Theme Issue Article

Stroke and thromboembolism in atrial fibrillation: A systematic review of stroke risk factors, risk stratification schema and cost effectiveness data

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Summary

The risk of stroke in atrial fibrillation (AF) needs to be assessed in each patient to determine the clinical and cost-effectiveness of thromboprophylaxis, with the aim of appropriate use of antithrombotic therapy. To achieve this, stroke risk factors in AF populations need to be identified and stroke risk stratification models have been devised on the basis of these risk factors. In this article, we firstly provide a systematic review of studies examining the attributable stroke risk of various clinical, demographic and echocardiographic patient characteristics in AF populations. Secondly, we performed a systematic review of published stroke risk stratification models, in terms of the results of the review of stroke risk factors and their ability to accurately discriminate between different levels of stroke risk. Thirdly, we review the health economic evidence relating to the cost-effectiveness of anticoagulation and antiplatelet therapy as thromboprophylaxis in AF patients. The studies included in the systematic review of stroke risk factors identified history of stroke or TIA, increasing age, hypertension and structural heart disease (left-ventricular dysfunction or hypertrophy) to be good predictors of stroke risk in AF patients. The evidence regarding diabetes mellitus, gender and other patient characteristics was less consistent. Three stroke risk stratification models were identified that were able to discriminate between different categories of stroke risk to at least 95% accuracy. Few models had addressed the cumulative nature of risk factors where a combination of risk factors would confer a greater risk than either factor alone. In patients at high risk of stroke, anticoagulation is cost effective, but not for those with a low risk of stroke. With the evidence available for stroke risk factors and the various alternative stroke risk stratification models, a review of these models in terms of the evidence on which they are devised and their performance in representative AF populations is important. The appropriate administration of thromboprophylaxis in AF patients would need to balance the risks and benefits of antithrombotic therapy with its cost-effectiveness.

Keywords

Atrial fibrillation, stroke, thromboembolism, echocardiography, risk modeling, thromboprophylaxis, stroke prevention, cost-effectiveness, anticoagulation

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Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke and thromboembolism and results in an independent increase in mortality *per se* (1). AF increases the risk of stroke by five-fold, and the use of anticoagulation reduces this risk by two-thirds whilst antiplatelet therapy reduces stroke by one-fifth (2, 3). However, the risk of stroke in AF is not homogeneous, and varies according to various risk factors. For example, stroke risk varies according to age and the presence of hypertension, diabetes mellitus, previous stroke or transient ischemic attack (TIA) and poor cardiac function. Transthoracic and transoesophageal echocardiography features have also been associated with a high risk of stroke. Although most stroke risk stratification criteria lay emphasis on clinical risk factors, there is a perception that transthoracic echocardiography (TTE) is mandatory to decide on antithrombotic therapy. In one study, however, echocardiography revealed cardiac abnormalities in many AF patients, although most

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Study	N	Age risk factor	P-value
Hart RG, 1999[11]	2,012	Incremental risk per decade	<0.001
Hart RG, 2000[13]	460	Incremental risk per decade	<0.001
Laupacis A, 1994[10]	1,593	Incremental risk per decade	<0.05
Nakagami H, 1998[19]	290	Incremental risk per decade	NS
SPAF Investigators., 1992[18]	568	Incremental risk per decade	NS
The SPAF III Writing Committee, 1998[12]	892	Incremental risk per decade	0.01
van Latum JC, 1995[16]	375	Incremental risk per decade	NS
Wang TJ, 2003[14]	705	Incremental risk per decade	<0.05
Petersen P, 1990[17]	336	Correlation with increasing age	NS
Stollberger C, 2004[15]	409	Correlation with increasing age	0.0006
Moulton AW, 1991[22]	265	Age > 75	<0.05
Cabin HS, 1990[20]	272	Age > 70	NS
Inoue H, 2000[21]	740	Age > 65	0.0001

N = sample size; NS = not significant (p>0.05).

Table 1: Summary of results for increasing age as a risk factor for stroke in terms of whether or not the study reported increasing age as a significant risk factor.

had other clinical risk factors for thromboembolism and often echocardiography did not alter the management decision (4). Also, transoesophageal echocardiography (TOE) can also be used by specialists to help assess the risk of stroke and thromboembolism (5). Echocardiography therefore complements risk stratification on clinical grounds.

The recognition of various stroke risk factors has enabled the formulation of stroke risk stratification models (RSMs), which are able – in varying degrees – to assign AF patients to a category of stroke risk based on the presence of stroke risk factors. Stroke risk may then be managed by administering antithrombotic therapy concordant with the cost-effectiveness associated with such therapy as measured by the risk of stroke and the efficacy and cost of the therapy. In particular, the administration of oral anticoagulation as thromboprophylaxis may be cost effective in high-risk patients, but not cost effective in lower risk patients. In those patients in whom oral anticoagulation is not cost effective, antiplatelet therapy may be more appropriate, or no treatment.

