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The Intracranial-B_2LEED_3S Score and the Risk of Intracranial Hemorrhage in Ischemic Stroke Patients Under Antiplatelet Treatment

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Key Words

Low body mass index · Blood pressure · Lacune · Elderly · Asian ethnicity · Cardiovascular disease · Cerebrovascular disease · Dual antithrombotic treatment or anticoagulant · Sex

Abstract

Background: Chronic antiplatelet therapy in the post-acute phase of non-cardioembolic ischemic stroke is limited by the risk of intracranial hemorrhage (ICH) complications. ***Methods:*** We developed an ICH risk score based on the PERFORM trial cohort (n = 19,100), which included patients with a non-cardioembolic ischemic stroke or transient ischemic attack, and externally validated this score in one contemporary trial of very similar size and inclusion criteria, the PRoFESS trial (n = 20,332 patients). Outcome was ICH over 2 years. A Cox proportional-hazard regression analysis identified risk factors. Discrimination was quantified with c-statistics and calibration was assessed by comparing predicted and observed ICH risk in PERFORM and PRoFESS. ***Results:*** ICH occurred within 2 years in 263 (1.4%) patients in PERFORM trial and in 246 (1.2%) patients in PRoFESS trial. A 13-point score based on 9 items (Intracranial-B_2LEED_3S score – low body mass in-

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dex, blood pressure, lacune, elderly, Asian ethnicity, coronary artery or cerebrovascular disease history, dual antithrombotic agent or oral anticoagulant, gender) was derived from the PERFORM trial. In PERFORM, the observed 2-year ICH risk varied from 0.75% in low-risk (score ≤2) to 2.44% in high-risk patients (score ≥5) with an acceptable calibration but a low discrimination both in PERFORM (c-statistic 0.64, 95% CI 0.61–0.68) and on external validation in PRoFESS (0.58, 95% CI 0.55–0.62). ***Conclusion:*** The Intracranial-B_2LEED_3S score helps identify patients who are at a high risk of bleeding. However, other variables need to be identified to improve the score (e.g., microbleeds) (Clinical Trial Registration Information ISRCTN66157730). URL: http://www.isrctn.com/ISRCTN66157730?totalResults=5&pageSize=10&page=1&searchType=basic-search&offset=3&q=&filters=conditionCategory%3ACirculatory+System%2CrecruitmentCountry%3ATaiwan%2CrecruitmentCountry%3AAustria&sort=.

Introduction

Chronic antiplatelet therapy in the post-acute phase of non-cardioembolic ischemic stroke is limited by the risk of intracranial hemorrhage (ICH) complications, as shown by clinical trials of antiplatelet agents. In patients with ischemic stroke or transient ischemic attack (TIA) randomized in the placebo group of the Swedish Aspirin Low dose Trial (SALT) [1], the 2-year risk of ICH was 0.34%. On aspirin, the 2-year ICH risk ranged from 0.52% in the Clopidogrel Aspirin in Prevention of Recurrent Ischemic Event (CAPRIE) trial to 1.14% in SALT [1, 2]. It was 0.37% on clopidogrel in CAPRIE. Dual antiplatelet therapy (clopidogrel plus aspirin) compared to single therapy of clopidogrel showed a doubling in the 2-year risk of ICH (1.41 vs. 0.6%, respectively) [3].

Acute coronary syndrome (ACS) patients with a history of ischemic stroke or TIA carry a higher risk of ICH than other ACS patients [4–7]. Consequently, considerable caution exists to develop new antiplatelet agents in ischemic stroke patients, regardless of whether or not they have a history of ACS. However, the residual risk of further ischemic vascular event after a stroke under best medical therapy is very high and needs to be addressed as much as in patients with coronary artery disease (CAD). The population with ischemic stroke or TIA represents more than 10 millions patients per year worldwide and strongly needs new potent antiplatelet treatment, more effective than those currently recommended by guidelines that reduce the risk of ischemic stroke by only less than 20%.

It is therefore of utmost importance to develop a risk score that would allow the detection of ischemic stroke patients at the highest risk of ICH complication under an antiplatelet regimen in order to exclude them from future clinical trials evaluating new antithrombotic agents.

To this end, we developed an ICH risk score based on the PERFORM trial cohort [8], which included 19,100 patients with a non-cardioembolic ischemic stroke or TIA, and validated this score externally in one contemporary trial of very similar size and inclusion criteria, the PRoFESS trial (n = 20,332 patients) [9].

