Stroke and Thromboembolism in Atrial Fibrillation – Systematic Review of Stroke Risk Factors and Risk Stratification Schema –

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We performed a systematic review of the available evidence on the relationship between the individual clinical, echocardiographic and laboratory characteristics of patients with atrial fibrillation (AF) and the risk of stroke. A systematic review was also performed of all published stroke risk stratification models, as well as the accuracy of their discriminative ability between risk strata. Third, we reviewed the literature on cost-effectiveness analyses with oral anticoagulation in AF. From the systematic review on stroke risk factors, a prior stroke or transient ischemic attack (15/16 studies positive, risk ratio [RR] 2.86), hypertension (11/20 studies positive, RR 2.27), aging (9/13 studies positive, RR 1.46 per decade increase), structural heart disease (9/13 studies positive, RR 2.0) and diabetes (9/14 studies positive, RR 1.62) were found to be good independent predictors of stroke. Supportive evidence was found for sex (8/22 studies positive, RR 1.67), vascular disease (6/17 studies positive, RR 2.61) and heart failure (7/18 studies positive, RR 1.85). The various risk stratification schemes classified variable proportions as low, moderate and high risk, but the CHA₂DS₂-VASc score classified the smallest proportion of patients as 'low risk'. Anticoagulation with vitamin K antagonists and dabigatran is cost-effective in patients at high risk of stroke, but not in patients without any other stroke risk factor beside AF. Continued efforts are warranted to improve the antithrombotic management of AF patients to identify, and challenge, risk factors and refine risk stratification models in order to realize an individualized tailored, risk factor-based approach. (*Circ J* 2012; **76**: 2289–2304)

Key Words: Atrial fibrillation; Risk factors; Stroke prevention

Atrial fibrillation (AF) is the most common sustained arrhythmia¹ and confers an independent risk of stroke and death.² The individual AF patient's risk of stroke depends on the presence of other demographic, clinical, biochemical and echocardiographic risk factors.^{3,4} Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) reduces the incidence of stroke by 64% and mortality by 26% compared to control or placebo, and is superior compared to the protection offered by antiplatelet agents.⁵ Recently, three novel OACs, 1 oral direct thrombin inhibitor (dabigatran) and 2 oral factor Xa inhibitors (rivaroxaban, apixaban), have been proven to match or even surpass the already impressive stroke risk reduction of VKAs.^{6–8}

Transforming the data on stroke risk factors in AF patients into a user-friendly format that would be suitable for everyday clinical practice has been the rationale behind the development of the many risk stratification models (RSMs). RSMs initially aimed to classify patients into clinically relevant stroke

risk categories (high-, intermediate- and low-risk) that could subsequently facilitate the choice of the most appropriate antithrombotic treatment. However, in clinical practice this translated into identifying the 'high-risk' AF patients who could be targeted for the 'inconvenient' VKAs, whereas all other AF patients could be treated with the less effective therapy, aspirin (ie, low- and intermediate-risk patients, or those who refuse VKAs) or no therapy.^{9–11}

Over the past few years, a growing body of evidence has emerged to demonstrate that OAC, including VKAs, is beneficial even in patients with a 'moderate' stroke risk, including those with 1 stroke risk factor.^{12,13} Improvements in warfarin control, with a high percentage of time in therapeutic range (TTR), have contributed to lower bleeding rates (as well as low stroke rates).¹⁴

Thus, there has been a paradigm shift towards identification of 'truly low risk' individuals with AF who do not need any antithrombotic therapy, and those with ≥ 1 stroke risk factors

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MeSH terms for database searches:

("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]). The total number of hits (references) was 10,100.

Other searches pulled up similar references, for example:

((("patients"[MeSH Terms] OR "patients"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields])) AND (("risk"[MeSH Terms] OR "risk"[All Fields] OR "risk of"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])). Total hits (references) = 3293.

((("patients"[MeSH Terms] OR "patients"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields]) AND ("thromboembolism"[MeSH Terms] OR "thromboembolism"[All Fields])). Total hits (references) = 1251.

("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND (("risk"[MeSH Terms] OR "risk"[All Fields]) AND fibrillation[All Fields]).

Figure. PRISMA flow chart for identification and selection of studies reporting risk factors for stroke in patients with AF. AF, atrial fibrillation.

who can be offered effective stroke prevention, which essentially is OAC—whether with well-controlled warfarin or one of the new OACs. Thus, a stroke risk factor (and not a category)-based approach to thromboprophylaxis reflects current practice.^{15,16} In 2010, the European guidelines on the management of AF acknowledged the aforementioned evidence and subsequently adopted the revised, risk factor-based approach and emphasized that OAC is the recommended antithrombotic treatment for most patients with AF.¹⁷

The present analysis aimed to systematically review (a) the independent risk factors for stroke in AF patients, (b) the published RSMs and (c) the published cost-effectiveness data of (new) oral anticoagulant and antiplatelet agents for stroke prevention in AF patients.

Methods

Studies were selected for review based on the published abstract content (or full paper if no abstract was available) by 2 of the authors (R.P. and G.Y.H.L.). They evaluated all studies to see if they met the inclusion criteria to be considered for review. In case of disagreement, a third author was consulted. All decisions to exclude a study were unanimous. Details of the study selection criteria, outcome measures, systematic review methodology for the stroke risk factors/risk stratification methods and the cost-effectiveness review are provided in [Appendix S1](#).

Results

Stroke Risk Factors

The systematic literature search yielded a total of 3,154 records leading to review for inclusion based on the full article in 432, of which 405 were excluded (see PRISMA flowchart in [Figure](#)). The remaining 27 studies were critically appraised. This systematic review allowed several studies that were derived from similar clinical trial populations to be included, because none of them used exactly the same populations or risk models.

Age Nine studies used a cut-off value (predominantly age ≥ 75 years)^{15,18–25} and another 15 used increment per (half a) decade or age as a continuum for assessing its independent effect on stroke.^{4,19,24,26–35} Of the 24 studies, 17 reported age to be an independent risk of stroke,^{4,19–23,25,27–29,33,34,36} whereas the other 7 studies did not ([Table 1](#)).^{15,18,24,30–32,40}

A recent study by Hobbs et al studied the incremental risk per 5 years among 665 elderly patients (all aged ≥ 75 years) and did not reveal age to be an independent stroke risk factor.³⁰ However, the vast majority of the studies that looking at incremental risk per decade did find age to be an independent stroke risk factor.^{19,24,27–29,33,36} The evidence supporting age as an independent stroke risk factor also remains when it is considered for every decade of age increase,^{20–23} with only 2 negative results in a very small, older cohort¹⁸ and a medium-size cohort of 1,577 patients across Europe.¹⁵

Sex Of the 21 studies considering biological sex as a risk factor for stroke ([Table 2](#)),^{4,15,18,20,21,23–25,27–32,34–39} only 7 demonstrated that female sex was an independent risk factor for stroke.^{15,18,24,28,29,36,39} Another older study identified male sex as an independent risk factor for stroke in paroxysmal AF patients.²⁰

Stroke, Transient Aschemic Attack (TIA) or Systemic Embolism All but one¹⁵ of 16 studies considering a history of stroke or TIA and 1 study considering thromboembolism found it to be a significant independent risk factor for recurrent

stroke ([Table 3](#)).^{4,21,24,25,28–30,33–36,38,40}

Hypertension In total, 29 studies looked at whether hypertension was an independent stroke risk factor ([Table 4](#)).^{4,15,18,21–25,27–30,32–38,40–42} Only 9 studied a cut-off value of systolic blood pressure, mostly >160 mmHg, as being predictive of stroke.^{24,25,28,29,36,41} This proved to be the case in 5 studies.^{24,25,28,29,36,41} The other 20 studies considered hypertension in general, including unspecified use of antihypertensive drugs and a history of hypertension, as a risk factor for stroke.^{4,15,18,21–23,27–30,32–35,37,38,40,42}

In 13 of the 20 studies,^{4,21,22,27–29,35,37,40,42} including the largest of the 4 most recent studies in this regard, hypertension was an independent stroke risk factor, but this was not the case in the remaining 7 studies.^{15,18,23,30,32–34,38} Left ventricular hypertrophy, defined as a left ventricular mass >110 g/m² in women and >134 g/m² in men, was found to be a significant independent risk factor for stroke in 2 studies.^{38,41}

Chronic Kidney Disease Only 2 studies examined the relationship between chronic kidney disease and stroke, with 1 not demonstrating an independent association with the risk of stroke²¹ and the other study reported a correlation between decreasing glomerular filtration rate and stroke risk in conjunction with proteinuria as an independent stroke risk factor.⁴³

Structural Heart Disease Structural heart disease in general was recently found not to be predictive of stroke in a UK primary care study considering valvular and congenital cardiac disease,²³ whereas an older, single study did show the predictive ability of structural heart disease¹⁸ ([Table 5A](#)). Valvular heart disease in general, and mitral stenosis specifically, were found to be independent risk factors for stroke in 2 studies,^{25,38} but not in another,³⁰ and there was no relationship between annular calcification and stroke.³⁷

A meta-analysis of 3 clinical trials did not demonstrate that any degree of mitral valve prolapse or regurgitation was an independent predictor of stroke or thromboembolism.³⁴ A dilated left atrium³⁷ and increasing left atrial size per body surface area²⁶ were found to be independent stroke risk factors.

