Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack

a pooled analysis of individual patient data from cohort studies

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Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic therapy after ischaemic stroke or TIA: a pooled analysis of individual patient data from cohort studies

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Abstract

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

Methods We did a pooled analysis of individual-patient data from the Microbleeds International Collaborative Network, which comprises 38 hospital-based prospective cohort studies from 18 countries. All studies recruited participants with previous IS or TIA, acquired baseline MRI allowing quantification of CMBs, and followed up participants for IS and ICH. We excluded participants not taking antithrombotic drugs. We developed Cox regression models to predict the five-year risks of ICH and IS, 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. We registered the study with the PROSPERO register of systematic reviews (registration: CRD42016036602).

Findings The included studies recruited participants between 28th August 2001 and 4th February 2018. 15,766 participants had follow-up for ICH, and 15,784 for IS. Over a median follow-up of two years, 184 ICH and 1,048 IS occurred. The risk models we developed included CMB burden and simple clinical variables. Optimism-adjusted c-indices were 0·73 (95% CI 0·69-0·77) for ICH and 0·63 for IS (95% CI 0·62-0·65); calibration slopes were 0·94 (95% CI 0·81-1·06) and 0·97 (95% CI 0·87-1·07) respectively, indicating good calibration.

Interpretation The MICON risk scores, incorporating clinical variables and CMBs, offer predictive value for the long-term risks of ICH 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 1st January 1996 to 1st February 2020 using the following search strategy: (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 which 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 (n=40,450) of patients with atrial fibrillation anticoagulated for stroke prevention found poor performance in predicting ICH 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 (n=182,678) assessing HASBLED and HEMORRH2HAGES in patients with atrial fibrillation also found limited performance, with c-indices between 0·58 and 0·62 in participants prescribed antithrombotics. Models developed for predicting ICH in patients taking antiplatelets specifically (including Intracranial-B2LEED3S and S2TOP-BLEED) also showed only moderate performance, with the highest reported c-index being 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 ICH 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-ICH score suggests it can usefully stratify patients by risk of antithrombotic-associated ICH in clinical practice. Our results also suggest that cerebral microbleeds add considerable value for predicting ICH, 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 greater predicted risk of ICH 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 ICH 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 highest risk of ICH may facilitate timely and accurate prognostication to allow mitigation of reversible risk factors for bleeding (e.g. intensive blood pressure control), and selection of participants for clinical trials. While more complex combinations of clinical, biochemical, and radiological markers might further improve stroke risk prediction, balancing accuracy with simplicity will remain important.

Introduction

Antithrombotic therapy is a key component of secondary prevention after ischaemic stroke or transient ischaemic attack. In patients without atrial fibrillation (AF), antiplatelet treatment reduces overall stroke risk by one-quarter,[1] while oral anticoagulation in patients with AF reduces this risk by two-thirds.[2,3] Although antithrombotic treatment increases the risk of intracranial haemorrhage (ICH) (by around one-quarter for antiplatelets, one-half for direct oral anticoagulants (DOACs), and two-fold for vitamin K antagonists (VKAs)),[1-3] the substantially-lower incidence of ICH 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. Ideally, this decision would be based on an individualised assessment of the risks of ischaemic stroke and ICH. To this end, risk scores for ischaemic stroke and major bleeding have been developed, mainly in patients with AF. 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 ICH have shown more limited performance, with c-indices between 0·50 and 0·62 in anticoagulated patients,[7,8] and 0·58 – 0·65 in patients taking antiplatelet drugs.[8,9]

Most risk scores for ischaemic stroke and ICH only include clinical variables. More recently, scores using serum biomarkers have been developed, which may offer improved performance.[10–12] However, the role of magnetic resonance imaging (MRI) biomarkers for cerebrovascular disease (increasingly obtained as part of standard stroke care) in improving risk prediction remains uncertain. Cerebral microbleeds (CMBs) are an 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 CMBs in predicting ICH has attracted particular interest. In a prospective observational study, the addition of CMB presence improved the c-index for ICH of the HASBLED bleeding risk score from 0·41 to 0·66,[14] while a recent large individual patient data meta-analysis confirmed a strong association between CMBs and ICH in patients with previous ischaemic stroke or TIA.[15] This study also found that CMBs are associated with IS risk, with a higher absolute risk of ischaemic stroke than ICH across all levels of CMB burden investigated.

Given these findings, we aimed to establish the added predictive value of CMBs for ICH and ischaemic stroke, by using the same large international dataset to develop risk models based on CMB burden and simple clinical variables, and to compare these to models using clinical variables alone. We aimed to derive from our models simple risk scores which 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 ICH than ischaemic stroke, and whether they performed better than existing risk scores.

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] Briefly, MICON comprises 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 TIA, baseline MRI including blood-sensitive paramagnetic sequences to detect CMBs, and at least three months' follow-up for ischaemic stroke, ICH, or a composite of both. We identified eligible cohorts through a systematic search of Medline and Embase from 01/01/1996 to 01/12/2018, 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 CMB 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 ICH.

The study was approved by the UK Health Research Authority (reference: 8/HRA/0188). Included cohorts obtained ethical and regulatory approvals according to local requirements. Only fully-anonymised data was shared, so that individual consent was not required for this individual patient data pooled analysis. We registered the study protocol with the PROSPERO register of systematic reviews on April 5, 2016 (registration number: CRD42016036602, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=36602).

Outcomes

Our outcomes for prediction were the five-year risks of symptomatic ICH (including intracerebral, subdural, subarachnoid, and extradural haemorrhage) and ischaemic stroke (excluding TIA).

Prediction model development

We developed separate prediction models for ICH and ischaemic stroke using Cox regression, with robust standard errors calculated using the Huber-White sandwich estimator to allow for clustering within cohorts.[18] We prespecified our candidate predictors, based on biological relevance and availability in the majority of our 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 TIA; previous

ICH; known AF; antithrombotic treatment after index event; CMB burden.; and type of MRI sequence used to detect CMBs (2D T2*-weighted gradient-recall echo (GRE) or susceptibility-weighted imaging (SWI, also including SWAN, SWIp and VenoBOLD sequences), in view of strong external evidence that CMB counts are systematically higher on these sequences than on GRE (*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 South-East Asia), given the higher incidence of intracerebral haemorrhage and intracranial atherosclerosis in this region.[19] We categorised antithrombotic treatment as antiplatelet therapy only, anticoagulation with a VKA, or anticoagulation with a DOAC. The antiplatelet category included patients taking dual antiplatelets, and anticoagulant categories included participants taking a concomitant antiplatelet. We categorised CMB 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 CMB 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.

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] using five folds consisting of whole cohorts, repeated 20 times to reduce variance. We quantified discrimination using Harrell's c-index, and calibration through the calibration slope. We further assessed calibration by calculating predicted five-year risk for each outcome on the basis of the integer risk score,

dividing participants into lower, intermediate and highest-risk groups of roughly equal sizes, and comparing predicted to observed risk using Kaplan-Meier plots.

To test the contribution of CMB burden to ICH and ischaemic stroke prediction, we developed purely clinical models in the same way as our main models, but excluding CMB burden and MRI sequence type. We compared their discrimination to our main models, and tested if adding CMB burden and MRI sequence type improved their fit. Next, we compared the performance of our CMB-based ICH risk score (the form of our model that could most easily be used in clinical practice) to existing bleeding risk scores (ATRIA, ORBIT and 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 INR' component as 0. As we made these comparisons in a subset of the model development data, we adjusted for optimism using bootstrapping.

We performed two sensitivity analyses. Firstly, we assessed the added predictive value of additional variables that we considered potentially clinically relevant by adding each variable individually to our final model for each outcome and testing if it improved model fit using 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; CMB 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. Secondly, we tested the performance of our ICH model for intracerebral haemorrhage specifically.

Finally, we determined the number of participants with a predicted risk of ICH greater 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 report, or the decision to submit it for publication. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Figure 1 describes the identification of studies in the MICON collaboration. From all 38 studies and 20,322 participants in the collaboration, we excluded one study comprising 3,335 participants that collected follow-up for a composite 'any stroke' outcome only. From the remaining 37 cohorts, we excluded 979 participants not taking antithrombotic medication, and a further 204 participants lacking follow-up for both ICH and ischaemic stroke, leaving a final study population of 15,784 participants, recruited between 28th August 2001 and 4th February 2018. Their characteristics are summarised in *Table 1*, and described by cohort in *appendix pp4-6*. All 15,784 participants had follow-up for ischaemic stroke, and 15,766 had follow-up for ICH. We imputed 2,747/15,784 (17.4%) observations for previous ICH, 2,002/15,784 (12.7%) for diabetes, and 1,097/15,784 (6.6%) for ischaemic stroke before index ischaemic stroke or TIA. We imputed fewer than 1% of observations for all other candidate predictors. During a total follow-up of 32,001 person-years for ICH (median 1·99yrs, IQR 0·61-2·87) and 31,468 person-years for ischaemic stroke (median 1·98yrs, IQR 0·56-2·80), 184 ICH

(including 146 intracerebral haemorrhages) and 1,048 ischaemic strokes occurred. The annualised incidences were 0·57% for ICH, and 3·33% for ischaemic stroke.

Table 2 shows the hazard ratios from our final models for ICH and IS, and the resulting integer risk scores. Both models included age, CMB burden, MRI sequence type used to assess CMB burden, history of ischaemic stroke prior to the index ischaemic stroke or TIA, and East Asian centre location. Our ICH model also included previous ICH 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 AF (p = 0·0040), consistent with the known superior efficacy of anticoagulants for stroke prevention in AF. We represented this in our model by combining AF, antithrombotic treatment type, and their interaction into a single four-level variable, as the hazard ratios for DOAC and VKA treatment were very similar. *Appendix p7* shows the results of our other tests for interactions. Apart from an interaction for ICH risk between antiplatelet use and previous ICH (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 ICH model was 0·73 (95% CI 0·69–0·77), and the calibration slope 0·94 (95% CI 0·81-1·06), indicating moderate discrimination and excellent calibration. For our final ischaemic stroke model, the c-index was 0·63 (95% CI 0·62-0·65) and the calibration slope 0·97 (95% CI 0·87-1·07), indicating reasonable discrimination and excellent calibration.

