings where CTA is often or routinely used, and clinicians have to decide whether or not to perform MRI/MRA and/or IADSA after a negative CTA. The DIAGRAM prediction score may help to weigh the probability of finding a macrovascular cause against the risk of complications of IADSA.

Performance of the model based on patient characteristics and NCCT diminished in the external validation cohort. This is likely due to differences between the development

and validation cohorts in terms of patient selection and choice of reference standard. Selection of patients influences prevalence of macrovascular causes and may affect predictor outcome associations, which in turn affect model performance. By selection of patients who underwent IADSA in the validation cohort, the prior probability of finding a macrovascular abnormality in this cohort was higher, which resulted in a systematically underestimated risk of finding a macrovascular cause by the prediction models. Simple recalibration improved correspondence between observed and predicted risks, supporting the hypothesis that differences in outcome incidence were an important source of miscalibration. Selection of more high-risk patients may also have altered predictor-outcome associations. As a consequence, the discriminatory ability of the model may have decreased. Given differences between development and validation cohorts, validation of the DIAGRAM prediction model in a prospective cohort is necessary to further establish the robustness of the model.

Strengths of our study include the prospective nature of the development cohort and the standardized radiological work-up. Another strength is the external validation in a setting outside of the Dutch healthcare system. Our study also has limitations. First, the models were developed in a preselected group of patients with a relatively high likelihood of finding a macrovascular cause, excluding those older than 70 years of age, and patients over the age of 45 years with hypertension and deep ICH or ICH in the posterior fossa. This preselected group represents patients in whom the diagnostic dilemma is most pressing in clinical practice. Generalisability to older patients with non-traumatic ICH remains to be established. In the elderly, diagnostic tests to search for macrovascular causes of ICH are often performed in only a small proportion of patients.[20] Second, not all patients in the development cohort underwent IADSA. As a consequence, small AVMs or dAVFs may have been missed. However, patients were followed-up for one year to assess occurrence of rebleeds and register possible causes of ICH identified during follow-up. Third, the association between CTA and presence of a macrovascular cause may have been overestimated, as CTA was also part of the reference standard. However, when we restricted our analyses in the development cohort to the patients who underwent IADSA, the discriminatory performance of the model remained similar. Fourth, MRI/MRA was not systematically performed in the validation cohort, which may have led to underestimation of the number of patients in whom a cavernoma was the cause of ICH.

The current models may facilitate selection of patients for further diagnostic work-up. The results of the model based on patient characteristics and NCCT suggest that in the absence of SVD, some form of angiographic imaging (CTA/MRA/IADSA) should be performed in all patients under 70 years of age, regardless of ICH location. If signs of SVD are seen on NCCT, CTA should still be considered in young patients (18-50 years old) with lobar and posterior fossa ICH, and in elderly patients (51-70 years old) with posterior fossa ICH. In settings where it is feasible to perform CTA in all patients shortly after ICH, the DIAGRAM+ score is particularly useful in patients in whom CTA was negative to guide the decision to perform these additional tests. Following a negative CTA, there is still a substantial chance of

finding a macrovascular cause in patients without signs of SVD, both in young and in older patients. In these patients, performance of MRI/MRA and IADSA deserves consideration, especially in patients with lobar and posterior fossa ICH. It should be noted that also in patients with a deep ICH who do not have SVD nor hypertension (as defined by the inclusion criteria), there is an around 9% (in those 18 to 50 years) and 3% (in those 51 to 70 years) chance of finding a macrovascular cause of the ICH after a negative CTA. Whether or not in these patients further imaging will be performed should be determined as part of a shared decision making process between the patient and the team responsible for their care. Because the AVMs or dAVFs that are sought for with IADSA after a negative CTA will be small, IADSA should be performed in centres with ample experience in detecting such lesions. Although the prediction charts can provide guidance in decision-making, it should be noted that there is a degree of uncertainty around the presented estimates, as shown by the confidence intervals in supplementary figure 4.

In conclusion, the DIAGRAM prediction charts can help to predict the probability of finding a macrovascular cause in both low and high resource settings. External validation of the models in other prospective cohorts and in elderly patients is needed to gain further insight in the robustness of the models.

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## SUPPLEMENT

### Supplementary methods. Assessment of small vessel disease on admission non-contrast CT

All non-contrast CTs (NCCT) were rated independently by two experienced neuroradiologist for presence of small vessel disease (SVD). Disagreements were resolved by a third observer. Characteristics of interest were:

- Presence of white matter lesions (WML), and if so: WML location (periventricular, subcortical or both) and severity (<1 cm, >1 cm, or confluent);
- Presence of a hypodensity elsewhere on NCCT, and if so: location.

Signs of small vessel disease on NCCT was defined as presence of white matter lesions, or an ischaemic lesion in basal ganglia, thalamus or posterior fossa.

**Supplementary table 1. Regression equations of multivariable models**

| Regression equation model based on patient characteristics and NCCT |
|---|
| -2.1828-0.0408*AGE+2.1224*no SVD+1.6923*Lobar+2.5472*Posterior fossa |
| Regression equation model based on patient characteristics, NCCT and CTA |
| -3.4045-0.0281*AGE+2.1585*no SVD+1.2038*Lobar+2.0049*Posterior fossa+2.4201*CTA |

No SVD no signs of small vessel disease; CTA positive or inconclusive CTA.

**Supplementary table 2: Calculation of the DIAGRAM and DIAGRAM+ prediction scores**

| | DIAGRAM score | DIAGRAM + score |
|---|---|---|
| | Points | Points |
| Age ≤50 | 1 | 1 |
| Absence of small vessel disease | 2 | 2 |
| ICH location | | |
| Deep | 0 | 0 |
| Lobar | 2 | 1 |
| Posterior fossa | 3 | 2 |
| Positive CTA | - | 3 |

NCCT non contrast CT; ICH intracerebral haemorrhage
An individual DIAGRAM or DIAGRAM+ score is the sum of the points assigned to each of the predictors. The maximum score is 6 for the model based on patient characteristics and NCCT (DIAGRAM score), and 8 for the model based on additional CTA (DIAGRAM + score).

**Supplementary table 3: Overview of prediction models for macrovascular causes and external validation studies**

**Model development**

| Model | Prospective/ retrospective | Patient selection | N | Mean age | MVC (%) | Reference standard | C-statistic |
|---|---|---|---|---|---|---|---|
| SICH score[1] | R | Patients who underwent CTA within 24h | 623 | 65 | 15 | CTA | 0.86 (0.83-0.89) |
| Simple ICH score[2] | R | Patients who underwent DSA | 160 | 41 | 51 | DSA | 0.65 (0.56-0.73) |
| DIAGRAM score | P | Patients < 70 y, excl of patients >45 y with HT and deep ICH or post fossa ICH | 298 | 53 | 23 | 1y FU | 0.83 (0.78-0.88)* 0.91 (0.88-0.94)‡ |