Vascular Disease Ischemic heart disease was not an independent stroke risk factor in 3 studies.^{21,27} A similar conclusion was drawn from 2 other studies in respect to angina.^{4,30} History of myocardial infarction was considered in 6 studies, with 2 identifying^{32,37} and 4 disputing^{4,21,30,38} its predictive capability regarding stroke risk.

More recently, peripheral artery disease alone has been examined as a stroke risk factor in 2 cohorts, both identifying it as an independent stroke risk factor.^{21,23} Two other studies investigated vascular disease as a combination of peripheral artery and/or coronary artery disease,^{15,44} with 1 reporting an independent relationship,⁴⁴ whereas the other¹⁵ did not identify this combination of vascular disease to be an independent stroke risk factor.

Congestive Heart Failure (CHF) A history or current episode of CHF was considered as a risk factor for stroke in 12 studies.^{4,15,21,25,27,28,30,33–35,40} Nine studies found that CHF was not an independent risk factor for stroke.^{4,15,28,30,33–35,40} The remaining 3, including the largest cohort of the most recent studies, reported that CHF independently predicted stroke.^{21,25,34}

Left ventricular dysfunction (LVD), being a mix of definitions of recent CHF or more quantitative measures (left ventricular fractional shortening $\leq 25\%$ or left ventricular ejection fraction ≤ 50 or 40%), was considered in 8 studies,^{15,26,28,33,35,38,41} with only half reporting that LVD was a significant independent stroke risk factor.^{26,34,38,41}

Other Risk Factors [Table 5B](#) provides an overview of the studies which considered other (predisposing factors of) car-

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

Study	n	Age risk factor	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Cabin HS, 1990 ¹⁸	272	Age >70 vs. ≤70 years	13%	7%	NA (bivariate analysis)	NS
Petersen P, 1990 ³²	336	Correlation with increasing age	NA	NA	LR Enter 0.01	NS
Moulton AW, 1991 ²²	265	Age >75 vs. ≤75 years	NA	NA	OR 1.72 (1.04–2.84)	<0.05
SPAF Investigators, 1992 ⁴⁰	568	Incremental risk per decade	NA	NA	RR 1.2 (0.9–1.6)	NS
Laupacis A, 1994 ⁴ (AF Invest. 1994)	1,593	Incremental risk per decade	NA	NA	RR 1.4	<0.05
Van Latum JC, 1995 ²⁴	375	≥60–69 vs. <60 years	NA	NA	HR 0.8 (0.3–1.9)	NS
		≥70–79 vs. <60 years	NA	NA	HR 0.9 (0.4–2.1)	NS
		≥80 vs. <60 years	NA	NA	HR 0.6 (0.2–1.6)	NS
Ezekowitz M, 1998 ³⁴ (using clinical factors alone)	1,066	Incremental risk per decade	NA	NA	RR 1.5 (1.1–1.9)	0.008
Ezekowitz M, 1998 ³⁴ (using clinical and echo-cardiographic features)	1,010	Incremental risk per decade	NA	NA	RR 1.5 (1.1–2.0)	0.006
Nakagami H, 1998 ³¹	290	Incremental risk per decade	NA	NA	OR 1.33 (1.04–1.71)	NS
SPAF III, 1998 ²⁷	892	Incremental risk per decade	NA	NA	RR 1.7 (1.1–2.6)	0.01
Stollberger C, 1998 ³⁵	409	Correlation with increasing age	NA	NA	RR 1.1 (1.0–1.11)	<0.001
Hart RG, 1999 ²⁸	2,012	Incremental risk per decade	NA	NA	RR 1.8	<0.001
Hart RG, 2000 ²⁹ (paroxysmal AF)	460	Incremental risk per decade	NA	NA	RR 2.1	<0.001
Hart RG, 2000 ²⁹ (persistent AF)	1,552	Incremental risk per decade	NA	NA	RR 1.7	<0.001
Inoue H, 2000 ²⁰	740	Age >65 years	NA	NA	RR 3.33 (1.92–5.81)	0.0001
Wang TJ, 2003 ³⁶	705	Incremental risk per decade	NA	NA	HR 1.32 (1.02–1.76) (for stroke)	<0.05
		Incremental risk per decade	NA	NA	HR 2.13 (1.86–2.44) (for stroke or death)	<0.05
Stollberger C, 2004 ³³	409	Correlation with increasing age	NA	NA	RR 1.05 (1.02–1.09)	0.0006
Frost L, 2007 ¹⁹	141,493	Age 70–74 vs. 40–44 years (for men)	NA	NA	HR 6.31 (4.78–8.33)	<0.05
Ruigómez A, 2009 ²³	831	Age >80 vs. 40–59 years	NA	NA	RR 5.8 (1.9–17.6)	<0.05
Lip GYH, 2010 ¹⁵	1,577	Age >75 vs. ≤75 years	3.6%	1.8%	OR 1.46 (0.63–3.65)	NS
Hobbs FD, 2011 ³⁰	665	Incremental risk per 5 years	NA	NA	HR 1.26 (0.93–1.72)	NS
Lin LY, 2011 ²¹	7,920	Age ≥75 vs. 20–64 years	NA	NA	OR 1.652 (1.313–2.080)	<0.001
Van Staa TP, 2011 ²⁵	79,844	Age 50–59 vs. 60–69 years	NA	NA	RR 0.44 (0.28–0.69)	<0.05
		Age <50 vs. 60–69 years	NA	NA	RR 0.14 (0.06–0.34)	<0.05
		Age ≥80 vs. 60–69 years	NA	NA	RR 2.22 (1.78–2.76)	<0.05
		Age 70–79 vs. 60–69 years	NA	NA	RR 1.42 (1.12–1.78)	<0.05

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; LR, likelihood ratio; n, sample size; NA, not available; NS, not significant ($P>0.05$); OR, odds ratio; RR, risk ratio.

