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Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES

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Aims The pattern of atrial fibrillation (AF) occurrence—paroxysmal, persistent, or permanent—is associated with progressive stages of atrial dysfunction and structural changes and may therefore be associated with progressively higher stroke risk. However, previous studies have not consistently shown AF pattern to predict stroke but have been hampered by methodological shortcomings of low power, variable event ascertainment, and variable anticoagulant use.

Methods and results We analysed the rates of stroke and systemic embolism in 6563 aspirin-treated patients with AF from the ACTIVE-A/AVERROES databases. There was thorough searching for events and adjudication. Multivariable analyses were performed with the adjustment for known risk factors for stroke. Mean age of patients with paroxysmal, persistent, and permanent AF was 69.0 $\pm$ 9.9, 68.6 $\pm$ 10.2, and 71.9 $\pm$ 9.8 years ($P < 0.001$). The CHA_2DS_2-VASc score was similar in patients with paroxysmal and persistent AF (3.1 $\pm$ 1.4), but was higher in patients with permanent AF (3.6 $\pm$ 1.5, $P < 0.001$). Yearly ischaemic stroke rates were 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively, with adjusted hazard ratio of 1.83 ($P < 0.001$) for permanent vs. paroxysmal and 1.44 ($P = 0.02$) for persistent vs. paroxysmal. Multivariable analysis identified age $\geq$ 75 year, sex, history of stroke or TIA, and AF pattern as independent predictors of stroke, with AF pattern being the second strongest predictor after prior stroke or TIA.

Conclusion In a large population of non-anticoagulated AF patients, pattern of AF was a strong independent predictor of stroke risk and may be helpful to assess the risk/benefit for anticoagulant therapy, especially in lower risk patients.

Keywords Atrial fibrillation • Paroxysmal • Permanent • Stroke

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and patients with AF are at an increased risk of cardioembolic stroke. Anticoagulation with INR-adjusted warfarin[1] or with non-VKA oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban is highly effective in reducing the risk of stroke, but is associated with an increased risk of bleeding.[1,2] Although the NOACs offer a more favourable safety profile than warfarin, the bleeding risk is not negligible, and the potential benefit of anticoagulant therapy still needs to be balanced against this risk. Therefore, the decision on whether and how to treat individual patients should be based on the predicted absolute risk of stroke in the absence of anticoagulation, and the predicted risk of bleeding with a specific anticoagulant.

Studies in non-anticoagulated AF patients have identified several clinical characteristics predictive of stroke, such as age, sex, previous stroke, hypertension, heart failure, diabetes mellitus, and peripheral

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arterial disease.[3–9] Clinical risk factors have been combined into risk scores to allow a more convenient evaluation of stroke risk,[3–7] and guidelines recommend their use to guide the decision on whether or not to anticoagulate a patient.[10]

Atrial fibrillation has been classified according to its pattern of occurrence; permanently or intermittently, however, the terminology has not always been consistent. Recent guidelines have proposed a consensus definition for the classification of the temporal occurrence of AF: paroxysmal AF episodes are self-limiting and shorter than 1 week, episodes lasting longer than 7 days are referred to as persistent, and permanent AF refers to AF without any intercurring sinus rhythm.[10] Previous studies of the relation between AF pattern of occurrence and the risk of stroke have yielded conflicting results.[11–25] Although some recent trials have reported higher stroke rates in patients with permanent compared with paroxysmal AF,[11,13,15,17,23] other studies did not report a significant difference.[12,14,16,18–22,24–27] Current guidelines recommend that the pattern of AF should not influence the decision on whether or not to treat patients with anticoagulants.[10]

The available data comparing stroke risk in patients with paroxysmal and permanent AF are limited by methodological issues, such as a small sample sizes with limited number of events,[11,12,19,25] or differential use of anticoagulation in patients with paroxysmal AF compared with permanent AF.[18,20,24] In many cohort studies, event ascertainment is likely to be incomplete and verification is poor, with lumping of ischaemic and haemorrhagic stroke and poor discrimination of systemic embolism.

In order to further investigate whether the pattern of AF is associated with the risk of stroke, we have pooled the data on aspirin-treated patients from the ACTIVE-A and AVERROES study. The pattern of AF in this large group of non-anticoagulated patients was defined according to recent guidelines as well as by objective baseline ECG criteria, and all events were rigorously detected and adjudicated.