In internal-external cross-validation, mean discrimination for ICH was 0.71, with a slightly reduced mean calibration slope (0.85), partly explained by the reduced sample for model development. Mean discrimination for IS was 0.60 and the mean calibration slope 0.76. For each outcome, after combining participants into three groups on the basis of their total risk

score, we observed excellent agreement between predicted and observed risk (*Figure 2, appendix p 10*). *Figure 3 and appendix p11* show detailed calibration results for each outcome across ten similarly-sized groups. Absolute ICH risk was moderately over-predicted in the highest-risk decile. As 98.2% of participants received the same prediction across all five imputations, we show calibration plots for the first imputation only.

The clinical-only models generated for comparison with our main, MRI-based models, included the same variables as the main models apart from CMB burden and MRI sequence type. The clinical-only model for ICH showed reduced model fit and substantially lower discrimination (difference in c-index 0·05, 95% CI 0·02 – 0·09, p < 0·0001). The clinical-only model for ischaemic stroke showed worse model fit (p = 0·00020) but similar discrimination (c = 0·63 (95% CI 0·61–0·64)).

Table 3 shows the results of comparisons between our new ICH risk score and the HASBLED, ORBIT and ATRIA risk scores. Eleven cohorts from eight countries contributed to the comparison for HASBLED, and eight cohorts from six countries to the comparison for ATRIA and ORBIT. All comparisons included East Asian and European centres. For each comparison, the estimate for the c-index of the new ICH risk score was higher, both in participants taking any antithrombotics and when restricted to participants taking OAC. The optimism-adjusted difference in c-index was substantial (range: 0·04 – 0·27) in all comparisons *(Table 3*), though estimates were imprecise and the 95% confidence interval 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 ICH or ischaemic stroke (*appendix p 8).* The optimism-adjusted c-index of our ICH model in predicting intracerebral haemorrhage specifically (rather than intracranial haemorrhage in general) was 0·77 (95% CI 0·73-0·81), with calibration slope 0·95 (0·83-1·07). Having found evidence that using information on CMB burden from MRI

improves ICH prediction, we performed an additional sensitivity analysis testing the performance of our ICH prediction model according to MRI sequence type used. Performance was acceptable in both groups (*appendix p12)*.

Of 11,953 participants for whom both risk scores could be calculated without imputed data, only 104 (0·87%) were in the 'highest risk' tertile for ICH and the 'lower risk' tertile for ischaemic stroke, in which the predicted five-year risks of ICH and ischaemic stroke were similar (6.7% and 7.2% respectively). Their baseline characteristics are described in *appendix p9*. An additional 999/11,953 participants (8·4%) were allocated to the 'highest risk' group for ICH and the 'intermediate risk' group for ischaemic stroke (predicted five-year risks 6.7% and 11·6% respectively). *Appendix p13* shows the full distribution of risk score predictions.

Discussion

Our most important result is the description of a novel risk score (MICON-ICH), including clinical variables and MRI-detected cerebral microbleeds, to predict ICH in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack. The addition of CMBs to a score based on clinical variables alone substantially improved performance, while a direct comparison with three existing bleeding risk scores also suggested superior discrimination of the new ICH risk score. Our risk score for ischaemic stroke showed modest discrimination, and CMBs appeared less important for predicting IS than ICH; nevertheless, this score can be used alongside our ICH score for straightforward and simultaneous estimation of ICH and ischaemic stroke risk. Both our scores showed excellent calibration in bootstrap validation, providing accurate estimates of absolute risk across low, medium, and high-risk groups. Discrimination was similar and calibration remained acceptable in internal-external validation. A sensitivity analysis suggested that our ICH score might show higher

discrimination for the prediction of intracerebral haemorrhage specifically, the most serious form of non-aneurysmal ICH and the form most closely associated with cerebral microbleeds. Overall, the performance of our scores suggests they may be useful to estimate 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 stroke patient, and CMBs are familiar in stroke clinical practice (for example, in the diagnosis of cerebral amyloid angiopathy). CMBs are discrete lesions, which can be counted with very good inter-rater reliability,[25] and the blood-sensitive GRE and SWI 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, as in the ABC bleeding score.[9] Our scores include relatively few variables, allowing diagrammatic representation for quick reference (*appendix pp14-15)* and easy conversion to an online calculator or app. Finally, our scores are applicable to nearly all ischaemic stroke or TIA patients, whether taking antiplatelets or anticoagulants, with or without AF.

Our scores are intended for use in patients in whom antithrombotic treatment is planned after ischaemic stroke or TIA. They 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 (i.e. antiplatelet or anticoagulant), as this would require randomised data, rather observational data in which the relationship between antithrombotic type and outcomes is attenuated by selection bias. Rather, 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 ICH risk might lead to more aggressive treatment of modifiable bleeding

risk factors, such as hypertension and alcohol intake, review of concurrent medication, and consideration of non-pharmacological stroke prevention strategies if applicable, such as left atrial appendage occlusion in patients with AF. Our scores might also have applications in the selection of patients at high ICH risk for future clinical trials and mechanistic studies of ICH.

The principal methodological strength of our study is the use of a large, multi-centre and truly international study population, increasing generalisability and allowing 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, while we accounted statistically for within-cohort clustering. We performed both internal validation using bootstrapping and internal-external cross-validation, in accordance with TRIPOD guidelines and expert recommendations.[22, 24] While we omitted some potentially clinically relevant variables from our model due to missing data, additional analyses suggested this did not reduce model performance.

We acknowledge the limitations of our study. In particular, to maximise precision we used all available data to develop our scores. External validation of our scores in new data should be undertaken. While we compared our new ICH score to three existing bleeding risk scores, further comparison in a large, truly independent cohort would clarify the relative performance of these scores. Our model is applicable to antiplatelet and anticoagulant-treated patients, but we lacked data to make direct comparison with antiplatelet-specific scores such as Intracranial-B2LEED3S and S2TOP-BLEED,[9, 26–28] which should also be undertaken. Although large, our study cohort contained relatively few patients with very high CMB counts, reducing the precision of our estimates for ICH and ischaemic stroke risk in very high-risk categories. We lacked data on MRI field strength, which can influence CMB count, and on some additional risk factors which might have improved identification of high risk patients, notably cortical

superficial siderosis, alcohol abuse, renal insufficiency and labile INR in VKA-treated patients. Hypertension, diabetes, and hyperlipidaemia were diagnosed according to local criteria for each cohort; we lacked data on their treatment, and on antithrombotic medication adherence. These factors may have reduced the association between these predictors and outcomes – for example, the unexpected absence of an association between hypertension and ICH. We did not have central formal adjudication of outcome events. Though we present data on the relative predicted risks of ICH and ischaemic stroke in our study sample, conclusions about the appropriateness of antithrombotic treatment are limited by the observational nature of our data. We also lacked data on functional outcomes, and it should be borne in mind that the morbidity and mortality of ICH is around twice that of ischaemic stroke.[29] Finally, our risk estimates are obtained from organised care systems with access to MRI, and may not be applicable to less developed settings.

In summary, the MICON-ICH and MICON-IS scores we present here provide a new means by which to assess the long-term risk of ICH 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 CMBs for ICH and ischaemic stroke, and may facilitate the design of future randomised controlled trials of alternative stroke prevention strategies (e.g. of novel antithrombotic agents with potentially lower ICH risk) in patients at high predicted risk of ICH.

Contributors

DJWe, DW, GA, and JM-F drafted the initial protocol, which was reviewed with critical revisions and approval 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 contributed to data acquisition, management, and brain imaging analyses. All authors contributed to critical revision of the manuscript and approved the final manuscript for submission.