Methods

Study Patients

The derivation dataset included 19,100 patients of PERFORM trial cohort, which is an international multicenter randomised controlled trial designed to assess the superiority of terutroban (an antagonist of thrombin receptor of platelets) compared with aspirin in the prevention of cardiovascular ischemic events in patients with recent non-cardioembolic stroke. The design, baseline characteristics and main findings have been reported [8, 10, 11]. Patients aged ≥55 years with a non-cardioembolic ischemic stroke or TIA were enrolled between February 2006 and April 2008.

The validation dataset included 20,332 patients of PRoFESS trial cohort with noncardio-embolic ischemic stroke or TIA. They were randomized to either clopidogrel vs. aspirin plus extended-released dipyridamole, or telmisartan vs. its placebo in a 2 × 2 factorial design. The design, baseline characteristics and main findings have been reported [9, 12].

Predictor Variables

Predictor variables were considered if they were viewed as commonly measured and available in randomized trials and with potential evidence of an association with ICH risk. Candidate variables included age, gender, ethnic origin, body mass index (BMI), systolic and diastolic blood pressure at inclusion, medical history (hypertension, stroke, diabetes, myocardial infarction, hypertriglyceridaemia, CAD and smoking), use of dual antiplatelet or anticoagulant therapy, and lacunar stroke etiology. Angina and hypertriglyceridaemia were unavailable in the PRoFESS trial cohort.

Primary Outcome

The primary outcome was ICH occurring within the 2-year follow-up. This end-point was specifically adjudicated in both trials by an independent endpoint committee.

Statistical Analysis

Main baseline characteristics were described for both derived and validation datasets. Continuous variables were reported as means ± SDs and categorical variables were expressed as frequencies and percentages. Since information on the potential predictors in validation dataset was available for 99.4% (n = 19,006) and for 100% of the outcome measure, no imputation procedure was applied to handle missing data [13]. Predictions of ICH risk were based on Cox proportional-hazards regression models, treating

Table 1. Baseline characteristics of patients in development (PERFORM trial) and validation cohort trial (PRoFESS trial)

	Derivation cohort trial (n = 19,100)	Validation cohort trial (n = 20,332)
Age, years	67±8	66±9
Gender, male	11,950 (62.6)	13,022 (64.0)
Asian	2,244 (11.7)	2,994 (14.7)
BMI, kg/m^2	27.1±4.3	26.8±5.0
Systolic blood pressure, mm Hg	138±17	144±17
Diastolic blood pressure, mm Hg	80±9	84±10
Medical history		
Hypertension	15,964 (83.6)	15,048 (74.0)
Stroke	2,893 (15.1)	3,708 (18.2)
Diabetes	5,299 (27.7)	5,743 (28.2)
Myocardial infarction	1,475 (7.7)	1,366 (6.7)
CAD	4,119 (21.6)	3,304 (16.3)
Hypercholesterolemia	9,183 (48.1)	9,493 (46.8)
Smoking	5,074 (26.6)	4,308 (21.2)
Lacunar stroke	3,940 (20.6)	10,578 (52.1)
Dual antiplatelet or anticoagulant	2,644 (13.8)	10,181 (50.1)

Data are means ± SD or number (percentage).

death from non-ICH cause as censoring event. All potential predictors were considered for the inclusion in the multivariable Cox regression model and the full model was simplified with a backward selection procedure by using a removal criterion of 0.05. In terms of the weight of evidence in the literature as regards the impact of dual antiplatelet or oral anticoagulant treatment on ICH risk [3], dual antiplatelet or oral anticoagulant was forced into the model. The proportional hazards assumption for each predictor, and for the prognostic index derived from the final model, was assessed by plotting the Schoenfeld residuals against the rank of survival time [14]. The log-linearity assumption of continuous predictors (age, BMI, systolic and diastolic blood pressure) was assessed, first using Martingale residual plots and second using restricted cubic spline functions [15]. Prognosis models derived from multivariable regression analysis are known to overestimate regression coefficients, which results in overestimated predictions when applied in future patients. Therefore, we performed an internal validation by using bootstrap resampling with 200 repetitions to estimate shrinkage factors and the c-statistic corrected for over-optimism. We examined the performance of the final model by determining its calibration and discrimination. Discrimination was evaluated using the Harrell's C-index of agreement [16]. It indicates to what extent the model distinguished between patients who had ICH from those who had no ICH. This c-statistic has a typical range of 0.60–0.85 for survival data [16]. Calibration is the agreement between the predicted and observed ICH risk, and was evaluated by comparing the predicted mean event curves to the Kaplan–Meier event curves in 4 risk groups [16], divided by quartiles of prognostic index (low risk, moderate risk, high risk and very high risk).