Methods

Patient selection

We pooled the data on aspirin-treated patients from ACTIVE-A and AVERROES. The patient selection criteria for these trials have been published previously.[28,29] In short, ACTIVE-A was a double-blind, randomized, multi-centre placebo-controlled trial comparing clopidogrel 75 mg with placebo on top of low-dose aspirin in patients with AF and at least one clinical risk factor for stroke, and who had a contraindication for oral anticoagulation. AVERROES was a double-blind, double-dummy randomized, multi-centre placebo-controlled trial comparing apixaban 5 mg twice daily with aspirin 81–324 mg once daily in patients with AF and at least one clinical risk factor for stroke, and who were deemed unsuitable for vitamin K antagonists.

Documentation of AF required either AF on baseline ECG, or at least one (AVERROES) or two (ACTIVE-A) episodes of AF in the 6 months prior to randomization, by ECG, rhythm strip, or at least 30 min of pacemaker-detected AF. In addition, patients were eligible for AVERROES if they had at least one of the following risk factors: prior stroke or TIA; age $\geq$75 years; arterial hypertension on treatment; diabetes mellitus; heart failure (New York Heart Association class $\geq$2 at time of enrolment or left ventricular ejection fraction $\leq$35% documented within 6 m of enrolment); or documented peripheral arterial disease. Patients were eligible for ACTIVE-A if they had any of the following risk factors: age of 75 years or older; treatment for hypertension; history of stroke, transient ischaemic attack, or non-central nervous system systemic embolism; left ventricular ejection fraction of less than 45%; peripheral vascular disease; or age of 55–74 years plus either diabetes mellitus or coronary artery disease.

Definitions

Pattern of atrial fibrillation occurrence

Investigators characterized patients as having one of the following AF patterns: paroxysmal, persistent, or permanent. We also characterized patients into two groups according to their baseline ECG: those with sinus rhythm on ECG and those with all other rhythms than sinus rhythm, including AF, atrial flutter, atrial and ventricular paced rhythm, ventricular paced, atrial paced, and other (denoted by AF/FL/other in tables and figures).

Clinical events

In both ACTIVE-A and AVERROES, there were systematic procedures in place to identify all potential stroke and systemic embolic events; and all reported outcome events were rigorously adjudicated by experts. All strokes were classified as ischaemic or haemorrhagic, or unspecified (not classified as definitely ischaemic or haemorrhagic). The outcome of interest for the current analysis was the composite outcome of ischaemic or unspecified stroke or systemic embolism.

Statistical analyses

Analyses were conducted according to the intention-to-treat principle. All patients randomized to aspirin in ACTIVE-A and AVERROES trials were included in the analysis. The outcome events were observed from the randomization until either study end or loss to follow-up or death. The outcome variable was the time to the first occurrence of either ischaemic or unspecified stroke or systemic embolism. Annual event rates (% per year) were calculated as number of first events per 100 patient-years of follow-up. Kaplan–Meier cumulative hazard rates were plotted according to clinical presentation of AF (paroxysmal, persistent, permanent) and baseline ECG assessment of sinus or non-sinus (AF/FL/other) rhythms.

Baseline characteristics of patients with paroxysmal, persistent, or permanent AF, and patients with baseline ECG showing sinus rhythm or AF/FL/other were summarized as mean $\pm$ SD for continuous variables and frequencies and percentages for categorical variables, and were compared using Pearson Chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. Cox proportional hazards regression models stratified by trial were used to assess the effects of permanent vs. paroxysmal/persistent and permanent/persistent vs. paroxysmal AF on the risk of ischaemic or unspecified stroke or systemic embolism in subgroups of baseline characteristics and CHA_2DS_2-VASc score categories of 0–1, 2–3, and $\geq$4. Significance of the interactions between the AF pattern and the baseline characteristics and CHA_2DS_2-VASc score were tested using Cox modes fitted to all patients. Similar subgroup analyses and tests of interaction were carried out for AF/FL/other vs. sinus rhythm.