Recently published evidence-based national guidelines for the management of AF in the United Kingdom (6) have systematically reviewed the recognized stroke risk factors, and established an algorithm-based RSM. These national guidelines, issued by the National Institute for Health and Clinical Excellence (NICE) are different from other expert consensus guidelines issued by learned societies (7), as the methodology is based on systematic literature reviews following specification of the guideline scope (8). In addition, a systematic review of the cost-effectiveness of anticoagulation was undertaken as part of the guideline development process. The guideline recommendations were formulated by a multidisciplinary panel of physicians, patient representatives and health service researchers given the results of the systematic literature reviews (that were critically appraised) and guideline scope.

The aim of this document was firstly, to provide a systematic review of studies examining the attributable stroke risk of various clinical, demographic and echocardiographic patient characteristics in AF populations. Secondly, we performed a systematic review of published stroke RSMs, in terms of the results of the review of stroke risk factors and their ability to accurately discriminate between different levels of stroke risk. Thirdly, we review the health economic evidence relating to the cost-effectiveness of anticoagulation and antiplatelet therapy as thromboprophylaxis in AF patients.

Methods

Full details of the methods used for formulating this Systematic Review are provided in a Supplementary file which can be viewed online at www.thrombosis-online.com. In addition, the full NICE guideline is available from the NICE webpage (http://www.nice.org.uk/page.aspx?o = cg36). The guideline is also published in full (6), with all the evidence tables from the various systematic reviews, as follows: http://rcplondon.ac.uk/pubs/books/af/index.asp.

Results

Stroke risk factors

The systematic literature searches resulted in a total of 2,817 abstracts which were reviewed for relevance. For the systematic review of risk factors, based on the information contained in the abstract a total of 2,743 studies were excluded and 95 reviewed based on the complete study report. Seventy-six of these studies were subsequently rejected for not meeting the study inclusion criteria and 19 were critically appraised. The most common reason for exclusion was the inclusion of anticoagulated patients in the study population. One study (9) was excluded following critical appraisal due to baseline data being recorded following the outcome event. The summary study characteristics of the 18 studies included in the systematic review of risk factors are shown in in the Supplementary Table at www.thrombosis-online.com. Although the data from the same clinical trial populations were analysed in multiple studies, none of these studies used

Table 2: Summary of results for gender as a risk factor for stroke in terms of whether or not the study reported gender as a significant risk factor.

Study	N	Reference gender	P-value
Hart RG, 2000[13]*	460	Female	0.004
Wang TJ, 2003[14]	705	Female	<0.05
Hart RG, 1999[11]	2,012	Female	0.01
Aronow WS, 1989[23]	110	Female	NS
Cabin HS, 1990[20]	272	Female	0.014
Aronow WS, 1998[24]	312	Female	NS
Petersen P, 1990[17]	336	Female	NS
SPAF III Writing Committee, 1998[12]	892	Female	NS
Nakagami H, 1998[19]	290	Female	NS
Hart RG, 2000[13]**	460	Female	NS
Inoue H, 2000[21]	740	Male	0.0291
van Latum JC, 1995[16]	375	Female	0.05

*Result in those with sustained AF; **Result in those with intermittent AF. N = sample size; NS = not significant (p>0.05).

exactly the same populations or risk models and all were therefore included.

Age

When measuring the independent risk associated with age either as a continuous variable or as incremental decades, six studies (10–15) found increasing age have an independent affect on the risk of stroke, while the remaining four studies (16–19) did not find a significant effect (Table 1). Of note, one study (18), based on the data from patients enrolled in the control arm of the first Stroke Prevention in Atrial Fibrillation trial, failed to find an independent affect of increasing age, while another study (10), which used the same data alongside data from four smaller trials, did find an independent affect.

When measuring age as a risk factor by classifying patients as young or old based on a threshold age value, one observational stud (20) involving approximately 748 patient years follow-up did not find that being over 70 years of age to be a significant stroke risk factor. In another observational study (21) based in patients with paroxysmal AF at enrolment and involving approximately 2,516 patient years follow-up, being over 65 years of age was found to be a significant risk factor (risk ratio [RR] 3.3, 95% confidence interval [CI] 1.92 to 5.81). Similarly, in another, smaller, observational study (22), being aged over 75 years was found to be a significant risk factor for stroke (odds ratio [OR] 1.72, 95% CI 1.04 to 2.84).

Gender

Ten studies considered gender as a risk factor for stroke in general AF populations for primary and/or secondary prevention. Five studies (11, 13, 14, 16, 20) found being female to be a significant independent risk factor for stroke, whilst the remaining studies (12, 17, 19, 23, 24) did not find that being female to be a significant independent predictor (Table 2). One study (21) based in a population with intermittent AF found being male to be a significant independent risk factor for stroke. This result is consistent in another study based in a population with intermittent AF (13) which did not find being female to be a significant independent risk factor, although it did find it significant in those with sustained AF.

