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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 transient ischaemic attack

a pooled analysis of individual patient data from cohort studies

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

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158 **Abstract**

159

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

165

166 **Methods** We did a pooled analysis of individual-patient data from the Microbleeds
167 International Collaborative Network, which comprises 38 hospital-based prospective cohort
168 studies from 18 countries. All studies recruited participants with previous IS or TIA, acquired
169 baseline MRI allowing quantification of CMBs, and followed up participants for IS and ICH.
170 We excluded participants not taking antithrombotic drugs. We developed Cox regression
171 models to predict the five-year risks of ICH and IS, selecting candidate predictors on biological
172 relevance and simplifying models using backward elimination. We derived integer risk scores
173 for clinical use. We assessed model performance in internal validation, adjusted for optimism
174 using bootstrapping. We registered the study with the PROSPERO register of systematic
175 reviews (registration: CRD42016036602).

176

177 **Findings** The included studies recruited participants between 28th August 2001 and 4th
178 February 2018. 15,766 participants had follow-up for ICH, and 15,784 for IS. Over a median
179 follow-up of two years, 184 ICH and 1,048 IS occurred. The risk models we developed
180 included CMB burden and simple clinical variables. Optimism-adjusted c-indices were 0.73
181 (95% CI 0.69-0.77) for ICH and 0.63 for IS (95% CI 0.62-0.65); calibration slopes were 0.94
182 (95% CI 0.81-1.06) and 0.97 (95% CI 0.87-1.07) respectively, indicating good calibration.

183

184 **Interpretation** The MICON risk scores, incorporating clinical variables and CMBs, offer
185 predictive value for the long-term risks of ICH and ischaemic stroke in patients prescribed
186 antithrombotic therapy for secondary stroke prevention. External validation is warranted.

187

188 **Funding** British Heart Foundation and Stroke Association

189 **Research in context**

190

191 *Evidence before this study*

192 We searched Medline from 1st January 1996 to 1st February 2020 using the following search
193 strategy: (stroke[tiab] OR bleeding[tiab] OR haemorrhage[tiab] OR hemorrhage[tiab]) AND
194 (prediction[tiab] OR risk stratification[tiab] OR risk score[tiab]). We identified studies in
195 English which described or validated risk scores for ischaemic stroke or major bleeding, in
196 patients taking antiplatelets or anticoagulants, with or without atrial fibrillation. Very few
197 studies of bleeding risk scores reported their performance for intracranial haemorrhage
198 specifically. A large cohort study (n=40,450) of patients with atrial fibrillation anticoagulated
199 for stroke prevention found poor performance in predicting ICH for all bleeding risk scores
200 assessed, including HEMORR2HAGES, HAS-BLED, ATRIA and ORBIT. The highest c-
201 index obtained was 0.53, for HASBLED. A nationwide registry-based cohort study
202 (n=182,678) assessing HASBLED and HEMORRH2HAGES in patients with atrial fibrillation
203 also found limited performance, with c-indices between 0.58 and 0.62 in participants
204 prescribed antithrombotics. Models developed for predicting ICH in patients taking
205 antiplatelets specifically (including Intracranial-B2LEED3S and S2TOP-BLEED) also showed
206 only moderate performance, with the highest reported c-index being 0.65, for S2TOP-BLEED.
207 Risk scores for ischaemic stroke (including CHADS₂, CHAD₂S₂VASc and ATRIA) performed
208 moderately, with c-indices typically between 0.60 and 0.70.

209

210 *Added value of this study*

211 We present new clinical-radiological risk scores using cerebral microbleeds, an MRI marker
212 of small vessel fragility, to predict ICH and ischaemic stroke in patients taking antithrombotic
213 drugs for secondary prevention after ischaemic stroke or transient ischaemic attack, derived

214 from studies in the Microbleeds International Network (MICON), a large international
215 collaboration of prospective cohort studies. The performance of our MICON-ICH score
216 suggests it can usefully stratify patients by risk of antithrombotic-associated ICH in clinical
217 practice. Our results also suggest that cerebral microbleeds add considerable value for
218 predicting ICH, but not ischaemic stroke, clarifying the relative predictive importance of
219 cerebral microbleeds for these outcomes. Our scores did not identify many patients with similar
220 or greater predicted risk of ICH than ischaemic stroke, even in those with high cerebral
221 microbleed burden and other risk factors. Our MICON scores are simple and widely applicable.

222

223 *Implications of all the available evidence*

224 Risk scores including cerebral microbleeds offer increased discrimination over clinical
225 variables alone for the prediction of antithrombotic-associated ICH in a large, multicentre,
226 international population. Although external validation is needed, this finding provides new
227 evidence of how neuroimaging biomarkers can contribute to clinical prediction models.
228 Identifying people at highest risk of ICH may facilitate timely and accurate prognostication to
229 allow mitigation of reversible risk factors for bleeding (e.g. intensive blood pressure control),
230 and selection of participants for clinical trials. While more complex combinations of clinical,
231 biochemical, and radiological markers might further improve stroke risk prediction, balancing
232 accuracy with simplicity will remain important.

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239 **Introduction**

240

241 Antithrombotic therapy is a key component of secondary prevention after ischaemic stroke or
242 transient ischaemic attack. In patients without atrial fibrillation (AF), antiplatelet treatment
243 reduces overall stroke risk by one-quarter,¹ while oral anticoagulation in patients with AF
244 reduces this risk by two-thirds.^{2,3} Although antithrombotic treatment increases the risk of
245 intracranial haemorrhage (ICH) (by around one-quarter for antiplatelets, one-half for direct oral
246 anticoagulants (DOACs), and two-fold for vitamin K antagonists (VKAs)),¹⁻³ the substantially-
247 lower incidence of ICH overall means that antithrombotic treatment is recommended for most
248 patients. However, deciding on appropriate antithrombotic therapy for a given patient can be
249 challenging, especially in those with additional risk factors for bleeding. Ideally, this decision
250 would be based on an individualised assessment of the risks of ischaemic stroke and ICH. To
251 this end, risk scores for ischaemic stroke and major bleeding have been developed, mainly in
252 patients with AF. Although these scores show reasonable discrimination for ischaemic stroke^{4,5}
253 and all-cause major bleeding,^{5,6} studies validating existing bleeding risk scores in predicting
254 ICH have shown more limited performance, with c-indices between 0.50 and 0.62 in
255 anticoagulated patients,^{7,8} and 0.58 – 0.65 in patients taking antiplatelet drugs.^{8,9}

256 Most risk scores for ischaemic stroke and ICH only include clinical variables. More recently,
257 scores using serum biomarkers have been developed, which may offer improved
258 performance.¹⁰⁻¹² However, the role of magnetic resonance imaging (MRI) biomarkers for
259 cerebrovascular disease (increasingly obtained as part of standard stroke care) in improving
260 risk prediction remains uncertain. Cerebral microbleeds (CMBs) are an MRI biomarker of
261 vascular fragility, associated with hypertensive microangiopathy (also known as
262 arteriolosclerosis or deep perforator arteriopathy) and cerebral amyloid angiopathy, the two
263 cerebral small vessel diseases that cause most spontaneous intracerebral haemorrhage.¹³

264 Accordingly, the potential of CMBs in predicting ICH has attracted particular interest. In a
265 prospective observational study, the addition of CMB presence improved the c-index for ICH
266 of the HASBLED bleeding risk score from 0.41 to 0.66,¹⁴ while a recent large individual
267 patient data meta-analysis confirmed a strong association between CMBs and ICH in patients
268 with previous ischaemic stroke or TIA.¹⁵ This study also found that CMBs are associated with
269 IS risk, with a higher absolute risk of ischaemic stroke than ICH across all levels of CMB
270 burden investigated.