Univariate and multivariable Cox proportional hazards regression models were used to assess an independent effect of the AF pattern defined based on AF pattern (paroxysmal, persistent, permanent) or based on baseline ECG assessment (sinus rhythm, AF/FL/other) on the risk of ischaemic or unspecified stroke or systemic embolism, unadjusted and adjusted for (i) age $\geq$75 years, sex, prior stroke or TIA, hypertension, diabetes, heart failure, and peripheral arterial disease; (ii) CHA_2DS_2-VASc score (0–1, 2–3, $\geq$4). Analyses were performed using SAS

software, version 9.2 of the SAS System for SunOS (SAS Institute Inc., Cary, NC, USA). All tests of significance were two-sided. Significance was established at the 5% level.

Results

Baseline characteristics

A total of 6573 patients were treated with aspirin alone in the combined data sets of ACTIVE-A ($N = 3782$) and AVERROES ($N = 2791$) patients. Atrial fibrillation pattern at baseline was paroxysmal in 1576 (24%), persistent in 1136 (17%), and permanent in 3854 (59%) patients. Baseline ECG showed sinus rhythm in 1539 patients (23%) and AF/flutter/other in 5024 patients (77%). Mean age was slightly higher in patients with permanent AF compared with paroxysmal AF. Paroxysmal AF patients were more likely to be female than permanent AF patients (47.7 vs. 39.8%), and fewer patients with paroxysmal AF had a history of stroke or TIA (9.6 and 16.2%, respectively), or of heart failure (25.4 and 40.3%, respectively). Overall, this resulted in a mean CHA_2DS_2-VASc score of 3.1 ± 1.4 for patients with paroxysmal AF, compared with 3.6 ± 1.5 for patients with permanent AF. Patients with persistent AF had a similar mean CHA_2DS_2-VASc score as patients with paroxysmal AF (*Table 1*). Baseline medication use was also different among patients with paroxysmal, persistent, and permanent AF, with higher use of beta-blockers, amiodarone, and statins in patients with paroxysmal AF, and higher use of digoxin in patients with permanent AF (*Table 1*).

On average, baseline characteristics of patients with sinus rhythm on baseline ECG were comparable with those of patients subjectively categorized as paroxysmal AF, and baseline characteristics of patients with AF/flutter/other rhythm on baseline ECG were comparable with those of patients with permanent AF (*Table 1*).

Classification of atrial fibrillation

When assessed by rhythm on the baseline ECG, patients with sinus rhythm at baseline were classified as having paroxysmal AF in 1075 (70.1%), persistent AF in 438 (28.5%), and permanent AF in 21 (1.4%) patients. Just over two-thirds of patients with non-sinus rhythm at baseline were classified as having permanent AF (3829, 72.6%) (see Supplementary material online, *Table S1*).

Risk of embolic events

The rate of embolic events (ischaemic or unspecified stroke or systemic embolism) was 2.1%/year in patients with paroxysmal AF, 3.0%/year in patients with persistent AF, 4.2% in patients with permanent AF, resulting in a hazard ratio (HR) for non-paroxysmal vs. paroxysmal of 1.91 [95% confidence interval (CI) 1.50–2.43; $P < 0.001$] (*Table 2*). This trend of increase in risk of embolic events with progression from paroxysmal to persistent to permanent AF pattern was highly consistent in all subgroups of the individual risk factors. Furthermore, outcome rates were higher in patients with permanent and persistent AF compared with patients with paroxysmal AF within each CHA_2DS_2-VASc category. There were no significant interactions between individual CHA_2DS_2-VASc risk factors or risk category and

Table 1 Baseline characteristics of the patients by pattern of atrial fibrillation and by baseline ECG showing sinus rhythm or AF/FL