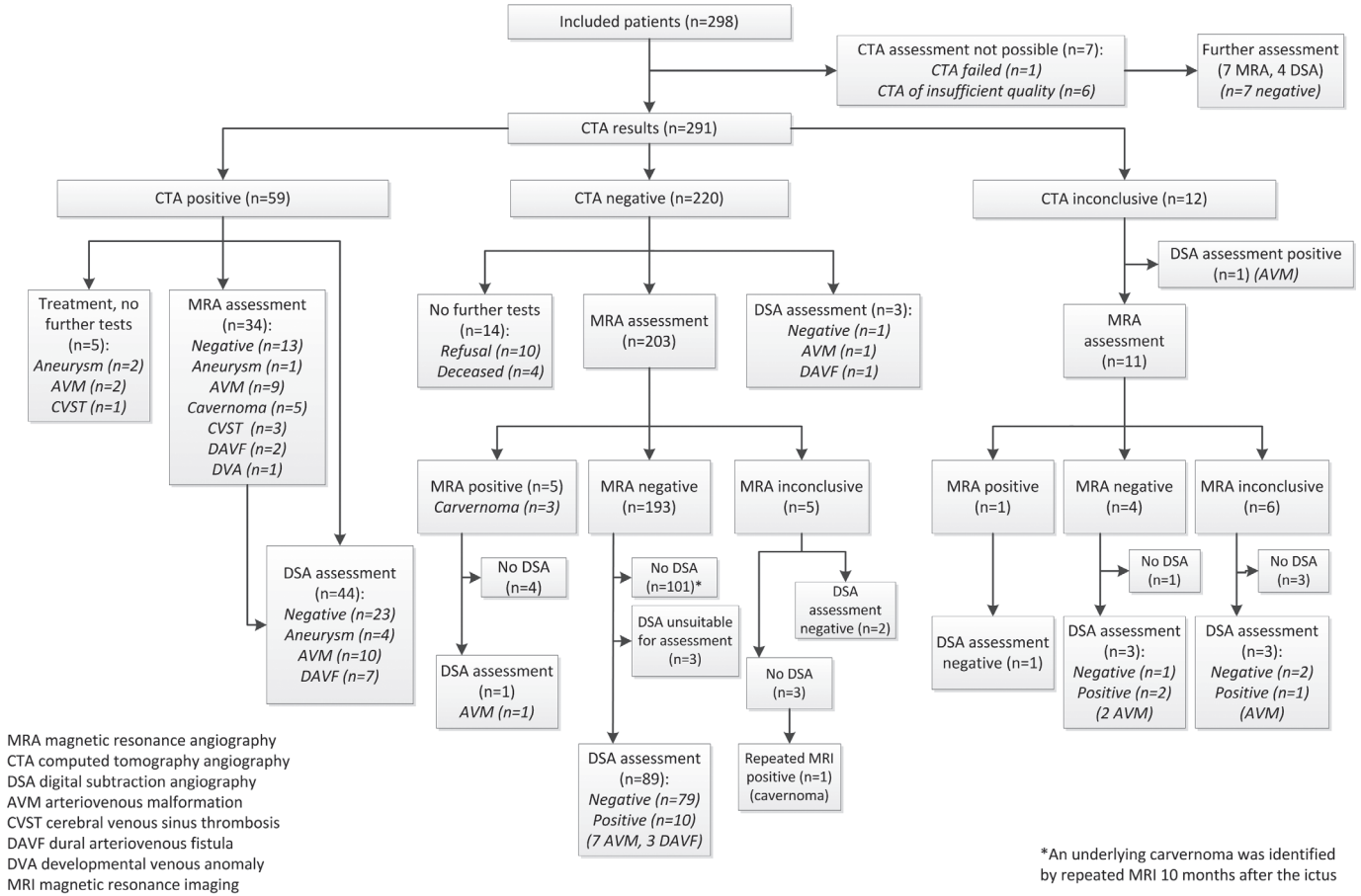
R retrospective; P prospective; y year; FU follow-up; MVC macrovascular cause; HT hypertension. *model based on patient characteristics and non contrast CT, ‡model based on patient characteristics, non contrast CT and CTA.

**Model validation**

| Model | Prospective/ retrospective | Patient selection | N | Mean age | MVC (%) | Reference standard | C-statistic |
|---|---|---|---|---|---|---|---|
| SICH score[1] | P (temporal) | Patients who underwent CTA | 222 | 67 | 13 | CTA | 0.87 (0.82-0.91) |
| SICH score[3] | R (external) | Patients who underwent DSA or neurosurgical evacuation | 341 | 57 | 18 | DSA or neurosurgical inspection | 0.82 (0.78-0.86) |
| SICH score[4] | R (external) | Patients who underwent CTA, MRA, DSA or pathological examination | 204 | ? | 24 | CTA, MRA, DSA, neurosurgical or pathological inspection | 0.73 (0.65-0.80) |
| Simple ICH score[2] | P | Patients who underwent CTA, MRA or DSA. | 106 | 57 | 32 | CTA, MRA or DSA | 0.67 (0.55-0.79) |
| DIAGRAM score | R | Patients who underwent CTA and DSA | 173 | 49 | 45 | DSA | 0.66 (0.58-0.74)* 0.88 (0.83-0.94)‡ |

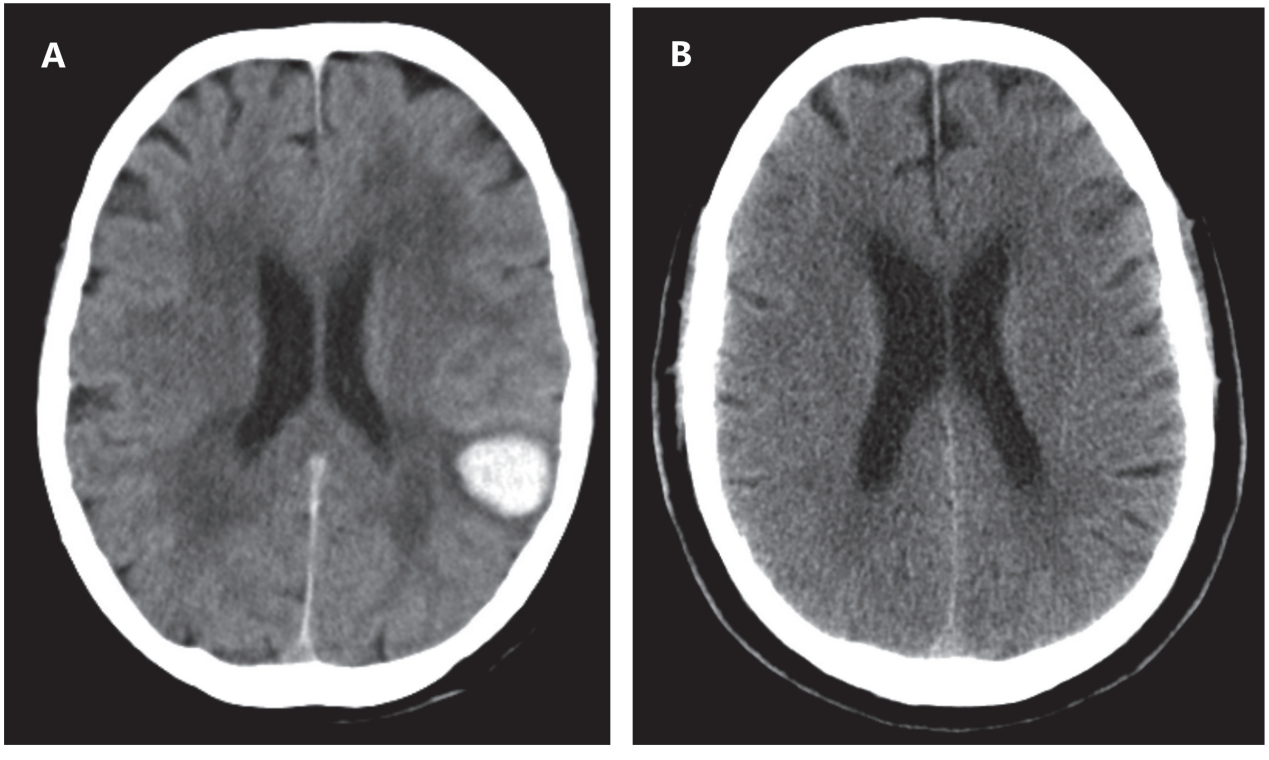
R retrospective; P prospective; MVC macrovascular cause. *model based on patient characteristics and non contrast CT, ‡model based on patient characteristics, non contrast CT and CTA, [1,2,3,4] references, please see final page of supplementary file.