Table 3: Summary of results for hypertension as a risk factor for stroke in terms of whether or not the study reported gender as a significant risk factor. a) systolic blood pressure greater than 160 mm Hg as a risk factor for stroke in terms of whether or not the study reported SBP > 160 mm Hg as a significant risk factor. b) the presence of hypertension (including a history of hypertension) as a risk factor for stroke in terms of whether or not the study reported hypertension as a significant risk factor.

a)

Study	N	P-value
Hart RG, 1999[11]	2,012	<0.001
Hart RG, 2000[13]	460	NS*
Hart RG, 2000[13]	460	<0.001**
van Latum JC, 1995[16]	375	NS

*In patients with intermittent AF; **In patients with sustained AF. N = sample size; NS = not significant (p>0.05).

b)

Study	N	P-value
Laupacis A, 1994[10]	1,593	<0.05
Hart RG, 1999[11]	2,012	<0.001
SPAF III Writing Committee, 1998[12]	892	0.001
Aronow WS, 1998[24]	312	NS
Hart RG, 2000[13]	460	0.008
Moulton AW, 1991[22]	265	<0.05
Aronow WS, 1989[23]	110	<0.01
SPAF Study, 1995[28]	854	0.004
Seidl K, 1998[27]	191	<0.05
Petersen P, 1990[17]	336	NS
SPAF Investigators., 1992[18]	568	0.02
Stollberger C, 2004[15]	409	NS
Cabin HS, 1990[20]	272	NS

N = sample size; NS = not significant (p>0.05).

Smoking status

One study (10) failed to find being a smoker to be a significant independent risk factor for stroke. The study did find a higher incidence of stroke in smokers than non-smokers (p<0.05).

Hypertension

Thirteen studies considered hypertension (controlled or uncontrolled) as a risk factor for stroke in a variety of populations, including those with intermittent AF and those with atrial flutter (Table 3). Nine studies (10–13, 18, 22, 23, 27, 28) found hypertension to be a significant independent risk factor. The remaining

Table 4: Summary of results for the presence of structural heart disease (SHD) as a risk factor for stroke in terms of whether or not the study reported SHD as a significant risk factor.

Study	N	SHD definition	P-value
SPAF III Writing Committee, 1998[12]	892	Ischaemic heart disease	NS
Cabin HS, 1990[20]	272	Structural heart disease	0.037
Laupacis A, 1994[10]	1,593	Angina	NS
SPAF Investigators, 1992[18]	568	CHF	0.01
SPAF Investigators, 1998[12]	892	CHF	NS
Laupacis A, 1994[10]	1,593	CHF	NS
Stollberger C, 2004[15]	409	NYHA > II	NS
SPAF Study, 1995[28]	854	LV dysfunction	0.02
Aronow WS, 1998[24]	312	LV dysfunction	0.003
Ezekowitz et al., 1998[25]	1,066	LV dysfunction	<0.001
Pearce, 1992[26]	568	LV dysfunction	0.003
Aronow WS, 1989[23]	110	LV hypertrophy	<0.01
Aronow WS, 1998[24]	312	LV hypertrophy	0.0001
Aronow WS, 1989[23]	110	Aortic stenosis	NS
Aronow WS, 1989[23]	110	Mitral annular calcification	NS
Ezekowitz et al., 1998[25]	1,066	Mitral valve prolapse	NS
Ezekowitz et al., 1998[25]	1,066	Mitral valve regurgitation	NS

N = sample size; NS = not significant (p>0.05); CHF = congestive heart failure; NYHA = New York Heart Association heart failure stage; LV = left ventricular.

Table 5: Summary of results for prior stroke or transient ischaemic attack (TIA) as a risk factor for stroke in terms of the risk ratio (RR), odds ratio (OR) or hazard ratio (HR). N = sample size.

Study	N	Risk / odds / hazard ratio	P-value
Aronow WS, 1998[24]	312	OR 1.6	0.009
Hart RG, 1999[11]	2,012	RR 2.9	<0.001
Hart RG, 2000[13]	460	RR 4.1	0.01
Hart RG, 2000[13]	460	RR 2.7	<0.001
Laupacis A, 1994[10]	1,593	RR 2.5	<0.05
SPAF Investigators., 1992[18]	568	RR 2.1	0.04
Stollberger C, 2004[15]	409	OR 2.14	0.045
van Latum JC, 1995[16]	375	HR 1.6	<0.05
Wang TJ, 2003[14]	705	HR 1.88	<0.05

four studies (15, 17, 20, 24) did not find hypertension to be a significant independent risk factor. Three studies (11, 13, 16) found systolic blood pressure greater than 160 mm Hg to be a significant independent risk factor for stroke in general AF populations, while one study (13) failed to find it to be a significant independent risk factor specifically in patients with intermittent AF.

Structural heart disease

One study (20) found the presence of structural heart disease to be a significant independent risk factor for stroke (Table 4). One study (12) did not find the presence of ischaemic heart disease to be a significant independent risk factor for stroke. A similar result was found in the case of angina in another study (10).

Three studies (10, 12, 18) considered a history and/or the presence of an episode of congestive heart failure (CHF) as possible stroke risk factors. Two (10, 18) found CHF to be a significant risk factor for stroke. The remaining study (15) did not find a NYHA class greater than II to be a significant independent risk factor for stroke. Four studies considered a history of myocardial infarction (MI) as a risk factor for stroke. Three studies (10, 17, 23) found MI to be a significant independent risk factor. The remaining study (24), based in an elderly population, did not find MI to be a significant independent risk factor.