Table 2. Summary of Results for Sex as a Risk Factor for Stroke in Terms of Whether or Not the Study Reported Sex as a Significant Risk Factor

Study	n	Sex comparison	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Aronow WS, 1989 ³⁷	110	F vs. M	NA	NA	OR 0.85	NS
Cabin HS, 1990 ¹⁸	272	F vs. M	14%	6%	NA (bivariate analysis) CRC 1.0	0.023 0.014
Petersen P, 1990 ³²	336	F vs. M	NA	NA	LR Enter 0.48	NS
Laupacis A, 1994 (AF Investig. 1994) ⁴	1,593	F vs. M	NA	NA	NA	NS
Van Latum JC, 1995 ²⁴	375	F vs. M	NA	NA	HR 1.5 (1.0–2.4)	NR
Ezekowitz M, 1998 ³⁴ (using clinical factors alone)	1,066	F vs. M	NA	NA	NA	NS
Aronow WS, 1998 ³⁸	312	M vs. F	NA	NA	RR 0.98 (0.67–1.43)	NS
Nakagami H, 1998 ³¹	290	F vs. M	NA	NA	OR 0.98 (0.55–1.72)	NS
SPAF III, 1998 ²⁷	892	F vs. M	NA	NA	NA	NS
Stollberger CM, 1998 ³⁵	409	F vs. M	NA	NA	NS	NS
Hart RG, 1999 ²⁸	2,012	F vs. M	NA	NA	RR 1.6	0.01
Hart RG, 2000 ²⁹ (paroxysmal AF)	460	F vs. M	NA	NA	NA	NS
Hart RG, 2000 ²⁹ (persistent AF)	1,552	F vs. M	NA	NA	RR 1.8	0.004
Inoue H, 2000 ²⁰	740	M vs. F	NA	NA	OR 2.00 (1.07–3.72)	0.0291
Wang TJ, 2003 ³⁶	705	F vs. M	NA	NA	1.92 (1.20–3.07)	<0.05
Fang M, 2005 ³⁹	13,559	F vs. M	3.5%	1.8%	RR 1.6 (1.3–1.9)	<0.05
Ruigomez A, 2009 ²³	831	M vs. F	NA	NA	RR 1.0 (0.6–1.7)	NS
Lip GYH, 2010 ¹⁵	1,084	F vs. M	3.6%	1.4%	OR 2.53 (1.08–5.92)	0.03
Hobbs FD, 2011 ³⁰	665	F vs. M	NA	NA	HR 0.99 (0.57–1.70)	NS
Lin LY, 2011 ²¹	7,920	F vs. M	NA	NA	OR 0.942 (0.787–1.127)	NS
Van Staa TP, 2011 ²⁵	79,844	M vs. F	NA	NA	RR 0.95 (0.84–1.06)	NS

CRC, Cox regression coefficient; F, female; M, male; NR, not reported. Other abbreviations as in Table 1.

Table 3. Summary of Results for Prior Stroke or TIA as a Risk Factor for Stroke in Terms of the RR, OR or HR

Study	n	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
SPAF I, 1992 ⁴⁰	568	NA	NA	RR 2.1 (1.0–4.2)	0.04
Laupacis A, 1994 ⁴ (AF Investig. 1994)	1,593	NA	NA	RR 2.5	<0.05
Van Latum JC, 1995 ²⁴	375	NA	NA	HR 1.6 (1.0–2.6)	<0.05
Ezekowitz M, 1998 ³⁴ (using clinical factors alone)	1,066	NA	NA	RR 3.4 (1.8–6.6)	<0.001
Ezekowitz M, 1998 ³⁴ (using clinical and echo-cardiographic features)	1,010	NA	NA	RR 3.5 (1.8–6.7)	<0.001
Aronow WS, 1998 ³⁸	312	NA	NA	RR 1.574 (1.12–2.21)	0.009
Stollberger C, 1998 ³⁵	409	NA	NA	RR 3.7 (1.5–7.5)	0.002
Hart RG, 1999 ²⁸	2,012	NA	NA	RR 2.9	<0.001
Hart RG, 2000 ²⁹ (paroxysmal AF)	460	NA	NA	RR 4.1	0.01
Hart RG, 2000 ²⁹ (persistent AF)	1,552	NA	NA	RR 2.7	<0.001
Wang TJ, 2003 ³⁶	705	NA	NA	HR 1.88 (1.09–3.26)	<0.05
Stollberger C, 2004 ³³	409	NA	NA	RR 2.14 (1.02–4.51)	0.0454
Hobbs FD, 2011 ³⁰	665	NA	NA	HR 2.59 (1.36–4.90)	0.003
Lin LY, 2011 ²¹	7,920	NA	NA	OR 2.752 (2.06–3.68)	<0.001
Lip GYH, 2010 ¹⁵	1,577	5.9%	2.0%	OR 2.22 (0.78–6.35)	NS
Van Staa TP, 2011 ²⁵	79,844	NA	NA	RR 2.86 (2.53–3.22)	<0.05

TIA, transient ischemic attack. Other abbreviations as in Tables 1,2.

diovascular disease as risk factors for stroke. Of these, 2 studies failed to find that being a smoker was an independent risk factor for stroke.^{4,23} Obesity was considered in 3 studies and only to be found predictive of stroke in one. One study considered alcohol abuse and hyperlipidaemia, but neither was found to be independent stroke risk factor.²³

Nine studies found diabetes mellitus to be an independent risk factor for stroke.^{4,21,25,28,30,34,36} Five other studies, 1 in a general population,¹⁵ 1 in patients with atrial flutter,⁴² 1 in an elderly cohort³⁸ and 2 in low-risk AF patients,^{27,32} failed to find that diabetes mellitus was an independent stroke risk factor.

Hormone replacement therapy was found to independently

Table 4. Summary of Results for Htn as a Risk Factor for Stroke in Terms of Whether or Not the Study Reported Htn as a Significant Risk Factor

Study	n	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
(A) SBP >160 mmHg as a risk factor for stroke in terms of whether or not the study reported SBP >160 mmHg as a significant risk factors					
SPAF study, 1995 ⁴¹	854	NA	NA	RR 2.2 (1.3–3.6)	0.004
Van Latum JC, 1995 ²⁴	375	NA	NA	HR 1.7 (1.0–2.9)	NR
Hart RG, 1999 ²⁸	2,012	NA	NA	RR 2.3	<0.001
Hart RG, 2000 ²⁹ (paroxysmal AF)	460	NA	NA	NA	NS
Hart RG, 2000 ²⁹ (persistent AF)	1,552	NA	NA	RR 2.8	<0.001
Wang TJ, 2003 ³⁶ (per 10 mmHg increase)	705	NA	NA	HR 1.06 (0.97–1.17) (for stroke)	NS
		NA	NA	HR 1.06 (1.02–1.11) (for stroke or death)	<0.05
van Staa TP, 2011 ²⁵ (140–159 vs. <120 mmHg)	79,844	NA	NA	RR 2.74 (1.21–6.19)	<0.05
van Staa TP, 2011 ²⁵ (160–179 vs. <120 mmHg)	79,844	NA	NA	RR 1.49 (0.55–4.00)	NS
van Staa TP, 2011 ²⁵ (≥180 vs. <120 mmHg)	79,844	NA	NA	RR 4.28 (1.25–14.64)	<0.05
(B) Presence of Htn (including a history of Htn) as a risk factor for stroke in terms of whether or not the study reported Htn as a significant risk factor					
Aronow WS, 1989 ³⁷	110	NA	NA	OR 12.51	<0.01
Cabin HS, 1990 ¹⁸	272	12%	8%	NA (bivariate analysis)	NS
Petersen P, 1990 ³²	336	NA	NA	LR Enter 0.8	NS
Moulton AW, 1991 ²²	265	NA	NA	OR 1.89 (1.15–3.10)	<0.05
SPAF Investigators, 1992 ⁴⁰	568	NA	NA	RR 2.2 (1.1–4.3)	0.02
Laupacis A, 1994 ⁴ (AF Investig. 1994)	1,593	NA	NA	RR 1.6	<0.05
Ezekowitz M, 1998 ²⁷ (using clinical factors alone)	1,066	NA	NA	RR 1.5 (0.9–2.5)	0.11
Ezekowitz M, 1998 ³⁴ (using clinical and echocardiographic features)	1,010	NA	NA	RR 1.5 (0.9–2.5)	0.13
Aronow WS, 1998 ³⁸	312	NA	NA	RR 1.254 (0.847–1.855)	NS
Seidl K, 1998 ⁴²	191	NA	NA	OR 6.5 (1.5–45)	<0.05
SPAF III, 1998 ²⁷	892	3.6% per year	1.1% per year	RR 3.3 (1.7–6.9)	0.001
Stollberger C, 1998 ³⁵	409	NA	NA	RR 3.6 (1.8–8.4)	0.001
Hart RG, 1999 ²⁸	2,012	NA	NA	RR 2.0	<0.001
Hart RG, 2000 ²⁹ (paroxysmal AF)	460	NA	NA	RR 3.4	0.003
Hart RG, 2000 ²⁹ (persistent AF)	1,552	NA	NA	RR 1.8	0.008
Stollberger C, 2004 ³³	409	NA	NA	NA	NS
Ruigomez A, 2009 ²³	831	NA	NA	RR 0.6 (0.3–1.1)	NS
Lip GYH, 2010 ¹⁵	1,084	2.6%	1.7%	OR 1.01 (0.38–2.66)	NS
Hobbs FD, 2011 ³⁰	665	NA	NA	HR 1.10 (0.62–1.95)	NS
Lin LY, 2011 ²¹	7,920	NA	NA	OR 2.656 (2.140–3.296)	<0.001