**Supplementary figure 1: Flowchart of angiographic examinations in DIAGRAM[5]**



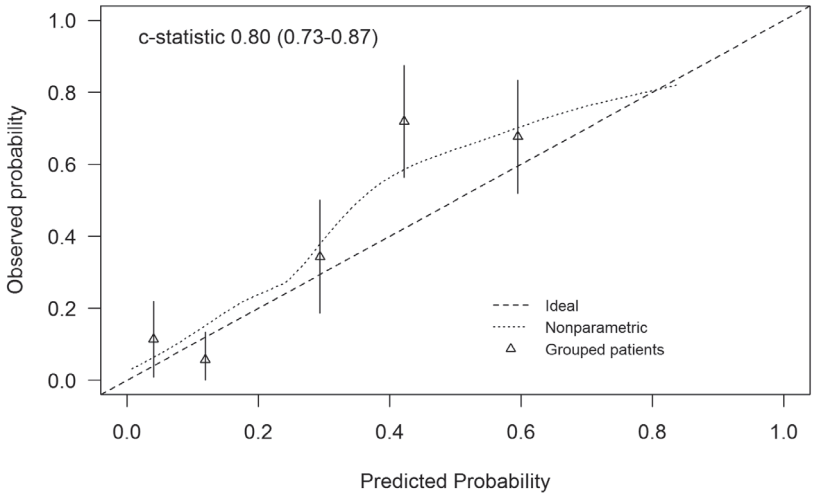
**Supplementary figure 2: CT scan of a patient with (A) and without (B) white matter hypodensities indicative of small vessel disease**



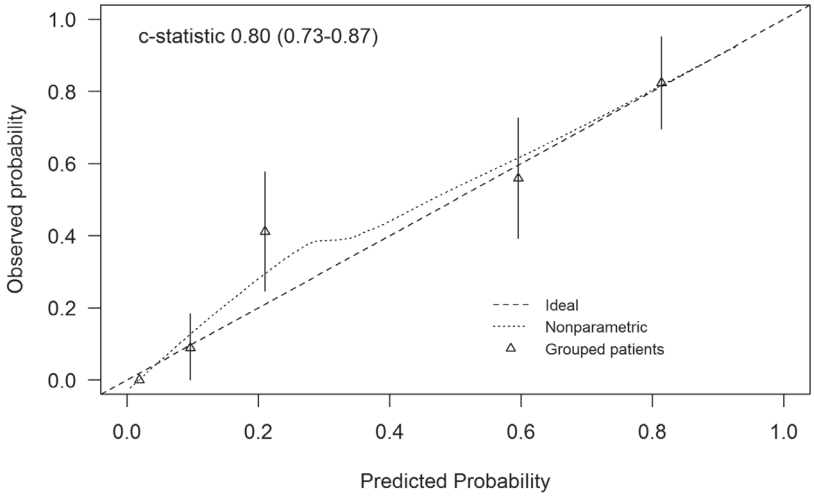


**Supplementary figure 3: Calibration plots and c-statistics of DIAGRAM models excluding DIAGRAM patients who did not undergo DSA according to the study protocol. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)**

**A.**

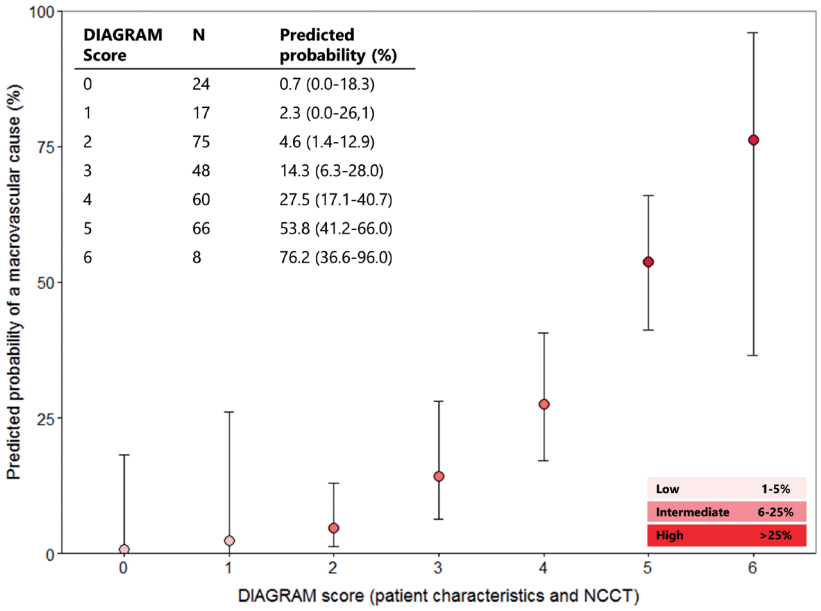



**B.**

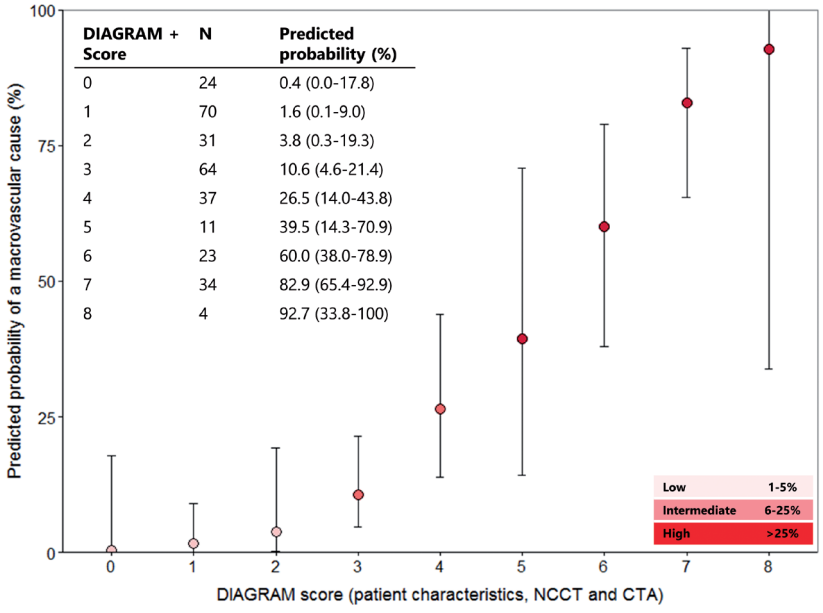


**Supplementary figure 4: Predicted one year probability of an underlying macrovascular cause based on the DIAGRAM prediction scores. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)**

**A.**

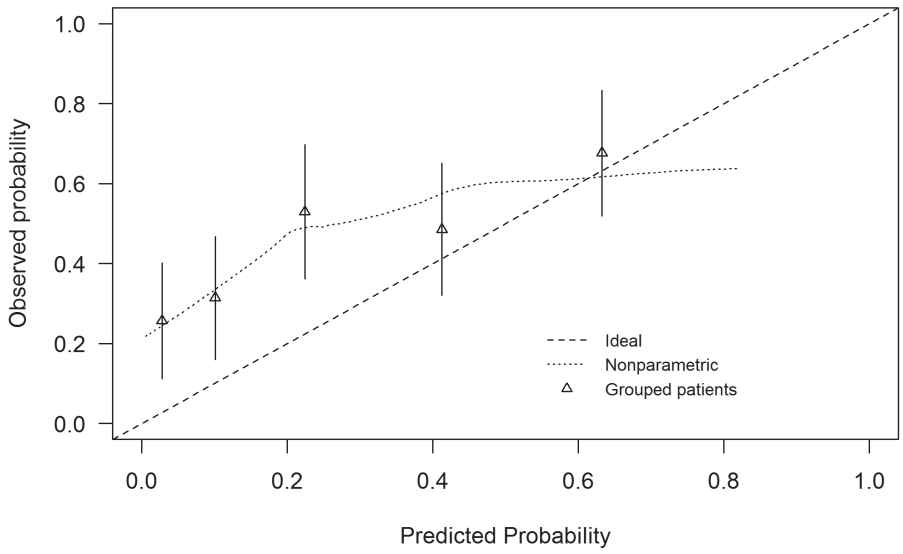



**B.**

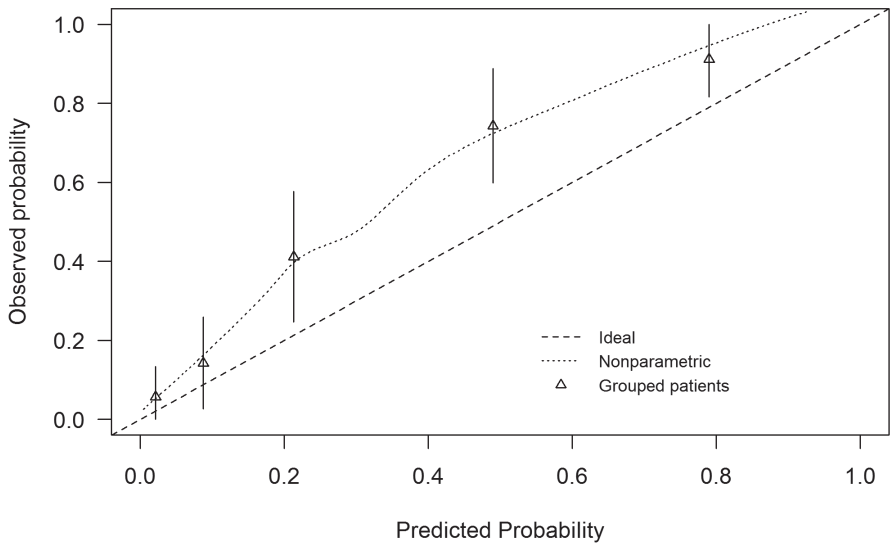


**Supplementary figure 5: Calibration plots of DIAGRAM models in validation cohort before recalibration. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)**

**A.**




**B.**



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# CHAPTER 11

GENERAL DISCUSSION

## GENERAL DISCUSSION

In this thesis we investigated prediction of major bleeding on antithrombotic treatment following a TIA or ischaemic stroke, and studied whether bleeding risk assessment can individualise decisions for antithrombotic treatment. Although there is no doubt about the efficacy of antithrombotic treatment in secondary stroke prevention,[1,2] bleeding is a serious and potentially life-threatening side effect of antithrombotic drugs. Identifying those patients who benefit from treatment without being severely harmed may help to improve secondary stroke prevention.