Four studies (24–26, 28) considered left-ventricular dysfunction (LVD), defined variously in terms of recent congestive heart failure, left-ventricular fractional shortening less than 25% or an ejection fraction less than 50%. All four studies found LVD to be a significant independent risk factor for stroke, although three of the studies (25, 26, 28) contained overlapping clinical trial populations.

Two studies (24, 28) found left-ventricular hypertrophy, defined as left-ventricular mass greater than 110 g/m^2 in women and 134 g/m^2 in men, to be a significant independent risk factor for stroke.

One study (23) did not find aortic stenosis or mitral annular calcification to be an independent predictor of stroke or thromboembolism. A meta-analysis using the data from three clinical trials (25) failed to find either mitral valve prolapse or regurgitation (of any degree) to be independent predictors of stroke or thromboembolism.

History of stroke, TIA or systemic embolism

Seven studies (10, 11, 13–15, 18, 24) found a history of stroke or TIA to be a significant independent risk factor for secondary stroke (Table 5). Another study (16) based in a population with a prior stroke or TIA found that a previous non-cerebrovascular thromboembolism to be a significant independent risk factor for secondary stroke.

Diabetes mellitus

Two studies (10, 14) found the presence of diabetes to be a significant independent risk factor for stroke in a general AF population (Table 6). Another study (24) based on an elderly population did not find it to be an independent risk factor. Two studies (12, 17) based on AF populations without a previous stroke (17) or without any risk factor, including previous stroke and presence of CHF or left-ventricular dysfunction (12) did not find diabetes to be a significant independent risk factor for stroke. One study (27) based on a population with atrial flutter did not find diabetes to be a significant independent risk factor for stroke.

AF subtype and duration

Two studies (15, 20), one with a follow-up of 3,442 patient years (15), the other with a follow-up of 748 patient years (20) did not find AF subtype (paroxysmal or non-paroxysmal) to be a signifi-

cant independent risk factor for stroke. Another study (16) with a follow-up of 594 patient-years and based in a high-risk population with a previous stroke or TIA, found that an AF duration greater than one year to be a significant independent risk factor for secondary stroke.

Obesity

One study (24) with a follow-up of 936 patient-years did not find obesity to be a significant independent risk factor for stroke.

Left atrial structure and function

One observational study (23), found left atrial dilatation to be a significant independent predictor of stroke. In another study based in a clinical trial population (26), increasing left atrial diameter per body surface area was found to be a significant independent predictor of stroke.

Stroke risk stratification models

For the systematic review of RSMs, the same list of 2,817 abstracts identified for the systematic review of stroke risk factors were reviewed for relevance. Based on the information contained in the abstract 2,752 studies were excluded and 65 reviewed based on the complete study report. Fifty-four of these studies were subsequently rejected for not meeting the study inclusion criteria and 11 were critically appraised. Three studies (10, 12, 16) were excluded following critical appraisal. One study (10) was excluded because the results for all age groups combined were not reported, one (12) was excluded because the outcome event was not reported for each risk category, and one (16) was excluded because confidence intervals were not reported. The summary study characteristics of the eight studies included in the systematic review of RSMs are shown in Table 7a.

Table 6: Summary of results for diabetes mellitus as a risk factor for stroke in terms of whether or not the study reported diabetes as a significant risk factor.

Study	N	P-value
Aronow WS, 1998[24]	312	NS
Laupacis A, 1994[10]	1,593	<0.05
Petersen P, 1990[17]	336	NS
Seidl K, 1998[27]	191	NS
SPAF Investigators, 1998[12]	892	NS
Wang TJ, 2003[14]	705	<0.05

N = sample size; NS = not significant (p>0.05).

Table 7: Published risk stratification models. a) Reviewed models. b) Stroke risk factors included in each RSM. c) Summary of results of model evaluation studies in terms of reported C statistics.

a)

RSM (Year)	Ref	Derivation	Stratification	Derivation populations/ organisations
ACCP 1 (1998)	Laupacis A, 1998[29]	Consensus	3 Categories	ACCP (1998)†
ACCP 2 (2004)	Singer DE, 2004[31]	Consensus	3 Categories	ACCP (2004)
AFI 1 (1994)	Laupacis A, 1994[10]	Evidence	2 Categories**	AFASAK, BATAAF, CAFA, SPAF, SPINAF
AFI 2 (1999)	Lip GYH, 1996[32]	Consensus	3 Categories	None*
AFI 3 (2003)	van Walraven C, 2003[33]	Evidence	2 Categories	AFASAK, SPAF I – III, PATAF
AHA/ACC/ESC (2001)	Fuster V, 2001[30]	Consensus	2 Categories	AHA/ACC/ESC (2001)
CHADS2 (2001)	Gage BF, 2001[34]	Consensus	Score 0 to 6	None*
EAFT (1995)	van Latum JC, 1995[16]	Evidence	3 Categories	EAFT
Framingham (2003)	Wang TJ, 2003[14]	Evidence	Score 0 to 31	Framingham Heart Study
SPAF I (1992)	SPAF Investigators, 1992[18]	Evidence	3 Categories	SPAF I
SPAF 2 (1995)	SPAF Investigators, 1995[28]	Evidence	2 Categories	SPAF I, SPAF II
SPAF 3 (1998)	SPAF III Writing Committee, 1998[12]	Evidence	3 Categories	SPAF III
SPAF 4 (1999)	Hart RG, 2000[13]	Evidence	3 Categories	SPAF III
SPAF 5 (1999)	Hart RG, 1999[11]	Evidence	3 Categories	SPAF I, SPAF II, SPAF III