271 Given these findings, we aimed to establish the added predictive value of CMBs for ICH and
272 ischaemic stroke, by using the same large international dataset to develop risk models based
273 on CMB burden and simple clinical variables, and to compare these to models using clinical
274 variables alone. We aimed to derive from our models simple risk scores which could be easily
275 used for risk stratification in clinical practice. We investigated whether the resulting scores
276 identified a group of patients at similar or higher predicted risk of ICH than ischaemic stroke,
277 and whether they performed better than existing risk scores.

278

279 **Methods**

280

281 *Study design and participants*

282 We used pooled individual patient data from the Microbleeds International Collaborative
283 Network (MICON) of prospective observational studies, for which the full methodology and
284 composition has been published.¹⁵ Briefly, MICON comprises 38 cohorts from 18 countries in
285 North America, Europe, the Middle East, Asia, and Australasia, collectively including 20,322
286 participants with previous ischaemic stroke or TIA, baseline MRI including blood-sensitive
287 paramagnetic sequences to detect CMBs, and at least three months' follow-up for ischaemic
288 stroke, ICH, or a composite of both. We identified eligible cohorts through a systematic search
289 of Medline and Embase from 01/01/1996 to 01/12/2018, clinical trial databases, scientific

290 abstracts, and the international METACOHORTS consortium of studies in cerebral small
291 vessel disease.¹⁶ Published and unpublished studies were eligible. We assessed all studies
292 identified for quality and risk of bias, including selection bias, using the Cochrane
293 Collaboration tool.¹⁷ All included studies adjudicated events blinded to CMB burden. In the
294 current prediction model development study, we included all MICON participants who were
295 taking antithrombotic therapy and were followed up separately for ischaemic stroke or ICH.
296 The study was approved by the UK Health Research Authority (reference: 8/HRA/0188).
297 Included cohorts obtained ethical and regulatory approvals according to local requirements.
298 Only fully-anonymised data was shared, so that individual consent was not required for this
299 individual patient data pooled analysis. We registered the study protocol with the PROSPERO
300 register of systematic reviews on April 5, 2016 (registration number: CRD42016036602,
301 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=36602).

302

303 *Outcomes*

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

307

308 *Prediction model development*

309 We developed separate prediction models for ICH and ischaemic stroke using Cox regression,
310 with robust standard errors calculated using the Huber-White sandwich estimator to allow for
311 clustering within cohorts.¹⁸ We prespecified our candidate predictors, based on biological
312 relevance and availability in the majority of our cohort, as: age; sex; presentation with transient
313 ischaemic attack or ischaemic stroke; clinical history of hypertension; clinical history of type
314 1 or type 2 diabetes mellitus; previous ischaemic stroke before index stroke or TIA; previous

315 ICH; known AF; antithrombotic treatment after index event; CMB burden.; and type of MRI
316 sequence used to detect CMBs (2D T2*-weighted gradient-recall echo (GRE) or susceptibility-
317 weighted imaging (SWI, also including SWAN, SWIp and VenoBOLD sequences), in view of
318 strong external evidence that CMB counts are systematically higher on these sequences than
319 on GRE (*appendix, p 3*). We accounted for missing data using multiple imputation with chained
320 equations (five imputations). We included a cluster-level variable indicating East Asian centres
321 (Japan, Korea, China and South-East Asia), given the higher incidence of intracerebral
322 haemorrhage and intracranial atherosclerosis in this region.¹⁹ We categorised antithrombotic
323 treatment as antiplatelet therapy only, anticoagulation with a VKA, or anticoagulation with a
324 DOAC. The antiplatelet category included patients taking dual antiplatelets, and anticoagulant
325 categories included participants taking a concomitant antiplatelet. We categorised CMB burden
326 as none, one, two to four, five to ten, 11-19, and 20 or more, and assessed whether an interaction
327 term between MRI sequence type and CMB burden was required. We investigated whether
328 separate models were required for patients taking anticoagulants or antiplatelets using
329 interaction terms and Wald tests. We simplified our models through backwards elimination at
330 the 20% level ($p=0.20$). We scaled and rounded regression coefficients to produce integer
331 scores for ease-of-use in clinical practice.

332

333 *Statistical analyses*

334 We internally validated our models using bootstrapping.²⁰ As an additional test of model
335 performance, we did internal-external cross validation,^{21,22} using five folds consisting of whole
336 cohorts, repeated 20 times to reduce variance. We quantified discrimination using Harrell's c-
337 index, and calibration through the calibration slope. We further assessed calibration by
338 calculating predicted five-year risk for each outcome on the basis of the integer risk score,

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

341 To test the contribution of CMB burden to ICH and ischaemic stroke prediction, we developed
342 purely clinical models in the same way as our main models, but excluding CMB burden and
343 MRI sequence type. We compared their discrimination to our main models, and tested if adding
344 CMB burden and MRI sequence type improved their fit. Next, we compared the performance
345 of our CMB-based ICH risk score (the form of our model that could most easily be used in
346 clinical practice) to existing bleeding risk scores (ATRIA, ORBIT and HASBLED). Each
347 comparison used all participants for whom the additional variables required for calculation of
348 the existing bleeding risk score were available. To apply HASBLED to patients not taking
349 vitamin K antagonists, we scored the 'labile INR' component as 0. As we made these
350 comparisons in a subset of the model development data, we adjusted for optimism using
351 bootstrapping.

352 We performed two sensitivity analyses. Firstly, we assessed the added predictive value of
353 additional variables that we considered potentially clinically relevant by adding each variable
354 individually to our final model for each outcome and testing if it improved model fit using a
355 Wald test²³, before comparing the discrimination of the base and augmented models if it did.
356 The additional variables were: clinical history of hypercholesterolaemia; current smoking
357 status; CMB distribution (strictly deep, strictly lobar, and mixed); and burden of white matter
358 hyperintensities on MRI assessed using the highest recorded Fazekas score from periventricular
359 and deep white matter regions. Secondly, we tested the performance of our ICH model for
360 intracerebral haemorrhage specifically.

361 Finally, we determined the number of participants with a predicted risk of ICH greater than
362 that of ischaemic stroke, and investigated their baseline characteristics.

363 Our statistical analyses used Stata version 16, and are reported following the TRIPOD
364 guideline.²⁴

365

366 *Role of the funding source*

367 The funders of the study had no role in its design, the collection, analysis and interpretation of
368 data, the writing of the report, or the decision to submit it for publication. All authors had full
369 access to all the data in the study and final responsibility for the decision to submit for
370 publication.