Declaration of Interests

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610

611 **Data Sharing Statement**

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

615

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Figure Titles

Figure 1: Study flowchart

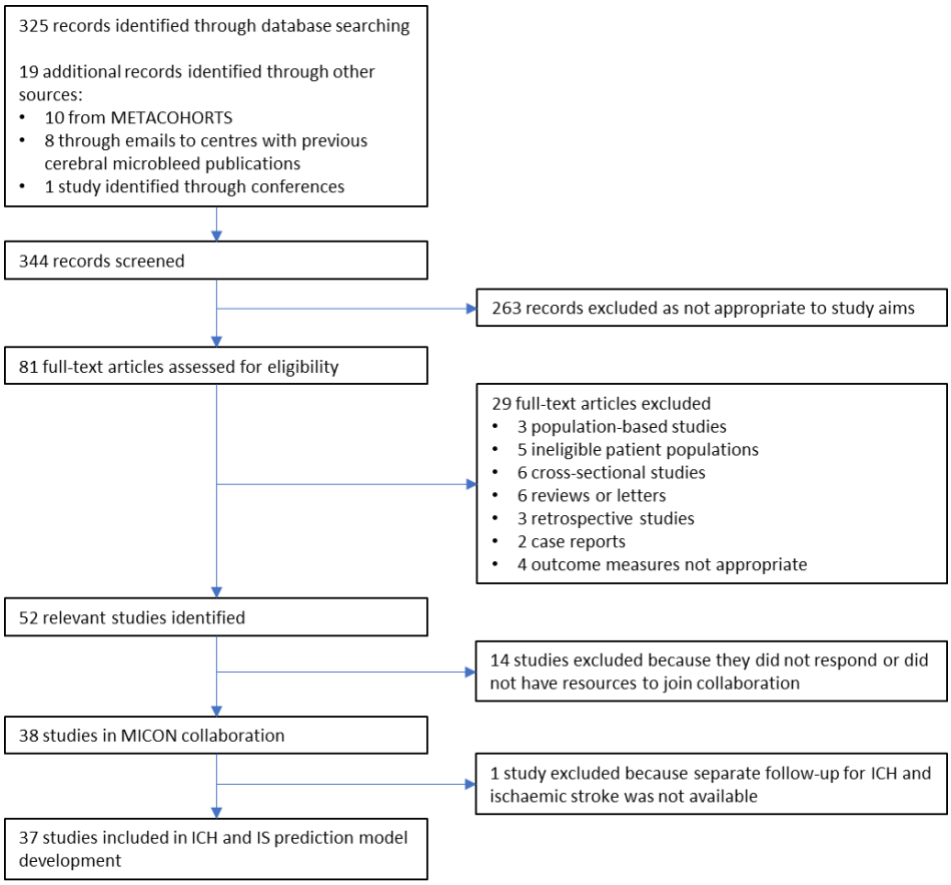


Figure 2: Kaplan-Meier plot and risk table for symptomatic ICH

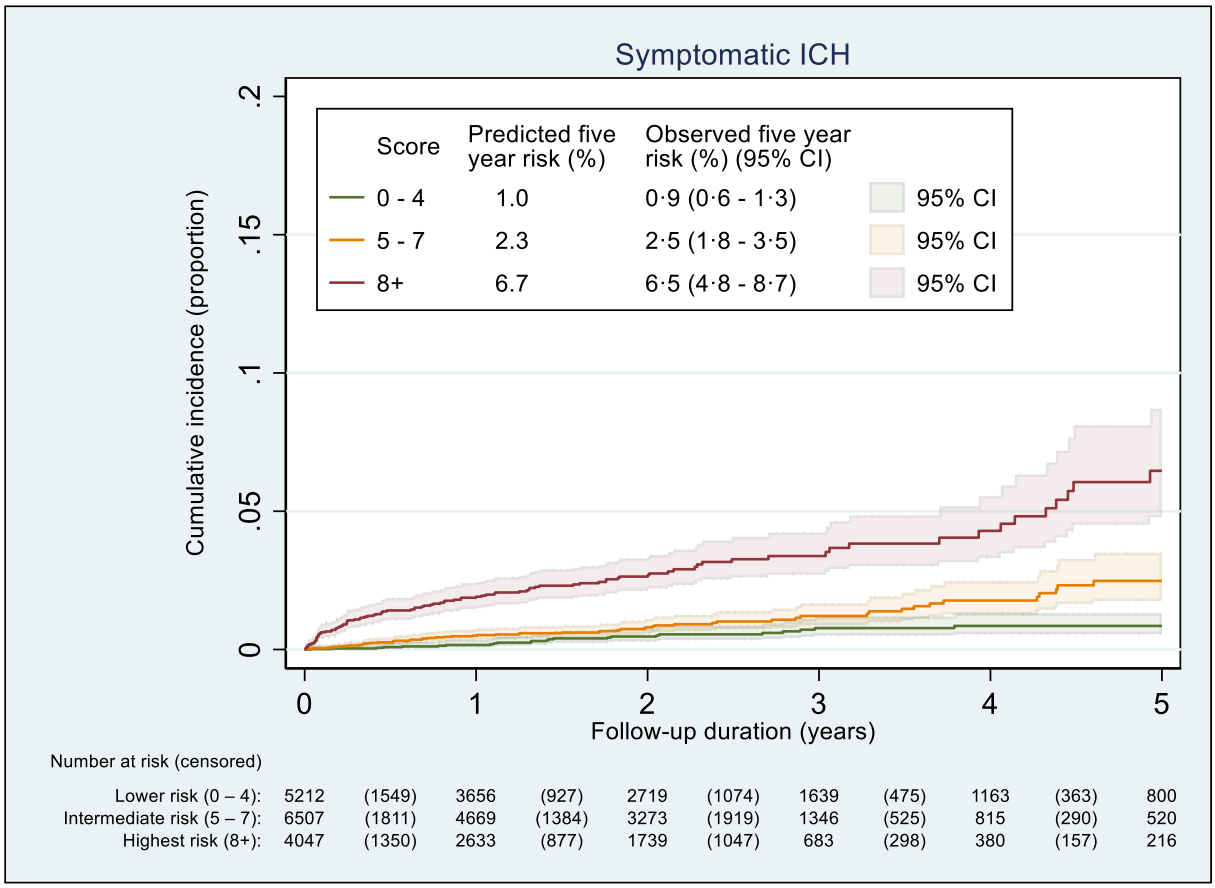
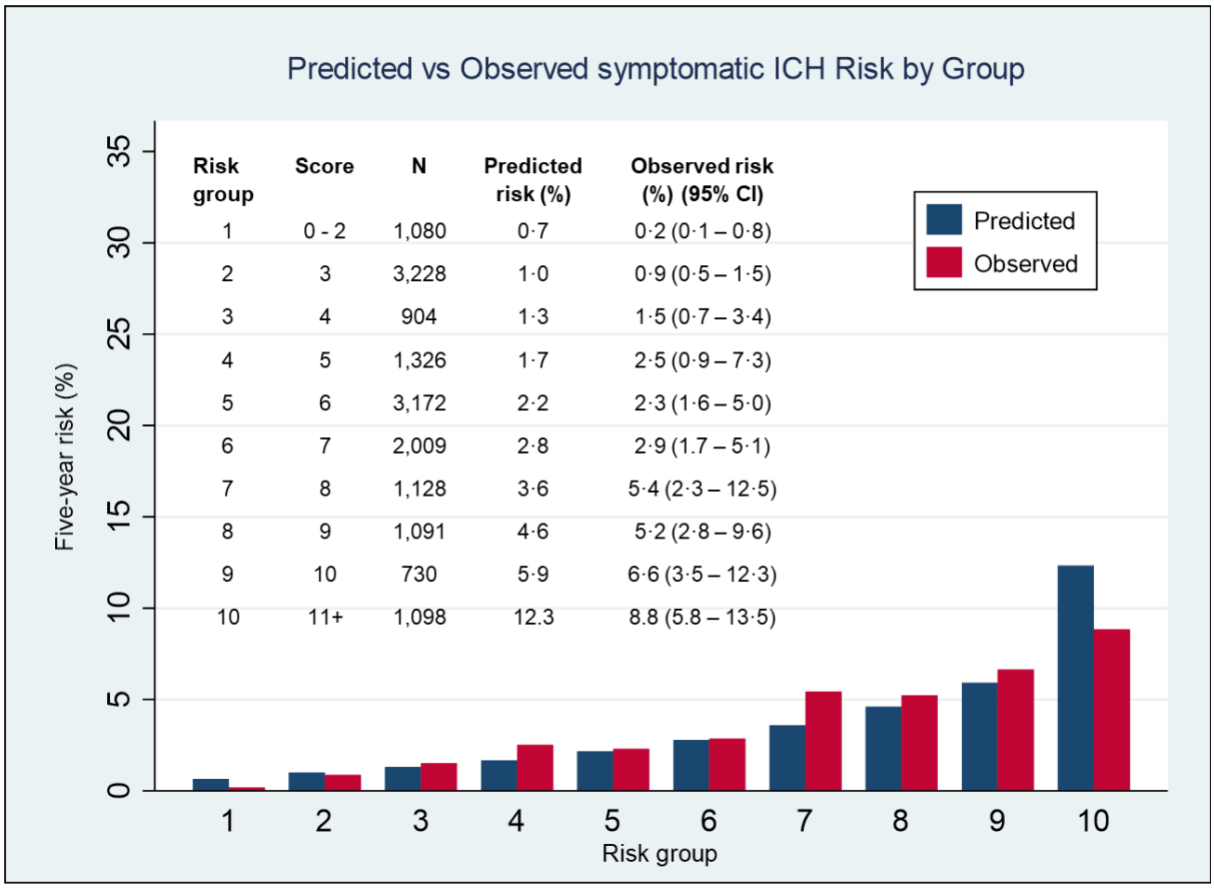


Figure 3: Model calibration – ICH



Tables

Table 1: Baseline characteristics

Values show prevalence for categorical variables, and mean (SD) for continuous variables.

Variable		**Antiplatelet (n = 8,736)**	**Anticoagulant (n = 7,048)**	**Overall (n = 15,784)**
Age		67·4 (12·4)	74·7 (10·8)	70·7 (12·2)
Female sex		3,444/8,736 (39·4%)	3,253/7,048 (46·2%)	6,697/15,784 (42·4%)
Male sex		5,292/8,736 (60·6%)	3,795/7,048 (53·8%)	9,087/15,784 (57·6%)
East Asian population		2,405/8,736 (27·5%)	2,185/7,048 (31·0%)	4,590/15,784 (29·1%)
Hypertension		5,931/8,726 (68·0%)	5,291/7,024 (75·33%)	11,222/15,750 (71·3%)
Atrial fibrillation		527/8,687 (6·1%)	5,906/7,039 (83·9%)	6,433/15,726 (40·9%)
Diabetes mellitus (type 1 or 2)		1,720/7,013 (24·5%)	1,490/6,769 (22.0%)	3,208/13,782 (23.3%)
Ischaemic stroke before presenting stroke/TIA		1,001/7,781 (12·9%)	1,299/6,906 (18·8%)	2,300/14,687 (16·5%)
Previous ICH		80/6,549 (1.22%)	85/6,403 (1.31%)	165/12,872 (1.27%)
Presentation with ischaemic stroke (vs TIA)		6,632/8,735 (75·9%)	6,172/7,039 (87·7%)	12,804/15,774 (81·2%)
CMB burden	0	6,418/8,733 (73·5%)	5,202/6,970 (74·6%)	11,620/15,703 (74.0%)
	1	942/8,733 (10·8%)	812/6,970 (11·7%)	1,754/15,703 (11.2%)
	2-4	785/8,733 (9·0%)	671/6,970 (9·6%)	1,456/15,703 (9.3%)

	5-10	316/8,733 (3·6%)	162/6,970 (2·3%)	478/15,703 (3.0%)
	11-19	157/8,733 (1·8%)	59/6,970 (0·85%)	216/15,703 (1.4%)
	20 +	115/8,733 (1·3%)	64/6,970 (0·92%)	179/15,703 (1.1%)
SWI sequence used (vs T2* GRE)		2,422/8,734 (27·7%)	2,335/7,025 (33·2%)	4,757/15,759 (30·2%)
Antithrombotic treatment	AP only	8,736/8,736 (100%)	NA	8,733/15,773 (55.4%)
	Warfarin or VKA	NA	4,752/7,037* (67·4%)	4,752/15,773 (30.1%)
	DOAC	NA	2,288/7,037 (32·5%)	2,288/15,773 (14.5%)
Concomitant antiplatelet with anticoagulant		NA	1,360/7,048 (19·3%)	1,360/15,784 (8·6%)

*Type of anticoagulant unknown for 11 participants

AP: antiplatelet; CMB: cerebral microbleed; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; SWI: susceptibility-weighted imaging; GRE – gradient-recall echo

