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Summary

Background Balancing the risks of recurrent ischaemic stroke and intracranial haemorrhage is important for patients treated with antithrombotic therapy after ischaemic stroke or transient ischaemic attack. However, existing predictive models offer insufficient performance, particularly for assessing the risk of intracranial haemorrhage. We aimed to develop new risk scores incorporating clinical variables and cerebral microbleeds, an MRI biomarker of intracranial haemorrhage and ischaemic stroke risk.

Methods We did a pooled analysis of individual-patient data from the Microbleeds International Collaborative Network (MICON), which includes 38 hospital-based prospective cohort studies from 18 countries. All studies recruited participants with previous ischaemic stroke or transient ischaemic attack, acquired baseline MRI allowing quantification of cerebral microbleeds, and followed-up participants for ischaemic stroke and intracranial haemorrhage. Participants not taking antithrombotic drugs were excluded. We developed Cox regression models to predict the 5-year risks of intracranial haemorrhage and ischaemic stroke, selecting candidate predictors on biological relevance and simplifying models using backward elimination. We derived integer risk scores for clinical use. We assessed model performance in internal validation, adjusted for optimism using bootstrapping. The study is registered on PROSPERO, CRD42016036602.

Findings The included studies recruited participants between Aug 28, 2001, and Feb 4, 2018. 15 766 participants had follow-up for intracranial haemorrhage, and 15 784 for ischaemic stroke. Over a median follow-up of 2 years, 184 intracranial haemorrhages and 1048 ischaemic strokes were reported. The risk models we developed included cerebral microbleed burden and simple clinical variables. Optimism-adjusted c indices were 0·73 (95% CI 0·69–0·77) with a calibration slope of 0·94 (0·81–1·06) for the intracranial haemorrhage model and 0·63 (0·62–0·65) with a calibration slope of 0·97 (0·87–1·07) for the ischaemic stroke model. There was good agreement between predicted and observed risk for both models.

Interpretation The MICON risk scores, incorporating clinical variables and cerebral microbleeds, offer predictive value for the long-term risks of intracranial haemorrhage and ischaemic stroke in patients prescribed antithrombotic therapy for secondary stroke prevention; external validation is warranted.

Funding British Heart Foundation and Stroke Association.

Research in context

Evidence before this study

We searched Medline from Jan 1, 1996, to Feb 1, 2020, using the search terms (stroke[tiab] OR bleeding[tiab] OR haemorrhage[tiab] OR hemorrhage[tiab]) AND (prediction[tiab] OR risk stratification[tiab] OR risk score[tiab]). We identified studies in English that described or validated risk scores for ischaemic stroke or major bleeding in patients taking antiplatelets or anticoagulants with or without atrial fibrillation. Very few studies of bleeding risk scores reported their performance for intracranial haemorrhage specifically. A large cohort study of 40 450 patients with atrial fibrillation who received anticoagulants for stroke prevention found poor performance in predicting intracranial haemorrhage for all bleeding risk scores assessed, including HEMORR2HAGES, HAS-BLED, ATRIA, and ORBIT. The highest c index obtained was 0·53, for HASBLED. A nationwide registry-based cohort study of 182 678 patients with atrial fibrillation also found poor to moderate performance of HASBLED and HEMORR2HAGES, with c indices between 0·58 and 0·62 in participants prescribed antithrombotics. Models developed for predicting intracranial haemorrhage in patients taking antiplatelets specifically (including Intracranial-B2LEED3S and S2TOP-BLEED) also showed only moderate performance, with the highest reported c index of 0·65 for S2TOP-BLEED. Risk scores for ischaemic stroke (including $CHADS_2$, $CHAD_2S_2VASc$, and ATRIA) performed moderately, with c indices typically between 0·60 and 0·70.

Added value of this study

We present new clinical-radiological risk scores using cerebral microbleeds, an MRI marker of small vessel fragility, to predict intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic drugs for secondary prevention after ischaemic stroke or transient ischaemic attack, derived from studies in the Microbleeds International Network (MICON)—a large international collaboration of prospective cohort studies. The performance of our MICON-intracranial haemorrhage score (c index 0·73) suggests it can usefully stratify patients by risk of antithrombotic-associated intracranial haemorrhage in clinical practice. Our results also suggest that cerebral microbleeds add considerable value for predicting intracranial haemorrhage, but not ischaemic stroke, clarifying the relative predictive importance of cerebral microbleeds for these outcomes. Our scores did not identify many patients with similar or higher predicted risk of intracranial haemorrhage than ischaemic stroke, even in those with high cerebral microbleed burden and other risk factors. Our MICON scores are simple and widely applicable.

Implications of all the available evidence

Risk scores including cerebral microbleeds offer increased discrimination over clinical variables alone for the prediction of antithrombotic-associated intracranial haemorrhage in a large, multicentre, international population. Although external validation is needed, this finding provides new evidence of how neuroimaging biomarkers can contribute to clinical prediction models. Identifying people at high-risk of intracranial haemorrhage might facilitate timely and accurate prognostication to allow mitigation of reversible risk factors for bleeding (eg, intensive blood pressure control), and selection of participants for clinical trials. Although more complex combinations of clinical, biochemical, and radiological markers might improve stroke risk prediction, balancing accuracy with simplicity will remain important in clinical practice.