	Pattern of AF			*P*-value[a]	Baseline ECG		*P*-value[a]
	Paroxysmal (*N* = 1576)	Persistent (*N* = 1136)	Permanent (*N* = 3854)		Sinus rhythm (*N* = 1539)	AF/FL/other (*N* = 5024)	
Age, years, mean ± SD	69.0 ± 9.9	68.6 ± 10.2	71.9 ± 9.8	<0.001	67.7 ± 9.9	71.5 ± 9.9	<0.001
Age ≥ 75 years, *n* (%)	496 (31.5)	347 (30.5)	1734 (45.0)	<0.001	417 (27.1)	2156 (42.9)	<0.001
Female, *n* (%)	752 (47.7)	480 (42.3)	1535 (39.8)	<0.001	740 (48.1)	2026 (40.3)	<0.001
Prior stroke or TIA, *n* (%)	151 (9.6)	120 (10.6)	626 (16.2)	<0.001	132 (8.6)	764 (15.2)	<0.001
Hypertension, *n* (%)	1407 (89.3)	990 (87.1)	3319 (86.1)	0.01	1393 (90.5)	4321 (86.0)	<0.001
Diabetes mellitus, *n* (%)	283 (18.0)	203 (17.9)	799 (20.7)	0.02	261 (17.0)	1025 (20.4)	0.003
Heart failure, *n* (%)	400 (25.4)	352 (31.0)	1554 (40.3)	<0.001	411 (26.7)	1896 (37.7)	<0.001
Peripheral arterial disease, *n* (%)	46 (2.9)	32 (2.8)	123 (3.2)	0.76	34 (2.2)	167 (3.3)	0.03
CHA_2DS_2-VASc score, mean ± SD	3.1 ± 1.4	3.1 ± 1.4	3.6 ± 1.5	<0.001	3.0 ± 1.4	3.5 ± 1.5	<0.001
CHA_2DS_2-VASc score, *n* (%)							
0–1	201 (12.8)	159 (14.0)	265 (6.9)		226 (14.7)	400 (8.0)	
2–3	795 (50.5)	565 (49.7)	1677 (43.5)		782 (50.8)	2252 (44.8)	
≥4	579 (36.8)	412 (36.3)	1911 (49.6)	<0.001	531 (34.5)	2371 (47.2)	<0.001
Medication use at baseline, *n* (%)							
Beta-blocker	918 (58.3)	642 (56.6)	2068 (53.7)	0.01	873 (56.8)	2755 (54.9)	0.20
Digoxin	229 (14.5)	243 (21.4)	1672 (43.5)	<0.001	151 (9.8)	1992 (39.7)	<0.001
Amiodarone	313 (19.9)	231 (20.4)	294 (7.6)	<0.001	360 (23.4)	477 (9.5)	<0.001
Statin	569 (36.1)	373 (32.9)	1031 (26.8)	<0.001	549 (35.7)	1426 (28.4)	<0.001

[a] *P*-value is from the two-sample Wilcoxon test (for comparison of sinus rhythm and AF/FL) or Kruskal–Wallis test (for comparison among paroxysmal, persistent, and permanent AF) for continuous variables and Chi-square test for categorical variables.

Table 2 Risk of ischaemic or unspecified stroke or systemic embolism according to clinical presentation of AF in subgroups of baseline characteristics