In order to present a risk score, each continuous predictor in the final model was divided into clinically meaningful categories (age <75 vs. ≥75 years; BMI <25 vs. ≥25 kg/m^2) and then included as categorical predictors in the final model. Based on the regression coefficients of this last model, each predictor was assigned 0–2 points, given a total score ranged from 0 to 13 points. One point was attributed for dual antiplatelet or oral anticoagulant therapy. Patients were then divided into 4 risk groups. A Cox's regression model was fitted with the total point score as a single continuous predictor. The predictive accuracy of this point-score model was assessed by the same measures of discrimination and calibration used for the primary analysis.

Finally, we performed an external validation of the point-score risk system as a single continuous predictor by assessing the point-score model calibration and discrimination performances in the validation dataset.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using SAS software package, release 9.3 (SAS Institute, Cary, N.C., USA).

Results

Baseline Characteristics

Table 1 shows baseline characteristics of both data sets. In PERFORM, patients were predominantly male (63%) and the mean age was 67 years. Approximately 84% had hypertension. Fourteen percent of patients were on dual antiplatelet therapy or oral anticoagulants at randomisation and 20% had lacunar strokes. The population of PRoFESS was quite similar except for having twice as many lacunar strokes. Of the 19,100 patients in the

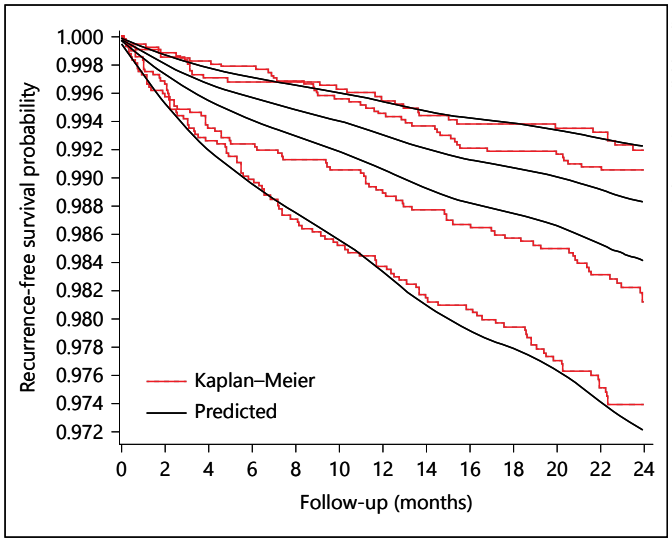

Fig. 1. Calibration plot for ICH-free survival probability in the derivation dataset (PERFORM trial). The 4 risk groups (Intracranial-B_2LEED_3S scores 0–2, 3, 4, and ≥5) were defined according to quartiles of prognostic index derived by Cox's regression model (continuous model). Black lines: cumulative probability of remaining free of recurrent ICH as predicted in the derivation dataset. Red lines: Kaplan–Meier estimates.

Color version available online

Table 2. ICH risk score (Intracranial-B_2LEED_3S score)

Predictor	Points
B, low BMI, kg/m^2	
<25	1
≥25	0
B, high blood pressure	
No	0
Yes	2
L, lacune, small vessel disease	
No	0
Yes	1
E, elderdy, years	
<75	0
≥75	1
E, Asian ethenicity	
Non-Asian	0
Asian	2
D, cardiovascular disease	
No	0
Yes	2
D, cerebrovascular disease	
No	0
Yes	2
D, dual antithrombotic treatment or anticoagulant	
No	0
Yes	1
S, sex	
Female	0
Male	1

Total point score is obtained by adding the number of points associated with each predictor. For example, a 65-year-old Asian man with a BMI of 26 kg/m^2, hypertension, no lacune, no cardiovascular disease but cerebrovascular disease and with dual antithrombotic treatment or anticoagulant will have a total score of (0 + 2 + 1 + 0 + 2 + 0+ 0 + 2 + 1 = 8).

PERFORM data set, 263 (1.4%) patients had an ICH during follow-up; in PRoFESS, 246 (1.2%) ICH occurred. The median follow-up time in PERFORM was 2.3 years (interquartile range (IQR) 2.0–2.8) and 2.4 (IQR 0–4.4) years in PRoFESS.

Derivation and Validation of Model

The multivariable model of predictors of ICH was obtained using data from 19,006 patients with no missing covariate values and included all patients that had an ICH. The backward stepwise selection retained age, gender, BMI, Asian ethnicity, previous hypertension, myocardial infarction and stroke, and lacunar stroke (online suppl. table I; for all online suppl. material, see www.karger.com/doi/10.1159/000453459). The shrinkage factor of the model (including dual antiplatelet or anticoagulant agent) calculated with bootstrapping was 0.87. After shrinkage of the coefficients, the c-statistic of the final model was 0.64 (95% CI 0.61–0.68). As shown in figure 1, the calibration is reasonable, but the risk was overpredicted in the moderate-risk group, and underpredicted in the high-risk group.