## METHODOLOGICAL CONSIDERATIONS

Part of this thesis was based on an analysis of individual patient data (IPD) from randomised clinical trials. Use of IPD is considered the "gold standard" for meta-analysis in intervention research,[3,4] and its application has risen since 1990.[4] Also in diagnostic and prognostic research, individual patient data meta-analysis (IPD-MA) is increasingly popular.[5] In contrast with intervention studies, the aim of prediction research is to quantify the absolute risk of a certain outcome with a combination of patient characteristics, rather than estimating the relative effect of a certain treatment. As a result, specific advantages and challenges arise when using IPD for prediction research.

### Advantages

A main advantage of IPD of multiple studies is the increase in sample size.[5,6] Larger sample size reduces the possibility of chance findings and increases precision of the result. A small number of events per variable (EPV) may easily lead to overfitting of prediction models, which will in turn result in poor performance when the model is applied to an independent sample.[7,8] Simulation studies have shown that the amount of bias in estimates of predictive accuracy (c-statistic, observed/expected ratio) decreases with increasing EPV, underlining the importance of sufficient EPV to develop a robust model.[9-11] Furthermore, combining data form multiple sources will increase case-mix variability on top of larger EPV, which will likely improve generalisability to future patients.[5,12] Also, IPD provides the possibility to standardise inclusion criteria and definitions across studies.[5] Last, a major advantage is that model development and validation can be performed simultaneously through internal-external cross validation.[13,14] In this approach, a model is developed in all studies but one and subsequently validated in the remaining study. This process is repeated for all combinations of studies and ensures that the majority of IPD is used for model development, while predictive performance can be appraised across all studies simultaneously. This approach allows to explore sources of heterogeneity across different subgroups, settings or countries and adjust the model to a specific setting if necessary.

**Challenges**

Some challenges need to be considered when undertaking an IPD-MA, of which the first and foremost is the process of gathering IPD. Researchers have recognized this as a time consuming task that requires intensive effort.[15,16] Collecting IPD for the current study has taken over five years and a recent meta-analysis has shown that in only 25% of IPDs all eligible studies have eventually been included.[17]

Other challenges associated with IPD for prognostic studies mainly relate to the application of adequate statistical techniques. A central issue in the analysis of IPD is 'clustering', the fact that data originated from different sources.[14] Clustering should be taken into account when dealing with systematically missing data, which arise when variables are not measured in certain trials and are thus lacking completely (as opposed to sporadically missing data).[18,19] Imputation strategies should ensure that grouping is preserved within clusters, otherwise, heterogeneity in predictor effects will be masked. This could incorrectly suggesting consistent performance across the studies and adequate generalisability.[20] Also, care should be given to develop a prediction model that takes between-study heterogeneity into account. Simple stacking of IPD is often not justified and may lead to inconsistent model performance at external validation.[14] Preferred strategies include the use of random effects models or stratified models, with subsequent application of internal-external cross validation to explore generalisability across studies. Although guidance on IPD-MA with logistic regression is emerging,[5,21] there is less guidance specific for time-to-event data. Survival analysis represents additional challenges including the choice of a specific model (semi-parametric versus parametric), selection and presentation of the baseline hazard and dealing with effects of treatment.

Despite the opportunity to simultaneously develop and validate a model in an internal-external cross validation procedure, this does not necessarily overcome the need for further external validation, as generalisability issues may still play a role despite access to data from multiple studies, as was demonstrated in this thesis. By combining results from multiple trials the variation in included patients may have increased, but all trials did exclude the same patients with a high risk of bleeding, necessitating further validation in a non-trial cohort.[22]

A limitation specific to our study is the fact that, even though we had individual patient level data, the level of detail was insufficient to uniformly redefine major bleeds. This has likely contributed to variation in absolute risk observed in our study. Standardised definitions have been introduced for major bleeding by the International Society on Thrombosis and Haemostasis[23] and will hopefully lead to more uniform assessment of major bleeding in the future.

IPD-MA for prediction studies provides great advantages, but care should be given to the previously mentioned challenges when an IPD-MA is undertaken. A possible way to overcome at least some of the challenges is to plan prospective IPD-MA, where investigators set up collaborations at the time of designing a study and ensure similar quality criteria

and definitions across studies. In the field of cerebrovascular diseases various initiatives have been undertaken to facilitate IPD-MA[24] and collaborations have been set up to perform prospective IPD-MA.[25,26]

## BLEEDING ON ANTIPLATELET TREATMENT

This thesis describes a series of studies aimed at predicting risk of major bleeding on antiplatelet treatment after a TIA or noncardioemoblic ischaemic stroke. Following a literature review and external validation study, we concluded that available models could not accurately identify patients at high risk of bleeding on antiplatelet treatment after cerebral ischaemia (*chapter 2).* We proceeded with the development of the $S_2$TOP-BLEED score for major bleeding on antiplatelet treatment after a TIA or ischaemic stroke (*chapter 3*), for which we pooled individual patient data from six randomised clinical trials. Development of a prediction model on trial data inherently has limitations: trial participants are not representative for the entire spectrum of patients with a TIA or ischaemic stroke.[27] Also, variables of interest may not have been measured in the original trials or may have served as exclusion criteria. To overcome these limitations, we externally validated the $S_2$TOP-BLEED score in a population-based cohort and compared its performance with other risk scores for bleeding *(chapter 4).* Subsequently, we investigated the added value of predictors that could not be measured in the development phase *(chapter 5).*-

The $S_2$TOP-BLEED score can provide a reasonably accurate estimate of an individuals' bleeding risk, based on ten readily available characteristics (age, sex, ethnicity, BMI, smoking, hypertension, diabetes, prior stroke, modified Rankin Scale score and type of antiplatelet treatment). Although the discriminatory ability of the $S_2$TOP-BLEED score is modest at best (c-statistic 0.63; 0.61-0.64 at model development and 0.61; 0.59-0.63 and 0.69; 0.64-0.73 in two subsequent external validation studies), the score seems to perform best compared with two other risk scores for major and intracranial bleeding. Moreover, the $S_2$TOP-BLEED score shows accurate calibration in an unselected patient population, indicating that the there is good agreement between observed and predicted risks. The overall three-year risk of major bleeding of 4-5% can be individualized to a risk as low as 2% (in younger patients (45-54 years) without additional risk factors), to over 10% (in elderly patients (≥75 years) with multiple risk factors).

