Predictors of risk of intracerebral haemorrhage in patients with a history of TIA or minor ischaemic stroke

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We developed a model identifying patients with previous cerebral ischaemia at increased risk of intracerebral haemorrhage (ICH). Based on data from eight cohorts, 107 ICHs were found to have occurred among 12,648 patients. Multivariate Cox regression analysis identified the following predictors: age (≥60 years, hazard ratio (HR) 2.07), blood glucose level (≥7 mmol/l, HR 0.33), systolic blood pressure (≥140 mm Hg, HR 2.17), and antihypertensive drugs (HR 1.53). The highest risk quartile was associated with five times more ICHs than the lowest quartile.

Each year approximately 1 million strokes occur in the European Union,1 of which approximately 80% are ischaemic strokes, 15% are intracerebral haemorrhages (ICHs), and 5% are subarachnoid haemorrhages.2 As the risk of stroke after a transient ischaemic attack (TIA) or ischaemic stroke is approximately 12% in the first year,3 preventive measures, such as anticoagulant or antiplatelet treatment, are indicated. However, antithrombotics may have detrimental adverse effects, the most devastating of which is an ICH; the incidence of this type of bleeding is far higher in patients after cerebral ischaemia (300–3700 per 100,000 per year4 5–7) than in the general population (20–35 per 100,000 per year8–9).

Determining which patients are at increased risk of ICH is important so as to better target antithrombotic treatment in these subjects. In this study a model was developed to identify patients with previous cerebral ischaemia at highest risk of ICH.

METHODS
The Cerebrovascular Cohort Studies Collaboration (CCSC) is a joint undertaking in which individual patient data from cohort studies in patients with a previous episode of cerebral ischaemia are pooled.4 The current analysis is based on data from eight cohorts in which there was adequate brain imaging after follow up strokes such that haemorrhagic strokes could be reasonably reliably identified (for extra references see supplementary information available at http://jnnp.com/supplemental). Patients with ischaemic stroke or TIA aged 18 years and above and a Rankin grade ≤3 at baseline were studied. Data on presenting events, baseline characteristics, results of baseline investigations including brain and vascular imaging, and all recorded follow-up events were obtained. Detailed consideration was given to the definition of each variable used in the original studies. Where definitions were identical, data were merged. When possible, differences in definitions of variables between studies were resolved by reconstructing definitions to achieve comparability. Since only few patients had a follow up longer than 7 years, we only included follow up data collected during the 7 years after inclusion in our analyses.

Symptomatic ICH was the predicted outcome of interest and was based on CT scan or autopsy. All of the studies differentiated between ICHs and subarachnoid haemorrhages or subdural haemorrhages. In none of the studies were cases classified as ICHs without good evidence on brain imaging.

DATA ANALYSIS
Using Cox regression analysis, we assessed as a first step the univariable associations between potential predictors and the occurrence of ICH. It was not feasible to adjust for source of study, because risk of ICH in patients with cerebral ischaemia in the separate studies was low. Therefore, to study the effect of the different trials from which patients originated, we compared the maximum likelihood estimate (MLE) of the model with one of the potential predictors and risk of ICH with the MLE of the model with origin of trial and risk of ICH. If there was no statistically significant difference between these two MLEs, then there was no confounding influence of origin of study.

In a second step we selected candidate predictor variables that were associated with ICH in the univariable analyses (p<0.05). These variables were entered into the multivariate Cox regression analyses using forward stepwise selection to develop a multivariate model. The variables associated with risk of ICH in the multivariable analyses were dichotomised using clinically meaningful cut offs. To adjust for overfitting in the modelling process, we performed bootstrapping to shrink the regression coefficients. We multiplied the shrunk regression coefficients by 10 and rounded them to the nearest integer to calculate a risk score and categorised the score into quartiles. To assess the relative increase in risk of ICH per score category, we performed a Cox regression analysis with score category and risk of ICH. For external validation, we will have to wait until new data are added to the CCSC data set.

RESULTS
A total of 107 ICHs occurred in 53,761 person years; the incidence of ICH was 1.9% in 5 years (95% confidence interval (CI): 0.8 to 2.2) (see web table 1 available at http://jnnp.com/supplemental). The mean follow up was 4.3 years. Comparison of the MLEs of the models showed no confounding by origin of study for the variables associated with ICH in the univariable analyses. Therefore, we concluded that origin of study did not influence the results.

Factors that were associated with ICH in the univariable analyses were age, systolic and diastolic blood pressure, use of antihypertensive drugs, blood glucose level, history of angina, and daily smoking (see web table 2 available at http://jnnp.com/supplemental). In the multivariate Cox regression analyses, age (hazard ratio (HR) 2.07), blood glucose level (HR 0.33), systolic blood pressure (HR 2.17), and use of antihypertensive drugs (HR 1.53) were associated with ICH.

Abbreviations: CCSC, Cerebrovascular Cohort Studies Collaboration; CI, confidence interval; ICH, intracerebral haemorrhage; MLE, maximum likelihood estimate; TIA, transient ischaemic attack
glucose level (HR 0.33), systolic blood pressure (HR 2.17), and use of antihypertensive drugs (HR 1.53) appeared to be independent predictors of ICH (table 1). After bootstrapping, the regression coefficients were shrunk by 14% to adjust for overfitting. From the shrunken regression coefficients we calculated a risk score, which ranged from −10 to 17 in individual patients. We categorised the patients into risk quartiles (Q) of the total population: −10 to 4 (Q1), 6 to 10 (Q2), 11 to 13 (Q3), and 17 (Q4). The 5 year rate of ICH was 0.4% for Q1, 0.6% for Q2, 1.3% for Q3, and 2.0% for Q4. The Kaplan-Meier curves are shown in fig 1. Patients in Q4 were five times more likely to suffer an ICH than those in Q1 (HR 5.17, 95% CI: 2.49 to 10.7).

**DISCUSSION**

Independent predictors of ICH were age, blood glucose level, systolic blood pressure, and use of antihypertensive drugs. With this model it was possible to select a group at higher risk of ICH (HR 5.17). However, the absolute risk of ICH in these patients is still low. Although we consider this not to be clinically insignificant, patients in the highest risk stratum would not be good candidates for the more aggressive forms of antithrombotic treatment, that is, oral anticoagulation or combination antiplatelet treatment.

In the Cerebrovascular Cohort Study Collaboration we have individual patient data available from the cohort studies in individual patients. We categorised the patients into risk quartiles (Q) of the total population: −10 to 4 (Q1), 6 to 10 (Q2), 11 to 13 (Q3), and 17 (Q4). The 5 year rate of ICH was 0.4% for Q1, 0.6% for Q2, 1.3% for Q3, and 2.0% for Q4. The Kaplan-Meier curves are shown in fig 1. Patients in Q4 were five times more likely to suffer an ICH than those in Q1 (HR 5.17, 95% CI: 2.49 to 10.7).

**Figure 1** Cumulative proportion of intracerebral haemorrhage.
REFERENCES


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