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

			ICH		IS		ICH score	IS score
Predictor		**Category**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**(/24)**	**(/34)**
Number of CMBS		0	1	<0·001	1	<0·001	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?		Yes	1·72 (0·80 - 3·70)	0·16	1·54 (0·82 - 2·89)	0·18	2	3
Age in years		< 50	1	<0·001	1	<0·001	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		Yes	1·85 (0·82 - 4·15)	0·14	1·62 (0·78 - 3·37)	0·19	2	4
IS before presenting stroke/TIA		Yes	1·36 (1·00 - 1·87)	0·053	1·85 (1·48 - 2·31)	<0·001	1	5
ICH score only	Previous ICH	Yes	3·91 (2·40 - 6·36)	<0·001	-	-	5	-
	Antithrombotic	AP only	1·23 (0·69 - 2·18)	0·51	-	-	1	-

	treatment	Warfarin/VKA	1·30 (0·82 - 2·05)		-	-	1	-
		DOAC	1		-	-	0	-
IS score only	Presentation with ischaemic stroke	Yes	-	-	1·34 (0·91 - 1·98)	0·14	-	2
	Diabetes mellitus	Yes	-	-	1·32 (1·09 - 1·58)	0.004	-	2
	Antithrombotic treatment	AP, has AF	-	-	3·14 (1·84 - 5·35)	<0·001	-	9
		AP, no AF	-	-	1·70 (1·16 - 2·51)		-	4
		OAC, other reason	-	-	1.36 (0·81 - 2·27)		-	2
		OAC, for AF	-	-	1		-	0

Baseline five-year survival for full ICH model: 99·53%; for full IS model: 97·15%

* Category merged with preceding category to prevent inconsistent (non-monotonic) scoring

AF: atrial fibrillation; AP: antiplatelet; CMB: cerebral microbleed; DOAC: direct oral anticoagulant; GRE – gradient-recall echo; OAC (including vitamin K antagonists and direct oral anticoagulants); VKA: vitamin K antagonist

Table 3: Comparison of MICON-ICH score with existing bleeding risk scores

Comparator	**Antithrombotics**	**N**	**C-index (Comparator)**	**C-index (MICON)**	**Optimism-adjusted difference (95% CI)**
HASBLED*	All	5,510	0·47	0·75	0·27 (0·18 – 0·37)
	OAC only	4,017	0·47	0·67	0·20 (0·06 – 0·34)
ATRIA#	All	3,340	0·63	0·71	0·06 (-0·06 – 0·18)
	OAC only	2,677	0·61	0·67	0·04 (-0·08 – 0·17)
ORBIT#	All	3,340	0·60	0·71	0·09 (-0·01 – 0·18)
	OAC only	2,677	0·58	0·67	0·08 (-0·03 – 0·19)

* Cohorts used for comparison: CROMIS-2, Graz, HERO, Kushiro City, NOACISP, IPAAC-Warfarin, SAMURAI-NVAF, TABASCO, UCLH, Wurzburg, Soo

Cohorts used for comparison: CROMIS-2, Graz, NOACISP, IPAAC-Warfarin, SAMURAI-NVAF, TABASCO, Soo

Appendix

Table of Contents

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Supplementary Table 1: MRI sequence type and cerebral microbleed detection

Summarises studies comparing SWI and SWAN sequences to 2D GRE in the same patients

Study*	**Population**	**N**	**Sequence**	**Prevalence (%) (SWI/SWAN)**	**Prevalence (%) (GRE)**	**Summary statistics# (SWI/SWAN)**	**Summary statistics# (GRE)**
Vernooij 2008[1]	General older population	200	SWI	71/200 (35.5)	42/200 (21.0)	Median 2.5 IQR: 1 – 9.5	Median 1 IQR: 1 - 4
Mori 2008[2]	Moya-Moya disease	50	SWI	21/50 (42.0)	16/50 (32.0)	-	-
Nandigam 2009[3]	Cerebral amyloid angiopathy	3	SWI	3/3 (100.0	3/3 (100.0)	Mean: 103.3	GRE: 34.3
Goos 2011[4]	Memory clinic patients	141	SWI	56/141 (39.7)	32/141 (22.7)	Median: 2 Range: 1 - 129	Median: 1 Range: 1 - 144
Cheng 2013[5]	Cerebral amyloid angiopathy	9	SWI	-	-	Median: 111 IQR: 48 – 192	Median: 57 IQR: 45 - 187
	Healthy controls	21	SWI	4/21 (19.0)	3/21 (14.3)	Median: 2	Median: 1
Guo 2013[6]	Hypertensive older population	273	SWI SWAN	SWI: 83/273 (30.4) SWAN: 88/273 (32.2)	54/273 (19.8)	SWI: Median: 8 Range: 1 – 15 SWAN: Median 8 Range: 1 - 17	GRE: Median 3 Range: 1 - 11
Shams 2015[7]	Memory clinic patients	246	SWI	50/246 (20.3)	43/246 (17.5)	Mean: 2.15	Mean: 1.48
Shao 2017[8]	Lacunar ischaemic stroke	60	SWI	26/60 (43.3)	15/60 (25.0)	-	-
	Healthy controls	60	SWI	8/60 (13.3)	4/60 (6.7)	-	-

For patients with microbleeds detected

Supplementary Table 2: Baseline characteristics by cohort

Cohort	Location	N	Age (y)	Female Sex	AF	HTN	DM	Previous IS	Previous ICH	Index Event IS	SWI Used	CMB Presence	AP Only	VKA	DOAC	Follow Up (y)	ICH events (%)	IS events (%)
CROMIS-2[9]	UK	1435	75.9 (10.4)	605/1435 (42.2)	1435/1435 (100.0)	897/1413 (63.5)	241/1434 (16.8)	137/1412 (9.7)	8/1416 (0.6)	1199/1435 (83.6)	0/1435 (0.0)	300/1435 (20.9)	36/1435 (2.5)	874/1435 (60.9)	525/1435 (36.6)	2.34 (1.00)	14 (0.98)	56 (3.9)
HBS	US	504	67.7 (15.4)	209/504 (41.5)	120/504 (23.8)	373/504 (74.0)	140/504 (27.8)	116/504 (23.0)	-	454/504 (90.1)	2/504 (0.4)	71/504 (14.1)	394/504 (78.2)	109/504 (21.6)	1/504 (0.2)	0.23 (0.05)	0 (0)	0 (0)
Bern[10]	Switzerland	245	66.6 (13.8)	106/245 (43.3)	79/202 (39.1)	144/245 (58.8)	32/245 (13.1)	33/245 (13.5)	-	245/245 (100.0)	245/245 (100.0)	49/245 (20.0)	171/245 (69.8)	66/245 (26.9)	8/245 (3.3)	0.30 (0.09)	0 (0)	5 (2)
CU-STRIDE[11]	Hong Kong	516	67.5 (11.1)	217/516 (42.1)	32/516 (6.2)	362/516 (70.2)	173/516 (33.5)	67/516 (13.0)	9/516 (1.7)	437/516 (84.7)	231/516 (44.8)	117/516 (22.7)	492/516 (95.3)	24/516 (4.7)	0/516 (0.0)	1.31 (0.37)	2 (0.39)	14 (2.7)
TABASCO[12]	Israel	378	67.4 (9.8)	171/378 (45.2)	29/374 (7.8)	221/374 (59.1)	89/374 (23.8)	0/378 (0.0)	0/378 (0.0)	275/378 (72.8)	0/378 (0.0)	59/378 (15.6)	345/378 (91.3)	33/378 (8.7)	0/378 (0.0)	4.06 (1.39)	0 (0)	54 (14)
Graz	Austria	385	65.9 (12.4)	142/385 (36.9)	91/385 (23.6)	299/385 (77.7)	84/385 (21.8)	77/385 (20.0)	5/385 (1.3)	342/385 (88.8)	0/385 (0.0)	75/385 (19.5)	315/385 (81.8)	58/385 (15.1)	12/385 (3.1)	1.75 (1.85)	13 (3.4)	52 (14)
PERFORM-MRI[13]	France	1056	67.7 (8.0)	370/1056 (35.0)	16/1056 (1.5)	887/1056 (84.0)	324/1056 (30.7)	120/1056 (11.4)	3/1056 (0.3)	929/1056 (88.0)	0/1056 (0.0)	381/1056 (36.1)	1056/1056 (100.0)	0/1056 (0.0)	0/1056 (0.0)	2.32 (0.68)	10 (0.95)	94 (8.9)
PARISK[14]	Netherlands	220	70.9 (9.1)	65/220 (29.5)	0/220 (0.0)	151/220 (68.6)	50/220 (22.7)	64/220 (29.1)	3/220 (1.4)	98/220 (44.5)	0/218 (0.0)	59/220 (26.8)	220/220 (100.0)	0/220 (0.0)	0/220 (0.0)	2.09 (0.46)	0 (0)	10 (4.5)
SAMURAI-NVAF[15]	Japan	1051	77.2 (9.8)	445/1051 (42.3)	1051/1051 (100.0)	977/1051 (93.0)	208/1051 (19.8)	225/1051 (21.4)	19/1051 (1.8)	1007/1051 (95.8)	771/1051 (73.4)	250/1051 (23.8)	12/1051 (1.1)	598/1051 (56.9)	441/1051 (42.0)	1.63 (0.72)	10 (0.95)	72 (6.9)
RUNDMC[16]	Netherlands	178	64.7 (8.7)	63/178 (35.4)	19/178 (10.7)	144/178 (80.9)	36/178 (20.2)	46/178 (25.8)	1/178 (0.6)	90/178 (50.6)	0/178 (0.0)	35/178 (19.7)	159/178 (89.3)	19/178 (10.7)	0/178 (0.0)	4.76 (0.75)	2 (1.1)	23 (13)
Wurzburg	Germany	343	70.7 (13.3)	154/343 (44.9)	99/343 (28.9)	276/343 (80.5)	73/343 (21.3)	77/343 (22.4)	12/343 (3.5)	270/343 (78.7)	151/343 (44.0)	75/343 (21.9)	219/341 (64.2)	40/341 (11.7)	82/341 (24.0)	0.34 (0.22)	1 (0.29)	19 (5.5)
Monash Stroke[17]	Australia	356	75.0 (10.7)	172/356 (48.3)	356/356 (100.0)	283/356 (79.5)	92/355 (25.9)	97/356 (27.2)	6/356 (1.7)	305/356 (85.7)	336/356 (94.4)	153/356 (43.0)	0/356 (0.0)	319/356 (89.6)	37/356 (10.4)	1.74 (1.24)	7 (2)	9 (2.5)
Basel TIA[18]	Switzerland	181	69.3 (12.3)	67/181 (37.0)	24/181 (13.3)	134/181 (74.0)	31/181 (17.1)	13/181 (7.2)	-	0/181 (0.0)	0/181 (0.0)	20/181 (11.0)	148/181 (81.8)	33/181 (18.2)	0/181 (0.0)	0.25 (0.00)	0 (0)	24 (13)
Yonsei[19]	South Korea	488	70.3 (10.5)	278/488 (57.0)	488/488 (100.0)	381/488 (78.1)	117/488 (24.0)	87/488 (17.8)	13/488 (2.7)	460/488 (94.3)	0/488 (0.0)	146/488 (29.9)	1/488 (0.2)	487/488 (99.8)	0/488 (0.0)	2.63 (1.58)	7 (1.4)	46 (9.4)