	Paroxysmal		Persistent		Permanent		Permanent vs. paroxysmal/persistent[a]		*P*-value for interaction[b]	Permanent/persistent vs. paroxysmal[a]		*P*-value for interaction[b]
	No. of events/ patients	Event rate (%/year)	No. of events/ patients	Event rate (%/year)	No. of events/ patients	Event rate (%/year)	Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value	
Overall	77/1576	2.1	74/1136	3.0	385/3854	4.2	1.74 (1.44–2.11)	<0.001		1.91 (1.50–2.43)	<0.001	
Age												
<75 years	43/1080	1.6	39/789	2.2	172/2120	3.4	1.76 (1.35–2.29)	<0.001	0.27	1.85 (1.33–2.57)	<0.001	0.70
≥75 years	34/496	3.1	35/347	4.6	213/1734	5.4	1.48 (1.13–1.94)	0.005		1.73 (1.21–2.48)	0.003	
Sex												
Male	29/824	1.5	28/656	1.9	187/2319	3.4	2.01 (1.49–2.70)	<0.001	0.32	2.06 (1.40–3.04)	<0.001	0.75
Female	48/752	2.7	46/480	4.3	198/1535	5.6	1.68 (1.31–2.14)	<0.001		1.93 (1.42–2.63)	<0.001	
Prior stroke or TIA												
No	65/1424	1.9	60/1016	2.6	277/3228	3.6	1.64 (1.33–2.03)	<0.001	0.72	1.78 (1.36–2.32)	<0.001	0.93
Yes	12/151	4.2	14/120	6.7	108/626	7.9	1.53 (0.99–2.35)	0.06		1.85 (1.02–3.36)	0.04	
Hypertension												
No	11/168	2.8	10/146	3.5	52/535	4.3	1.39 (0.83–2.31)	0.21	0.35	1.50 (0.79–2.85)	0.22	0.41
Yes	66/1407	2.0	64/990	2.9	333/3319	4.2	1.80 (1.47–2.21)	<0.001		1.98 (1.52–2.57)	<0.001	
Diabetes mellitus												
No	63/1292	2.0	60/933	2.8	305/3055	4.2	1.78 (1.44–2.19)	<0.001	0.70	1.91 (1.46–2.49)	<0.001	>0.99
Yes	14/283	2.2	14/203	3.5	80/799	4.4	1.59 (1.03–2.45)	0.04		1.88 (1.07–3.30)	0.03	
Heart failure												
No	64/1175	2.2	46/784	2.5	232/2300	4.1	1.74 (1.39–2.19)	<0.001	0.89	1.66 (1.27–2.18)	<0.001	0.08
Yes	13/400	1.5	28/352	4.1	153/1554	4.5	1.67 (1.18–2.36)	0.004		2.87 (1.64–5.05)	<0.001	
Peripheral arterial disease												
No	75/1529	2.1	71/1104	2.9	372/3731	4.2	1.75 (1.44–2.12)	<0.001	0.95	1.89 (1.48–2.41)	<0.001	0.68
Yes	2/46	1.9	3/32	4.8	13/123	5.1	1.66 (0.59–4.69)	0.34		2.55 (0.59–11.1)	0.21	
CHA_2DS_2-VASc score												
0–1	4/201	0.8	6/159	1.7	7/265	1.0	0.91 (0.35–2.41)	0.86	0.50	1.57 (0.51–4.81)	0.43	0.31
2–3	38/795	2.0	24/565	1.9	127/1677	3.2	1.60 (1.18–2.17)	0.002		1.43 (1.00–2.04)	0.05	
≥4	35/579	2.6	44/412	5.0	251/1911	5.7	1.61 (1.25–2.07)	<0.001		2.11 (1.49–3.00)	<0.001	

[a] Hazard ratios were estimated using Cox proportional hazards models fitted separately in subgroups of patients. The *P*-value is from the Wald test.
[b] *P*-value for interaction is from the Wald test of interaction between AF pattern and baseline characteristic. Interactions were tested in Cox models fitted to all patients.

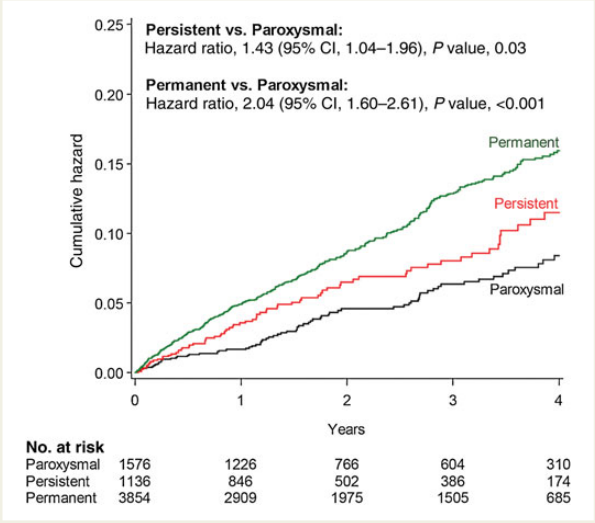

Figure 1 Kaplan–Meier cumulative hazard rates of embolic events according to the pattern of atrial fibrillation occurrence.