[1,2,3, etc… refers to published versions of the particular RSM.] *Risk factors were identified from other stratification schemes; **each category applied to three different age ranges, although in AFI 2 and AFI 3 models, age was incorporated as a risk factor.
†Although the recommendations of each ACCP guideline supersede the previous version, the 1998 version contained an RSM that was externally validated, and is referenced only for this reason.

b)

RSM	AF duration	Age	DM	Female	Htn	SHD	Stroke/TE	Thyrotox
ACCP 1 (1998)[29]	No	Yes	Yes	No	Yes	Yes	No	Yes
ACCP 2 (2004)[31]	No	Yes	Yes	No	Yes	Yes	Yes	No
AFI 1 (1994)[10]	No	No	Yes	No	Yes	No	Yes	No
AFI 2 (1999)[32]	No	Yes	Yes	No	Yes	No	Yes	No
AFI 3 (2003)[33]	No	No	Yes	No	Yes	Yes	Yes	No
AHA/ACC/ESC (2001)[30]	No	Yes	Yes	No	Yes	Yes	No	Yes
CHADS2 (2001)[34]	No	Yes	No	No	Yes	Yes	Yes	No
EAFT (1995)[16]	Yes	Yes	No	No	Yes	Yes	Yes	No
Framingham (2003)[14]	No	Yes	Yes	Yes	Yes	No	Yes	No
SPAF 1 (1992)[18]	No	No	No	No	Yes	Yes	Yes	No
SPAF 2 (1995)[28]	No	Yes	No	Yes	Yes	Yes	Yes	No
SPAF 3 (1998)[12]	No	Yes	No	Yes	Yes	Yes	Yes	No
SPAF 4 (1999)[13]	No	Yes	Yes	Yes	Yes	No	Yes	No
SPAF 5 (1999)[11]	No	Yes	Yes	Yes	Yes	No	Yes	No

[1,2,3, etc… refers to published versions of the particular RSM] DM = diabetes mellitus; Htn = hypertension; SHD = structural heart disease (including myocardial infarction and angina); TE = thromboembolism; Thyrotox = thyrotoxicosis.

c)

RSM	Gage BF, 2001[34]	Gage BF, 2004[35]
ACCP 1 (1998)[29]	NR	0.58
AFI 1 (1994)[10]	0.68	0.63
CHADS2 (2001)[34]	0.82	0.70
Framingham (2003)[14]	NR	0.69
SPAF 3 (1998)[12]	NR	0.64
SPAF 5 (1999)[11]	0.74	NR

NR = not reported. [1,2,3, etc… refers to published versions of the particular RSM]. The c-statistic (concordance statistic) is the proportion of possible combinations of cases and non-cases in the sample for which the logistic model assigns a higher probability of an event occurring to the case. The c-statistic is analogous to the area under the receiver operating characteristic (ROC) curve and measures the discriminating ability of the model.

Table 7: Published risk stratification models (a). b) Stroke risk factors included in each RSM. c) Summary of results of model evaluation studies in terms of reported C statistics.

Each of the RSMs were evaluated in terms of their inclusion of stroke risk factors identified in the systematic review of stroke risk factors for which there was evidence supporting their significance as a risk factor for stroke in AF (Table 7b).

Each RSM included only risk factors that had been identified as statistically significant by at least one study included in the systematic review of stroke risk factors, with the exception of two (29, 30). Both of these RSMs were developed on the basis of consensus by professional organisations (the American College of Chest Physicians [29] and the American Heart Association and European Society of Cardiology [30]) and included thyrotoxicosis as a risk factor (whether alone or in combination with other risk factors) for stroke. All RSMs included either hypertension as a stroke risk factor, defined either as a history of hypertension or uncontrolled (>160 mm Hg systolic) blood pressure. Not all RSMs included a history of stroke or thromboembolism, despite it being identified as a stroke risk factor by all of the studies in the systematic review of stroke risk factors above. This exclusion may have been due to some guidelines being targeted at primary stroke prevention.

The systematic search of papers that evaluated stroke risk models found nine studies (10, 11, 18, 28, 33–37). One study (10) was subsequently excluded because it substratified risk by age group. The remaining eight studies included evaluations of RSMs that were performed in AF populations other than that used to formulate the model (external evaluations), as well as studies that evaluated the performance of the stroke risk model in the same population used to derive it (internal evaluations). A total of 16 model evaluations were performed across 10 models.