Htn, hypertension. Other abbreviations as in Tables 1,2.

predict the risk of stroke in AF patients in 1 study,²⁸ but not another.³⁹

One population-based prospective study investigating whether or not the blood coagulation markers, von Willebrand factor, soluble P-selectin and fibrinogen were independent predictors of stroke and cardiovascular mortality in AF patients failed to demonstrate an independent risk for stroke associated with any of these parameters.⁴⁵ Another study identified C-reactive protein as a predictor risk of stroke.²⁵

AF Type Paroxysmal vs. non-paroxysmal clinical type of AF was not found to independently predict stroke in any of the 3 studies that considered it.^{18,33,46} In only 1 study was a longer history of AF found to be an independent stroke risk factor.²⁴

Stroke Risk Stratification Models

The same 3,154 abstracts were used for the systematic review of RSMs. The abstract and full text information led to the exclusion of 3,135 studies and inclusion of 19 studies. A general overview of all included studies in the systematic review of RSMs is shown in [Table 6A](#).

First, the incorporation of independent risk factors of stroke derived from the systematic review of stroke risk factors into the RSMs was checked ([Table 6B](#)). The risk factors used in all RSMs were acknowledged to be independent risk factors of stroke by at least one of the studies from the systematic review, except for 2.^{47,48} These RSMs were both based on expert consensus. Although some definition of hypertension could be found in all RSMs, this was not the case for the strongest independent risk factor of stroke: prior stroke or thromboem-

Table 5. Summary of Results for (A) the Presence of SHD as a Risk Factor for Stroke in Terms of Whether or Not the Study Reported SHD as a Significant Risk Factor and (B) Other Cardiovascular Conditions and Risk Factors in Terms of Whether or Not the Study Reported the Respective Condition

(A)						
Study	n	SHD definition	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
SPAF III, 1998 ²⁷	892	Ischemic heart disease	NA	NA	NA	NS
Stollberger CM, 1998 ³⁵	409	Ischemic heart disease	NA	NA	NA	NS
Aronow WS, 1989 ³⁷	110	MI	NA	NA	OR 4.84	<0.01
Petersen P, 1990 ³²	336	MI	28%/2 y	11%/2 y	LR 4.33	0.0375
Laupacis A, 1994 ⁴ (AF Investig. 1994)	1,593	MI	NA	NA	RR 1.2	NS
Aronow WS, 1998 ³⁸	312	MI	NA	NA	RR 0.87 (0.60–1.26)	NS
Hobbs FDR, 2011 ³⁰	665	MI	NA	NA	HR 0.52 (0.18–1.50)	NS
Lin LY, 2011 ²¹	7,920	Coronary artery disease	NA	NA	OR 1.07 (0.83–1.36)	NS
Lin LY, 2011 ²¹	7,920	MI	NA	NA	OR 1.42 (0.91–2.23)	NS
Cabin HS, 1990 ¹⁸	272	Structural heart disease	14%	5%	NA	0.02
		Structural heart disease	NA	NA	CRC 0.9	0.037
Ruigomez A, 2009 ²³	831	Structural heart disease (other cardiac disease)	NA	NA	RR 0.8 (0.2–3.2)	NS
Laupacis A, 1994 ⁴ (AF Investig. 1994)	1,593	Angina	NA	NA	NA	NS
Hobbs FD, 2011 ³⁰	665	Angina	NA	NA	HR 1.12 (0.30–2.44)	NS
SPAF Investig., 1992 ²⁶	568	CHF	NA	NA	RR 2.0 (0.8–4.7)	NS
Laupacis A, 1994 ⁴ (AF Investigators 1994)	1,593	CHF	NA	NA	RR 1.4	NS
Ezekowitz M, 1998 ³⁴ (using clinical factors alone)	1,066	CHF	NA	NA	RR 1.7 (1.1–2.7)	0.03
Ezekowitz M, 1998 ³⁴ (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	CHF	NA	NA	RR 1.4 (0.8–2.3)	0.16
SPAF III, 1998 ²⁷	892	CHF	NA	NA	NA	NS
Hart RG, 1999 ²⁸	2,012	CHF	NA	NA	NA	NS
Lip GYH, 2010 ¹⁵	1,577	CHF	2.4%	2.3%	OR 0.72 (0.27–1.88)	NS
Hobbs FD, 2011 ³⁰	665	CHF	NA	NA	HR 0.78 (0.36–1.68)	NS
Lin LY, 2011 ²¹	7,920	CHF	NA	NA	OR 1.611 (1.299–1.999)	<0.001
Van Staa TP, 2011 ²⁵	79,844	CHF	NA	NA	RR 1.26 (1.11–1.42)	<0.05
SPAF Investig., 1992 ²⁶	568	LV dysfunction	NA	NA	RR 2.0 (1.0–4.0)	0.05
SPAF Study, 1995 ⁴¹	854	LV dysfunction	NA	NA	1.8 (1.2–3.0)	0.02
AFI Echo, 1998 ³⁴ (AF Investig. 1998) (Using clinical and echocardiographic features)	1,010	LV dysfunction (moderate to severe vs. none to mild)	NA	NA	RR 2.5 (1.5–4.4)	<0.001
Aronow WS, 1998 ³⁸	312	LV ejection fraction	NA	NA	RR 1.795 (1.214–2.653)	0.003
Stollberger CM, 1998 ³⁵	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 2004 ³³	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 1998 ³⁵	409	NYHA >II	NA	NA	NA	NS
Stollberger CM, 2004 ³³	409	NYHA >II (vs. no heart failure)	NA	NA	NA	NS
Hart RG, 1999 ²⁸	2,012	LV dysfunction	NA	NA	NA	NS
Lip GYH, 2010 ¹⁵	1,577	LV ejection fraction <40%	0.8%	2.1%	0.34 (0.04–2.73)	NS
Aronow WS, 1989 ³⁷	110	LV hypertrophy	NA	NA	OR 6.56	<0.01
Aronow WS, 1998 ³⁸	312	LV hypertrophy	NA	NA	RR 2.792 (1.784–4.370)	0.0001
AFI Echo, 1998 ³⁴ (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	Mitral valve prolapse	NA	NA	NA	NS
AFI Echo, 1998 (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	Mitral valve regurgitation	NA	NA	NA	NS
Aronow WS, 1998 ³⁸	312	Mitral stenosis	NA	NA	RR 1.98 (1.09–3.58)	0.025
Aronow WS, 1998 ³⁸	312	Mitral annular calcification	NA	NA	RR 1.210 (0.774–1.892)	NS
Nakagami, 1998 ³¹	290	Mitral valve regurgitation (≤mild vs. ≥moderate)	25%	9%	OR 0.45 (0.2–0.97)	<0.05

(Table 4 continued the next page.)