Introduction

Antithrombotic therapy is a key component of secondary prevention after ischaemic stroke or transient ischaemic attack. In patients without atrial fibrillation, antiplatelet treatment reduces overall stroke risk by a quarter,[1] whereas oral anticoagulation in patients with atrial fibrillation reduces this risk by two-thirds.[2,3] Although antithrombotic treatment increases the risk of intracranial haemorrhage (by about a quarter for antiplatelets, half for direct oral anticoagulants, and two-times for vitamin K antagonists),[1–3] the substantially lower absolute incidence of intracranial haemorrhage overall means that antithrombotic treatment is recommended for most patients. However, deciding on appropriate antithrombotic therapy for a given patient can be challenging, especially in those with additional risk factors for bleeding, such as uncontrolled hypertension, previous intracerebral haemorrhage, or severe cerebral small vessel disease. Ideally, this decision would be based on an individualised assessment of the risks of ischaemic stroke and intracranial haemorrhage. To this end, risk scores for ischaemic stroke and major bleeding have been developed, mainly in patients with atrial fibrillation. Although these scores show reasonable discrimination for ischaemic stroke[4,5] and all-cause major bleeding,[5,6] studies validating existing bleeding risk scores in predicting intracranial haemorrhage have shown poor to moderate performance, with c indices between 0·50 and 0·62 in patients who received anticoagulants[7,8] and 0·58–0·65 in patients who received antiplatelet drugs.[8,9]

Most risk scores for ischaemic stroke and intracranial haemorrhage only include clinical variables, although scores using serum biomarkers have been developed, which might offer improved performance.[10–12] However, the role of MRI biomarkers for cerebrovascular disease (increasingly obtained as part of standard stroke care) in improving risk prediction remains uncertain. Cerebral microbleeds are a MRI biomarker of vascular fragility, associated with hypertensive microangiopathy (also known as arteriolosclerosis or deep perforator arteriopathy) and cerebral amyloid angiopathy, the two cerebral small vessel diseases that cause most spontaneous intracerebral haemorrhage.[13] Accordingly, the potential of cerebral microbleeds to predict intracranial haemorrhage has attracted particular interest. In a prospective observational study, the addition of cerebral microbleeds to the HASBLED bleeding risk score improved the c index for intracranial haemorrhage

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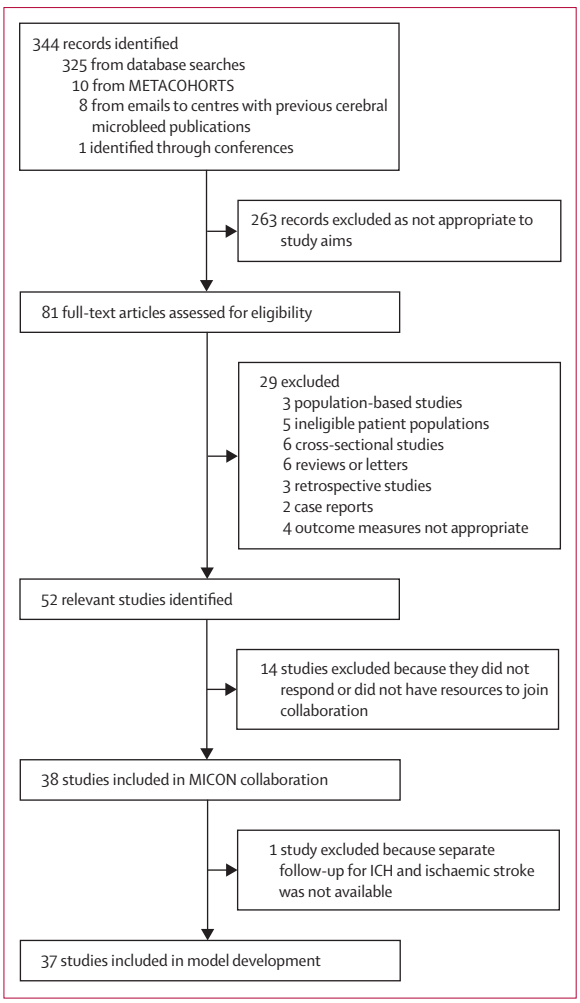

Figure 1: **Study profile**
Records are publications indexed in Medline or Embase and other studies identified through METACOHORTS, correspondence with other groups, and conference publications. ICH=intracranial haemorrhage. MICON=Microbleeds International Collaborative Network.

from 0·41 to 0·66,[14] and a large individual patient data meta-analysis confirmed a strong association between cerebral microbleeds and intracranial haemorrhage in patients with previous ischaemic stroke or transient ischaemic attack.[15] This study[15] also found that cerebral microbleeds are associated with ischaemic stroke risk, with a higher absolute risk of ischaemic stroke than intracranial haemorrhage across all levels of cerebral microbleed burden investigated.

Given these findings, we aimed to establish the added predictive value of cerebral microbleeds for intracranial haemorrhage and ischaemic stroke, by using the same large international dataset to develop risk models based on cerebral microbleed burden and simple clinical variables, and to compare these with models using clinical variables alone. From our models, we aimed to derive simple risk scores that could be easily used for risk stratification in clinical practice. We investigated whether the resulting scores identified a group of patients at similar or higher predicted risk of intracranial haemorrhage than ischaemic stroke and whether our new intracranial haemorrhage risk score performed better than existing methods.

