

Online Supplementary Material

Hughes and Lip: “Stroke and thromboembolism in atrial fibrillation: A systematic review of stroke risk factors, risk stratification schema and cost effectiveness data” (TH-07-08-0508) in *Thromb Haemost* 2008; 99 (2)

Details of methods used for formulating this systematic review

One reviewer (MH) selected studies for review based on the information published in the study abstract (or full paper where no abstract was available). All of these studies were then evaluated by two reviewers (MH and GYHL) for inclusion based on the criteria for considering studies for this review and the types of outcome measures described above. Studies were evaluated in terms of their methods according to a study appraisal system used by the UK National Institute for Health and Clinical Excellence (NICE)⁸. This appraisal system assigns a grade of either ‘++’, ‘+’ or ‘-’ to each study. Studies that were graded as ‘-’ were excluded. There were no cases of disagreement between the reviewers on the exclusion of studies.

Systematic review of independent stroke risk factors in AF

A systematic review of the published literature was conducted to identify all of those studies that report the independent risk attributable to demographic, clinical or echocardiographic patient characteristics in a population of AF patients. The methodological quality of these studies was appraised and the results summarised with the objective of identifying those patient characteristics whose presence indicate a statistically significant and independent elevated stroke risk in AF patients. Of note, it was not assumed that the risk factors for stroke in AF patients are necessarily overlapping with those characteristics that are established stroke risk factors in non-AF patients. This is of particular importance considering the differential stroke mechanisms thought to be involved in AF versus non-AF patients.

Systematic review of stroke risk stratification models

A further systematic review was conducted, based on the same literature search as used for the systematic review of independent stroke risk factors, to identify all of those studies that either derived an evidence-based RSM or conducted a formal validation exercise on an existing RSM. The methodological quality of these studies was appraised and their results used to make a systematic comparison between models based on the following: (a) their incorporation of statistically significant and independent stroke risk factors identified in the systematic review of stroke risk factors; and (b) their accurate categorisation of stroke risk in terms of their ability to distinguish between different risk categories at the 95% confidence level and Harrell’s C statistic, where reported.

Review of cost-effectiveness of antithrombotic therapy

To complement the systematic reviews of stroke risk factors and RSMs, a further review of health economic studies and models was made. The conclusions of such models are an important consideration in assessing the efficacy of stroke thromboprophylaxis in AF and the ability to estimate stroke risk based on a RSM.

Study selection criteria

(a) Types of studies

A tailored search expression (available from the corresponding author on request) was used to search for relevant studies in the Medline, Cinahl, EMBASE and Cochrane CENTRAL electronic databases. The results were combined into a single file with duplicates deleted. Further studies were also included following manual cross-referencing and expert consultation. The search encompassed all studies referenced in any of the above databases until the 4th July, 2005. The systematic literature search covered both English language studies, and those published in other languages whose abstracts were available in English. Non-English language studies were translated if it was agreed – based on the information contained in the abstract – that a) the same study had not been republished in English, and b) it met all of the inclusion criteria

(b) Types of participants

For the systematic reviews of stroke risk factors and stroke risk models, studies were considered for inclusion if they were based in a population of non-anticoagulated AF patients (studies that included a minority of atrial flutter patients were also considered) and excluded those with significant co-morbid prothrombotic conditions such as active cancer or overt heart failure.

(c) Types of outcome event

Adequately confirmed cerebrovascular accidents, including both strokes and – where reported - transient ischaemic attacks (TIAs) were considered. Confirmation was considered adequate through clinical diagnosis or neuroimaging. Because the types of participants considered in this review exclude those receiving antithrombotic therapy, it was assumed that the incidence of haemorrhagic stroke would be clinically insignificant relative to the incidence of ischaemic stroke. Studies that did not discriminate between stroke aetiology were therefore included, in addition to those studies that considered only ischaemic stroke as the main outcome event.

Outcome Measures

(a) Stroke risk factors

Studies were considered for inclusion if they reported a measurement for the independent risk of stroke in patients with AF for at least one objectively quantifiable patient characteristic. Independent risk was assumed to be measurable only through either (i) the appropriate use of regression models where the occurrence of a bleeding event is defined as the dependent variable, and multiple clinically plausible risk factors are defined as the set of independent variables, or (ii) the use of a matched case-control study design with cases and controls defined in terms of a single clinically plausible risk factor. Acceptable measures of independent stroke risk included risk ratios expressed as relative risk, odds ratio or hazard ratio with reported p values or 95% confidence intervals, or differences in the frequency of risk factors in between case and control cohorts.