Study	n	SHD definition	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Hobbs FD, 2011 ³⁰	665	Valvular disease	NA	NA	HR 0.96 (0.58–3.13)	NS
Van Staa TP, 2011 ²⁵	79,844	Valvular disease	NA	NA	RR 1.65 (1.01–2.71)	<0.05
Aronow WS, 1989 ³⁷	110	Left atrial enlargement	NA	NA	OR 4.91	<0.05
SPAF Investigators, 1992 ⁴⁰	568	Left atrial enlargement (size 2.5 vs. 2.0 cm/m ²)	NA	NA	RR 1.6 (1.0–2.5)	0.04
(B)						
Study	n	(Predisposing) cardio-vascular condition	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Go AS, 2009 ⁸⁶	10,908	Proteinuria	NA	NA	HR 1.54 (1.29–1.85)	<0.05
Lin LY, 2011 ²¹	7,920	Chronic kidney disease	NA	NA	OR 1.066 (0.834–1.361)	NS
Ruigomez A, 2009 ²³	831	Peripheral vascular disease	NA	NA	RR 2.6 (1.3–5.1)	<0.05
Lip, 2010 ¹⁵	1,577	Vascular disease	3.6%	1.5%	OR 2.27 (0.94–5.46)	0.063
Lin LY, 2011 ²¹	7,920	Peripheral artery disease	NA	NA	OR 1.81 (1.19–2.77)	0.006
Rasmussen LH, 2011 ⁴⁴	57,053	Vascular disease	20.8%	8.0%	HR 1.91 (1.44–2.54) (Stroke or death)	<0.05
		Vascular disease	8.6%	4.6%	HR 0.80 (0.53–1.20) (Stroke)	NS
Ruigomez A, 2009 ²³	831	Alcohol abuse (10–19 vs. 0–1 units/week)	NA	NA	RR 0.7 (0.2–2.2)	NS
		Alcohol abuse (≥ 20 units/week vs. 0–1)	NA	NA	RR 0.3 (0.1–2.4)	NS
Aronow, 1998 ³⁸	312	BMI (obesity)	NA	NA	RR 1.093 (0.565–2.114)	NS
Ruigomez A, 2009 ²³	831	BMI (25–29.9 vs. 20–24.9 kg/m ²)	NA	NA	RR 1.0 (0.6–2.3)	NS
		BMI (≥ 30 vs. 20–24.9 kg/m ²)	NA	NA	RR 0.7 (0.3–1.9)	NS
Van Staa TP, 2011 ²⁵	79,844	BMI <20 vs. 20–25.9 kg/m ²	NA	NA	RR 1.31 (1.06–1.61)	<0.05
Laupacis A, 1994 ⁴ (AF Investigators)	1,593	Smoking status (smoker vs. non-smoker)	NA	NA	NA	NS
Ruigomez A, 2009 ²³	831	Smoking status (smoker vs. non-smoker)	NA	NA	RR 1.6 (0.7–3.7)	NS
		Smoking status (ex-smoker vs. non-smoker)	NA	NA	RR 0.9 (0.4–2.4)	NS
Ruigomez A, 2009 ²³	831	Hyperlipidemia	NA	NA	RR 1.2 (0.4–3.4)	NS
Petersen P, 1990 ³²	336	DM	NA	NA	LR Enter 0.16	NS
Laupacis A, 1994 ⁴ (AF Investig. 1994)	1,593	DM	NA	NA	RR 1.7	<0.05
Ezekowitz M, 1998 ³⁴ (using clinical factors alone)	1,066	DM	NA	NA	RR 1.7 (1.0–2.8)	0.05
Ezekowitz M, 1998 ³⁴ (using clinical and echocardiographic features)	1,010	DM	NA	NA	RR 1.7 (1.0–2.9)	0.05
Aronow WS, 1998 ³⁸	312	DM	NA	NA	RR 0.83 (0.56–1.22)	NS
Seidl K, 1998 ⁴²	191	DM	NA	NA	NA	NS
SPAF III, 1998 ²⁷	892	DM	NA	NA	NA	NS
Stollberger CM, 1998 ³⁵	490	DM	NA	NA	NA	NS
Hart RG, 1999 ²⁸	2,012	DM	NA	NA	RR 1.9 (for disabling/fatal stroke)	0.02
Wang TJ, 2003 ³⁶	705	DM	NA	NA	HR 1.80 (1.43–3.13) (for stroke)	<0.05
			NA	NA	HR 1.40 (1.07–1.83) (for stroke or death)	<0.05
Lip GYH, 2010 ¹⁵	1,577	DM	4.3%	1.9%	OR 1.79 (0.73–4.40)	NS
Hobbs FD, 2011 ³⁰	665	DM	NA	NA	HR 2.06 (1.07–3.98)	0.03
Lin LY, 2011 ²¹	7,920	DM	NA	NA	OR 1.341 (1.092–1.648)	0.005
Van Staa TP, 2011 ²⁵	79,844	DM	NA	NA	RR 1.33 (1.14–1.55)	<0.05

BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; NYHA, New York Heart Association heart failure stage; LV, left ventricular; MI, myocardial infarction; SHD, structural heart disease. Other abbreviations as in Tables 1,2.

Table 6. Published Risk Stratification Models

(A) Reviewed models									
RSM (year)	Ref.	Derivation	Stratification	Derivation population/organization					
ACCP (1998)	Laupacis A, 1998	Consensus	3 categories	ACCP (1998) [†]					
ACCP (2004)	Singer DE, 2004 ⁸⁷	Consensus	3 categories	ACCP (2004)					
ACCP (2008)	Singer DE, 2008	Consensus	3 categories	ACCP (2008)					
AFI (1994)	Laupacis A, 1994 ⁴	Consensus	2 categories**	AFASAK, BATAAF, CAFA, SPAF, SPINAF					
AFI (1996)	Lip GYH, 1996 ⁸⁸	Consensus	3 categories	None*					
AFI (2003)	vanWalraven C, 2003 ⁵¹	Evidence	2 categories	AHA/ACC/ESC (2001)					
AHA/ACC/ESC (2001)	Fuster V, 2001 ⁴⁷	Consensus	2 categories	AHA/ACC/ESC (2001)					
AHA/ACC/ESC (2006)	Fuster V, 2006 ⁸⁹	Consensus	3 categories	AHA/ACC/ESC (2006)					
CHADS ₂ (2001)	Gage BF, 2001 ⁴⁹	Consensus	Score 0–6	None*					
EAFT (1995)	Van Latum JC, 1995 ²⁴	Evidence	3 categories	EAFT					
Framingham (2003)	Wang TJ, 2003 ³⁶	Evidence	Score 0–31	Framingham Heart Study					
SPAF (1992)	SPAF Investigators, 1992 ⁴⁰	Evidence	3 categories	SPAF I					
SPAF (1995)	SPAF Investigators, 1995 ⁴¹	Evidence	2 categories	SPAF II, SPAF II					
SPAF (1998)	Ezekowitz, 1998 ²⁷	Evidence	3 categories	SPAF III					
SPAF (1999)	Hart RG, 2000 ²⁹	Evidence	3 categories	SPAF III					
SPAF (1999)	Hart RG, 1999 ²⁸	Evidence	3 categories	SPAF I, SPAF II, SPAF III					
Revised CHADS ₂ (2008)	Rietbrock S, 2008 ⁹⁰	Consensus	Score (max. 14)	GPRD					
NICE guidelines (2006)	Lip GYH, 2006 ⁹¹	Evidence	Algorithm based approach	SPAF III					
CHA ₂ DS ₂ -VASc (2010)	Lip GYH, 2010 ¹⁵	Evidence	Score 0–9	SPAF III, Euro Heart Survey					
(B) Stroke risk factors included in each RSM									
RSM (year)	AF duration	Age	DM	Female	Htn	Vasc	SHD	Stroke/TE	Thyrottox
ACCP (1998)	–	+	+	–	+	–	+	–	+
ACCP (2004) ⁸⁷	–	+	+	–	+	–	+	+	–
AFI (1994) ⁴	–	–	+	–	+	–	–	+	–
AFI (1999)	–	+	+	–	+	–	–	+	–
AFI (2003) ⁵¹	–	–	+	–	+	–	+	+	–
AHA/ACC/ESC (2001) ⁴⁷	–	+	+	–	+	–	+	–	+
CHADS ₂ (2001) ⁴⁹	–	+	+	–	+	–	+	+	–
EAFT (1995) ²⁴	+	+	–	–	+	–	+	+	–
Framingham (2003) ³⁶	–	+	+	+	+	–	–	–	–
SPAF (1992) ⁴⁰	–	–	–	–	+	–	+	+	–
SPAF (1995) ⁴¹	–	+	–	+	+	–	+	+	–
SPAF (1998) ²⁷	–	+	–	+	+	–	+	+	–
SPAF (1999) ²⁹	–	+	+	+	+	–	–	–	–
SPAF (1999) ²⁸	–	+	+	+	+	–	–	–	–
Rietbrock-CHADS ₂ (2008) ⁹⁰	–	+	+	+	+	–	–	+	–
CHA ₂ DS ₂ -VASc (2010) ¹⁵	–	+	+	+	+	+	+	+	–
(C) Summary of results of model evaluation studies in terms of reported C statistics regarding prediction of stroke									
RSM	Gage BF, 2001 ⁴⁹	Gage BF, 2004 ⁵²	Lip, GYH, 2010 ¹⁵	Olesen JB, 2011 ¹⁶	Hobbs FD, 2011 ³⁰				
ACCP (1998)	NR	0.58	NR	NR	NR				
ACCP (2008)	NA	NA	0.57	NR	0.60				
AFI (1994) ⁴	0.68	0.63	0.57	NR	NR				
CHADS ₂ (2001) ⁴⁹	0.82	0.70	0.56	0.72	0.55				
Framingham (2003) ³⁶	NR	0.69	0.64	NR	0.59				
SPAF (1998) ²⁷	NR	0.64	NR	NR	NR				
SPAF (1999) ²⁹	0.74	NR	0.55	NR	NR				
AHA/ACC/ESC (2006) ⁸⁹	NA	NA	0.57	NR	0.61				
Rietbrock-CHADS ₂ (2008) ⁹⁰	NA	NA	0.59	NR	0.62				
CHA ₂ DS ₂ -VASc (2010) ¹⁵	NA	NA	0.61	0.85	0.60				

(Table 6's footnote is on the next page.)