371

372 **Results**

373

374 *Figure 1* describes the identification of studies in the MICON collaboration. From all 38 studies
375 and 20,322 participants in the collaboration, we excluded one study comprising 3,335
376 participants that collected follow-up for a composite ‘any stroke’ outcome only. From the
377 remaining 37 cohorts, we excluded 979 participants not taking antithrombotic medication, and
378 a further 204 participants lacking follow-up for both ICH and ischaemic stroke, leaving a final
379 study population of 15,784 participants, recruited between 28th August 2001 and 4th February
380 2018. Their characteristics are summarised in *Table 1*, and described by cohort in *appendix*
381 *pp4-6*. All 15,784 participants had follow-up for ischaemic stroke, and 15,766 had follow-up
382 for ICH. We imputed 2,747/15,784 (17.4%) observations for previous ICH, 2,002/15,784
383 (12.7%) for diabetes, and 1,097/15,784 (6.6%) for ischaemic stroke before index ischaemic
384 stroke or TIA. We imputed fewer than 1% of observations for all other candidate predictors.
385 During a total follow-up of 32,001 person-years for ICH (median 1.99yrs, IQR 0.61-2.87) and
386 31,468 person-years for ischaemic stroke (median 1.98yrs, IQR 0.56-2.80), 184 ICH

387 (including 146 intracerebral haemorrhages) and 1,048 ischaemic strokes occurred. The
388 annualised incidences were 0.57% for ICH, and 3.33% for ischaemic stroke.

389 *Table 2* shows the hazard ratios from our final models for ICH and IS, and the resulting integer
390 risk scores. Both models included age, CMB burden, MRI sequence type used to assess CMB
391 burden, history of ischaemic stroke prior to the index ischaemic stroke or TIA, and East Asian
392 centre location. Our ICH model also included previous ICH and antithrombotic treatment type.
393 We chose to retain antithrombotic treatment in this model on clinical grounds. Our ischaemic
394 stroke model also included presentation with ischaemic stroke and history of diabetes mellitus,
395 and we found strong evidence of an interaction between antiplatelet treatment and AF ($p =$
396 0.0040), consistent with the known superior efficacy of anticoagulants for stroke prevention in
397 AF. We represented this in our model by combining AF, antithrombotic treatment type, and
398 their interaction into a single four-level variable, as the hazard ratios for DOAC and VKA
399 treatment were very similar. *Appendix p7* shows the results of our other tests for interactions.
400 Apart from an interaction for ICH risk between antiplatelet use and previous ICH ($p = 0.011$),
401 which we attributed to treatment bias and chose to exclude, we found no compelling evidence
402 that other interaction terms were required.

403 The optimism-adjusted c-index for our final ICH model was 0.73 (95% CI 0.69–0.77), and the
404 calibration slope 0.94 (95% CI 0.81–1.06), indicating moderate discrimination and excellent
405 calibration. For our final ischaemic stroke model, the c-index was 0.63 (95% CI 0.62–0.65)
406 and the calibration slope 0.97 (95% CI 0.87–1.07), indicating reasonable discrimination and
407 excellent calibration.

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

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

417 The clinical-only models generated for comparison with our main, MRI-based models,
418 included the same variables as the main models apart from CMB burden and MRI sequence
419 type. The clinical-only model for ICH showed reduced model fit and substantially lower
420 discrimination (difference in c-index 0.05, 95% CI 0.02 – 0.09, $p < 0.0001$). The clinical-only
421 model for ischaemic stroke showed worse model fit ($p = 0.00020$) but similar discrimination
422 ($c = 0.63$ (95% CI 0.61–0.64)).

423 *Table 3* shows the results of comparisons between our new ICH risk score and the HASBLED,
424 ORBIT and ATRIA risk scores. Eleven cohorts from eight countries contributed to the
425 comparison for HASBLED, and eight cohorts from six countries to the comparison for ATRIA
426 and ORBIT. All comparisons included East Asian and European centres. For each comparison,
427 the estimate for the c-index of the new ICH risk score was higher, both in participants taking
428 any antithrombotics and when restricted to participants taking OAC. The optimism-adjusted
429 difference in c-index was substantial (range: 0.04 – 0.27) in all comparisons (*Table 3*), though
430 estimates were imprecise and the 95% confidence interval for comparisons with ATRIA and
431 ORBIT did not exclude 0.

432 In our planned sensitivity analyses, we found no evidence that any of the additional variables
433 tested improved model fit for ICH or ischaemic stroke (*appendix p 8*). The optimism-adjusted
434 c-index of our ICH model in predicting intracerebral haemorrhage specifically (rather than
435 intracranial haemorrhage in general) was 0.77 (95% CI 0.73–0.81), with calibration slope 0.95
436 (0.83–1.07). Having found evidence that using information on CMB burden from MRI

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

440 Of 11,953 participants for whom both risk scores could be calculated without imputed data,
441 only 104 (0.87%) were in the ‘highest risk’ tertile for ICH and the ‘lower risk’ tertile for
442 ischaemic stroke, in which the predicted five-year risks of ICH and ischaemic stroke were
443 similar (6.7% and 7.2% respectively). Their baseline characteristics are described in *appendix*
444 *p9*. An additional 999/11,953 participants (8.4%) were allocated to the ‘highest risk’ group for
445 ICH and the ‘intermediate risk’ group for ischaemic stroke (predicted five-year risks 6.7% and
446 11.6% respectively). *Appendix p13* shows the full distribution of risk score predictions.

447

448 **Discussion**

449

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

462 discrimination for the prediction of intracerebral haemorrhage specifically, the most serious
463 form of non-aneurysmal ICH and the form most closely associated with cerebral microbleeds.
464 Overall, the performance of our scores suggests they may be useful to estimate stroke risk and
465 inform prognostication in clinical practice.

466 Our scores have several features to ensure their ease-of-use in the clinical setting. Most
467 importantly, they are simple: the clinical variables used are a standard part of the medical
468 history for any stroke patient, and CMBs are familiar in stroke clinical practice (for example,
469 in the diagnosis of cerebral amyloid angiopathy). CMBs are discrete lesions, which can be
470 counted with very good inter-rater reliability,²⁵ and the blood-sensitive GRE and SWI
471 sequences required to image them (accounted for in our scores) are quick to acquire, widely
472 available, and part of routine stroke imaging protocols in many centres. This offers an
473 advantage over the use of serum biomarkers not usually measured clinically, as in the ABC
474 bleeding score.⁹ Our scores include relatively few variables, allowing diagrammatic
475 representation for quick reference (*appendix pp14-15*) and easy conversion to an online
476 calculator or app. Finally, our scores are applicable to nearly all ischaemic stroke or TIA
477 patients, whether taking antiplatelets or anticoagulants, with or without AF.