BIO-STROKE/TIA[20]	Ireland	240	67.9 (13.3)	91/240 (37.9)	73/236 (30.9)	141/238 (59.2)	38/237 (16.0)	19/236 (8.1)	-	89/240 (37.1)	0/240 (0.0)	24/240 (10.0)	167/240 (69.6)	73/240 (30.4)	0/240 (0.0)	0.47 (0.35)	0 (0)	13 (5.4)
Kushiro City[21]	Japan	631	71.5 (11.1)	257/631 (40.7)	86/631 (13.6)	407/631 (64.5)	182/631 (28.8)	115/631 (18.2)	17/631 (2.7)	631/631 (100.0)	0/631 (0.0)	268/631 (42.5)	568/631 (90.0)	63/631 (10.0)	0/631 (0.0)	0.15 (0.21)	20 (3.2)	99 (16)
IPAAC-Warfarin[22]	Hong Kong	81	71.3 (9.1)	40/81 (49.4)	81/81 (100.0)	56/81 (69.1)	27/81 (33.3)	25/81 (30.9)	1/81 (1.2)	65/81 (80.2)	71/81 (87.7)	24/81 (29.6)	0/81 (0.0)	81/81 (100.0)	0/81 (0.0)	2.10 (1.03)	3 (3.7)	5 (6.2)
CASPER[23]	Netherlands	133	65.8 (10.6)	38/133 (28.6)	16/133 (12.0)	94/133 (70.7)	18/133 (13.5)	10/133 (7.5)	0/133 (0.0)	133/133 (100.0)	133/133 (100.0)	79/133 (59.4)	115/133 (86.5)	10/133 (7.5)	8/133 (6.0)	1.21 (0.17)	0 (0)	3 (2.3)
HERO[24]	Spain	935	77.6 (6.6)	487/935 (52.1)	856/933 (91.7)	693/933 (74.3)	212/932 (22.7)	246/933 (26.4)	8/933 (0.9)	803/925 (86.8)	0/935 (0.0)	247/935 (26.4)	1/934 (0.1)	623/934 (66.7)	310/934 (33.2)	1.92 (0.58)	18 (1.9)	32 (3.4)
HAGAKURE	Japan	350	73.1 (13.0)	141/350 (40.3)	102/350 (29.1)	263/347 (75.8)	116/350 (33.1)	50/350 (14.3)	10/349 (2.9)	317/350 (90.6)	28/350 (8.0)	127/350 (36.3)	197/350 (56.3)	93/350 (26.6)	60/350 (17.1)	2.15 (1.08)	9 (2.6)	23 (6.6)
Leuven[25]	Belgium	487	72.2 (9.4)	192/487 (39.4)	103/487 (21.1)	313/487 (64.3)	92/487 (18.9)	61/487 (12.5)	-	354/487 (72.7)	0/487 (0.0)	129/487 (26.5)	354/487 (72.7)	133/487 (27.3)	0/487 (0.0)	2.12 (0.72)	4 (0.82)	32 (6.6)
NOACISP	Switzerland	290	78.3 (9.1)	132/290 (45.5)	290/290 (100.0)	226/290 (77.9)	55/289 (19.0)	49/289 (17.0)	12/289 (4.2)	262/290 (90.3)	284/290 (97.9)	79/290 (27.2)	10/290 (3.4)	67/290 (23.1)	213/290 (73.4)	1.84 (0.74)	9 (3.1)	19 (6.6)
Min Lou[26]	China	106	64.4 (12.0)	34/106 (32.1)	16/106 (15.1)	80/106 (75.5)	-	18/106 (17.0)	7/106 (6.6)	106/106 (100.0)	106/106 (100.0)	36/106 (34.0)	92/106 (86.8)	7/106 (6.6)	7/106 (6.6)	0.39 (0.27)	0 (0)	2 (1.9)
MICRO[27]	Netherlands	397	65.3 (12.2)	165/397 (41.6)	30/396 (7.6)	218/397 (54.9)	54/397 (13.6)	35/397 (8.8)	0/397 (0.0)	35/397 (8.8)	0/397 (0.0)	72/397 (18.1)	357/397 (89.9)	40/397 (10.1)	0/397 (0.0)	3.25 (1.63)	11 (2.8)	21 (5.3)
Orken[28]	Turkey	452	71.9 (12.1)	233/452 (51.5)	353/452 (78.1)	356/452 (78.8)	150/452 (33.2)	123/452 (27.2)	0/452 (0.0)	432/452 (95.6)	250/452 (55.3)	132/452 (29.2)	0/452 (0.0)	321/452 (71.0)	131/452 (29.0)	2.59 (2.07)	3 (0.66)	8 (1.8)
CATCH[29]	Canada	392	67.6 (13.9)	154/392 (39.3)	26/392 (6.6)	218/392 (55.6)	54/392 (13.8)	0/392 (0.0)	0/392 (0.0)	236/392 (60.2)	0/392 (0.0)	62/392 (15.8)	325/392 (82.9)	67/392 (17.1)	0/392 (0.0)	0.26 (0.09)	1 (0.26)	13 (3.3)
MSS2[30]	UK	209	66.4 (11.4)	82/209 (39.2)	21/209 (10.0)	157/209 (75.1)	-	29/209 (13.9)	0/209 (0.0)	209/209 (100.0)	199/209 (95.2)	34/209 (16.3)	188/209 (90.0)	21/209 (10.0)	0/209 (0.0)	1.08 (0.30)	0 (0)	31 (15)
Sainte-Anne, Paris	France	302	78.6 (10.9)	154/302 (51.0)	302/302 (100.0)	215/302 (71.2)	56/302 (18.5)	39/302 (12.9)	6/302 (2.0)	302/302 (100.0)	0/279 (0.0)	80/302 (26.5)	0/302 (0.0)	122/302 (40.4)	180/302 (59.6)	1.53 (0.81)	5 (1.7)	20 (6.6)
STROKDEM	France	178	64.0 (12.7)	68/178 (38.2)	12/178 (6.7)	100/178 (56.2)	23/178 (12.9)	20/178 (11.2)	1/178 (0.6)	178/178 (100.0)	0/178 (0.0)	23/178 (12.9)	130/178 (73.0)	40/178 (22.5)	8/178 (4.5)	3.32 (1.61)	0 (0)	16 (9)
NUS (Chen)	Singapore	41	66.6 (10.2)	12/41 (29.3)	10/41 (24.4)	32/41 (78.0)	11/41 (26.8)	2/41 (4.9)	0/41 (0.0)	41/41 (100.0)	41/41 (100.0)	22/41 (53.7)	26/41 (63.4)	15/41 (36.6)	0/41 (0.0)	3.01 (1.32)	0 (0)	5 (12)
FUTURE	Netherlands	18	44.5 (5.3)	9/18 (50.0)	0/18 (0.0)	7/18 (38.9)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	12/18 (66.7)	18/18 (100.0)	1/18 (5.6)	18/18 (100.0)	0/18 (0.0)	0/18 (0.0)	0.67 (0.72)	0 (0)	4 (22)

Heidelberg[31]	Germany	607	64.3 (14.0)	225/607 (37.1)	110/607 (18.1)	465/607 (76.6)	-	92/607 (15.2)	1/607 (0.2)	501/607 (82.5)	607/607 (100.0)	138/607 (22.7)	488/607 (80.4)	109/607 (18.0)	10/607 (1.6)	4.00 (1.27)	3 (0.49)	28 (4.6)
NNI	Singapore	182	57.7 (11.5)	56/182 (30.8)	28/181 (15.5)	142/182 (78.0)	59/182 (32.4)	26/182 (14.3)	0/182 (0.0)	182/182 (100.0)	0/182 (0.0)	49/182 (26.9)	150/182 (82.4)	23/182 (12.6)	9/182 (4.9)	0.80 (0.63)	0 (0)	0 (0)
OXVASC[32]	UK	1067	68.3 (14.0)	508/1067 (47.6)	164/1066 (15.4)	581/1066 (54.5)	-	-	-	502/1067 (47.0)	0/1067 (0.0)	157/1067 (14.7)	949/1067 (88.9)	112/1067 (10.5)	6/1067 (0.6)	3.41 (1.53)	11 (1)	78 (7.3)
HKU[32]	Hong Kong	966	68.9 (12.2)	388/966 (40.2)	124/966 (12.8)	628/966 (65.0)	272/966 (28.2)	93/966 (9.6)	12/966 (1.2)	966/966 (100.0)	966/966 (100.0)	433/966 (44.8)	862/966 (89.2)	63/966 (6.5)	41/966 (4.2)	2.90 (1.49)	19 (2)	89 (9.2)
Soo[33]	Hong Kong	178	73.4 (9.6)	82/178 (46.1)	175/178 (98.3)	155/178 (87.1)	50/178 (28.1)	34/178 (19.1)	3/178 (1.7)	152/178 (85.4)	178/178 (100.0)	66/178 (37.1)	5/178 (2.8)	7/178 (3.9)	166/178 (93.3)	1.85 (1.44)	1 (0.56)	5 (2.8)
SIGNaL	UK	206	72.4 (14.0)	85/206 (41.3)	65/206 (31.6)	146/206 (70.9)	49/206 (23.8)	55/206 (26.7)	8/206 (3.9)	185/206 (89.8)	140/206 (68.0)	92/206 (44.7)	163/206 (79.1)	9/206 (4.4)	34/206 (16.5)	0.60 (0.20)	1 (0.49)	24 (12)
Total		15784	70.7 (12.2)	6697/15784 (42.4)	6882/15728 (43.8)	11222/15750 (71.3)	3208/13782 (23.3)	2300/14687 (15.7)	165/13037 (1.3)	12804/15774 (81.2)	4757/15759 (30.2)	4164/15784 (26.4)	8733/15781 (55.3)	4759/15781 (30.2)	2289/15781 (14.5)	2.03 (1.53)	184 (1.2)	1048 (6.6)

Values shown are prevalence (%) or mean (SD). “ICH event (%)” and “IS event (%)” refer to the number and percentage of each cohort who experienced an event during follow-up. Studies without references are unpublished. FUTURE: Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation study. HAGAKURE: Hypertension, Amyloid, and aGe Associated Kaleidoscopic brain lesions on CT/MRI Undertaken with stroke REgistry. HBS: Heart Brain Interactions Study. NNI: National Neuroscience Institute, Singapore. NOACISP: Novel Oral Anticoagulants in Stroke Patients, Basel; NCT02353585. SIGNaL: Stroke Investigation in North and Central London. STROKDEM: Study of Factors Influencing Post-stroke Dementia.