However, a prediction model will likely only be useful in clinical practice if it can actually inform or influence treatment decisions. For decisions on antiplatelet treatment this requires an assessment of the bleeding risk on the one hand and recurrent stroke risk on the other hand (*chapter 7*). Based on an analysis of previously described IPD from antiplatelet trials, we conclude that bleeding risk assessment based on patient characteristics should not guide the decision to treat, or the choice of a specific antiplatelet drug for long-term secondary prevention. Although there is notable variation in the absolute risk of bleeding on antiplatelet treatment for individual patients, the risk of a recurrent ischaemic event

increases in parallel along the risk of bleeding. Those patients who are most harmed by antiplatelet treatment, are also the ones who derive most benefit. Both outcomes share many similar risk factors, as reflected by the overlapping predictors in the $S_2$TOP-BLEED score and in risk scores for recurrent ischaemic events (e.g. age, smoking, hypertension, diabetes, and prior stroke), which explains to a large extent why we cannot easily distinguish patients with high bleeding risk and high ischaemic risk.[28-30]

It should be noted that these analyses were performed on selected trial participants who were followed-up for roughly two years. Whether the balance between benefits and risks might differ in the semi-acute phase after a TIA or stroke, or whether it differs among frail or very elderly patients could not be assessed with the available data. However, a lesson learned from anticoagulant treatment in atrial fibrillation is that we should be very cautious to withhold antithrombotic treatment in patients with high perceived bleeding risk. Even among patients with substantial bleeding risks, the benefits of oral anticoagulants were shown to outweigh the risks.[31,32] In the field of atrial fibrillation, the focus has therefore shifted from influencing antithrombotic management towards identification of modifiable risk factors for bleeding and initiation of preventive treatment.[33] Also in patients with a TIA or ischaemic stroke, assessing bleeding risk may help to identify modifiable risk factors and target preventive treatment.

Smoking has been repeatedly identified as a risk factor for major bleeding[34,35] and is one of the few modifiable risk factors. Increased bleeding risk is therefore another reason to encourage smoking cessation. Additionally, adequate blood pressure control should be achieved, as high blood pressure increases both the risk of intracerebral haemorrhage (ICH) and recurrent ischaemic stroke. Although the optimal target blood pressure to lower risk of ICH remains uncertain, high blood pressure (160 mmHg systolic and 100 mmHg diastolic) was associated with a 2-3 fold higher risk of ICH following stroke (*chapter 9*). Current national and international guidelines recommend a target blood pressure of <140/90 mmHg among patients with (non-lacunar) stroke, [36,37] based on studies suggesting that lower targets do not confer additional benefit or even cause harm.[38,39] However, a more recent meta-analysis showed a linear association between blood pressure and recurrent cerebrovascular evens.[40] Partly based on these findings, the revised American Heart Association guideline on hypertension suggests a more strict target of <130/80 mmHg among patients with a TIA or stroke and newly diagnosed hypertension.[41] Further research is needed to define optimal lower blood pressure limits.

Furthermore, initiation of preventive treatment to lower risk of bleeding should be considered among high-risk individuals. Preventive strategies mainly target GI bleeds, which make up 40-50% of all major bleedings. The efficacy of eradication of Helicobacter Pylori among low-dose aspirin users is currently being investigated in the Helicobacter Eradication Aspirin Trial (HEAT).[42] Alternatively, proton pump inhibitors (PPI) may be considered, which effectively reduce risk of upper GI bleeds by 70-90% in patients on antiplatelet therapy.[43] A recent population-based study has shown that the numbers needed

to treat (NNT) to prevent one upper GI bleed were very reasonable in patients aged 75 years and older (NNT 23 to prevent one major upper GI bleed at 5 years).[34] However, age is not the single driver of bleeding risk, and the $S_2$TOP-BLEED and $S_2$TOP-BLEED+ scores can be helpful tools to identify patients at high risk of bleeding as they work reasonably well for prediction of upper GI bleeds (*chapter 4 and 5).* If the results from the population-based study were to be followed, PPI treatment should be considered in patients with an annual risk of major bleeding of 2% (corresponding with the risk in patients aged 75-80 years), which would be similar to a $S_2$TOP-BLEED score of 12 points. However, observational studies have raised concern about the safety of long-term PPIs and suggested that PPIs are associated with dementia, renal impairment, pneumonia and hip fractures.[44,45] Evidence from intervention studies is needed to gain further insight in safety of long-term PPI use.

If our focus is on targeting gastro-protective treatments, we may try to further tailor prediction models towards GI-bleeds. Different risk factors underlie various major bleeds, and improvements in discrimination can likely be achieved by including subtype specific risk factors. This notion is supported by the result of the $S_2$TOP-BLEED+ score, which showed improved discriminatory ability for upper GI bleeds after addition of peptic ulcer and anaemia.

## FUTURE PERSPECTIVES

Despite advances in identifying patients at high risk of major bleeding on antiplatelet treatment, individualising antithrombotic treatment based on bleeding risk is not yet within reach. In order to meaningfully inform decisions of antithrombotic treatment, we should be able to identify which patients are at high risk of bleeding without equally having an increased risk of recurrent ischaemic events. A promising feature to identify patients at high risk of intracerebral haemorrhage is the presence of microbleeds on susceptibility-weighted or gradient-echo T2*-weighted MRI. Both the presence and the burden of microbleeds are associated with recurrent stroke, and are more strongly related to future intracerebral haemorrhages than to ischaemic stroke.[46] In a meta-analysis among patients with a TIA or ischaemic stroke who were predominantly on antiplatelet drugs, the presence of microbleeds increased risk of ICH six fold (compared with no microbleeds), while risk of ischaemic stroke was increased approximately twofold.[46] With increasing burden of microbleeds, the risk of ICH increased more steeply than the risk of ischaemic stroke. Particularly lobar and mixed location of microbleeds were associated with an increased risk of ICH. Among patients with a stroke on oral anticoagulants, similar but slightly weaker associations were observed.[47] A high burden of microbleeds might tip the balance between benefits and risks of antiplatelet and oral anticoagulant treatment. Larger prospective studies investigating the interaction between anticoagulants and microbleeds are underway (CROMIS-2[48] and Intracerebral Hemorrhage Due to Oral Anticoagulants: Prediction of the Risk by Magnetic Resonance (HERO; clinicaltrials.gov/ct2/show/NCT02238470)).

Of note, bleeding risk stratification may also be relevant in the future if the absolute risk of a recurrent ischaemic event following a TIA or stroke is further reduced by preventive treatments other than antiplatelet drugs. Over the past years the risk of recurrent ischaemic stroke has decreased, likely due to earlier diagnosis and improved secondary prevention.[49-51] If further reductions in absolute risk are achieved, the relative risk reduction of 13% achieved with aspirin compared with placebo in long-term secondary prevention might not outweigh the relative risk increase of about 70% in major bleeds. Continued evaluation of the balance between benefits and risks of antiplatelet treatment is therefore needed.

Although addressing bleeding risk could be one way to optimise antithrombotic treatment in secondary stroke prevention, bleeding represents only one side of the balance. The net benefit of antithrombotic treatment could also be improved if greater reductions in ischaemic events are achieved.

One possible way to improve efficacy of antiplatelet treatment is to treat more aggressively early after TIA or stroke. Work described in this thesis has mainly focussed on long-term secondary prevention, however growing evidence suggests that a distinction should be made between the early phase of secondary prevention, when risk of recurrence is highest and potential benefit of prevention greatest, and long-term secondary prevention.[52] The CHANCE trial showed improved outcome in patients treated with a short course of aspirin-clopidogrel compared with aspirin alone, without increasing harms.[53] This trial was done primarily in Chinese patients and generalisability to Caucasian patients is uncertain because of differences in secondary prevention strategies and distribution of stroke subtypes. The same treatment regimen is currently being investigated in the Platelet-Oriented Inhibition in New TIA and minor ischaemic stroke (POINT) trial in Western countries.[54] Early aggressive treatment could lead to additional reductions in early recurrent stroke, without exposing patients to risk of bleeding associated with long-term dual therapy.