478 Our scores are intended for use in patients in whom antithrombotic treatment is planned after
479 ischaemic stroke or TIA. They are not applicable to patients in whom antithrombotic treatment
480 is contraindicated, or for patients taking antithrombotics for primary prevention. They are not
481 designed to help select the type of antithrombotic therapy to use (i.e. antiplatelet or
482 anticoagulant), as this would require randomised data, rather observational data in which the
483 relationship between antithrombotic type and outcomes is attenuated by selection bias. Rather,
484 the MICON risk scores should be used to assess prognosis to inform clinical discussions and
485 other aspects of care once the intended antithrombotic treatment has been chosen. The finding
486 of a high predicted ICH risk might lead to more aggressive treatment of modifiable bleeding

487 risk factors, such as hypertension and alcohol intake, review of concurrent medication, and
488 consideration of non-pharmacological stroke prevention strategies if applicable, such as left
489 atrial appendage occlusion in patients with AF. Our scores might also have applications in the
490 selection of patients at high ICH risk for future clinical trials and mechanistic studies of ICH.
491 The principal methodological strength of our study is the use of a large, multi-centre and truly
492 international study population, increasing generalisability and allowing us to consider regional
493 differences in stroke risk. We screened the prospective studies included for quality and risk of
494 bias. These offered standardised baseline assessment and ascertainment of outcome events
495 within each cohort, an advantage over registry-based studies, while we accounted statistically
496 for within-cohort clustering. We performed both internal validation using bootstrapping and
497 internal-external cross-validation, in accordance with TRIPOD guidelines and expert
498 recommendations.^{22, 24} While we omitted some potentially clinically relevant variables from
499 our model due to missing data, additional analyses suggested this did not reduce model
500 performance.

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

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

524 In summary, the MICON-ICH and MICON-IS scores we present here provide a new means by
525 which to assess the long-term risk of ICH and ischaemic stroke. Although the MICON-ICH
526 score appears promising and clinically useful, external validation is still required. Our results
527 also clarify the relative predictive importance of CMBs for ICH and ischaemic stroke, and may
528 facilitate the design of future randomised controlled trials of alternative stroke prevention
529 strategies (e.g. of novel antithrombotic agents with potentially lower ICH risk) in patients at
530 high predicted risk of ICH.

531 Contributors

532 DJWe, DW, GA, and JM-F drafted the initial protocol, which was reviewed with critical
533 revisions and approval by all authors. JGB and GA did the statistical analysis. JGB, GA and
534 DJW accessed and verified the data, and wrote the first draft of the manuscript. All authors
535 contributed to data acquisition, management, and brain imaging analyses. All authors
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538