Supplementary Table 3: Interaction terms

Each interaction was tested individually as an addition to a model comprising all candidate predictors for each outcome. The association of each variable tested is shown at each level of the interacting variable, including the interaction but not the main effect of the interacting variable. When testing interactions with antiplatelet vs anticoagulant treatment, we omitted the three-level antithrombotic treatment to avoid collinearity. CMB recoded describes CMB burden following recategorisation as a four-level variable to reduce sparseness.

A: Interactions with antithrombotic treatment

Variable	Anticoagulant (HR, 95% CI)	Antiplatelet (HR, 95% CI)	P-value for interaction
ICH			
CMB 0	1	1	0.36
CMB 1	2.11 (1.28 – 3.48)	1.72 (0.94 – 3.19)	
CMB 2 - 4	2.01 (0.98 – 4.11)	2.33 (1.37 – 3.96)	
CMB 5 - 10	1.25 (0.32 – 4.90)	4.66 (2.47 – 8.80)	
CMB 11 - 19	5.67 (2.17 – 14.8)	4.53 (2.74 – 7.49)	
CMB 20+	3.15 (0.42 – 23.45)	15.01 (7.06 – 31.92)	
Age (years)	1.04 (1.02 – 1.06)	1.03 (1.02 – 1.05)	0.66
Female sex	1.16 (0.81 – 1.66)	0.87 (0.54 – 1.40)	0.29
Presentation with ischaemic stroke	1.19 (0.49 – 2.89)	0.91 (0.34 – 2.48)	0.71
SWI MRI sequence used	0.73 (0.43 – 1.23)	0.42 (0.14 – 1.26)	0.28
Atrial fibrillation present	0.70 (0.29 – 1.73)	1.68 (0.96 – 2.91)	0.09
Hypertension present	0.85 (0.55 – 1.30)	1.17 (0.62 – 2.23)	0.41
Diabetes present	1.63 (0.97 – 2.73)	0.83 (0.45 – 1.50)	0.10
Ischaemic stroke before index event	1.30 (0.92 – 1.84)	1.41 (0.84 – 2.39)	0.81
Previous intracranial haemorrhage	1.98 (0.83 – 4.74)	7.39 (4.11 – 13.29)	0.011
East Asian population	1.17 (0.70 – 1.99)	3.21 (0.96 – 10.7)	0.09
Ischaemic stroke			
CMB 0	1	1	054
CMB 1	0.92 (0.66 – 1.28)	1.16 (0.87 – 1.53)	
CMB 2 - 4	1.16 (0.91 – 1.48)	1.32 (1.06 – 1.66)	
CMB 5 - 10	0.95 (0.47 – 1.91)	1.98 (1.32 – 2.96)	
CMB 11 - 19	1.43 (0.69 – 2.93)	1.44 (0.68 – 3.06)	
CMB 20+	1.85 (0.78 – 4.39)	1.94 (1.29 – 2.92)	
Age (years)	1.02 (1.00 – 1.03)	1.02 (1.01 – 1.03)	0.69
Female sex	1.10 (0.88 – 1.38)	0.88 (0.71 – 1.09)	0.15
Presentation with ischaemic stroke	1.14 (0.71 – 1.82)	1.42 (0.93 – 2.15)	0.39
GRE MRI sequence used	0.94 (0.60 – 1.45)	0.50 (0.23 – 1.10)	0.04
Atrial fibrillation present	0.72 (0.43 – 1.21)	1.81 (1.30 – 2.50)	0.0040
Hypertension present	1.07 (0.79 – 1.45)	1.07 (0.74 – 1.55)	0.98
Diabetes present	1.37 (1.08 – 1.73)	1.25 (1.03 – 1.53)	0.53
Ischaemic stroke before index event	1.82 (1.22 – 2.71)	1.86 (1.48 – 2.34)	0.92
Previous intracranial haemorrhage	1.04 (0.49 – 2.22)	1.63 (0.79 – 3.35)	0.40
East Asian population	1.77 (1.12 – 2.81)	1.45 (0.49 – 4.28)	0.67

B: Interactions with MRI sequence type

Variable	GRE	SWI	P-value for interaction
ICH			
CMB 0	1	1	0.50
CMB 1	2.28 (1.59 – 3.26)	1.09 (0.35 – 3.40)	
CMB 2 - 4	2.50 (1.60 – 3.89)	1.32 (0.51 – 3.37)	
CMB 5 - 10	2.91 (1.27 – 6.66)	3.40 (1.21 – 9.48)	
CMB 11 - 19	5.09 (2.82 – 9.19)	4.20 (1.87 – 9.45)	
CMB 20+	9.14 (3.22 – 25.93)	8.35 (2.17 – 32.13)	
Ischaemic stroke			
CMB 0	1	1	0.0065
CMB 1	1.09 (0.80 – 1.49)	0.99 (0.69 – 1.41)	
CMB 2 - 4	1.30 (1.12 – 1.50)	1.17 (0.75 – 1.81)	
CMB 5 - 10	1.91 (1.24 – 2.93)	1.28 (0.77 – 2.14)	
CMB 11 - 19	2.19 (1.14 – 4.21)	0.44 (0.21 – 0.95)	
CMB 20+	1.92 (1.29 – 2.84)	1.83 (0.95 – 3.50)	
CMB recoded 0	1	1	0.18
CMB recoded 1	1.09 (0.80 – 1.49)	0.99 (0.69 – 1.41)	
CMB recoded 2 – 4	1.30 (1.12 – 1.50)	1.17 (0.75 – 1.81)	
CMB recoded 5+	1.97 (1.38 – 2.82)	1.17 (0.75 – 1.83)	

Supplementary Table 4: Additional variables

Predictor	Prevalence or Median	HR (95% CI)*	P-value
ICH			
Hyperlipidaemia	5,880/13,128 (44·8%)	1·02 (0·66-1·57)	0·94
Current smoker	1,708/10,357 (16·5%)	1·01 (0·67-1·53)	0·94
Fazekas score (continuous)	1 (IQR 1 – 2)	1·06 (0·71-1·59)	0·78
Fazekas score 2+	3,777/9,366 (40·2%)	1·47 (0·41-1·70)	0·21
Strictly deep CMBs	1005/11,877 (8·5%)	1·55 (0·73-3·31)	0·26
Strictly lobar CMBs	1,146/11,874 (9·7%)	0·69 (0·31-1·51)	0·36
Mixed CMBs	938/11,878 (8·2%)	0·87 (0·45-1·66)	0·67
IS			
Hyperlipidaemia	5,889/13,146 (44·8%)	0·93 (0·72-1·20)	0·57
Current smoker	1,709/10,375 (16·5%)	1·10 (0·86-1·41)	0·43
Fazekas score (continuous)	1 (IQR 1 – 2)	1·02 (0·80-1·31)	0·85
Fazekas score 2+	3,786/9,414 (40·2%)	1·12 (0·82-1·53)	0·47
Strictly deep CMBs	1,007/11,895 (8·5%)	1·20 (0·95-1·52)	0·080
Strictly lobar CMBs	1,146/11,892 (9·7%)	0·96 (0·71-1·30)	0·80
Mixed CMBs	971/11,896 (8·2%)	0·79 (0·54-1·15)	0·23

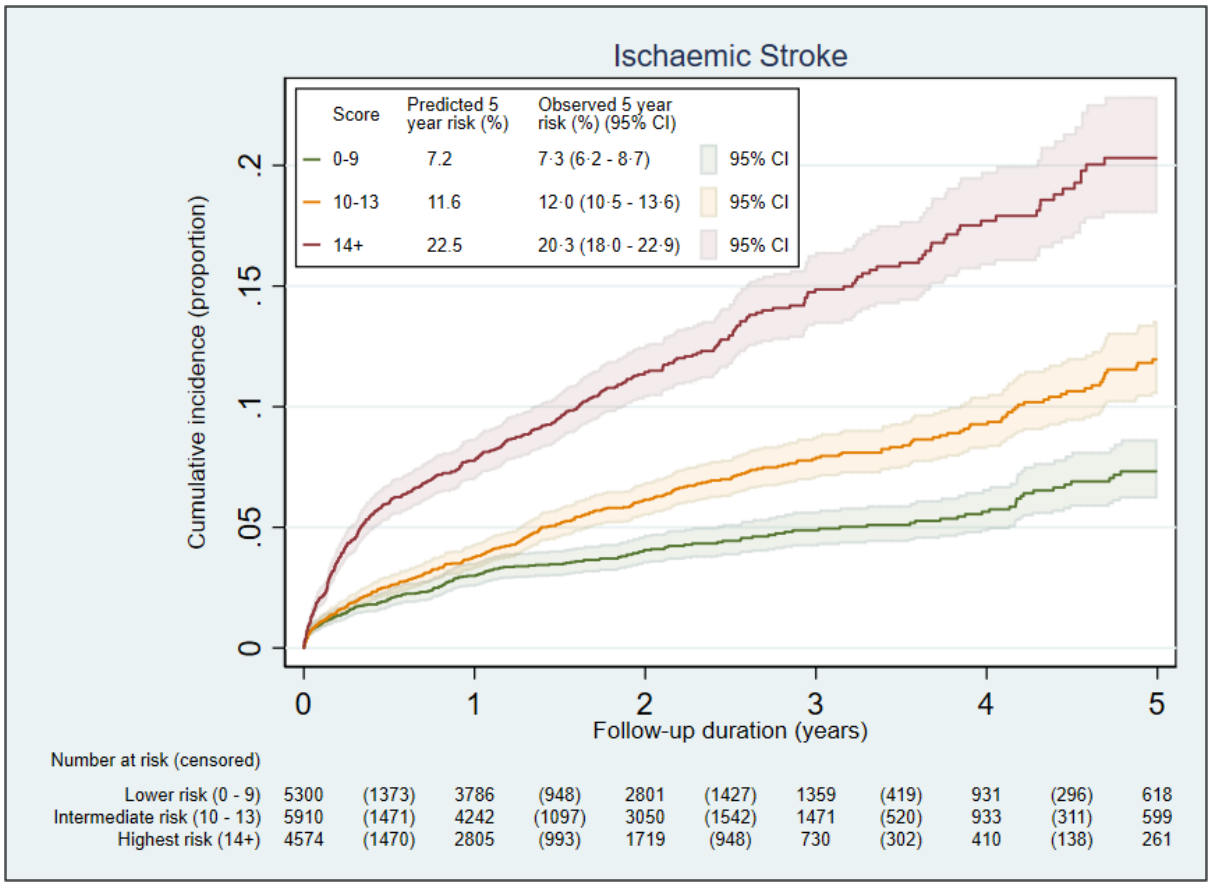
*****Adjusted for other components of main model
CMB: cerebral microbleed; ICH: intracranial haemorrhage; IS: ischaemic stroke