A second way to improve antithrombotic treatment is to target treatment based on stroke subtype. Many antithrombotic strategies that were proven to be effective in patients with acute coronary syndrome[55,56] are subsequently investigated among patients with a TIA or stroke.[57,58] However, unlike acute coronary syndromes which are caused by plaque rupture and thrombus formation in over 75% of cases,[59] TIA and stroke are heterogeneous clinical syndromes. Uniform treatment of all noncardioembolic strokes might therefore not be appropriate. For blood pressure reduction a distinction is already made between lacunar and non-lacunar strokes in some guidelines, with more strict BP targets for lacunar stroke patients.[36] Differential antiplatelet regimens for small vessel disease and large artery atherosclerosis strokes may also contribute to improved secondary prevention. Among patients with large artery atherosclerosis, plaque stabilisation and prevention of thrombus formation are most important. Therefore, aggressive antiplatelet treatment and statins seem most appropriate, particularly in the early phase when the risk of recurrence after large artery stroke is high.[60] Patients with small vessel disease are more prone to intracerebral haemorrhage,[61] and may benefit more from adequate treatment of

hypertension and diabetes than aggressive antiplatelet drugs. This notion is supported by results from a subgroup analysis from the SOCRATES trial, which showed a 30% (95% CI 11 to 45%) reduction in the risk of stroke, MI or death with ticagrelor over aspirin in patients with atherosclerosis and stenosis, but not in patients without ipsilateral stenosis (relative risk reduction 3%; -12 to 16%).[62] Furthermore, trials comparing a short course of aspirin-clopidogrel with aspirin alone in patients with atherosclerotic stenosis showed about 45% less micro-embolic signals, suggesting that aspirin-clopidogrel may indeed be beneficial in atherosclerotic stroke.[63,64] Future trials must selectively include patients with different stroke mechanisms and must focus on interventions that are most likely to be beneficial for the underlying aetiology.

A final method to achieve further reductions in recurrent ischaemic events is to explore the potential of more potent antithrombotic treatments. A promising development in the field of antithrombotic treatment is the introduction of direct oral anticoagulants (DOACs), currently prescribed for treatment of venous thromboembolism[65] and for prevention of stroke and systemic embolism in patients with atrial fibrillation.[33] DOACs have been shown to be at least as effective as warfarin in these patient groups and to cause less intracranial haemorrhages.[66] Among patients with acute coronary syndrome low-dose rivaroxaban on top of standard medical therapy provided additional reduction in risk of ischaemic event, although associated with an increase in bleeds.[67] Also, in patients with stable vascular disease benefit from low-dose rivaroxaban in addition to aspirin was observed.[68] Following these positive results, future trials might investigate the efficacy and safety of low-dose DOACs among patients with atherosclerotic stroke. A phase 2 trial of dabigatran for 30 days versus aspirin in patients with acute stroke is ongoing.[69]

Even if we would be able to predict bleeding more accurately in the future, it is unlikely that we will be able to fully prevent all major bleeds. It is therefore important to investigate the optimal antithrombotic management after a severe bleed. Although GI bleeding and intracranial bleeding are risk factors for recurrent bleeds in the same area, patients with a recent bleed are also at increased risk of future cardiovascular events, possibly due to (sudden) discontinuation of antithrombotic treatment. One small trial addressed the question whether antiplatelet treatment should be continued in patients with peptic ulcer bleeding and found a significant reduction in all-cause mortality when aspirin was continued.[70] This finding is supported by results from observational studies, both among patients on antiplatelet treatment and oral anticoagulants.[71-74] Based on these results guidelines recommend resumption of antithrombotic treatment following GI bleeding.[75,76] Evidence from randomised controlled trials on the safety and efficacy of restarting antithrombotic treatment following ICH is currently lacking. Although observational studies suggest that restarting antithrombotic treatment is associated with reduced risk of ischaemic stroke and all-cause mortality,[77,78] confounding by indication may have biased the results. A more definite answer to this question is expected from current trials that investigate the safety and efficacy of restarting antiplatelet and oral anticoagulant treatment

after ICH (REstart or STop Antithrombotics Randomised Trial (RESTART) and the Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation (APACHE-AF) trial).[79,80]

## CONCLUSIONS

To conclude, the individual risk of major bleeding on antiplatelet treatment following a TIA or ischaemic stroke can be predicted with the $S_2$TOP-BLEED score based on readily available characteristics. Bleeding risk prediction cannot individualise antiplatelet treatment or oral anticoagulant treatment following a TIA or stroke, but may still be useful to identify patients in whom preventive treatment should be considered. There is room for further improvement of bleeding risk scores, possibly with results from brain imaging. Alternative ways to improve net benefit of antithrombotic treatment in secondary stroke prevention should be investigated, including early aggressive treatment, tailoring towards stroke subtype and more potent antithrombotic treatment. Last, more insight is needed in the optimal antithrombotic management after a severe bleed.

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# APPENDICES

## SUMMARY

Antithrombotic treatment is a cornerstone in secondary prevention following a transient ischaemic attack (TIA) or ischaemic stroke, either with oral anticoagulants after a cardioembolic stroke, or with antiplatelet drugs after a stroke from presumed arterial origin. Current guidelines recommend aspirin, clopidogrel and aspirin-dipyridamole as first-line antiplatelet agents for secondary prevention after a noncardioembolic stroke or TIA. Although antithrombotic drugs successfully reduce the risk of a recurrent stroke or vascular event, their benefits are partly offset by an increased risk of bleeding. Determining which patients are at high risk of bleeding may provide opportunities to individualise antithrombotic treatment. In this thesis we investigated prediction of bleeding on antithrombotic treatment following a TIA or ischaemic stroke, and assessed the potential of bleeding risk stratification to inform treatment decisions for antithrombotic treatment.

**Chapter 2** presents an overview of currently available prediction models for major bleeding or intracranial bleeding on antiplatelet therapy, and evaluates the performance of these models among patients with cerebral ischaemia. This review showed that only two prediction models have been developed specifically for patients with a TIA or stroke. All models had some methodological shortcomings and relatively poor performance in TIA/stroke patients. Wide use of these models in clinical practice seems premature.

In **chapter 3** a new prediction model for major bleeding on antiplatelet treatment following a TIA or ischaemic stroke is presented. This model was derived from individual patient data (IPD) from six randomised clinical trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, PRoFESS) including 43,112 patients with a TIA or ischaemic stroke. Independent predictors for major bleeding were combined in the $S_2$TOP-BLEED score: male Sex, Smoking, Type of antiplatelet drug, Outcome on modified Rankin Scale, Prior stroke, high Blood pressure, Low BMI, Elderly, Asian Ethnicity, Diabetes. The model showed low discriminatory ability (c-statistic 0.63; 95% confidence interval (CI) 0.61-0.64) and accurate calibration in the development cohort. In an external validation cohort of 18,417 trial participants, the discriminatory performance of the $S_2$TOP-BLEED score was comparable (c-statistic 0.61; 0.59-63), but risk of major bleeding was slightly underestimated. The three-year predicted risk of major bleeding varied from 1% in patients aged 45-54 years old without additional risk factors, to more than 10% in patients aged 75 years and older with multiple risk factors.

The use of trial data for development of a prediction model inherently has limitations: trial participants are not representative for the entire population of patients with a TIA or stroke as patients are selected on the basis of strict in- and exclusion criteria. Furthermore, it might not be possible to investigate all predictors of interest because some variables may not have been measured or may have served as exclusion criteria in the original trials. Both issues were addressed in subsequent chapters of this thesis.

In **chapter 4** the external validity of the $S_2$TOP-BLEED score is assessed in a population-based cohort of 2,072 patients with a TIA or ischaemic stroke on antiplatelet

treatment, and its performance is compared with other risk scores for major bleeding. The $S_2$TOP-BLEED score showed a c-statistic of 0.69 (95% CI 0.64-0.73) in the validation cohort and accurate correspondence between the observed and predicted risks. Compared with two other models, the REACH score for major bleeding and the Intracranial-$B_2LEED_3S$ score for intracranial haemorrhage, the $S_2$TOP-BLEED score showed best performance.

**Chapter 5** describes an extension of the $S_2$TOP-BLEED score with variables that could not be investigated in the original trial cohorts but are known risk factors for bleeding. Among 2,072 patients with a TIA or ischaemic stroke we identified peptic ulcer (hazard ratio (HR) 1.72; 1.04-2.86), cancer (HR 2.40; 1.57-3.68), anaemia (HR 1.55; 0.99-2.44) and renal failure (HR 2.20; 1.57-4.28) as predictors for major bleeding on top of $S_2$TOP-BLEED risk factors. Discriminatory ability of the new $S_2$TOP-BLEED+ score increased to 0.73 (95% CI 0.69-0.78), and net reclassification improved over the entire range of the score (NRI 0.56; 0.36-0.76). In a validation cohort of 1,094 patients with a myocardial infarction, the c-statistic increased from 0.68 (95% CI 0.62-0.74) to 0.70 (95% CI 0.64-0.76). Future validation studies among patients with a TIA or stroke are required to fully establish the robustness of the $S_2$TOP-BLEED+ score as extension to the original $S_2$TOP-BLEED score.