539 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

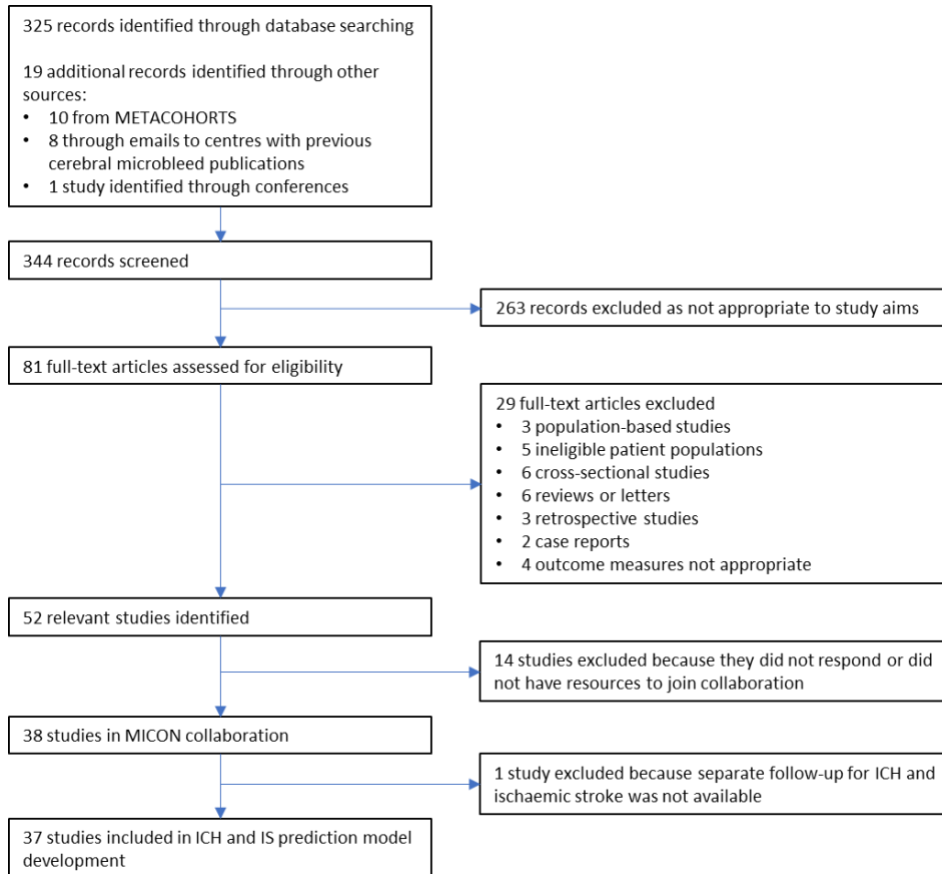


Figure 2: Kaplan-Meier plot and risk table for symptomatic ICH

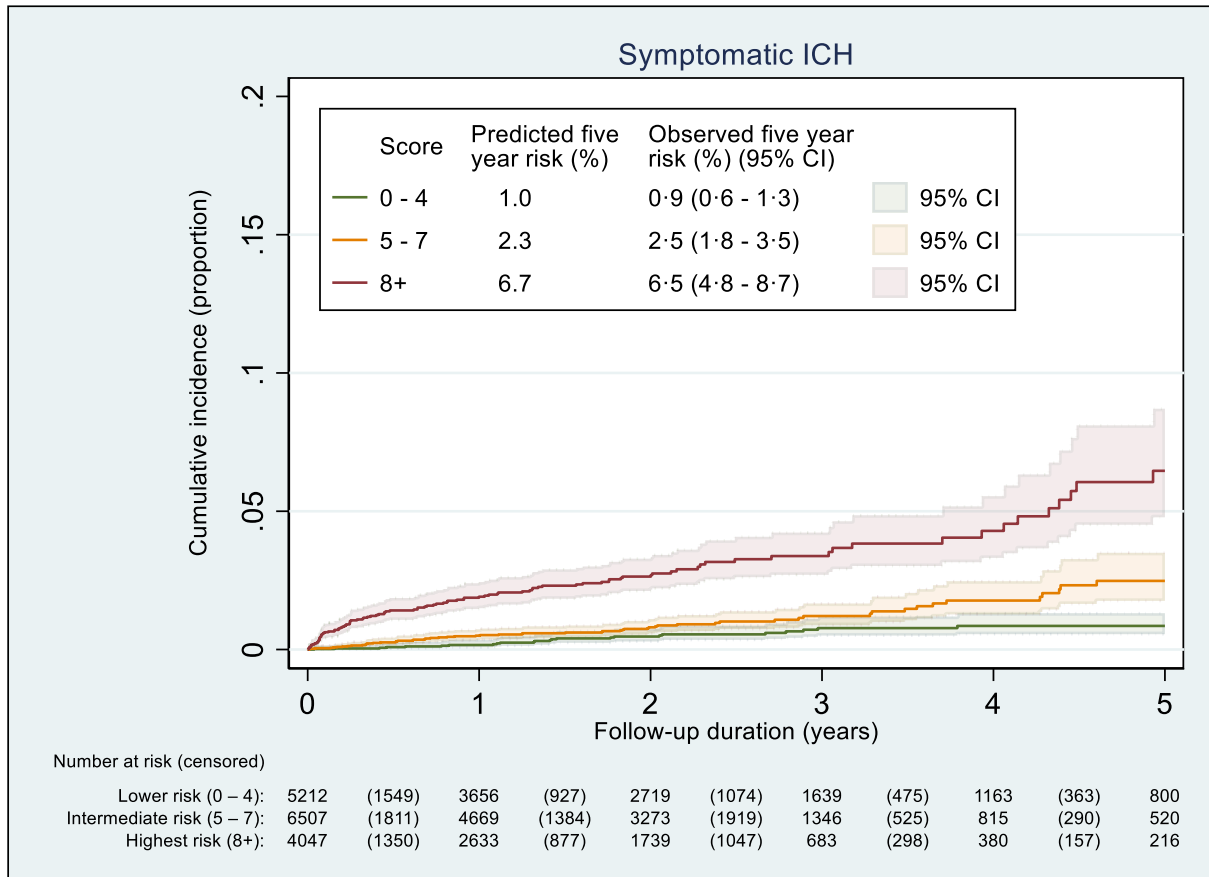
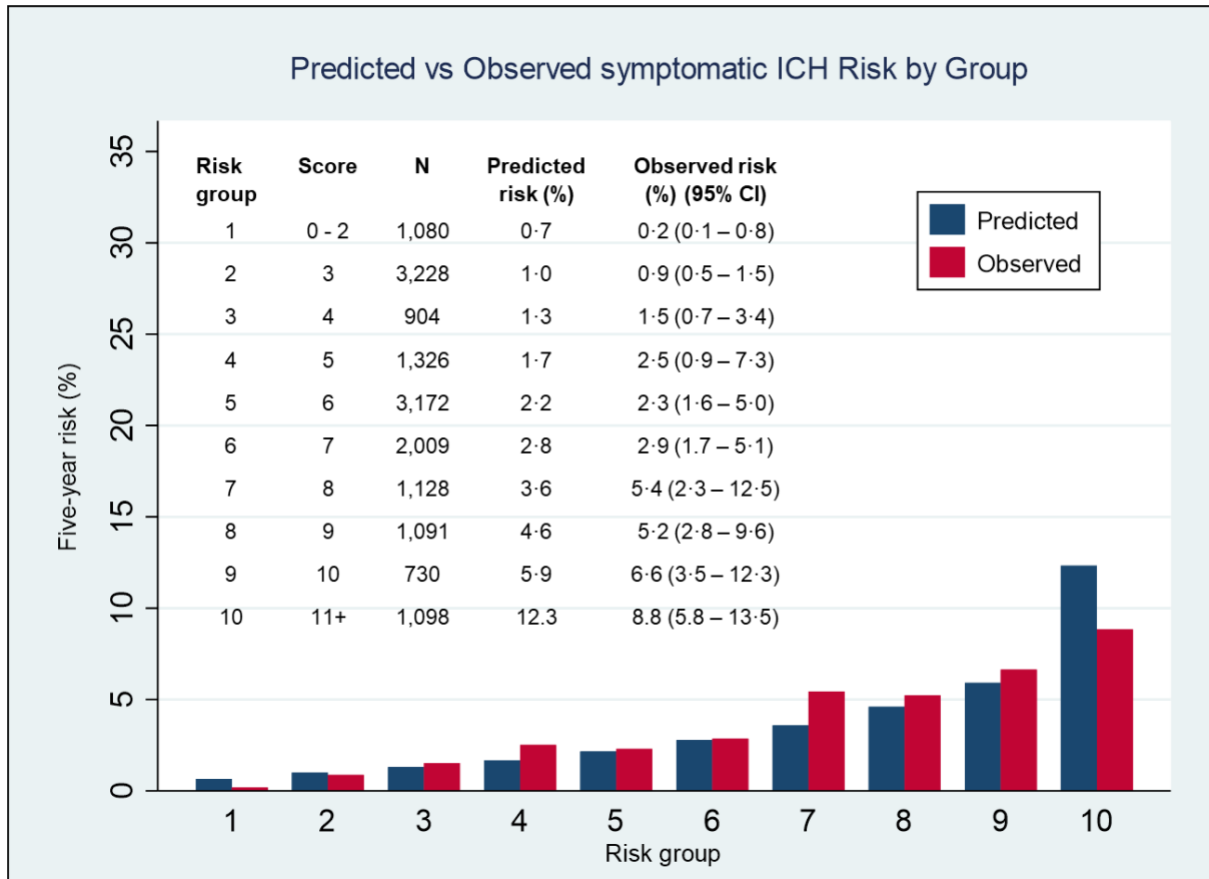


Figure 3: Model calibration – ICH



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)

Predictor	Category	ICH		IS		ICH score	IS score	
		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	
<i>ICH score only</i>	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	-
<i>IS score only</i>	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

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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)	219/343 (64.2)	40/343 (11.7)	82/343 (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)	92/356 (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)	856/935 (91.7)	693/933 (74.3)	212/935 (22.7)	246/935 (26.4)	8/933 (0.9)	803/925 (86.8)	0/935 (0.0)	247/935 (26.4)	1/934 (0.1)	623/935 (66.7)	310/935 (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 ³ ₁	Germany	607	64.3 (14.0)	225/60 7 (37.1)	110/60 7 (18.1)	465/607 (76.6)	-	92/607 (15.2)	1/607 (0.2)	501/607 (82.5)	607/60 7 (100.0)	138/607 (22.7)	488/60 7 (80.4)	109/60 7 (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)	150/18 2 (82.4)	23/182 (12.6)	9/182 (4.9)	0.80 (0.63)	0 (0)	0 (0)
OXVASC ³²	UK	106 7	68.3 (14.0)	508/10 67 (47.6)	164/10 66 (15.4)	581/106 6 (54.5)	-	-	-	502/1067 (47.0)	0/1067 (0.0)	157/1067 (14.7)	949/10 67 (88.9)	112/10 67 (10.5)	6/1067 (0.6)	3.41 (1.53)	11 (1)	78 (7.3)
HKU ³²	Hong Kong	966	68.9 (12.2)	388/96 6 (40.2)	124/96 6 (12.8)	628/966 (65.0)	272/96 6 (28.2)	93/966 (9.6)	12/966 (1.2)	966/966 (100.0)	966/96 6 (100.0)	433/966 (44.8)	862/96 6 (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)	175/17 8 (98.3)	155/178 (87.1)	50/178 (28.1)	34/178 (19.1)	3/178 (1.7)	152/178 (85.4)	178/17 8 (100.0)	66/178 (37.1)	5/178 (2.8)	7/178 (3.9)	166/17 8 (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)	140/20 6 (68.0)	92/206 (44.7)	163/20 6 (79.1)	9/206 (4.4)	34/206 (16.5)	0.60 (0.20)	1 (0.49)	24 (12)
Total		157 84	70.7 (12.2)	6697/1 5784 (42.4)	6882/1 5728 (43.8)	11222/1 5750 (71.3)	3208/1 3782 (23.3)	2300/1 4687 (15.7)	165/130 37 (1.3)	12804/15 774 (81.2)	4757/1 5759 (30.2)	4164/157 84 (26.4)	8733/1 5781 (55.3)	4759/1 5781 (30.2)	2289/1 5781 (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](https://clinicaltrials.gov/ct2/show/study/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	0.54
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