Supplementary Table 5: Characteristics of participants in highest-risk group for ICH and lower-risk group for IS

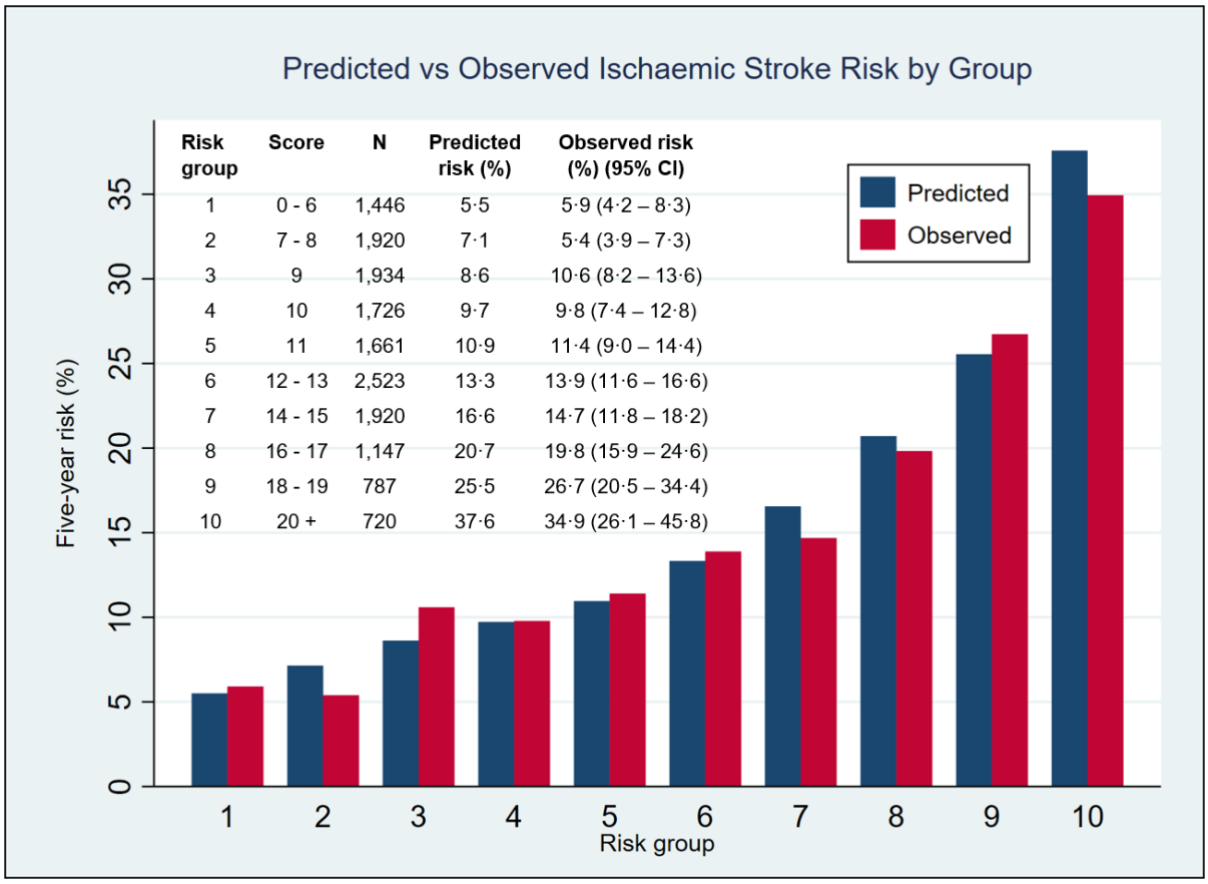
Values show prevalence for categorical variables, and mean (SD) or median (IQR) for continuous variables.

Variable		**Group (n = 104)**	**Remainder (n = 11,849)**
Age		80·9 (8·11)	71·4 (11·7)
Female sex		57/104 (54·8%)	5,055/11,849 (42·7%)
East Asian population		4/104 (3·85%)	4,423/711,849 (37·3%)
Hypertension		81/104 (77·9%)	8,613/11,849 (72·8%)
Atrial fibrillation		102/104 (98·1%)	5,898/11,849 (49.8%)
Previous IS		1/104 (0·96%)	1,878/11,849 (15·6%)
Previous ICH		17/104 (16·4%)	131/11,849 (1·11%)
Diabetes mellitus		9/104 (8·7%)	2,825/11,849 (23·8%)
Hyperlipidaemia		42/104 (41·6%)	5,236/11,849 (44·7%)
CMB burden	0	13/104 (12·5%)	8,531/11,849 (72·0%)
	1	60/104 (57·7%)	1,404/11,849 (11·9%)
	2 – 4	28/104(26·9%)	1,207/11,849 (10·2%)
	5 – 10	1/104 (1·0%)	382/11,849 (3·2%)
	11 - 19	1/104 (1·0%)	178/11,849 (1·5%)
	20 +	1/104 (1·0%)	147/11,849 (1·2%)
Antithrombotic treatment	AP only	2/104 (1·9%)	8,670/11,849 (48.6%)
	DOAC	19/104(18.3·3%)	2,215/11,849 (33·1%)
	Warfarin/VKA	83/104 (79.8·8%)	4,612/11,849 (18·3%)

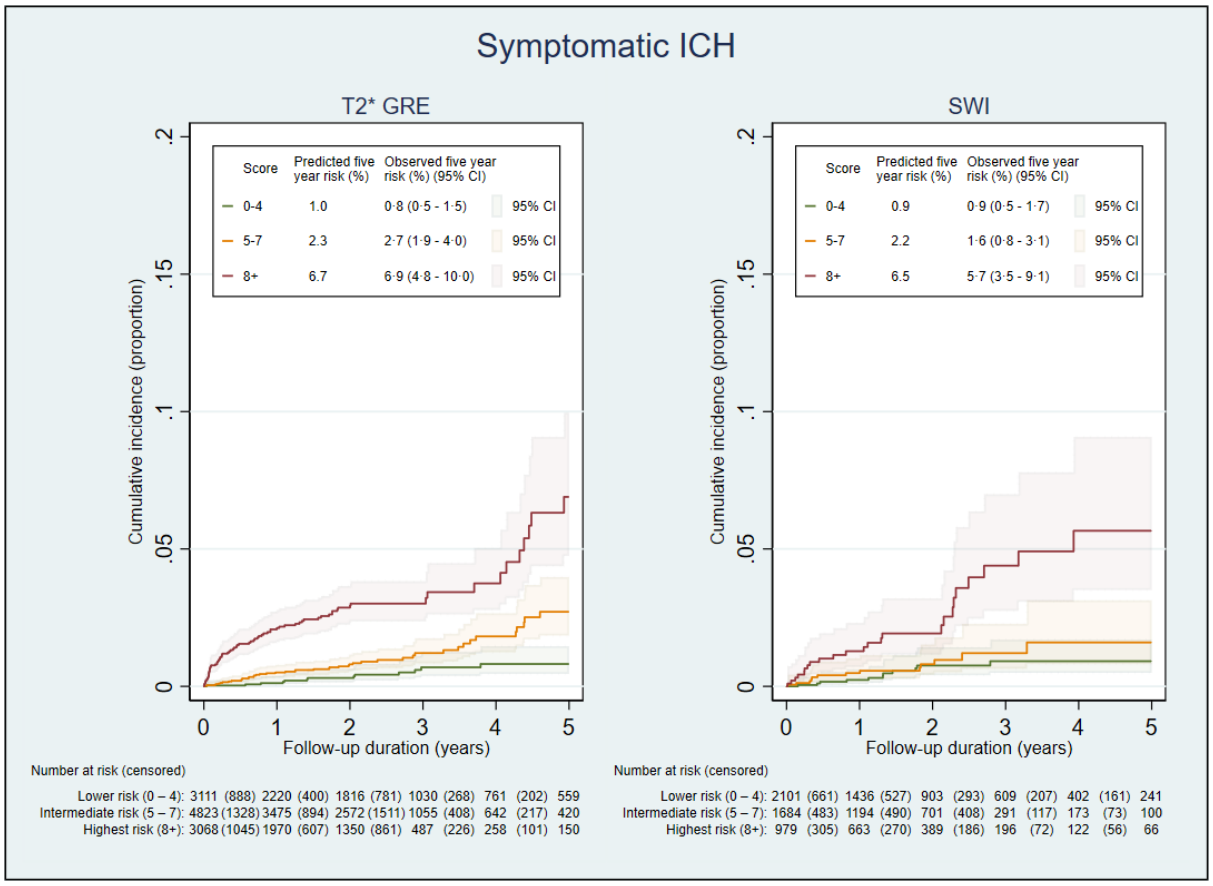
Supplementary Figure 1: Kaplan-Meier plot and risk table for ischaemic stroke model