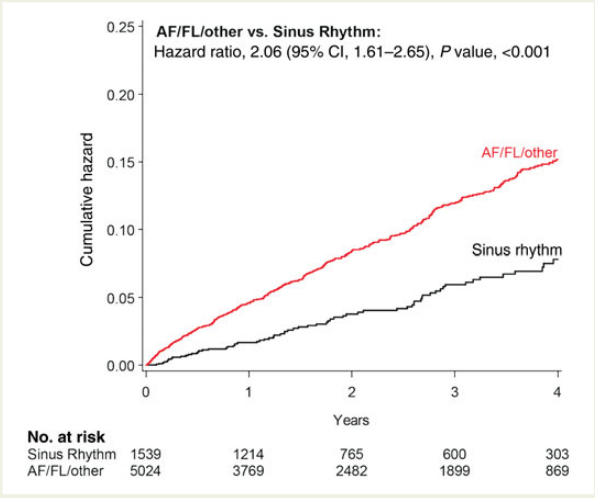

Figure 2 Kaplan–Meier cumulative hazard rates of embolic events according to the baseline ECG.

the pattern of AF (*Table 2*). Similar results were found when AF pattern was defined based on baseline ECG, with a two-fold increase in outcome rates in patients with non-sinus rhythm (4.0%/year) compared with those with sinus rhythm at baseline (1.9%/year, HR 2.06, $P < 0.001$) (see Supplementary material online, *Table S2*). Plots of the cumulative hazard rates show a separation of the curves from the start for different AF patterns, either investigator-defined or by baseline ECG assessment (*Figures 1* and *2*).

In a univariate analysis of baseline risk factors associated with stroke and systemic embolism, baseline ECG, age ≥75 years, sex, and prior stroke or TIA were found to be significant predictors of events (*Table 3*). Atrial fibrillation pattern remained predictive of stroke risk in a multivariable analysis, with an adjusted HR of 1.83 (95% CI, 1.43–2.35) for permanent vs. paroxysmal AF, and an adjusted HR of 1.44 (95% CI, 1.05–1.98) for persistent vs. paroxysmal AF. Permanent AF pattern was the second strongest predictor of stroke risk in this multivariate analysis, after a history of stroke or TIA (*Table 3*). No significant interactions were found between AF pattern and individual CHA_2DS_2-VASc risk factors or between AF pattern and CHA_2DS_2-VASc score (*Table 3*). Similarly, patients enrolling in ACTIVE-A or AVERROES with non-sinus rhythm on their baseline ECG had a HR of 1.83 (1.42–2.36) for stroke or systemic embolism compared with patients with sinus rhythm on their baseline ECG (see Supplementary material online, *Table S3*).

Discussion

Our data, based on non-anticoagulated aspirin-treated patients from the pooled ACTIVE-A and AVERROES studies, show that persistent and permanent AF are associated with an almost two-fold higher rate of stroke or systemic embolism than paroxysmal AF after adjustment for other independent predictors. Results were similar when AF pattern was assessed by baseline rhythm on ECG; stroke rates were about 50% lower when the baseline ECG showed sinus rhythm compared with AF/flutter.

An important question is whether the observed effect is indeed related to the pattern of AF, or is due to confounding factors. Previous studies have pointed out that patients with permanent AF are older and have a higher cardiovascular risk compared with patients with paroxysmal AF.[6,14,16,20,21] This was confirmed in our study. Atrial fibrillation pattern thus likely identifies patient groups with different disease state and comorbidities, which in turn may affect atrial mechanical and endothelial function. Nevertheless, we observed the same gradient of increased risk with increased chronicity (paroxysmal–persistent–permanent) independently in the low, moderate, and high risk patient groups, according to CHA_2DS_2-VASc scores. Furthermore, after correcting for all CHA_2DS_2-VASc risk factors in the multivariable analysis, AF pattern was still the second strongest predictor of risk of stroke or systemic embolism, after a history of stroke or TIA.

Various previous studies have reported that AF pattern was either not associated with stroke risk, or have concluded that observed differences in stroke risk are due to associated risk factors such as increased age.[14,16,18,20,22] In contrast, recent analyses of large contemporary trials have suggested an independently increased stroke risk with non-paroxysmal vs. paroxysmal AF.[17,23] Despite these conflicting results, there is a wide consensus that treatment decision for stroke prevention should not be influenced by AF pattern.[10]

There are several reasons why the findings from the present analysis are credible. Our results are based on data of a large number of exclusively non-anticoagulated patients over a wide range of CHA_2DS_2-VASc scores, with very substantial study power due to having more than 500 ischaemic strokes or embolic events during follow-up. All events were independently adjudicated by expert committees, and the same results were consistently seen in each of the ACTIVE-A and AVERROES data sets independently (see Supplementary material online, *Tables S4–S6*, and *Figure S1*).