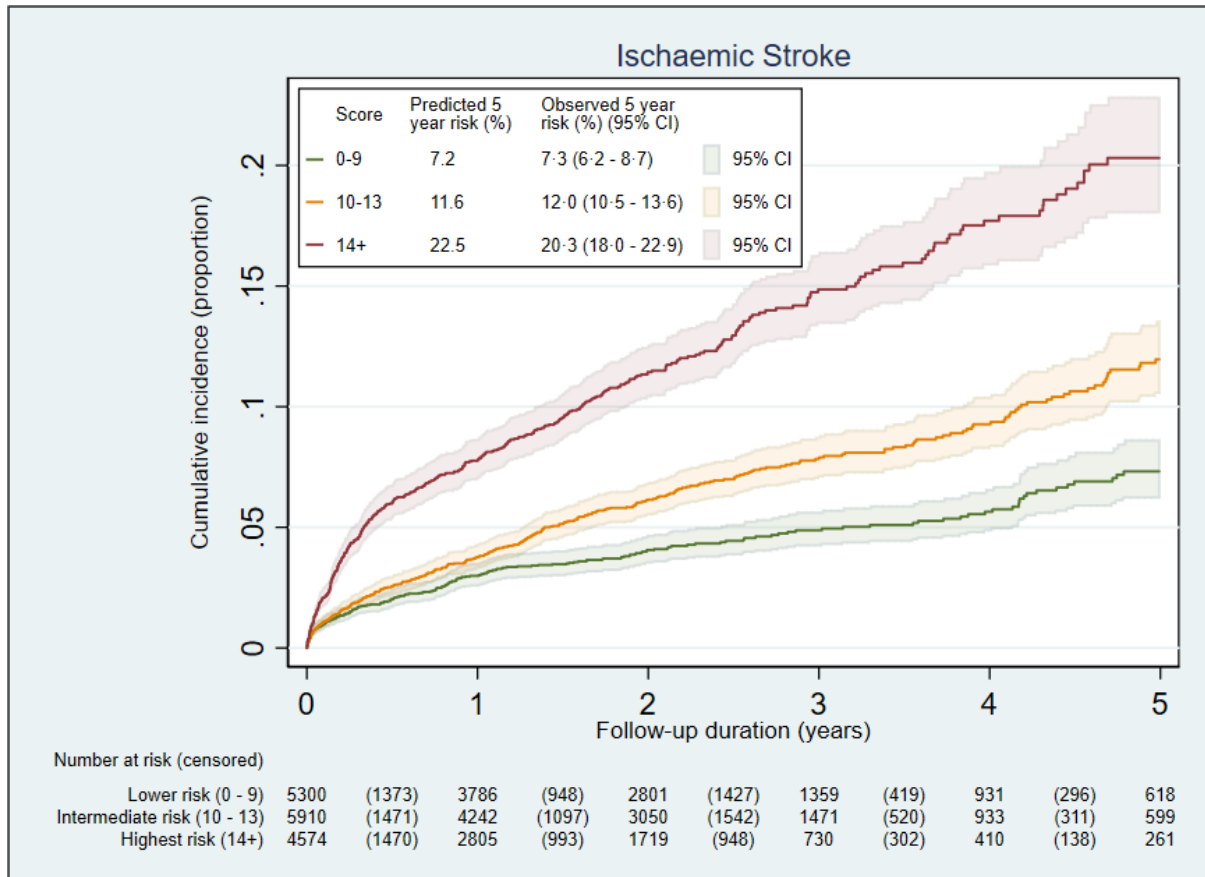
CMB: cerebral microbleed; ICH: intracranial haemorrhage; IS: ischaemic stroke

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

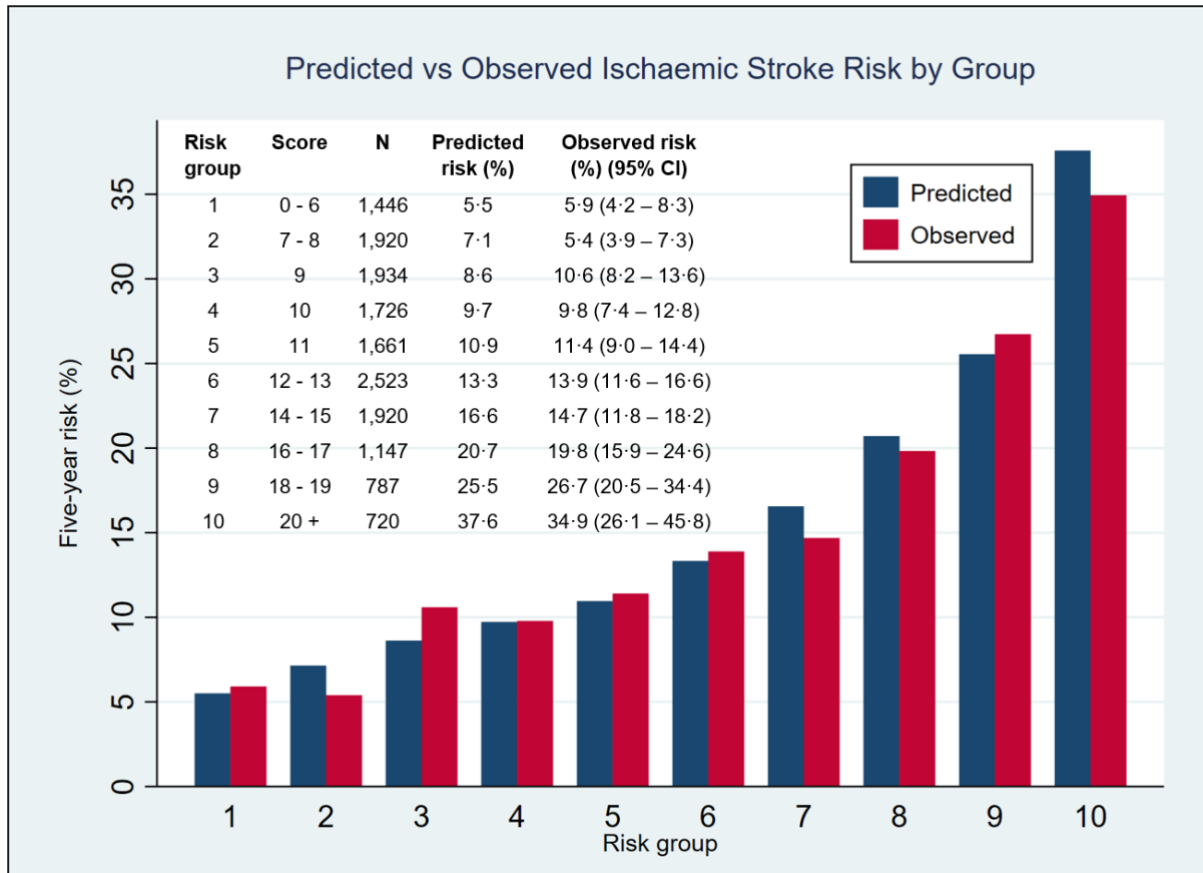
Values show prevalence for categorical variables, and mean (SD) or median (IQR) for continuous variables.