Only one stroke risk model comprising three risk strata (SPAF 5 [11]) achieved separation of each risk group at the 95% CI. Two stroke risk models comprising two risk strata achieved separation of each risk group at the 95% confidence level (SPAF 2 [28], AFI 3 [33]). The results are summarised in Figure 1, which represents the 95% CIs for the observed stroke incidence of each risk category for each RSM evaluation. Because of the

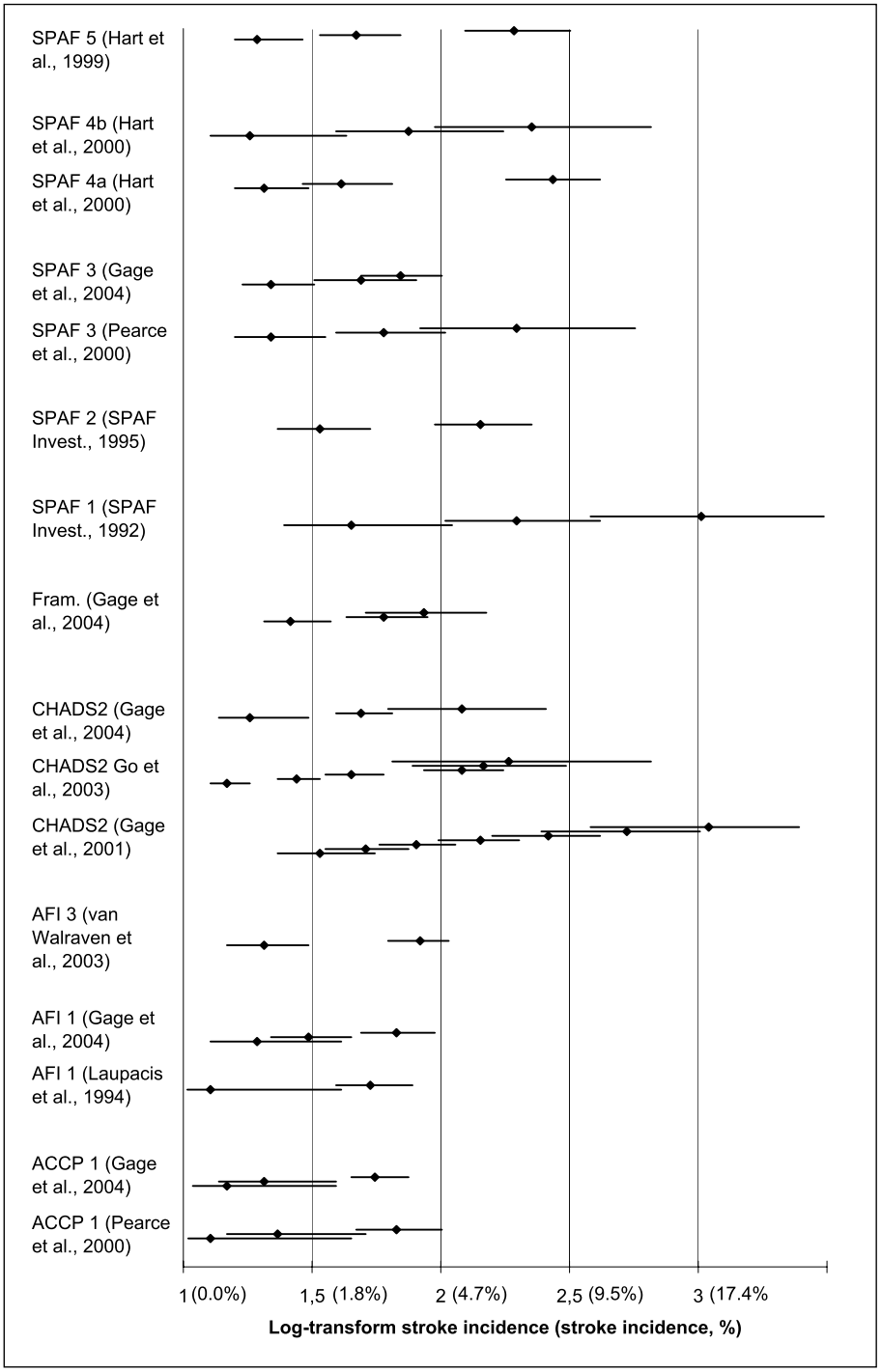

Figure 1: Forest plot of model evaluation results expressed as point estimates of observed stroke risk (percent stroke incidence per year) and 95% confidence intervals for each risk strata defined by the stroke risk model. For study acronyms, see text [1,2,3, etc… refers to published versions of the particular RSM]. Each line denotes the 95% confidence intervals in observed stroke incidence of a risk strata defined by a studied stroke risk model. The strata of each model are grouped together by model with the lowest risk at the bottom of the group. The points in each line denote the point estimate of observed stroke incidence. The degree of separation or overlap of the lines in each risk model may be considered to measure the degree of accuracy with which the model is able to distinguish between different levels of stroke risk within the studied population. Note that because of the wide range of observed stroke risks between different evaluation populations and risk strata, the stroke incidence is expressed on a log scale where a stroke risk of 0% corresponds to a value of 1. The actual stroke incidence corresponding to each point on the log scale is provided in parentheses.

wide range of observed stroke incidence, a logarithmic scale was used on the x-axis.