Methods

Study design and participants

We used pooled individual patient data from the Microbleeds International Collaborative Network (MICON) of prospective observational studies, for which the full methodology and composition has been published.[15] MICON includes 38 cohorts from 18 countries in North America, Europe, the Middle East, Asia, and Australasia, collectively including 20 322 participants with previous ischaemic stroke or transient ischaemic attack, baseline MRI—including blood-sensitive paramagnetic sequences to detect cerebral microbleeds—and at least 3 months' follow-up for ischaemic stroke or intracranial haemorrhage, or a composite of both. We identified eligible cohorts through a systematic search of Medline and Embase from Jan 1, 1996, to Dec 1, 2018, for clinical trial databases, scientific abstracts, and the international METACOHORTS consortium of studies in cerebral small vessel disease.[16] Published and unpublished studies were eligible. We assessed all studies identified for quality and risk of bias, including selection bias, using the Cochrane Collaboration tool.[17] All included studies adjudicated events blinded to cerebral microbleed burden. In the current prediction model development study, we included all MICON participants who were taking antithrombotic therapy and were followed up separately for ischaemic stroke or intracranial haemorrhage.

The study was approved by the UK Health Research Authority (8/HRA/0188). Included cohorts obtained ethical and regulatory approvals according to local requirements. Only fully anonymised data were shared, so that individual consent was not required for this individual patient data pooled analysis. The study protocol is registered on PROSPERO, CRD42016036602.

Outcomes

Our outcomes for prediction were the 5-year risks of symptomatic intracranial haemorrhage (including intracerebral, subdural, subarachnoid, and extradural haemorrhage) and ischaemic stroke (excluding transient ischaemic attack).

Procedures

We developed separate prediction models for intracranial haemorrhage and ischaemic stroke using Cox regression, with robust standard errors calculated with the Huber-White sandwich estimator to allow for clustering within cohorts.[18] We prespecified our candidate predictors—on the basis of biological relevance and availability in the cohort—as age; sex; presentation with transient ischaemic attack or ischaemic stroke; clinical history of hypertension; clinical history of type 1 or type 2 diabetes mellitus; previous ischaemic stroke before index stroke

or transient ischaemic attack; previous intracranial haemorrhage; known atrial fibrillation; antithrombotic treatment after index event; cerebral microbleed burden; and type of MRI sequence used to detect cerebral microbleeds (2-dimensional T2*-weighted gradient recalled echo sequences or susceptibility-weighted sequences, including susceptibility-weighted imaging [Siemens, Munich, Germany], susceptibility-weighted angiography [General Electric, Chicago, IL, USA], and susceptibility-weighted imaging with phase enhancement and venous blood oxygen level dependent [Philips, Amsterdam, The Netherlands] sequences), in view of strong external evidence that cerebral microbleed counts are systematically higher on susceptibility-weighted imaging sequences than on gradient-recall echo sequences (appendix p 3). We accounted for missing data using multiple imputation with chained equations (five imputations). We included a cluster-level variable indicating east Asian centres (Japan, Korea, China, and southeast Asia) because of higher incidence of intracerebral haemorrhage and intracranial atherosclerosis in this region.[19] We categorised antithrombotic treatment as antiplatelet therapy only, anticoagulation therapy as with a vitamin K antagonist or anticoagulation with a direct oral anticoagulant. The antiplatelet category included patients taking dual antiplatelets, and anticoagulant categories included participants taking a concomitant antiplatelet. We categorised cerebral microbleed burden as none, one, two to four, five to ten, 11–19, and 20 or more, and assessed whether an interaction term between MRI sequence type and cerebral microbleed burden was required. We investigated whether separate models were required for patients taking anticoagulants or antiplatelets using interaction terms and Wald tests. We simplified our models through backwards elimination at the 20% level (p=0·20). We scaled and rounded regression coefficients to produce integer scores for ease of use in clinical practice.

To test the contribution of cerebral microbleed burden to intracranial haemorrhage and ischaemic stroke prediction, we developed purely clinical models in the same way as the main models, but excluded cerebral microbleed burden and MRI sequence type. We compared their discrimination to the main models and tested whether adding cerebral microbleed burden and MRI sequence type improved their fit. Next, we compared the performance of our cerebral microbleed-based intracranial haemorrhage risk score (the form of the model that could most easily be used in clinical practice) to existing bleeding risk scores (AnTicoagulation and Risk factors In Atrial fibrillation [ATRIA], Older age, Reduced Haemoglobin, Bleeding history, Insufficient kidney function, Treatment [ORBIT], and Hypertension, Abnormal liver or renal function, Stroke, Bleeding, Labile INR, Elderly, Drugs [HASBLED]). Each comparison used all participants for whom the additional variables required for calculation of the existing bleeding risk score were available. To apply HASBLED to patients not taking vitamin K antagonists, we scored the labile international normalised ratio (INR) component as 0. Because we made these comparisons in a subset of the model development data, we adjusted for optimism using bootstrapping.