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%)	4,423/11,849 (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%)

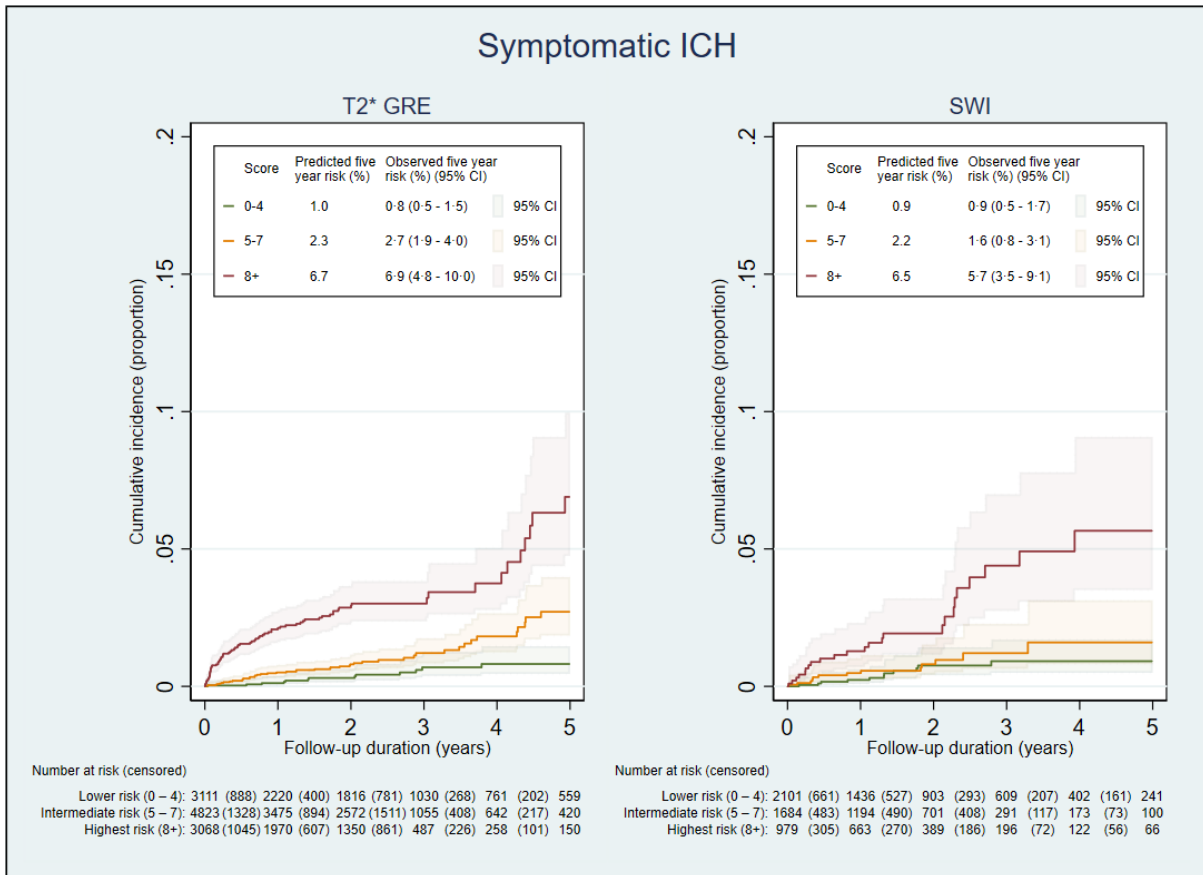
Supplementary Figure 1: Kaplan-Meier plot and risk table for ischaemic stroke model



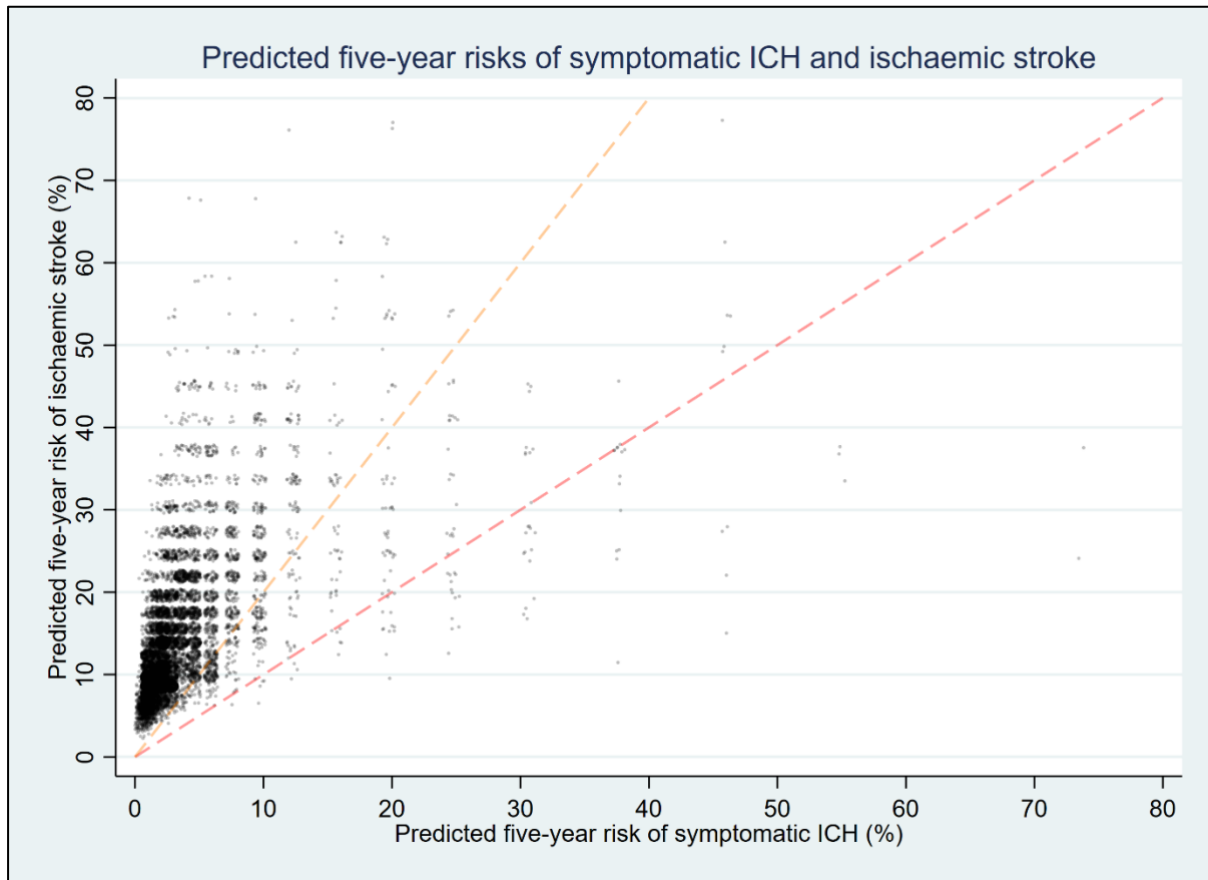
Supplementary Figure 2: Model calibration – ischaemic stroke