In terms of reported values of the C statistic for each RSM evaluation, two studies were found (34, 35). One study (34) reported the C statistic for an evaluation of three RSMs using the same sample population, and found the CHADS2 scheme to have the highest value of the C statistic. A similar result was found in the other study (35) which compared the value of the C statistic for the same population between five different RSMs. The results are summarised in Table 7c.

Cost effectiveness analyses

Anticoagulation versus no anticoagulation

In general patients with AF, anticoagulation treatment is relatively cost effective compared with no anticoagulation. Four studies (38–41) reported on cost effectiveness of warfarin compared with no warfarin in a general AF population. The only UK study (41) reported an incremental cost-effectiveness rate (ICER) ranging between £1,751 and £13,221 per life-year gained free from stroke. Another study based in the USA reported an ICER of US$1,907 (38). Another study (40) based in

Sweden estimated that the cost per stroke prevented stratified according to risk of bleeding to be SKR171,000 per stroke prevented if the risk of bleeding is 0.3%, to SKR417,000 if the risk of bleeding is 2%. The other study (39) estimated a reduction in healthcare costs of US$1,514 per year by anticoagulation use in AF patients.

Four studies (38, 42–44) compared anticoagulation with no anticoagulation in patients with a low risk of stroke. In this subgroup of patients anticoagulation was found not to be cost effective, with higher costs and loss in quality of life compared with no anticoagulation. In patients with medium to high risk for stroke, anticoagulation with warfarin was found to be cost effective and dominant (38, 42), with estimated ICERs ranging between US$1,434/QALY (43) and £6,000/QALY (44). One study (44) also found that the ICER decreased as blood pressure increased. In patients at high risk of stroke (more than two risk factors of stroke) four studies (38, 42–44) found that anticoagulation had lower costs and improved quality adjusted survival. In contrast, for low risk patients the opposite result was reported.

Anticoagulation versus antiplatelet therapy

Two studies (38, 39) compared anticoagulation treatment with aspirin in general patients with AF. One study (38) had an ICER of US$4484/ QALY while another study (39) found that warfarin treatment resulted in cost savings. Thus, in general patients with AF, warfarin was found to be cost effective compared with aspirin.

In low-risk patients, one study (42) estimated small improvements in QALYs which wererealised at substantial costs compared with aspirin (US$370,000/QALY for 65-year-olds and US$110,000/QALY for 75-year-olds). In patients with AF who have a medium to high risk of stroke, the study calculated an ICER of US$8,000/QALY for anticoagulation with warfarin. The cost-effectiveness advantage was found to decrease as the risk of bleeding increased. In elderly patients with a moderate risk of stroke, warfarin was cost effective compared with aspirin with an estimated ICER of US$500/QALY.

Discussion

Many of the studies used highly selected populations that would affect the relative risk of the factors considered. The main data appraised came from cohort studies, epidemiological studies and clinical trials. Many of the clinical trials randomised only a small proportion of those initially screened, and excluded patients with valvular heart disease, thyroid disease or intercurrent illnesses such as chest infections. Few had addressed the cumulative nature of risk factors where a combination of such factors (e.g. hypertension plus diabetes) would confer a greater risk than either alone. Three stroke risk stratification models were identified that were able to discriminate between different categories of stroke risk to at least 95% accuracy.

Based on the evidence, the following were identified as good risk factors for predicting stroke risk in AF: previous stroke or TIA; being elderly (aged over 75); structural heart disease; hypertension; and previous MI. The evidence for diabetes mellitus as an independent predictor of stroke in AF was not considered convincing, but overall was regarded as an important indicator for increased risk in the general AF population. While MI was identified as an independent stroke risk factor in some studies, underlying left ventricular dysfunction may confound this result. Echocardiographically demonstrated moderate-severe left ventricular dysfunction is a known risk factor for stroke, but heart failure cannot always be diagnosed on clinical grounds alone.

Other risk factors such as peripheral artery disease were debated, but limited evidence was available, especially since peripheral (and carotid) artery disease was not systematically assessed for, in the initial clinical trials that included non-warfarin treatment arms; these data have been used to inform the development of current risk stratification schema. However, coronary and peripheral artery diseases were regarded as part of the clinical spectrum of atherothrombotic vascular disease that contributed to stroke risk. For example, complex aortic plaque on TOE was an independent stroke risk factor (45) and ischaemic stroke in AF could be associated with carotid artery disease (46).

In most cases, risk stratification for stroke or thromboembolism and the decision to administer appropriate thromboprophylaxis can be made on purely clinical (non-echocardiographic) characteristics. However, the stroke risk may be unclear in some patients, in which case echocardiography may be useful in refining the risk. In particular, TOE may be used to identify the presence of left atrial dilatation (23, 26) and TTE may be used to identify left ventricular dysfunction or hypertrophy (23-26, 28) that may not be associated with overt heart failure (26).