	Antiplatelet-only (n=8736)	Anticoagulant (n=7048)	Overall (n=15 784)
Age	67·4 (12·4)	74·7 (10·8)	70·7 (12·2)
Sex			
Female	3444 (39·4%)/8736	3253 (46·2%)/7048	6697 (42·4%)/15 784
Male	5292 (60·6%)/8736	3795 (53·8%)/7048	9087 (57·6%)/15 784
East Asian population	2405 (27·5%)/8736	2185 (31·0%)/7048	4590 (29·1%)/15 784
Hypertension	5931 (68·0%)/8726	5291 (75·3%)/7024	11 222 (71·3%)/15 750
Atrial fibrillation	527 (6·1%)/8687	6355 (90·3%)/7041	6882 (43·8%)/15 728
Diabetes mellitus (type 1 or 2)	1720 (24·5%)/7013	1490 (22·0%)/6769	3208 (23·3%)/13 782
Ischaemic stroke before presenting stroke or TIA	1001 (12·9%)/7781	1299 (18·8%)/6906	2300 (15·7%)/14 687
Previous ICH	80 (1·2%)/6549	85 (1·3%)/6488	165 (1·3%)/13 037
Presentation with ischaemic stroke (*vs* TIA)	6632 (75·9%)/8735	6172 (87·7%)/7039	12 804 (81·2%)/15 774
Cerebral microbleed burden			
0	6418 (73·5%)/8733	5202 (74·6%)/6970	11 620 (74·0%)/15 703
1	942 (10·8%)/8733	812 (11·6%)/6970	1754 (11·2%)/15 703
2–4	785 (9·0%)/8733	671 (9·6%)/6970	1456 (9·3%)/15 703
5–10	316 (3·6%)/8733	162 (2·3%)/6970	478 (3·0%)/15 703
11–19	157 (1·8%)/8733	59 (0·8%)/6970	216 (1·4%)/15 703
≥20	115 (1·3%)/8733	64 (0·9%)/6970	179 (1·1%)/15 703
SWI sequence used (*vs* T2*GRE)	2422 (27·7%)/8734	2335 (33·2%)/7025	4757 (30·2%)/15 759
Antithrombotic treatment			
AP only	8736 (100%)/8736	NA	8736 (55·3%)/15 784
Warfarin or vitamin K antagonist	NA	4759 (67·5%)/7048	4759 (30·2%)/15 784
DOAC	NA	2289 (32·5%)/7048	2289 (14·5%)/15 784
Concomitant antiplatelet with anticoagulant	NA	1360 (19·3%)/7048	1360 (8·6%)/15 784

Date are n (%)/N or mean (SD). DOAC=direct oral anticoagulant. GRE=gradient-recalled echo. ICH=intracranial haemorrhage. NA=not applicable. SWI=susceptibility-weighted imaging. TIA=transient ischaemic attack. VKA=vitamin K antagonist.

Table 1: **Baseline characteristics by treatment category**

Statistical analyses

We internally validated our models using bootstrapping.[20] As an additional test of model performance, we did internal-external cross validation,[21,22] with five folds consisting of whole cohorts, which was repeated 20 times to reduce variance. We quantified discrimination using Harrell's c index, and calibration through the calibration slope. We also assessed calibration by calculating predicted 5-year risk for each outcome on the basis of the integer risk score, dividing participants into low-risk, intermediate-risk, and high-risk groups of roughly equal sizes, and comparing predicted to observed risk using Kaplan-Meier plots.

We did two sensitivity analyses. We assessed the added predictive value of additional variables that we considered

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	Intracranial haemorrhage		Ischaemic stroke		Intracranial haemorrhage score (out of 24)	Ischaemic stroke score (out of 34)
	HR (95% CI)	p value	HR (95% CI)	p value		
Number of cerebral microbleeds						
0	1 (ref)	<0·0001	1 (ref)	<0·0001	0	0
1	1·96 (1·38–2·80)	..	1·07 (0·86–1·34)	..	3	1
2–4	2·18 (1·43–3·33)	..	1·29 (1·08–1·53)	..	3	2
5–10	3·27 (1·71–6·24)	..	1·66 (1·21–2·27)	..	5	4
11–19	4·93 (2·93–8·29)	..	..†	..	6	4
≥20	9·26 (4·11–20·82)	..	1·91 (1·36–2·69)	..	9	5
T2* GRE sequence used?	1·72 (0·80–3·70)	0·16	1·54 (0·82–2·89)	0·18	2	3
Age (years)						
<50	1 (ref)	<0·0001	1 (ref)	<0·0001	0	0
50–59	1·05 (0·48–2·33)	..	1·03 (0·68–1·55)	..	0	0
60–69	..†	..	1·10 (0·77–1·57)	..	0	1
70–79	2·12 (0·95–4·75)	..	1·60 (1·11–2·29)	..	3	4
≥80	2·66 (1·19–5·96)	..	1·72 (1·15–2·56)	..	4	4
East Asian population	1·85 (0·82–4·15)	0·14	1·62 (0·78–3·37)	0·19	2	4
Ischaemic stroke before presenting stroke or transient ischaemic attack	1·36 (1·00–1·87)	0·053	1·85 (1·48–2·31)	<0·0001	1	5
Intracranial haemorrhage score only						
Previous intracranial haemorrhage	3·91 (2·40–6·36)	<0·0001	..	..	5	..
Antithrombotic treatment						
Antiplatelet only	1·23 (0·69–2·18)	0·51	..	..	1	..
Warfarin or vitamin K antagonist	1·30 (0·82–2·05)	..	..	..	1	..
DOAC	1 (ref)	..	..	..	0	..
Ischaemic stroke score only						
Presentation with ischaemic stroke	..	..	1·34 (0·91–1·98)	0·14	..	2
Diabetes mellitus	..	..	1·32 (1·09–1·58)	0·004	..	2
Antithrombotic treatment						
Received antiplatelet only had atrial fibrillation	..	..	3·14 (1·84–5·35)	0·0002	..	9
Received antiplatelet only no atrial fibrillation	..	..	1·70 (1·16–2·51)	..	..	4
Received OAC for other reason	..	..	1·36 (0·81–2·27)	..	..	2
Received OAC for atrial fibrillation	..	..	1 (ref)	..	..	0