Age and BMI were categorized using cut-off values of 75 years for age and 25 kg/m^2 for BMI. The C-index of this model was unchanged (C = 0.64, 95% CI 0.61–0.67) in the derivation data set, and was 0.59 (95% CI 055–0.62) in the validation data set. The final ICH risk score (named Intracranial-B_2LEED_3S score) ranged from 0 to 13 points (table 2). In our dataset, the maximal intracranial-B_2LEED_3S score observed was 12. After categorization, the score into quartiles, the observed 2-year ICH risk was 0.75% for patients with a score ≤2, 1.05% for patients with a score of 3, 1.68% with a score of 4 and 2.44% with a score of ≥5. The plot of predicted ICH risk according to the intracranial-B_2LEED_3S score is available in figure 2.

As shown in table 3, calibration of the intracranial-B_2LEED_3S score was acceptable in both derivation and validation datasets (table 3). An example of how to calculate the estimated risk for a fictive patient using the Cox model is presented in the online supplementary data.

Table 3. Model performance of the Intracranial-B_2LEED_3S score in the derivation and validation datasets: observed and predicted probabilities of ICH at 2 years

Risk group	Derivation		Validation	
	observed†	predicted††	observed†	predicted‡
2-Year ICH risk, %				
0–2	0.75	0.84	0.46	0.85
3	1.05	1.16	0.73	1.14
4	1.68	1.46	1.03	1.42
≥5	2.44	2.33	1.33	2.39
C-index (95% CI)	0.64 (0.61–0.67.5)		0.59 (0.55–0.62)	

The risk group was defined using the quartiles of B_2LEED_3S score from derivation dataset.
† Kaplan–Meier estimate.
†† Calculated as the mean predicted probabilities by the Cox regression model (using Intracranial-B_2LEED_3S score as continuous predictor).
‡ Predicted estimates used shrinkage factor based on bootstrap validation in the derivation dataset (see Methods).

Discussion

In this population where all patients were on antiplatelet therapy, age, blood pressure, and low BMI were, as expected, among the strongest predictors of ICH. Asian ethnicity was also a strong predictor, independently of low BMI, which has already been found in studies of oral anticoagulant in atrial fibrillation [17]. History of stroke or CAD was another strong predictor. Indeed, in ACS trials such as in TRACER and TRA-2P (with vorapaxar) [4, 5], PLATO (with ticagrelor) [6] and TRITON-TIMI38 (with prasugrel) trials [7], there was a doubling in ICH in patients randomized in the experimental arm compared to placebo, which was partially driven by patients with a past history of stroke or TIA. Consequently, in their label, stroke or TIA is a contra-indication of these agents in ACS patients. Hence, in an analysis of CAD patients enrolled in the REACH registry, we found that those with a past history of stroke, as compared to those without, had a doubling in the risk of ICH, but in absolute term, their 4-year risk of developing an ischemic stroke (11.6%) was 20 times higher than the risk of developing an ICH (0.6%) [18].

Less significant, but still independent, predictors were male gender and lacunes. In the SPS-3 trial, that evaluated clopidogrel plus aspirin vs. aspirin only in patients with symptomatic cerebral small vessel disease, there was an increased risk in mortality in the dual antiplatelet therapy arm, which was partly driven by ICH increase (2-year risk: 0.5% on aspirin vs. 0.84% on clopidogrel plus aspirin) [19]. An exploratory analysis of patients enrolled in the PERFORM-MRI substudy (online suppl. table II) indicates that the combination of microbleeds, severe leukoaraoisis, and superficial hemorrhagic suffusion have a 4-time higher risk of ICH risk than patients without. However, only 17 patients had an ICH in this population and it was not possible to perform a multivariable analysis. It is thus reasonable to think, but yet to be validated, that in the Intracranial-B_2LEED_3S score any of the three variables can be substituted to the 'lacune' variable.