Supplementary Figure 2: Model calibration – ischaemic stroke

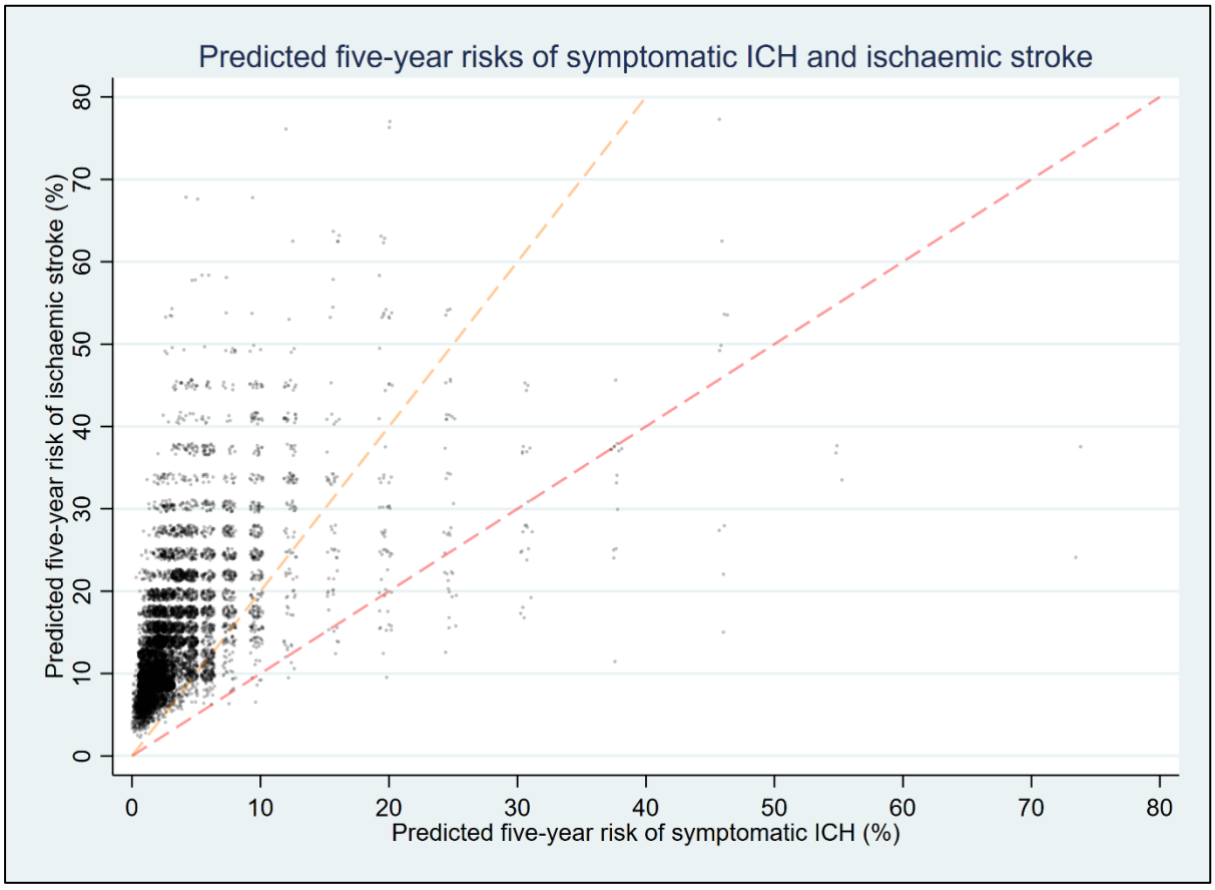


Supplementary Figure 3: ICH model performance by MRI sequence type



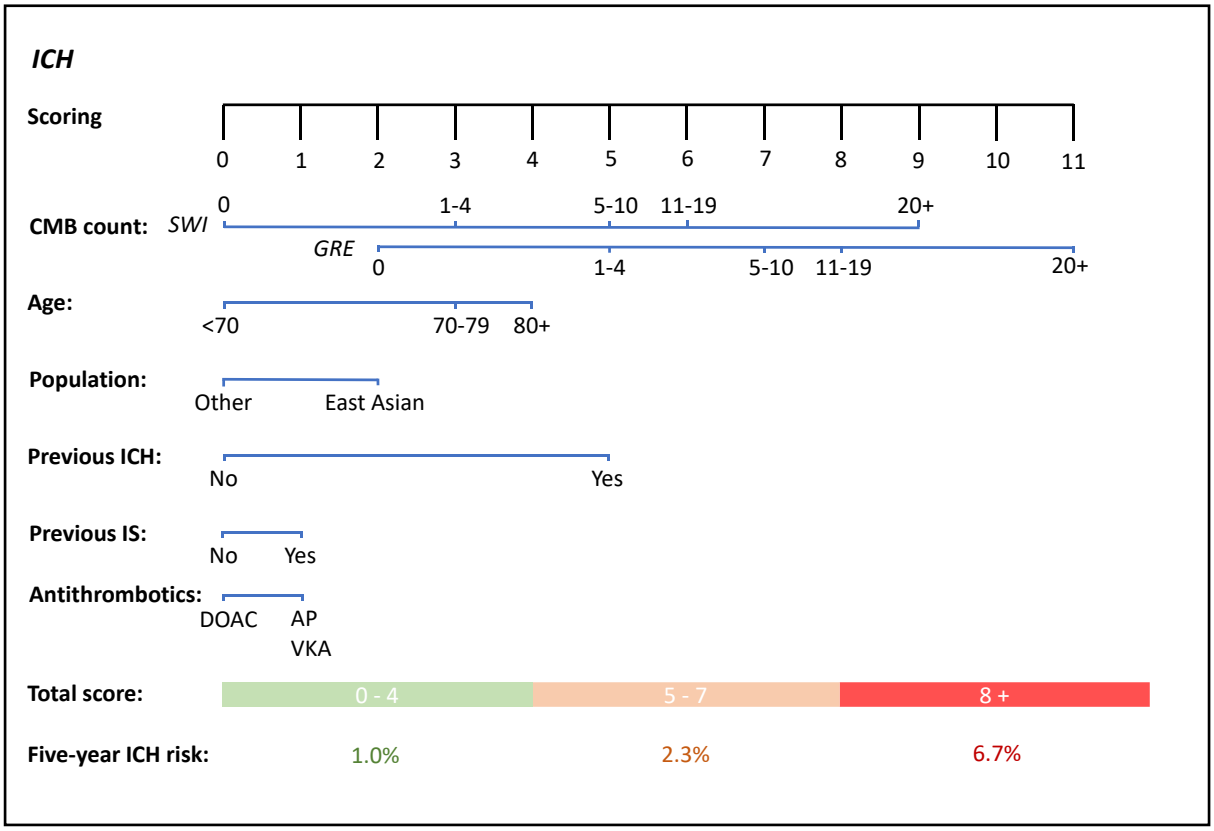
Performance measure	**T2* GRE**	**SWI**
C-index (optimism-adjusted)	0·75 (0·70 – 0·79)	0·70 (0·62 – 0·79)
Calibration slope	0·94 (0·76 – 1·12)	0·94 (0·79 – 1·09)

Supplementary Figure 4: Comparative risks of symptomatic ICH and ischaemic stroke



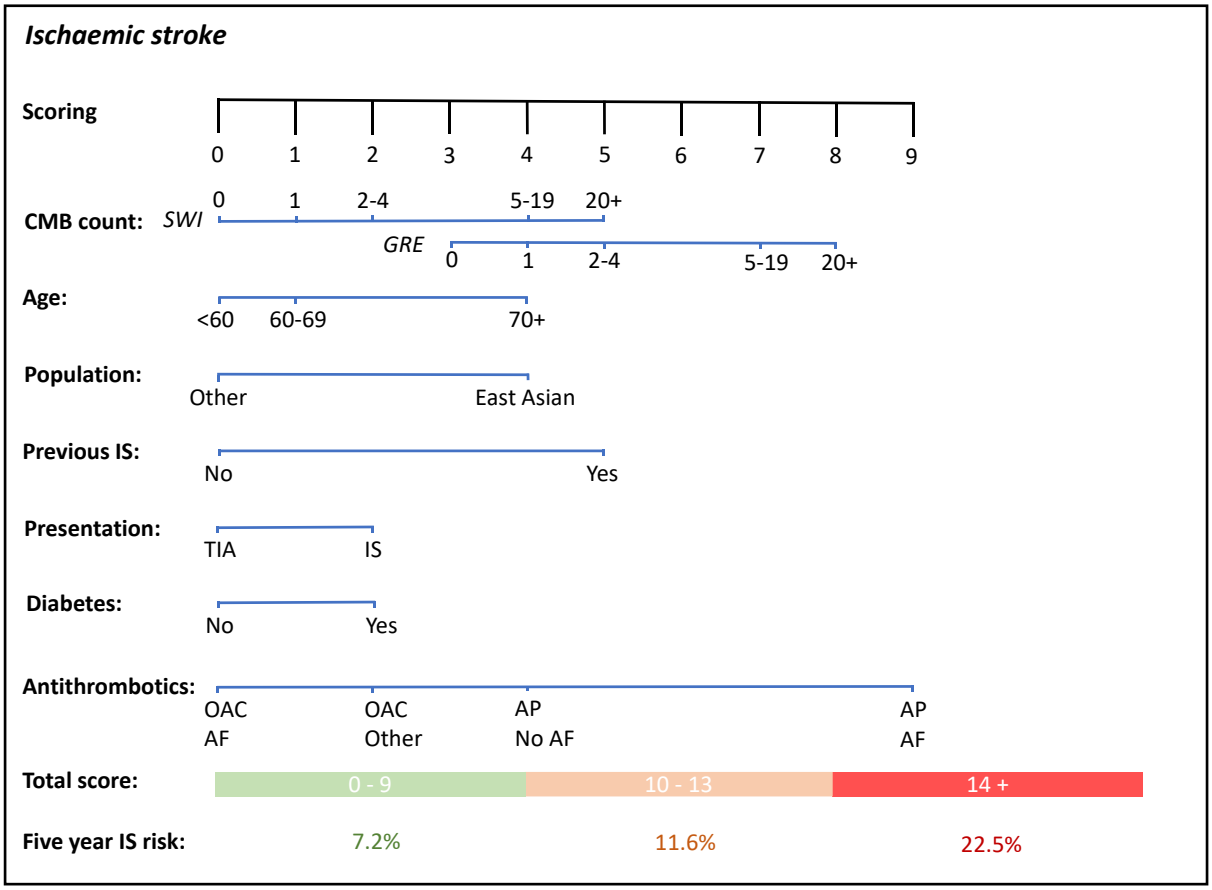
Predicted five-year risks from ICH and ischaemic risk scores for all 11,953 participants with all variables available without imputation. The red line indicates equality between predicted risks of ICH and IS; the orange line indicates predicted IS risk twice that of ICH. For presentation, markers are translucent and jittered.

Supplementary Figure 5: Nomogram for symptomatic ICH risk



For each variable, select the appropriate category, then read the score for that variable from the scoring bar. After summing the total score, select the corresponding 'total score' category and read the five-year ICH risk below.

Supplementary Figure 6: Nomogram for ischaemic stroke risk



For each variable, select the appropriate category, then read the score for that variable from the scoring bar. After summing the total score, select the corresponding 'total score' category and read the five-year IS risk below.

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