Baseline 5-year survival for full ICH model 99·5% and for full IS model 97·2%. DOAC=direct oral anticoagulant. GRE=gradient-recalled echo. HR=hazard ratio. ICH=intracranial haemorrhage. OAC=oral anticoagulant. MICON=Microbleeds International Collaborative Network. †Category merged with preceding category to prevent inconsistent (non-monotonic) scoring.

Table 2: **Final models and risk scores for symptomatic intracranial haemorrhage (MICON-ICH) and ischaemic stroke (MICON-IS)**

potentially clinically relevant by adding each variable individually to our final model for each outcome and testing if it improved model fit with a Wald test[23] before comparing the discrimination of the base and augmented models if it did. The additional variables were clinical history of hypercholesterolaemia, current smoking status, cerebral microbleed distribution (strictly deep, strictly lobar, and mixed), and burden of white matter hyperintensities on MRI, assessed using the highest recorded Fazekas score from periventricular and deep white matter regions. We also tested the performance of our intracranial haemorrhage model for intracerebral haemorrhage specifically.

We determined the number of participants with a predicted risk of intracranial haemorrhage higher than that of ischaemic stroke and investigated their baseline characteristics. Our statistical analyses used Stata (version 16) and are reported following the TRIPOD guideline.[24]

Role of the funding source

The funders of the study had no role in its design, the collection, analysis and interpretation of data, the writing of the Article, or the decision to submit it for publication.

Results

Of the 38 studies and 20 322 participants in the collaboration, one study comprising 3355 (16·5%) participants that collected follow-up for a composite of any stroke outcome only was excluded (figure 1). From the remaining 37 cohorts, 979 (4·8%) participants were excluded because they did not receive antithrombotic medication, and 204 (1·0%) participants were excluded because they were not followed-up for both intracranial haemorrhage and ischaemic stroke. 15 784 (77·7%) participants were included in the final study population, recruited between Aug 28, 2001, and Feb 4, 2018. Participant characteristics are summarised in table 1 and described by cohort in the appendix (pp 4–6). All 15 784 participants had follow-up for ischaemic stroke and 15 766 (99·9%) had follow-up for intracranial haemorrhage. 2747 (17·4%) of 15 784 observations were imputed for previous intracranial haemorrhage, 2002 (12·7%) were imputed for diabetes, and 1097 (7·0%) were imputed for ischaemic stroke before index ischaemic stroke or transient ischaemic attack. We imputed fewer than 1% of observations for all other candidate predictors (table 1). During a total follow-up of 32 001 person-years (median 1·99 years [IQR 0·61–2·87]) for intracranial haemorrhage and 31 468 person-years (median 1·98 years [0·56–2·80]) for ischaemic stroke, 184 intracranial haemorrhages (including 146 intracerebral haemorrhages) and 1048 ischaemic strokes were reported. The annualised incidences were 0·57% for intracranial haemorrhage and 3·33% for ischaemic stroke.

The hazard ratios from our final models for intracranial haemorrhage and ischaemic stroke and the resulting integer risk scores are reported in table 2. Both models included age, cerebral microbleed burden, MRI sequence type used to assess cerebral microbleed burden, history of ischaemic stroke before the index ischaemic stroke or transient ischaemic attack, and east Asian centre location. Our intracranial haemorrhage model also included previous intracranial haemorrhage and antithrombotic treatment type. We chose to retain antithrombotic treatment in this model on clinical grounds. Our ischaemic stroke model also included presentation with ischaemic stroke and history of diabetes mellitus, and we found strong evidence of an interaction between antiplatelet treatment and atrial fibrillation (p=0·0040), consistent with the known superior efficacy of anticoagulants for stroke prevention in atrial fibrillation. We represented this interaction in our model by combining atrial fibrillation and antithrombotic treatment type into a single-four level variable, with diract oral anticoagulants and vitamin K antagonist treatment categories merged because their hazard ratios were very similar. The results of our other tests for interactions are reported in the appendix (p 7).