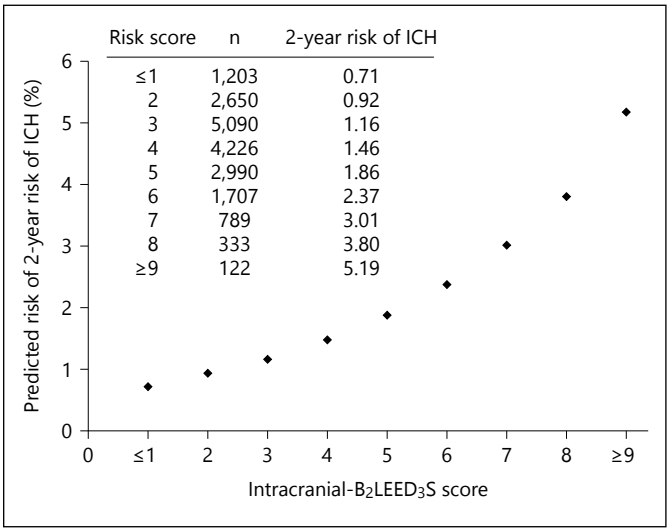

Fig. 2. Predicted 2-year risk of ICH according to the Intracranial-B_2LEED_3S score. Mean values are represented by little squares. Score of 0 and 1; and upper or equal to 9 were combined because of the low number of events.

Dual antithrombotic therapy or oral anticoagulant therapy just missed statistical significance. However, we forced this variable in the score because of a clear increased risk of ICH with vitamin K antagonist in previous trials (WARS, WASID, ESPRIT) [20–22], which was associated with too high INR, and with dual antiplatelet therapy in trials in ACS [4–6] and in non-cardioembolic ischemic stroke patients [3]. Excess in ICH risk in the CAD population of the REACH registry was 5 times higher in patients on dual antiplatelet therapy albeit confined to the first year of treatment [18]. In patients with ischemic stroke on dual antiplatelet therapy, such as in MATCH and in the PRoFESS trials, there was a significant increase risk of ICH [3, 9]. Only very early, short-term (21 days), dual antiplatelet treatment in the CHANCE trial did not show an increased risk in ICH compared with aspirin monotherapy (0.3% at 90 days in each arm) [23].

The strength of our analyses was the large, similar sample size in both derivation and validation cohorts. Both trials evaluated 2 antiplatelet strategies in non-cardioembolic strokes, in multi-ethnic, multicontinental trials, with careful evaluation of safety endpoints. In both studies, ICHs were adjudicated independently, and investigators were all experienced in stroke care and diagnosis.

Limitations included the lack of systematic collection of important MRI data such as severe leuko-araiosis, multilacunes, and microbleeds; all data have been associated with an increased risk of ICH [24–26]. It is likely that the rather low c-statistics that we observed with the Intracranial-B_2LEED_3S score was due to missing important variables in our database. Another important limit was exclusion from the randomization of patients deemed to have a high likelihood of bleeding complications such as patients who already bled on antithrombotic agents, had thrombophilia, or had a past history of ICH. Patients with history of falls or at high risk of it, as well as patients with cognitive impairment, both conditions that may increase the risk of ICH due to trauma or misusage of antithrombotic agents, were also likely not randomized in either trial. Patients with large, severe ischemic stroke with residual handicap measured by a modified Rankin score >3, who are more prone to bleed than those with minor ischemic stroke, were also excluded in both trials. Interaction with other drugs prescribed during the course of the trial may also be an important bleeding factor, such as paracetamol or ibuprofen prescriptions [27]. We found that these drugs were associated with almost a doubling in major hemorrhages [27]. It is thus reasonable to think, but yet to be validated, that in the Intracranial-B_2LEED_3S score addition of paracetamol or ibuprofen can be substituted by the 'dual antiplatelet therapy' variable. One other limitation was that in both trials patients with a past history of bleeding were excluded from randomization. When, in an exploratory analysis, we included in the model the variable 'minor and major bleeding (other than ICH) during the trial' we found a strong independent association with a doubling in the risk of ICH (2.05, 95% CI 1.05–4.00, p = 0.04) and an improvement in the c-statistics to 0.67. However, we built the score on baseline data. But this exploratory analysis shows that the Intracranial-B_2LEED_3S score could be improved by including the history of minor/major bleeding (again most patients with such a bleeding event prior randomization were not enrolled in either trial). Finally, although potentially helpful, the score is also not perfectly calibrated since it overestimated the risk in the validation cohort.

In conclusion, the Intracranial-B_2LEED_3S score helps identify patients at high-risk of bleeding on antiplatelet monotherapy. Further improvement will identify other variables in order to capture more patients at risk (e.g., microbleeds on magnetic resonance imaging).

Disclosure Statement

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K.M. Fox receives honoraria from Servier (lectures) and collaborates with Servier as consultant to EMEA and advisory boards.

P.G. Steg holds research grants from Sanofi and Servier (steering committee chair) and receives honoraria from Astrazeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GSK, Janssen, Lillly, Novartism Pfizer, regenereon, Roche, Sanofi, Servier, The Medecines Company and Amarin (steering committee) and Pfizer (event adjudication committee).

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