The use of data of a non-anticoagulated group of patients has several advantages. First, although aspirin also offers limited protection against AF-related stroke, event rates in aspirin-treated patients more accurately reflect the true risk in the absence of anticoagulant

Table 3 Pattern of atrial fibrillation, baseline risk factors, and risk of ischaemic or unspecified stroke or systemic embolism

	Unadjusted analysis		Adjusted for baseline characteristics		Adjusted for CHA_2DS_2-VASc score	
	Hazard ratio (95% CI)	*P*-value[a]	Hazard ratio (95% CI)	*P*-value[a]	Hazard ratio (95% CI)	*P*-value[a]
Pattern of AF						
Persistent vs. paroxysmal	1.43 (1.04–1.96)	0.03	1.44 (1.05–1.98)	0.02	1.44 (1.04–1.97)	0.03
Permanent vs. paroxysmal	2.04 (1.60–2.61)	<0.001	1.83 (1.43–2.35)	<0.001	1.84 (1.44–2.36)	<0.001
Age ≥ 75 years	1.79 (1.51–2.12)	<0.001	1.50 (1.25–1.78)	<0.001	~	~
Female	1.66 (1.40–1.97)	<0.001	1.59 (1.33–1.89)	<0.001	~	~
Prior stroke or TIA	2.39 (1.97–2.91)	<0.001	2.08 (1.70–2.53)	<0.001	~	~
Hypertension	0.91 (0.71–1.16)	0.43	0.92 (0.72–1.19)	0.54	~	~
Diabetes	1.09 (0.88–1.35)	0.41	1.06 (0.86–1.31)	0.61	~	~
Heart failure	1.19 (1.00–1.42)	0.06	1.07 (0.89–1.27)	0.48	~	~
Peripheral arterial disease	1.22 (0.76–1.96)	0.40	1.20 (0.75–1.92)	0.45	~	~
CHA_2DS_2-VASc score						
2–3 vs. 0–1	2.34 (1.42–3.84)	<0.001	~	~	2.22 (1.35–3.65)	0.002
≥4 vs. 0–1	4.44 (2.73–7.24)	<0.001	~	~	4.04 (2.48–6.59)	<0.001

[a]The *P*-value is from Wald test, Cox proportional hazards model.

treatment, allowing to accurately assess the predictive value of a certain factor.

Secondly, anticoagulant therapy may act as a confounder. The ACTIVE-W trial found a trend towards higher stroke rates in permanent compared with paroxysmal AF in non-anticoagulated patients, but not in warfarin-treated patients.[16] Similarly, the data from the Stockholm cohort did not show a significant overall difference in stroke rate according to AF pattern, but indicated a significant 48% increase in stroke in the subgroup of non-anticoagulated patients with permanent compared with paroxysmal AF.[20] This confounding effect of anticoagulants may be due to the efficacy of anticoagulants in preventing stroke, thus reducing power. Recent very large trials in anticoagulated AF patients with larger numbers of events reported lower stroke rates in paroxysmal vs. non-paroxysmal AF patients (SPORTIF,[19] ARISTOTLE,[17,23] and ENGAGE-AF[22,30]). Differential use of anticoagulant treatment may confound the association between AF pattern and risk of stroke in registries. The European Heart Survey showed no significant differences in stroke rate between paroxysmal and permanent AF patients (1.90 vs. 1.60%/year),[18] but anticoagulant therapy was used in only 50% of paroxysmal AF patients, compared with 71% of permanent AF patients.[18]

Although AF has typically been classified according to its pattern, the definitions have changed over time,[31] and a variety of terms have been used for both non-permanent (paroxysmal, intermittent) and permanent (sustained, persistent) AF. Even with the currently accepted definitions of clinical AF patterns, classification can be challenging, especially in patients who present with both short self-terminating AF episodes and longer episodes. We performed a sensitivity analysis using a more objective classification by means of baseline ECG rhythm. Baseline sinus rhythm correlated well with reported non-permanent AF, and about three quarters of patients without sinus rhythm on their baseline ECG where classified as permanent AF. Our main findings did not differ whether the AF pattern was assessed by the investigator or by single baseline ECG.