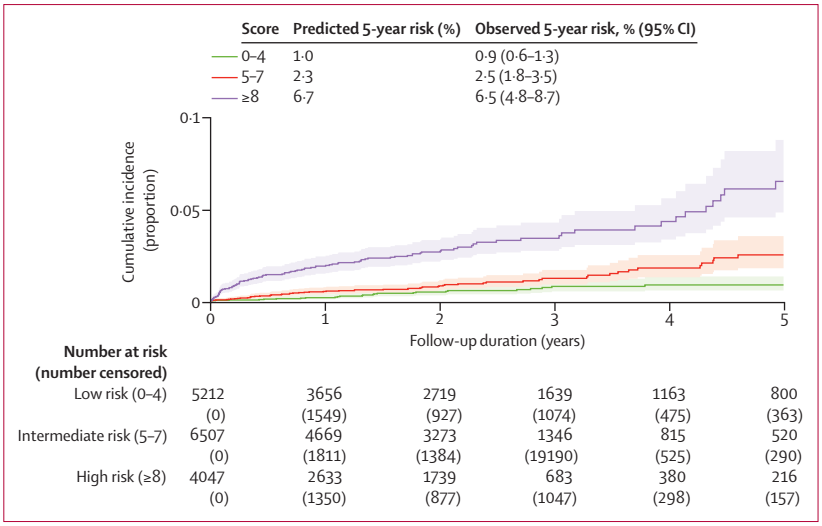

Figure 2: **Kaplan-Meier plot and risk table for symptomatic intracranial haemorrhage**
Shaded areas are 95% CI.

Apart from an interaction for intracranial haemorrhage risk between antiplatelet use and previous intracranial haemorrhage (p=0·011), which we attributed to treatment bias and chose to exclude, we found no compelling evidence that other interaction terms were required.

The optimism-adjusted c index for our final intracranial haemorrhage model was 0·73 (95% CI 0·69–0·77) and the calibration slope was 0·94 (0·81–1·06; appendix p 11). For our final ischaemic stroke model, the c index was 0·63 (0·62–0·65) and the calibration slope was 0·97 (0·87–1·07). Both c indices and calibration slopes indicated reasonable discrimination and excellent calibration.

In internal-external cross-validation, mean discrimination for intracranial haemorrhage was 0·71 (SD 0·05), with a slightly reduced mean calibration slope (0·85 [0·24]), partly explained by the reduced sample for model development. Mean discrimination for ischaemic stroke was 0·60 (0·05) and the mean calibration slope was 0·76 (0·35). For each outcome, after participants were combined into three groups—based on their total risk score—we observed excellent agreement between predicted and observed risk (figure 2; appendix p 10). The detailed calibration results for each outcome across ten similar sized risk groups are shown in figure 3, table 3, and the appendix (p 11). Absolute intracranial haemorrhage risk was moderately over-predicted in the high-risk decile. Because 15 487 (98·2%) of 15 766 participants received the same prediction across all five imputations, calibration plots were reported only for the first imputation.

The clinical-only models generated for comparison with our main MRI-based models included the same variables as the main models, apart from cerebral microbleed burden and MRI sequence type. The clinical-only model for intracranial haemorrhage showed reduced model fit and substantially lower discrimination (difference in c index 0·05 [95% CI 0·02–0·09], p<0·0001). The

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See Online for appendix

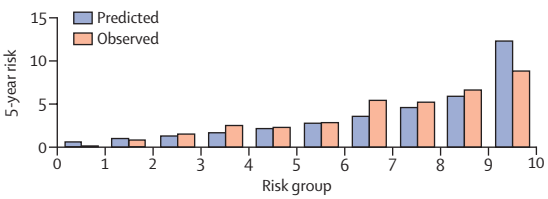

Figure 3: **Intracranial haemorrhage model calibration**
Predicted *vs* observed risk of symptomatic intracranial haemorrhage by risk group.

	Risk score	Number of patients	Predicted risk, %	Observed risk, % (95% CI)
1	0–2	1080	0·7	0·2 (0·1–0·8)
2	3	3228	1·0	0·9 (0·5–1·5)
3	4	904	1·3	1·5 (0·7–3·4)
4	5	1326	1·7	2·5 (0·9–7·3)
5	6	3172	2·2	2·3 (1·6–5·0)
6	7	2009	2·8	2·9 (1·7–5·1)
7	8	1128	3·6	5·4 (2·3–12·5)
8	9	1091	4·6	5·2 (2·8–9·6)
9	10	730	5·9	6·6 (3·5–12·3)
10	≥11	1098	12·3	8·8 (5·8–13·5)

Table 3: **Predicted and observed five year symptomatic intracranial haemorrhage risk for each risk group**

clinical-only model for ischaemic stroke showed worse model fit (p=0·00020) but similar discrimination (c index 0·63 [0·61–0·64]).

11 cohorts from eight countries contributed to the comparison between HASBLED and the new intracranial haemorrhage risk score, and seven cohorts from six countries contributed to the comparison with ATRIA and ORBIT. All comparisons included east Asian and European centres. For each comparison, the estimate for the c index of the new intracranial haemorrhage risk score was higher, both in participants taking any antithrombotics and when restricted to participants taking oral anticoagulants. The optimism-adjusted difference in c index was substantial (range 0·04–0·27) in all comparisons (table 4), although estimates were imprecise and the 95% CI for comparisons with ATRIA and ORBIT did not exclude 0.