*Risk factors were identified from other stratification schemes. **Each category applied to 3 different age ranges, although in the 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. GPRD, General Practice Research Database; SHD, structural heart disease (including MI and angina); RSM, risk stratification model; TE, thromboembolism; Thyrotox, thyrotoxicosis. Other abbreviations as in Tables 1–4. [number] reference number.

bolism.

The systematic search of papers evaluating both internally and externally validated stroke risk models resulted in 12 studies,^{4,28,40,41,43,49–52} following exclusion of 1 study because of substratification by age group.⁴ In total, 12 models were evaluated on 28 occasions.

When considering the 95% confidence intervals (CIs) for the observed stroke incidence of each risk category for each RSM, only one stroke risk model using 3 risk strata (low, moderate, high) reached separation of each risk group at the 95% CI level; that is, the Stroke Prevention in AF model.²⁸ The results of the studies found to have reported on discriminative capabilities of each RSM using the c-statistic are shown in [Table 6C](#).

One recent study reported the values of the c-statistic for 9 RSMs within the same population and found the Rietbrock modified CHADS₂-index to have the highest c-statistic.³⁰ The CHADS₂ score was found to have the highest c-statistic in the same population in another study comparing 5 different RSMs.⁵² The largest of all comparative studies, a nationwide cohort, found that the highest c-statistic for an evaluation of 2 RSMs using the same population was for the CHA₂DS₂-VASc score.¹⁶ The various risk stratification schemes classified variable proportions as low, moderate and high risk, but in general, the CHA₂DS₂-VASc score classified the lowest proportion of patients as 'low risk'.

Cost-Effectiveness

An overview of studies looking into the cost-effectiveness of antithrombotic therapy for AF can be found in [Table 7](#).

Vitamin K Antagonists vs. No Anticoagulation Anticoagulation treatment in a general AF population was found to be relatively cost-effective compared to no anticoagulation in all 9 studies reporting on it.^{53–61} The incremental cost-effectiveness rate (ICER) in a British study ranged from £1,751 and £13,221 per life-year gained free from stroke,⁵⁶ which is comparable to reports from North America and Sweden during the same time period, reporting, US\$1,907 and SKR171,000–417,000, respectively. The latter range depended on the perceived risk of bleeding being either low (0.3%) or more average (2%).

Caro et al found an annual reduction in total healthcare costs of US\$1,514 if anticoagulation was used in AF patients.⁵³ Cost-effectiveness of VKAs also depends on the risk of stroke. In patients at low risk (ie, only AF as a stroke risk factor), there is no perceived benefit when they are treated with VKAs, expressed by the increased costs and decreased quality-adjusted life years (QALY), whereas patients with more than 2 of the classical risk factors of stroke do benefit, with an ICER of US\$1,434 – £6,000 – per QALY.^{54,55,57,60}

Antiplatelet Therapy vs. Vitamin K Antagonists A UK study in a high risk, elderly (≥75 years) population found the total costs, associated with both hemorrhagic and thrombotic events, to be lower and QALY scores to be higher in patients receiving warfarin compared to those receiving aspirin.⁶² Another study in less elderly AF patients with a 'moderate' to high stroke risk also demonstrated the cost-effectiveness of vitamin K antagonists over aspirin (ICER US\$500/QALY).⁵⁵

Three other studies supported the cost-effectiveness of VKAs compared with aspirin.^{53,54,61} In addition to the stroke risk reduction playing an important role in treatment decisions, the quality of anticoagulation and discontinuation of the drug should also be considered.⁵⁹ The benefits for patients at low risk of stroke comes at the price of significantly increased costs over aspirin (US\$370,000/QALY in 65-year-old patients and US\$110,000/QALY in 75-year-old patients) compared to those at medium to high stroke risk (US\$8,000/QALY). Also, bleeding risk was found to have a negative effect on the cost-effectiveness of VKAs.⁵⁵

Dabigatran vs. Vitamin K Antagonists or Antiplatelet Therapy

Three studies reported on the cost-effectiveness of the new oral direct thrombin inhibitor, dabigatran, compared to other forms of antithrombotic therapy.^{63–65} One study found that, assuming an average risk of major bleeding, only aspirin was cost-effective for those at lowest risk of stroke (CHADS₂ score=0). Unless the TTR was poor (<57.1%) or the risk of major bleeding increased, warfarin was cost-effective in those at moderate risk of stroke (CHADS₂ score 1 or 2). Dabigatran 150mg twice daily was cost-effective in those with a CHADS₂ score >2, when the TTR was not excellent (>72.6%).⁶⁴ A lower dose (110mg twice daily) of dabigatran and clopidogrel, in addition to aspirin, was not found to be cost-effective in this analysis.⁶⁴ From a Canadian perspective, dabigatran etexilate was found to be cost-effective compared to VKAs (ICER \$10,440/QALY) in patients at moderate to high risk of stroke.⁶⁵ Another study found the price of dabigatran to be of importance, as the assumption of US\$13,80 for the high (150 twice daily) dose resulted in an ICER of US\$51,229/QALY for low-dose dabigatran and US\$ 45,372/QALY for high-dose dabigatran.⁶³

Discussion

This systematic review demonstrates that the strongest, independent predictors of stroke are a prior stroke or TIA, age >75 years, hypertension, diabetes mellitus and structural heart disease. Sex, heart failure and vascular disease cause more discussion because the available evidence favoring their use as risk factors in AF per se is not as convincing. The interplay of less powerful independent risk factors of stroke could potentially help explain apparent differences in predictive ability of (clinical) entities such as, for instance, heart failure.

Whereas the more clinical diagnosis of CHF fails to be an independent risk factor for stroke in AF patients, a more objective/quantitative approach (eg, LVD) does prove more consistently to be an independent stroke risk factor, but not always.⁶⁶ Although almost being ignored in the historical anticoagulation trials of 2 decades ago, most studies identified by our search and the nearly all of the most recent available epidemiological evidence clearly indicate the importance of vascular disease as an significant stroke risk predictor.^{66–71} However, it is important to further differentiate vascular disease (eg, aortic disease, peripheral vs. coronary artery disease or myocardial infarction), as the former seems to be the driving force behind vascular disease being an independent stroke risk factor in AF patients.⁷⁰

Table 7. Summary of Results for Cost-Effectiveness Studies of Different Antithrombotic Regimens Regarding the Prevention of Stroke in Patients With AF