Finally, the health economic analysis suggested that the studies comparing warfarin with no anticoagulation and warfarin with aspirin were of good quality and summarised the evidence as follows: i) In patients with AF, anticoagulation treatment is cost effective compared with no anticoagulation; ii) In patients at high risk of stroke, anticoagulation is cost effective, but not for those with a low risk of stroke; iii) Aspirin is cost effective in low-risk patients compared with warfarin, but not in higher risk patients.

Formulation of the NICE stroke risk stratification algorithm

During formulation of the NICE stroke risk stratification algorithm, the benefits and drawbacks of each stroke RSM shown in Table 1 were discussed, with emphasis on a balance between evidence, clinical applicability and practicality, as well as refinement for a UK population. In addition, it was accepted that patients' preferences should be considered as some patients will still decline anticoagulation treatment for a variety of reasons. These include: the inconvenience of dosing adjustments and regular blood tests to monitor INR levels; dietary restrictions; the risk of minor and major bleeding; and under-appreciation or lack of knowledge regarding the risk of stroke, or poor adherence to the treatment regimen. It was noted that none of the published algorithms had been derived or validated in a UK population but one had subsequently been modified for this purpose (32).

Various issues were discussed regarding the applicability of the published algorithms to the UK setting: i) With the exception of one model (14), non-warfarin trial participants had often been used as validation populations; ii) One was based on a complex mathematical model (14); iii) Some only used a two-tier model (low and moderate–high risk) to stratify patients (10, 28, 30, 33);

iv) One was based on a point scoring system (34), and was not inclusive of echocardiographic data; v) One did not necessarily identify a patient with a previous stroke or TIA alone as 'high risk' given that a score of 2 was 'moderate risk' (34); and vi) One model was only applicable for secondary prevention (16).

A revised RSM for the NICE guideline was adopted, based on the only model that had been optimised for use in a UK setting (32). This was based on a modification of the AF investigators' algorithm (10), but had been expanded into a three-tier model following consultation with primary and secondary care clinicians and was implemented (31/08/1997) and subsequently validated as a regional audit project in primary care by a large UK health authority. This algorithm has since been validated in a prospective cohort, where it performed similar to the popular CHADS2 scheme in predicting stroke and vascular events (47).

Bleeding risk

We reemphasise that this systematic review focuses on stroke risk factors and a review of the published stroke risk stratification schema. However, the use of anticoagulation has to be balanced against the increased risk of bleeding that in some patients may outweigh the benefits in reducing the risk of stroke (48). As part of the NICE guideline, the systematic search and appraisal of the published literature the following patient characteristics were identified as having supporting evidence for being risk factors for anticoagulation-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet drugs (48). The presence of diabetes mellitus, controlled hypertension and gender were not identified as significant risk factors.

Of note, some of the risk factors for anticoagulation-related bleeding are also factors indicating the use of anticoagulants in AF patients, and represents a need for further research in the area to enable physicians to balance the risks and benefits of anticoagulation in AF patients (48). This is consistent with recent registry data linking increasing stroke risk (e.g. by CHADS2 score) with increasing bleeding risk amongst elderly (49). In contrast, a recent clinical trial of elderly (age ≥75) subjects with AF in a primary care setting found that major bleeding rates were no different between warfarin and aspirin 75 mg daily, but a clear benefit for warfarin for stroke reduction was seen (50).

Limitations

With the recognition of AF as a major risk factor for stroke and the introduction of stroke risk stratification models and the widespread use of anticoagulation, significant reductions in stroke incidence have been achieved (51). Since this systematic review, an updated stroke risk stratification scheme has been published in updated joint American-European guidelines (7) – which is broadly based on CHADS2 – but has not been validated in a prospective cohort. Also, this systematic review does not aim to addresses the issue of rate or rhythm control, in relation to stroke risk. In addition, since the systematic review 'cut-off' date, other new data would have emerged for various risk factors, for example, linking AF to stroke in the setting of MI (52), as well as increasing recognition that asymptomatic AF may be an equally important contributor to stroke (53). Finally, we have not performed any metaanalysis, given the diverse nature of evidence (e.g. trial cohorts, observation studies, etc.) reviewed as part of the systematic reviews.

Conclusion

With the evidence now available for stroke risk factors in AF and a wide array of alternative stroke risk stratification models, a review of these models in terms of the evidence on which they are devised and their performance in representative AF populations is important. The appropriate administration of thromboprophylaxis in AF patients would need to balance the risks and benefits of antithrombotic therapy with its cost-effectiveness. Clearly, assessment of bleeding risk is also needed, given that risk factors for bleeding can be fairly similar to stroke risk factors.

Conflicts of interest

GL has received funding for research, educational symposia, consultancy and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. He was Clinical Adviser to the Guideline Development Group which wrote the United Kingdom National Institute for Health and Clinical Excellence (NICE) Guidelines on atrial fibrillation management (www.nice.org.uk). GL is also on the writing committee for the American College of Chest Physicians Guidelines on Antithrombotic Therapy.

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