Preliminary evidence suggests that risk of bleeding on dual antiplatelet therapy may be particularly high early after start of treatment. In **chapter 6** we investigated the time course of major, gastro-intestinal and intracranial bleeding on antiplatelet treatment among 45,195 patients with a TIA or ischaemic stroke, who were followed-up for a median of 1.9 years (interquartile range 1.2 to 2.4 years). The incidence of major bleeding on aspirin-clopidogrel and aspirin-dipyridamole was highest in the first 30 days: 5.8 and 4.9 per 100 person-years respectively, and was significantly higher than at 31-90 days (rate ratio (RR) 1.98; 95% CI 1.16-3.40 for aspirin-clopidogrel and 1.94; 1.24-3.03 for aspirin-dipyridamole). Incidence rates on aspirin and clopidogrel monotherapy were 2.8 and 2.5 per 100 person-years respectively in the first 30 days, with no significant change over time. The time course was similar for gastro-intestinal bleeds. There was no early excess of intracranial haemorrhage in patients on either dual or single antiplatelet therapy. Although the risk of early recurrent ischaemic events will likely outweigh the risk of bleeding, these findings draw attention to the high early risks of bleeding associated with dual antiplatelet therapy, which may have been underestimated previously.

The harms of antiplatelet treatment may offset the benefits in patients at high risk of bleeding and low risk of recurrent ischaemic events. In **chapter 7** we investigated the balance between benefits and risks according to baseline bleeding risk, and aimed to assess whether bleeding risk stratification can influence treatment decisions for antiplatelet therapy. Based on IPD from six trials we studied net benefit of antiplatelet treatment for three different scenarios: 1) aspirin compared with no antiplatelet treatment to assess the net benefit of antiplatelet treatment per se over a range of absolute bleeding risks, 2) aggressive dual antiplatelet therapy (aspirin-clopidogrel) versus monotherapy to assess if a specific subgroup might benefit from long-term dual therapy, and 3) aspirin-dipyridamole versus

clopidogrel to assess whether there is a preference for one of these guideline recommended treatments depending on the absolute bleeding risk. We observed that risk of major bleeding and recurrent ischaemic events increase in parallel across bleeding risk groups. The benefits of aspirin outweighed the risks irrespective of baseline bleeding risk. Among patients treated with aspirin-clopidogrel, the excess of major bleeds was larger than the reduction in ischaemic events. No clear preference was observed for either of two guideline recommended treatments (aspirin-dipyridamole or clopidogrel) according to bleeding risk. We concluded that bleeding risk assessment based on patient characteristics should not guide treatment decisions for antiplatelet drugs. However, bleeding risk assessment may still be useful to identify patients at high risk of bleeding in whom gastro-protective treatment should be considered.

Several risk scores have been developed to assess bleeding risk for individual patients with atrial fibrillation (AF) on oral anticoagulants (OAC), but performance of these risk scores in patients with a previous stroke is not well established. In **chapter 8** we investigated whether we can identify patients at high risk of bleeding on OAC and explored whether the net benefit of OAC treatment changes with increasing bleeding risk. We performed a post hoc subgroup analysis among 3,623 patients with a TIA or ischaemic stroke included in the RE-LY trial, of whom 266 had a major bleed. Available prediction models showed modest predictive performance in patients with a TIA or stroke and atrial fibrillation, but performance was comparable among patients with AF in general. The benefits of OAC outweighed harms in all bleeding risk groups, indicating that bleeding risk scores should not be used to guide treatment decisions for OAC.

Blood pressure control is another important aspect of secondary stroke prevention. Current guidelines recommend a target systolic blood pressure (SBP) of <140 mmHg, and <130 mmHg in patients with a recent lacunar stroke. However, hypertension is strongly associated with risk of intracerebral haemorrhage (ICH) and stricter blood pressure control might be beneficial to prevent ICH. In **chapter 9** we described the association between blood pressure levels and risk of ICH after ischaemic stroke among 20,332 patients included in the PRoFESS trial. We observed that the incidence rate of ICH increased with increasing systolic blood pressure (SBP) and diastolic blood pressure (DBP) categories. Risk of ICH was significantly higher in patients with SBP ≥160 mmHg (HR 2.27; 95% CI 1.34 to 3.86) compared with SBP of 130-<140 mmHg, and in patients with DBP ≥100mmHg (HR 3.08; 95% CI 1.78 to 5.34) compared with those with DBP of 80-<90 mmHg. The association between blood pressure and ICH did not differ for lacunar strokes versus other stroke subtypes. Based on these results it remains unclear whether blood pressure lowering below 140mmHg confers additional benefit, however, these data do emphasize the need for stringent blood pressure control to prevent ICH.

ICH has many potential causes, of which the majority is so called 'primary' ICH. Approximately 20% of ICHs are caused by an underlying macrovascular cause such as an arteriovenous malformation or aneurysm, also referred to as 'secondary' ICH. Identification

of secondary causes is important, as it has implications for both therapy and prognosis. **Chapter 10** describes the development and external validation of the DIAGRAM prediction score, which aims to predict the presence of a macrovascular cause in patients with a non-traumatic ICH. In a prospective cohort of 298 patients with non-traumatic ICH, 69 (23%) had an underlying macrovascular cause. Independent predictors for presence of a macrovascular cause were younger age, lobar or posterior fossa (versus deep) location of ICH and absence of signs of small vessel disease. These predictors were combined in the DIAGRAM score, which showed good performance in the development cohort (c-statistic 0.83; 95% CI 0.78-0.88) and moderate performance (c-statistic 0.66; 0.58-0.74) in an external validation cohort of 173 patients with non-traumatic ICH (79 macrovascular cause; 45%). When CTA results were added (DIAGRAM+ score), the c-statistic was excellent (0.91; 0.88-0.94), and good after external validation (0.88; 0.83-0.94). Predicted probabilities varied from 1% in patients aged 51-70 years with deep ICH and SVD, to more than 50% in patients aged 18-50 years with lobar or posterior fossa ICH without SVD. The DIAGRAM scores may facilitate selection of patients for diagnostic work-up following a non-traumatic ICH, but future validation studies are required to confirm the robustness of the scores and assess the generalisability to older patients with non-traumatic ICH.

In **chapter 11** we reviewed advantages and challenges associated with the use of IPD for the development of a prediction model. Furthermore, we reflected on the findings in this thesis and concluded that bleeding risk stratification based on patient characteristics cannot individualise antiplatelet treatment. However, bleeding risk assessment might still be useful to identify modifiable risk factors for bleeding and to identify patients in whom preventive treatment should be considered. Future studies may focus on refinement of bleeding risk prediction with radiological characteristics such as microbleeds, and should investigate other strategies to optimise antiplatelet treatment, including short-term aggressive antiplatelet treatment and differential treatment according to stroke subtype. Last, more insight is needed in the optimal antithrombotic management after a severe bleed.

## SAMENVATTING

Jaarlijks worden ruim 41.000 Nederlanders getroffen door een herseninfarct. Een herseninfarct ontstaat doordat de bloedtoevoer naar een gedeelte van de hersenen wordt afgesloten door een bloedstolsel. Ongeveer een kwart van alle patiënten die een herseninfarct hebben doorgemaakt krijgt binnen vijf jaar opnieuw een herseninfarct. Secundaire preventie – het voorkomen van een nieuw infarct – is daarom een belangrijk onderdeel van de behandeling. Bij patiënten die een herseninfarct of TIA ('transient ischaemic attack', een klein infarct dat binnen 24 uur restloos herstelt) hebben doorgemaakt, bestaat secundaire preventie uit leefstijladviezen, cholesterolverlaging, bloeddrukcontrole en behandeling met bloedverdunners. Afhankelijk van de oorzaak van het infarct wordt de keuze voor een bepaald type bloedverdunner gemaakt: een oraal antistollingsmiddel als het infarct een cardiale oorsprong heeft, of een plaatjesaggregatieremmer (zoals aspirine) als het een herseninfarct van arteriële oorsprong betreft. De belangrijkste bijwerking van bloedverdunners is dat ze het risico op een bloeding verhogen. Dit kunnen zowel relatief onschuldige neusbloedingen zijn, als ernstige hersenbloedingen met invaliditeit of zelfs overlijden tot gevolg.