Study	Comparison	Population	QALY	ICER
Gage BG, 1995 ⁵⁵	VKA vs. no OAC	Nonvalvular AF (NVAF). Base case: male, age 65 years, good candidates for warfarin. Risk factors: prior stroke or TIA, diabetes, Htn, heart disease	QALYs during next 10 years for base case [High risk] Warfarin: 6.51, No therapy: 6.01 [Medium risk] Warfarin: 6.70, No therapy: 6.23 [Low risk] Warfarin: 6.70, No therapy: 6.51	Costs in 1994 US\$ of prophylaxis, stroke, hemorrhage, and death in next 10 years. Marginal cost-effectiveness per QALY saved with warfarin during next 10 years (MCE) Cost \$12,500, Cost \$15,300, MCE: Warfarin preferred to no therapy Cost \$10,900, Cost \$11,400, MCE: Warfarin preferred to no therapy Cost \$9,000, Cost \$6,300, MCE: \$14,000 (range 7,700–24,000) vs. no therapy
Caro JJ, 1997 ⁵³	VKA vs. no OAC	NVAF	Warfarin: NR, No prophylaxis: NR	Costs per year in 1995 US\$ of prophylaxis, emboli and bleeding Cost \$2,599, Cost \$4,113, Net saving \$1,514
Eckman MH, 1998 ⁵⁴	VKA vs. no OAC	NVAF. Base case: 69-year-old man, prototypical of 5 clinical trials considered	QALY Warfarin: 7.60, No prophylaxis: 7.02	Costs over lifetime in 1998 US\$, including systemic embolism, bleeding and associated morbidity. Marginal cost-effectiveness ratio (MCER, \$ per additional QALY) Cost \$13,812, Cost \$12,704, MCER \$1,907
Lightowlers S, 1998 ⁵⁶	VKA vs. no OAC	NVAF. Base cases 1 and 2 from BAATAF trial 4-year data: case 1, hazard rates remained constant from end of 4th year to 10th year; case 2, mean hazard rates for years 1–4 remained for years 5–10. Cases 3 and 4 from meta-analysis data: case 3 used hazard rates for the whole group; case 4 used hazard rates for the group aged >75 years	Life-years gained (discounted) free from stroke over 10-year period with warfarin vs. no prophylaxis [Case 1] 0.33061 [Case 2] 0.5349 [Case 3] 0.9349 [Case 4] 1.908	Incremental cost-effectiveness ratio (ICER, cost per life-year gained, [benefits discounted]) in 1997 UK£, including anticoagulation, stroke and bleeding ICER £13,221.29 ICER £5,497.59 ICER £1,751.05 ICER –£400.45
Thomson R, 2000 ⁶⁰	VKA vs. no OAC	NVAF. 12 groups were defined according to combinations of sex and age. Overall, 1,512 combinations of sex, age, systolic blood pressure, and other risk factors were assessed	QALY NA	Cost per QALY gain in UK£, including stroke, warfarin treatment, GI bleeding In most cases, treatment led to lower costs. In 12/1,512 combinations (0.8%) there was a cost per QALY gained in the range £250–6,000
Desbiens NA, 2002 ⁵⁷	VKA vs. no OAC	NVAF. Assessed according to age and additional risk factors	QALY [Low risk (age 65 years+no risk factors)] Anticoagulation: 11.5, No anticoagulation: 11.8 [High risk (age 65 years, prior stroke or TIA, DM and Htn)] Anticoagulation: 11.7, No anticoagulation: 9.5 [High risk (age 85 years, prior stroke or TIA, DM and Htn)] [High risk (age 95 years, prior stroke or TIA and Htn)]	Costs in US\$ and MCER (\$ per additional QALY) NA Cost –\$1,434 and 2.2 QALY gained Cost –\$1,767 and 0.5 QALY gained MCER \$30,000 per QALY gained
Sorensen SV, 2009 ⁵⁹		NVAF at moderate to high risk of stroke. Base case age 70 years. Scenario 1: all patients start on warfarin and INR values are always in range. Scenario 2: all patients start on warfarin with trial-like INR control. Scenario 3: all patients start on warfarin with real-world INR control. Scenario 4: real-world prescription (and control) of warfarin, aspirin, or neither for warfarin-eligible patients	QALY	Costs over lifetime in 2006 US\$, including drug and monitoring, acute events, long-term care
Sorensen SV, 2009 ⁵⁹	VKA perfect INR vs. trial INR		Scenario 2 (trial-like INR): 6.92, Scenario 1 (perfect INR): 7.21	Cost \$77,764, Cost \$68,039, Scenario 1 vs. 2: Cost –\$5,981–13,775 and 0.38–0.76 QALY gained
Sorensen SV, 2009 ⁵⁹	VKA real-world INR vs. trial INR		Scenario 2 (trial-like INR): 6.92, Scenario 3 (real-world INR): 6.75	Cost \$77,764, Cost \$84,518, Scenario 3 vs. 2: Cost \$3,699–9,970 and –0.23–0.57 QALY gained
Sorensen SV, 2009 ⁵⁹	Real-world prescription (and INR) vs. trial INR		Scenario 2 (trial-like INR): 6.92, Scenario 4 (real-world warfarin, aspirin, or no treatment): 6.67	Cost \$77,764, Cost \$87,248, Scenario 4 vs. 2: Cost \$4,400–13,901 and –0.41–0.86 QALY gained

(Table 7 continued the next page.)

Study	Comparison	Population	QALY	ICER
Mercaldi CJ, 2011 ⁶¹	VKA vs. no VKA	NVAF patients in the Centers for Medicare and Medicaid Services 5% Sample Standard Analytic Files	Warfarin: NA, No warfarin: NA	Costs in 2006 US\$ per patient per year, including events, inpatient and outpatient utilization Cost \$18,621 (SD 38,249), Cost \$22,135 (SD 46,048), Difference -\$9,836 (P<0.0001)
Gage BG, 1995 ⁵⁵	VKA vs. AP	NVAF Base case: age 65 years, good candidate for warfarin. Risk factors: Prior stroke or TIA, diabetes, Htn, heart disease	QALYs during next 10 years for 65-year-old with NVAF [High risk (+≥2 risk factors)] Warfarin: 6.51, Aspirin: 6.27 [Medium risk (+≥1 risk factor)] Warfarin: 6.60, Aspirin: 6.46 [Low risk (age 60–69 years + no risk factors)] Warfarin: 6.70, Aspirin: 6.69	Marginal cost-effectiveness per QALY saved with warfarin during next 10 years (MCE). Costs in 1994 US\$ of prophylaxis, stroke, hemorrhage, and death in next 10 years Cost \$12,500, Cost \$13,200, MCE warfarin preferred to aspirin Cost \$10,900, Cost \$9,700, MCE \$8,000 (range 200–30,000) vs. aspirin Cost \$9,000, Cost \$5,400, MCE \$370,000 (range 66,000-aspirin preferred) vs. aspirin
Eckman MH, 1998 ⁵⁴	VKA vs. AP	NVAF. Base case: 69-year-old man, prototypical of 5 clinical trials considered	QALY Warfarin: 7.60, Aspirin: 7.20	Costs over lifetime in 1998 US\$, including systemic embolism, bleeding and associated morbidity. Marginal cost-effectiveness ratio (MCER, \$ per additional QALY) Cost \$13,812, Cost \$12,020, MCER \$4,484
Jowett S, 2011 ⁶²	VKA vs. AP	AF, ≥75 years of age	QALY over 4 years Aspirin: 1.665, Warfarin: 1.685, Difference 0.020 (95% CI -0.070 to 0.111) favoring warfarin (NS)	Cost in 1997 UK£ over 4 years, including clinical events, primary care, coagulation clinic visits Cost £1,548 (SD 2468), Cost £1382 (SD 2004), Difference -£166 (95% CI -452 to 89) NS
Caro JJ, 1997 ⁵³	AP vs. no OAC	NVAF	Aspirin: NR, Aspirin: NR, No prophylaxis: NR	Costs per year in 1995 US\$ of prophylaxis, emboli and bleeding Cost \$4,313 (excluding SPAF II trial), Cost \$3,139 (including SPAF II trial), Cost \$4,113, Net expense \$200 (excluding SPAF II trial), Net saving \$974 (including SPAF II trial)
Freeman JV, 2011 ⁶³	Dabigatran vs. VKA	Patients NVAF aged ≥65 years and with risk factors for stroke (CHADS ₂ score ≥1 or equivalent) and no contraindications to anticoagulation	QALY Warfarin: 10.28, DE 110 mg bid: 10.70 Warfarin: 10.28, DE 150 mg bid: 10.84	Costs and ICER in 2008 US\$ ICER Cost \$143,193, Cost \$164,576, ICER \$51,229 Cost \$143,193, Cost \$168,398, ICER \$45,372
Shah SV, 2011 ⁶⁴	Dabigatran vs. VKA	Hypothetical cohort of 70-year-old patients with AF who had a moderate risk of stroke and no contraindication to anticoagulant therapy, based on the RE-LY trial	QALY Warfarin: 8.40, DE 150 mg bid: 8.65 Warfarin: 8.40, DE 110 mg bid: 8.54 Warfarin: 8.40, Aspirin and clopidogrel: 8.32	Cost over 20 years and marginal cost per QALY (MCER) in 2010 US\$, including antithrombotic therapy, hemorrhage, neurological ischemia, dyspepsia and MI Cost \$23,000, Cost \$43,700, MCER \$86,000 Cost \$23,000, Cost \$44,300, MCER \$150,000 Cost \$23,000, Cost \$34,000, MCER Dominated
Sorensen SV, 2011 ⁶⁵	Dabigatran vs. VKA	AF and ≥1 additional risk factor for stroke, or AF and impaired LVEF; eligible for anticoagulation. Evaluated DE in a sequential dosing approach, with patients <80 years of age receiving 150 mg bid and patients ≥80 receiving 110 mg bid. Comparisons made with warfarin with trial-like INR control or real-world prescription (and control) of warfarin, aspirin, or neither	QALY Base case: Trial-like warfarin: 7.08, Sequential dosing DE: 7.29 Scenario 1: Real-world prescribing warfarin: 7.01, Sequential dosing DE: 7.29 Scenario 2: Trial-like warfarin: 6.68, DE 150 mg bid: 6.86 Scenario 3: Trial-like warfarin: 6.68, DE 110 mg bid: 6.82	ICER (2010 Canadian \$ per QALY) ICER \$10,440 ICER \$3,962 Scenario 2: 9,041 Scenario 3: 29,994
Shah SV, 2011 ⁶⁴	Dabigatran vs. AP	Hypothetical cohort of 70-year-old patients with AF who had a moderate risk of stroke and no contraindication to anticoagulant therapy, based on the RE-LY trial	QALY Aspirin: 8.17, DE 150 mg bid: 8.65 Aspirin: 8.17, DE 110 mg bid: 8.54 Aspirin: 8.17, Warfarin: 8.40 Aspirin: 8.17, Aspirin and clopidogrel: 8.32	Cost over 20 years and marginal cost per QALY (MCER) in 2010 US\$, including antithrombotic therapy, hemorrhage, neurological ischemia, dyspepsia and MI Cost \$20,000, Cost \$43,700, MCER \$50,000 Cost \$20,000, Cost \$44,300, MCER \$66,000 Cost \$20,000, Cost \$23,000, MCER \$12,500 Cost \$20,000, Cost \$34,000, MCER \$99,000