In our planned sensitivity analyses, we found no evidence that any of the additional variables tested improved model fit for intracranial haemorrhage or ischaemic stroke (appendix p 8). The optimism-adjusted c index of our intracranial haemorrhage model in predicting intracerebral haemorrhage specifically (rather than intracranial haemorrhage in general) was 0·77 (95% CI 0·73–0·81), with a calibration slope of 0·95 (0·83–1·07). Having found evidence that use of information on cerebral microbleed burden from MRI improves intracranial haemorrhage prediction, we did an additional sensitivity analysis testing the performance of our intracranial haemorrhage prediction model according to MRI sequence type used. Performance was acceptable in both groups (appendix p 12).

Of 11 953 participants for whom both risk scores could be calculated without imputed data, only 104 (0·9% were in the high-risk tertile for intracranial haemorrhage and the low-risk tertile for ischaemic stroke (appendix p 9), in which the predicted 5-year risks of intracranial haemorrhage (6·7%) and ischaemic stroke (7·2%) were similar (figure 2; appendix p 10). An additional 999 (8·4%) of 11 953 participants were allocated to the high-risk group for intracranial haemorrhage (predicted 5-year risk 6·7%) and the intermediate-risk group for ischaemic stroke (predicted 5-year risk 11·6%; appendix pp 10, 13).

Discussion

Our most important result is the description of the novel MICON-intracranial haemorrhage (MICON-ICH) risk score—which includes clinical variables and MRI-detected cerebral microbleeds—to predict intracranial haemorrhage in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack. The addition of cerebral microbleeds to a score based on clinical variables alone substantially improved performance, and a direct comparison with three existing bleeding risk scores also suggested superior discrimination of the MICON-ICH risk score. The novel MICON-ischaemic stroke (MICON-IS) risk score showed modest discrimination, and cerebral microbleeds appeared less important for predicting ischaemic stroke than intracranial haemorrhage; nevertheless, this score can be used alongside MICON-ICH for straightforward and simultaneous estimation of intracranial haemorrhage and ischaemic stroke risk. Both our scores showed excellent calibration in bootstrap validation, providing accurate estimates of absolute risk across lower-risk, intermediate-risk, and higher-risk groups. Discrimination was similar and calibration remained acceptable in internal-external validation. A sensitivity analysis suggested that MICON-ICH might show higher discrimination for the prediction of intracerebral haemorrhage, the most serious form of non-aneurysmal intracranial haemorrhage and the form most closely associated with cerebral microbleeds. Overall, the performance of our scores suggests they might be useful for estimating stroke risk and inform prognostication in clinical practice.

Our scores have several features to ensure their ease-of-use in the clinical setting. Most importantly, they are simple: the clinical variables used are a standard part of the medical history for any patient who has had a stroke, and cerebral microbleeds are familiar in stroke clinical practice (eg, in the diagnosis of cerebral amyloid angiopathy). Cerebral microbleeds are discrete lesions, which can be counted with very good inter-rater reliability,[25] and the blood-sensitive gradient-recall echo and susceptibility-weighted imaging sequences required to image them (accounted for in our scores) are quick to acquire, widely available, and part of routine stroke imaging protocols in many centres. This offers an advantage

over the use of serum biomarkers not usually measured clinically (eg, in the ABC bleeding score).[9] Our scores include relatively few variables, allowing diagrammatic representation for quick reference (appendix pp 14–15) and easy conversion to an online calculator or app. Our scores are also applicable to nearly all patients with ischaemic stroke or transient ischaemic attack, whether they are taking antiplatelets or anticoagulants, with or without atrial fibrillation.

Our scores are intended for use in patients in whom antithrombotic treatment is planned after ischaemic stroke or transient ischaemic attack. The scores are not applicable to patients in whom antithrombotic treatment is contraindicated or for patients taking antithrombotics for primary prevention. They are not designed to help select the type of antithrombotic therapy to use (ie, antiplatelet or anticoagulant) because this would require randomised data, rather than observational data in which the relationship between antithrombotic type and outcomes is attenuated by selection bias. The MICON risk scores should be used to assess prognosis to inform clinical discussions and other aspects of care once the intended antithrombotic treatment has been chosen. The finding of a high predicted intracranial haemorrhage risk might lead to more aggressive treatment of modifiable bleeding risk factors (eg, hypertension and alcohol intake), review of concurrent medication, and consideration of non-pharmacological stroke prevention strategies if applicable (eg, left atrial appendage occlusion in patients with atrial fibrillation). Our scores might also have applications in the selection of patients at high intracranial haemorrhage risk for future clinical trials and mechanistic studies of intracranial haemorrhage.

The principal methodological strength of our study is the use of a large, multicentre, and international study population, which increases generalisability and allows us to consider regional differences in stroke risk. We screened the prospective studies included for quality and risk of bias. These offered standardised baseline assessment and ascertainment of outcome events within each cohort—an advantage over registry-based studies—and we accounted statistically for within-cohort clustering. We did both internal validation using bootstrapping and internal-external cross-validation, in accordance with TRIPOD guidelines and expert recommendations.[22,24] Although we omitted some potentially clinically relevant variables from our model because of missing data, a sensitivity analysis suggested that this did not reduce model performance.