Supplementary Figure 3: ICH model performance by MRI sequence type

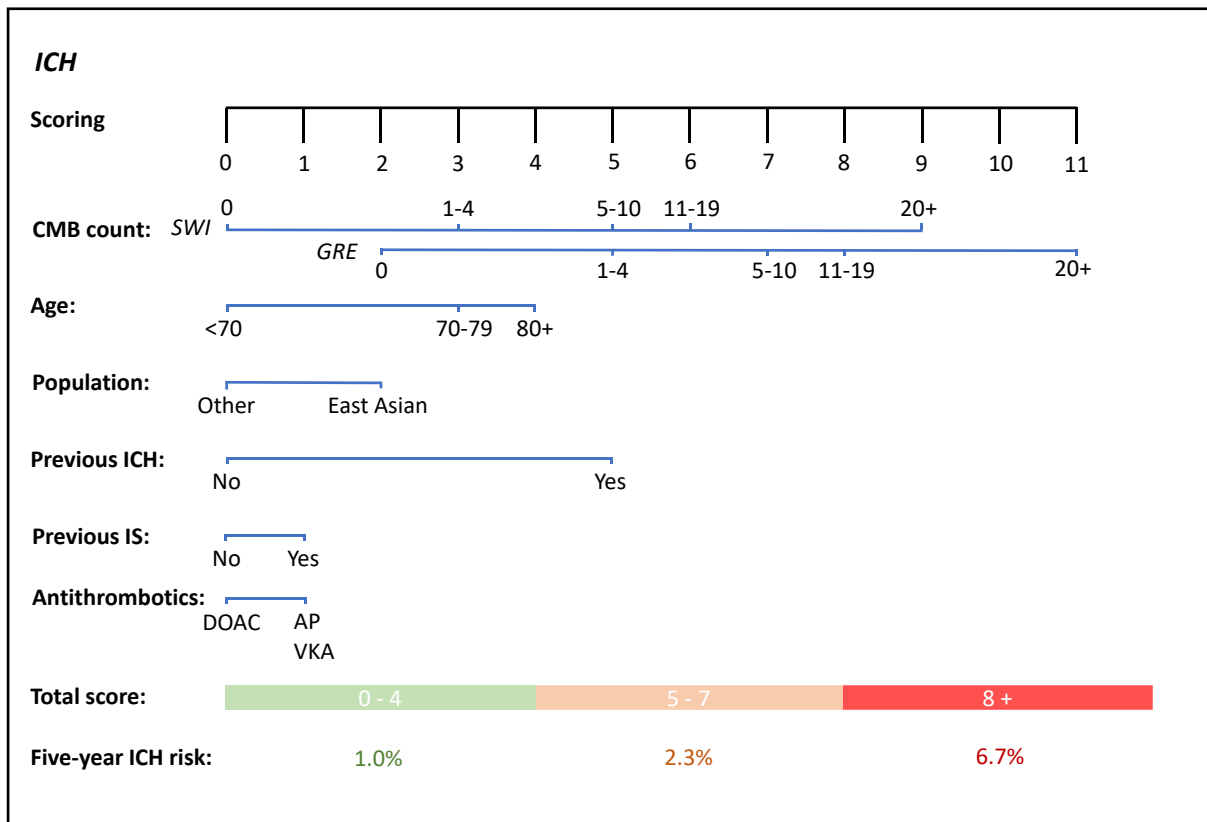


Performance measure	T2* GRE	SWI
C-index (optimism-adjusted)	0.75 (0.70 - 0.79)	0.70 (0.62 - 0.79)
Calibration slope	0.94 (0.76 - 1.12)	0.94 (0.79 - 1.09)

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

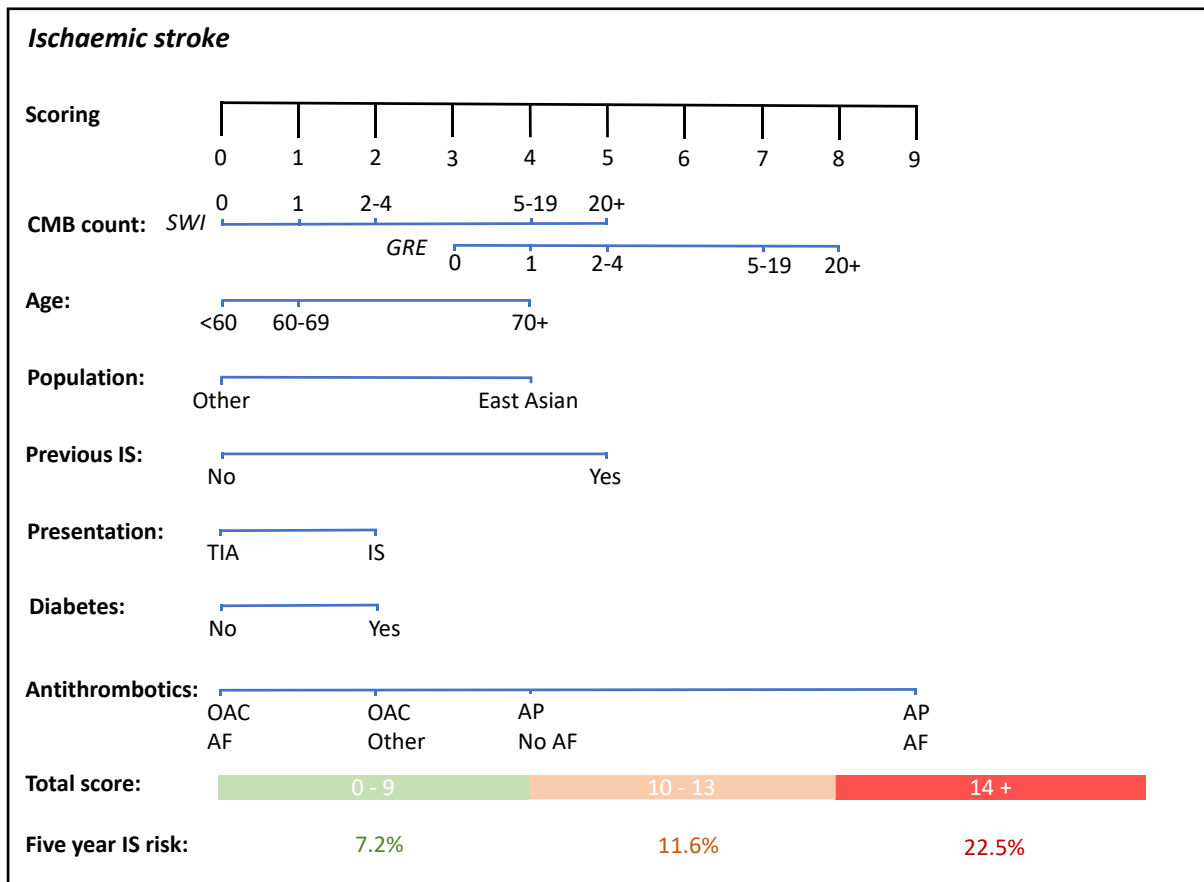
Predicted five-year risks from ICH and ischaemic risk scores for all 11,953 participants with all variables available without imputation. The red line indicates equality between predicted risks of ICH and IS; the orange line indicates predicted IS risk twice that of ICH. For presentation, markers are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