DE, dabigatran etexilate; NVAF, nonvalvular AF. Other abbreviations as in Tables 1–5. [number] reference number.

In recent years, female sex has also been identified as an independent stroke risk factor in some,^{15,39,72} but not all^{21,25,30} studies. Especially in light of recent developments in both stroke risk stratification and the availability of new oral anticoagulants, resulting into adjusted recommendations for the use of oral anticoagulation further studies for this matter are warranted.⁷²

Fortunately, readily available clinical risk factors are usually sufficient to adequately commence and review antithrombotic therapy. However, when in doubt, echocardiography can assist.^{26,34,37,38,41,73} Transthoracic echocardiography might show left ventricular hypertrophy, in the absence of aortic valve stenosis possibly reflecting end-organ damage caused by (undetected or masked) hypertension. Similarly, it might show a reduced left ventricular ejection fraction without the (clear) clinical syndrome of heart failure. A transesophageal echocardiogram^{26,37} adds further valuable data because it provides even more (reliable) local information on aspects such as vascular disease (aortic plaques) and structural heart disease (atrial dilatation). However, up to now there has been insufficient recent evidence to support the use of left atrial dimension as a stroke risk factor.

Although the searches identified a few recent studies that considered laboratory data/biomarkers as stroke risk factors, none of those studied parameters was found to be an independent predictor of stroke. Still, there is reason to be optimistic about the future possibilities of biomarkers when considering the prevention of AF-related stroke in the broadest sense.⁷⁴

Regarding the health economics analyses, the quality of the studies were good and suggests that OAC is cost-effective in patients at moderate to high risk of stroke,^{53–61} but that appears not to be so for those low-risk patients, for whom aspirin seems cost-effective,⁵⁵ although the option of no antithrombotic therapy as an alternative in this subset has not been tested. The new oral direct thrombin inhibitor, dabigatran, appears to be cost-effective in high risk patients and also those at moderate risk of stroke;^{63–65} however, actual cost price and the individual TTR may also be important factors that influence the latter consideration. Furthermore, limited data on the other new oral anticoagulants, rivaroxaban and apixaban, have been published recently.^{75,76} Even more data^{77–79} and comparative efforts are awaited to facilitate optimal decision making in the antithrombotic management of AF patients.

We emphasize that the focus of this review was on stroke risk assessment. However, at the same time we also acknowledge the well-known fact that the risk of stroke and major bleeding go, to some extent, hand in hand and the latter therefore also needs to be considered when dealing with antithrombotic therapy.

Recently, a novel user-friendly risk score called HAS-BLED was introduced.⁸⁰ The backbone of this bleeding risk stratification tool was derived from the literature on risk factors of anticoagulation-related to major bleeding which was systematically searched and appraised.⁸¹ It underwent additional fine-tuning and validation in a large European cohort of AF patients and further validations have recently been published,^{82,83} contributing to its incorporation into the latest European guidelines on the management of AF.¹⁷ Another bleeding risk assessment tool, the ATRIA bleeding score,⁸⁴ consists of 5 weighted factors, but appears to be less user-friendly and was recently outperformed by the HAS-BLED score regarding predictive ability for major bleeding.⁸³ More importantly, the goal of HAS-BLED or any other practical bleeding risk tool is not to provide a cut-off for when not to commence or continue antithrombotic therapy. It serves as a reminder to all physi-

cians dealing with antithrombotic drugs in AF patients of the risk factors for major bleeding and hopefully triggers appropriate prevention or active treatment to reduce risk. This approach seems very helpful, given the new oral anticoagulants^{6–8} and the recent evidence, both from clinical⁹ and ‘real-world’ data,^{11,85} that further support the limited role of aspirin as a suitable, safe alternative to OAC.

Study Limitations

The presented review data consists of epidemiological, cohort and clinical studies, all of which were not free from selection bias, to a substantial degree in some cases. Especially regarding the clinical studies, we must keep in mind that only a small minority of the screened patients were actually randomized and therefore included in the data presented. Furthermore, certain conditions (eg, vascular disease) were not consistently recorded or taken into account. Altogether, this could very well affect the relative risk of each of the considered risk factors. Only one of the recent studies made an attempt to consider the not uncommon scenario of coexistence of multiple stroke risk factors in a patient by providing some data on the cumulative risk vs. the risk of stand-alone risk factors. Optimal discrimination between risk strata, the absence of overlap of the respective CIs, was observed for 3 RSMs. Regarding the presented discriminative capability between RSMs, we must be aware that not all methods of calculating the c-statistic provide adequate discrimination levels, as well as that cross-study comparison being impaired by the differences in study populations. Finally, because of the heterogeneity of studies included in the systematic review, a meta-analysis of the data was not feasible.

Conclusion

The importance of stroke prevention in AF has led to worldwide focus on this topic, resulting in an (ever) increasing body of evidence on stroke risk factors and the development and validation of stroke RSMs. Recognizing the importance of establishing individual profiles through risk factor-based assessment for both risk of stroke and major bleeding, and to develop an integrative (‘net clinical benefit’) approach, is pivotal to reducing adverse clinical events in patients with AF.

Perhaps the best option is the clinical practice shift that is strongly recommended in the new 2012 focussed update of the European Society of Cardiology guidelines on atrial fibrillation, which is towards more focus on identification of ‘truly low-risk’ patients with AF (that is, ‘age <65 and lone AF (irrespective of gender) or CHA₂DS₂-VASc score=0’), who do not need any antithrombotic therapy) instead of trying to focus on identifying ‘high-risk’ patients.⁹²

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Supplementary Files

Supplementary File 1

Appendix S1.

Please find supplementary file(s);
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