Het hoofddoel van dit onderzoek was om in kaart te brengen welke patiënten een hoog risico hebben op het ontwikkelen van een ernstige bloeding bij het gebruik van bloedverdunners, en om te onderzoeken of de behandeling met bloedverdunners geïndividualiseerd kan worden op basis van het bloedingsrisico.

Een risicoscore of predictiemodel kan worden gebruikt om de kans op een ernstige bloeding te voorspellen voor een individuele patiënt. Wij zijn nagegaan of er al predictiemodellen beschikbaar zijn in de literatuur die de kans op een ernstige bloeding kunnen voorspellen (hoofdstuk 2). Er bleek slechts een zeer beperkt aantal predictiemodellen te zijn. De modellen die we vonden hadden een matige voorspellende waarde en hadden methodologische tekortkomingen. Om die reden ontwikkelden wij een nieuw model op basis van gegevens van ruim 40.000 patiënten met een TIA of herseninfarct die in onderzoeksverband plaatjesaggregatieremmers gebruikten (hoofdstuk 3). Factoren die het risico op een ernstige bloeding verhogen waren onder andere hogere leeftijd, mannelijk geslacht, roken, diabetes en een eerder herseninfarct. We combineerden de voorspellers in een risicoscore: de $S_2$TOP-BLEED score.

Vervolgens onderzochten we de voorspellende waarde van de $S_2$TOP-BLEED score in een onafhankelijke populatie (hoofdstuk 4). We zagen dat de risicoscore robuust was en generaliseerbaar naar een brede groep patiënten met een TIA of herseninfarct, maar dat het discriminerende vermogen matig was. Toevoeging van extra voorspellers zoals de aanwezigheid van nierfunctiestoornissen en bloedarmoede verbeterde de voorspellende waarde enigszins (hoofdstuk 5).

Het risico op een ernstige bloeding is afhankelijk van verschillende patiëntkenmerken en varieert van minder dan 2% na 3 jaar bij jonge patiënten zonder comorbiditeit, tot meer dan 10% bij patiënten ouder dan 75 jaar met comorbiditeit. Wij onderzochten of de baten van

bloedverdunners altijd opwegen tegen de risico's (hoofdstuk 7). Daartoe vergeleken we de winst van behandeling met verschillende bloedverdunners, in termen van het voorkomen van herseninfarcten, hartinfarcten en vasculaire uitkomsten, met de schade in termen van ernstige bloedingen. We zagen dat de baten van bloedverdunners groter zijn dan de risico's, ongeacht het onderliggende bloedingsrisico. Patiënten met het hoogste risico op een bloeding blijken ook het hoogste risico op een nieuw infarct te hebben. Dit is goed te begrijpen als we kijken naar de onderliggende risicofactoren voor bloedingen en infarcten, die in hoge mate overlappen (oudere leeftijd, roken, hypertensie, diabetes, eerdere hart- en vaatziekten). Het voorspelde bloedingsrisico blijkt ook niet van belang voor de keuze van het type plaatjesaggregatieremmer. Ook bij patiënten die orale antistolling gebruiken als secundaire preventie na een infarct van cardiale oorsprong blijken de baten van bloedverdunners groter te zijn dan de risico's (hoofdstuk 8). Op basis hiervan concluderen we dat het berekenen van het bloedingsrisico voor een individuele patiënt niet van invloed moet zijn op de beslissing om een bloedverdunner voor te schrijven of een specifiek soort bloedverdunner te kiezen. Desondanks kan het zinvol zijn het risico te berekenen, omdat bij patiënten met een hoog bloedingsrisico extra zorg kan worden besteed aan preventie van bloedingen, bijvoorbeeld door een maagbeschermer voor te schrijven.

Wij onderzochten daarnaast op welk moment ernstige bloedingen optraden (hoofdstuk 6). We zagen dat het risico op een maag-darmbloeding het hoogst was in de eerste 30 dagen na aanvang van de behandeling, met name als combinaties van plaatjesaggregatieremmers werden gebruikt. Het risico op hersenbloedingen blijkt niet extra verhoogd te zijn vroeg na het starten met de behandeling met plaatjesaggregatieremmers.

Adequate bloeddrukcontrole is een ander belangrijk aspect van secundaire preventie na een herseninfarct. Strikte bloeddrukregulatie verlaagt het risico op een nieuw infarct, maar er is onzekerheid over de optimale streefwaarde van de bloeddruk. We onderzochten het verband tussen bloeddruk en hersenbloedingen en namen waar dat het risico op een hersenbloeding toenam naarmate de systolische bloeddruk hoger werd (hoofdstuk 9). De groep met de hoogste bloeddrukken (systolisch >160 mmHg of diastolisch >100 mmHg) had een twee tot drie keer zo grote kans op een hersenbloeding. Op basis van deze resultaten blijft het onduidelijk of het verlagen van de bloeddruk onder 140 mmHg extra baten oplevert voor preventie van hersenbloedingen. Echter, deze resultaten onderstrepen het belang van bloeddrukregulatie voor preventie van hersenbloedingen.

In hoofdstuk 10 richtten we ons tot slot op de diagnostiek bij hersenbloedingen. Een hersenbloeding kan door verschillende mechanismen ontstaan. In de meeste gevallen gaat het om een zogenaamde 'primaire' bloeding, veroorzaakt door schade aan de kleine vaten. Ongeveer een vijfde van alle hersenbloedingen wordt veroorzaakt door een onderliggende macrovasculaire afwijking, zoals een arterioveneuze malformatie of aneurysma, ook wel 'secundaire' hersenbloeding genoemd. Het opsporen van een secundaire oorzaak is van belang omdat deze consequenties heeft voor zowel de behandeling als de prognose. Om beter in te schatten welke patiënten een hoge kans hebben op een macrovasculaire

afwijking, en dus aanvullend onderzoek moeten ondergaan, ontwikkelden we de DIAGRAM score. Hiermee kan op basis van drie kenmerken (leeftijd, locatie van de bloeding en aan- of afwezigheid van schade aan de kleine vaten zichtbaar op een CT-scan) de kans op een macrovasculaire afwijking worden ingeschat. De score kan dus bijdragen aan de selectie van de patiënten die aanvullend beeldvormend onderzoek moeten ondergaan. Echter, in de toekomst zullen validatiestudies moeten uitwijzen of de DIAGRAM score robuust is en generaliseerbaar is naar oudere patiënten met een hersenbloeding.

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## LIST OF PUBLICATIONS

### This thesis

NA Hilkens, A Algra, JP Greving. Prediction models for intracranial hemorrhage or major bleeding on antiplatelet therapy: a systematic review and external validation study. Journal of Thrombosis and Haemostasis, 2016;14:167-174

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## CURRICULUM VITAE

Nina Hilkens werd geboren op 5 juli 1990 te Vlaardingen. Na het behalen van haar gymnasiumdiploma in 2008 (Christelijk Lyceum Delft), studeerde ze geneeskunde aan de Universiteit Utrecht. Tijdens haar studie groeide haar interesse in wetenschappelijk onderzoek en specifiek in cerebrovasculaire ziekten. Ze deed onderzoek naar de waarde van angiografisch onderzoek bij intraventriculaire bloedingen en de behandeling van arterioveneuze malformaties in de hersenen, onder begeleiding van prof. dr. C.J.M. Klijn. Na het afronden van haar studie geneeskunde in 2014 begon ze aan een promotietraject bij het Julius Centrum voor Gezondheidswetenschapen en Eerstelijns Geneeskunde onder begeleiding van prof. dr. A. Algra en dr. ir. J.P. Greving, wat resulteerde in dit proefschrift. Tijdens haar promotietraject behaalde ze een masterdiploma klinische epidemiologie. In 2017 werkte ze vijf maanden als onderzoeker aan de Universiteit van Oxford onder begeleiding van prof. P.M. Rothwell, wat resulteerde in twee hoofdstukken van dit proefschrift. Sinds maart 2018 is Nina werkzaam als arts in opleiding tot neuroloog in het Radboudumc in Nijmegen (opleider dr. B. Post). In de toekomst hoopt ze klinisch werk en onderzoek te combineren.