While meta-analytic methods exist for estimating risk-based outcome measures across multiple studies, this is not a methodologically valid procedure for studies involving multivariate regression models. These studies typically exclude variables based on an absence of any statistically significant univariate association with the outcome variable in the first step, and subsequently exclude non-significant variables during the iterative regression procedure. Moreover, the estimated value of the independent risk as calculated by a multivariate regression model is dependent on the choice of independent variables selected by the study investigators, which varies between studies. The main outcome of interest in this review was therefore considered to be the statistical significance of the independent risk attributable to the patient characteristic, rather than an estimation of the independent risk parameter, however expressed. Specifically, whether $p < 0.05$ for each patient characteristic.

(b) Stroke risk stratification models

RSMs were compared in terms of the set of included stroke risk factors and whether these factors had been identified as significant independent predictors of stroke risk in the systematic review of stroke risk factors. Comparison was also made in terms of their ability to distinguish between different stroke risk categories. This comparison was made in terms of the C statistic (Harrell's 'C'), where reported and the absence of overlap in the reported 95% confidence intervals (CIs) of the stroke incidence in each risk category. While the C statistic has the advantage of measuring the ability to distinguish between multiple risk categories, regardless of the sample size of the study population, no convention exists as to an acceptable threshold value beyond which a RSM should be considered as clinically useful or statistically significant. In contrast, an absence of any overlap in the 95% CIs between risk categories is a clear demonstration of the ability to correctly predict stroke risk in at least 95% of the sample population. The absence of any overlap in the 95% CIs has the disadvantage of being dependent upon the number of risk categories – reducing the statistical power of the model – and the sample population size and variance in stroke risk.

Table: Summary of study characteristics included in the systematic review of stroke risk factors.

Study	N	Stroke freq. (%)	Mean age	Patients
Aronow et al., 1989 ²³	110	44 (40%)	82	Observational study in a long-term care facility
Aronow et al., 1998 ²⁴	312	NR	84	Observational study in a long-term care facility
Cabin et al., 1990 ²⁰	272	27 (10%)	NR	Observational study in an AF population
Ezekowitz et al., 1998 ²⁵	1,066	78 (7.3%)	67	Non anticoagulated patients enrolled in SPAF I, BATAAF and SPINAF trials
Hart et al., 1999 ¹¹	2012	130 (6%)	69	Patients enrolled in control arms of SPAF I-III
Hart et al., 2000 ¹³	460	27 (6%)	66	Patients with intermittent AF enrolled in control arms of SPAF I-III
Inoue et al., 2000 ²¹	740	55 (7%)	56	Observational study based in patients with paroxysmal AF
Laupacis et al., 1994 ¹⁰	1593	NR	69	Patients enrolled in control arms of stroke prevention studies (AFASAK, BAATAF, CAFA, SPAF, SPINAF)
Moulton et al., 1991 ²²	265	134 (51%)	77	Observational study of AF patients admitted to hospital
Nakagami et al., 1998 ¹⁹	290	68 (23%)	68	Observational study in an AF population with no prior thrombotic event
Pearce, 1992 ²⁶	568	46 (8.1)	67	SPAF I patients enrolled in placebo arm
Petersen, 1990 ¹⁷	336	25 (7%)	NR	Patients enrolled in the placebo arm of AFASAK
Seidl et al., 1998 ²⁷	191	12 (6%)	64	Observational study of cardioversion patients
SPAF III Writing Committee, 1998 ¹²	892	NR	67	Patients enrolled in control arm of SPAF III
SPAF Investigators, 1992 ¹⁸	568	46 (8%)	NR	Patients enrolled in the placebo arm of SPAF I

SPAF Investigators, 1995 ²⁸	854	NR	69	Patients enrolled in aspirin arms of SPAF I-II
Stollberger et al., 2004 ¹⁵	409	83 (20%)	62	Observational study in an AF population
van Latum et al., 1995 ¹⁶	375	116 (31%)	NR	Patients with a prior stroke/TIA enrolled in the placebo arm of EAFT
Wang et al., 2003 ¹⁴	705	83 (12%)	75	Observational study in the general population

SPAF Stroke Prevention in Atrial Fibrillation trial [these trials appear in different publications, as the dataset was used in various analyses of stroke risk factors.