Our study has limitations. To maximise precision we used all available data to develop our scores; as a result, external validation of our scores with new data should be done. Although we compared the new MICON-ICH score to three existing bleeding risk scores, comparison against a large, truly independent cohort would clarify the relative performance of these scores. Our model is applicable to patients who have received antiplatelet and anticoagulant therapy, but we had insufficient data to make direct comparison with antiplatelet-specific scores, such as Intracranial-B2LEED3S and S2TOP-BLEED,[9,26–28] which should also be done. Although large, our study cohort contained relatively few patients with very high cerebral microbleed counts, reducing the precision of our estimates for intracranial haemorrhage and ischaemic stroke risk in very high-risk categories. We had no data on MRI field strength, which can influence cerebral microbleed count, and on some additional risk factors that might have improved identification of high risk patients, including cortical superficial siderosis, alcohol use, renal insufficiency, and labile INR in patients treated with vitamin K antagonists. Hypertension, diabetes, and hyperlipidaemia were diagnosed according to local criteria for each cohort; we had no data on their treatment, and on antithrombotic medication adherence. These factors might have reduced the association between these predictors and outcomes (eg, the unexpected absence of an association between hypertension and intracranial haemorrhage risk). We did not have central formal adjudication of outcome events. Although we present data on the relative predicted risks of

	Number of patients	c index (Comparator)	c index (MICON-ICH)	Optimism-adjusted difference (95% CI)
HASBLED*				
All	5510	0·47	0·75	0·27 (0·18 to 0·37)
OAC only	4017	0·47	0·67	0·20 (0·06 to 0·34)
ATRIA†				
All	3340	0·63	0·71	0·06 (–0·06 to 0·18)
OAC only	2677	0·61	0·67	0·04 (–0·08 to 0·17)
ORBIT†				
All	3340	0·60	0·71	0·09 (–0·01 to 0·18)
OAC only	2677	0·58	0·67	0·08 (–0·03 to 0·19)

All groups include any anticoagulant or antiplatelet use. ATRIA=AnTicoagulation and Risk factors In Atrial fibrillation. HASBLED=Hypertension, Abnormal liver or renal function, Stroke, Bleeding, Labile INR, Elderly, Drugs. ICH=intracranial haemorrhage. MICON=Microbleeds International Collaborative Network. OAC=oral anticoagulation. ORBIT=Older age, Reduced Haemoglobin, Bleeding history, Insufficient kidney function, Treatment. *Cohorts used for comparison were Clinical Relevance Of Microbleeds In Stroke 2 (CROMIS-2), UK; Graz, Austria; Hemorrhage Predicted by Resonance in Patients Receiving Oral Anticoagulants (HERO), Spain; Kushiro City, Japan; Novel Oral Anticoagulants in Stroke Patients (NOACISP), Switzerland; IPAAC (Intracerebral Hemorrhage in Patients Taking Oral Anticoagulants for Atrial Fibrillation with Microbleeds)-Warfarin, Hong Kong; SAMURAI-NVAF (Stroke Acute Management With Urgent Risk-factor Assessment and Improvement Study on Anticoagulant Therapy) in Nonvalvular Atrial Fibrillation (NVAF), Japan; Tel-Aviv Brain Acute Stroke Cohort (TABASCO), Israel; Stroke Investigation in North and Central London (SIGNAL), UK; Würzburg, Germany; Soo, Hong Kong. †Cohorts used for comparison were CROMIS-2, Graz, Austria; and NOACISP, IPAAC-Warfarin, SAMURAI-NVAF, and TABASCO, Soo, Japan.

Table 4: **Comparison of MICON-ICH score with existing bleeding risk scores**

intracranial haemorrhage and ischaemic stroke in our study sample, conclusions about the appropriateness of antithrombotic treatment are limited by the observational nature of our data. Of note, we also had no data on functional outcomes, and the morbidity and mortality of intracranial haemorrhage is around twice that of ischaemic stroke.[29] Finally, our risk estimates were obtained from organised care systems with access to MRI, and might not be applicable to low-income and middle-income settings.

In summary, the MICON-ICH and MICON-IS risk scores provide a new means by which to assess the long-term risk of intracranial haemorrhage and ischaemic stroke. Although the MICON-ICH score appears promising and clinically useful, external validation is still required. Our results also clarify the relative predictive importance of cerebral microbleeds for intracranial haemorrhage and ischaemic stroke, and might facilitate the design of future randomised controlled trials of alternative stroke prevention strategies (eg, of novel antithrombotic agents with potentially lower intracranial haemorrhage risk) in patients at high predicted risk of intracranial haemorrhage.

Contributors

DJWe, DW, GA, and JM-F drafted the protocol, which was critically reviewed and approved by all authors. JGB and GA did the statistical analysis. JGB, GA, and DJW accessed and verified the data and wrote the first draft of the manuscript. All authors collected data, managed the study, and analysed brain images. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Requests for access to anonymised study data for legitimate academic purposes should be directed to the corresponding author. Approval by the study steering committee and the principal investigator of each cohort in the study will be required before data can be shared.

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