There is a biological plausibility to the higher stroke risk in patients with permanent AF. Although the mechanisms of thrombus formation in AF patients are not fully understood, stasis of blood in the left atrium and its appendage is thought to play an important role.[32] The electrical resulting mechanical abnormalities are present continuously in patients with permanent AF, but only intermittently in paroxysmal AF patients. Beyond stasis, pathophysiological changes in the atrial wall and endothelium are thought to promote activation of coagulation while impeding protective antithrombotic mechanisms such as nitric oxide. If AF is considered a 'spectrum' of disease, evolving from paroxysmal to permanent AF, these pathophysiological changes are likely to be more pronounced in persistent presentations of the arrhythmia. Indeed, the duration and burden of AF have been shown to be related to structural, functional, and electrical changes in the fibrillating atrium,[33,34] and levels of biomarkers associated with increased stroke risk in AF are higher in patients with permanent compared with paroxysmal AF.[7,35–37] Thus, rather than having a causal effect, AF pattern likely acts as a clinical surrogate marker reflecting increasing structural and functional changes which predispose to thrombus formation. This is further illustrated by the finding that progression from paroxysmal to sustained AF increased the risk of adverse cardiovascular events[38] and stroke.[11]

There are several limitations to the present study. First, AF pattern was assessed once, at baseline. Patients may have progressed from paroxysmal or persistent to permanent AF during the time of the follow-up; however, this would only dilute the findings. The number and duration of episodes of paroxysmal AF were not assessed; hence, our study does not inform on the burden of paroxysmal AF beyond the simple clinical assessment of overall AF pattern. Nevertheless, quantification of AF burden is not available in most patients, whereas assessment of current rhythm is done routinely

at each patient visit. Therefore, the finding that clinical AF pattern is associated with stroke risk is complementary to studies reporting the predictive value of AF burden in patients with continuous rhythm monitoring, such as the ASSERT trial.[39]

Second, for inclusion in ACTIVE-A and AVERROES, patients were deemed to be 'unsuited' for oral anticoagulant therapy. Although the overall stroke and bleeding risk profiles of these patients were comparable with that in other large double-blind trials of anticoagulants in AF[27,40,41] and in a large population registry,[42] this has to be taken into account when generalizing to a broad AF population.

Finally, our data set included relatively few patients at very low risk of stroke. There were no patients with a CHA_2DS_2-VASc score of 0, and only 10% of the patients had a CHA_2DS_2-VASc score of 1. A study by Scardi *et al.*[15] found that in young AF patients without additional risk factors, yearly stroke rates were 0.36% for paroxysmal, and 1.30% for permanent AF patients over a 10-year follow-up, suggesting that the AF pattern is also linked to stroke risk in low-risk patients.

What are the implications of our findings? Our data show that patients with permanent AF are at a higher risk of stroke compared with patients with non-permanent AF. Although permanent AF increased the risk of embolic events by 50–100% in patients with a CHA_2DS_2-VASc score of 2 or greater, patients with paroxysmal AF still had yearly stroke rates of at least 2%. This confirms the recommendations that patients with a high clinical risk of stroke should be anticoagulated regardless of their AF pattern. However, in deciding whether to offer anticoagulation to low-risk patients, where the risk to benefit ratio of anticoagulation is less clear, it may be useful to consider the pattern of AF occurrence, or perhaps more simply, whether the patient is currently in sinus rhythm or not.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
3. The Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. *Arch Intern Med* 1997;**157**:1237–1240.
4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
5. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999;**30**:1223–1229.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–272.
7. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049–1056.
8. Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. *Stroke* 1989;**20**:1000–1004.
9. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–554.
10. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–2429.
11. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;**17**:622–626.
12. Roy D, Marchand E, Gagne P, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. *Am Heart J* 1986;**112**:1039–1043.
13. Treseder AS, Sastry BS, Thomas TP, Yates MA, Pathy MS. Atrial fibrillation and stroke in elderly hospitalized patients. *Age Ageing* 1986;**15**:89–92.
14. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183–187.
15. Scardi S, Mazzone C, Pandullo C, Goldstein D, Poletti A, Humar F. Lone atrial fibrillation: prognostic differences between paroxysmal and chronic forms after 10 years of follow-up. *Am Heart J* 1999;**137**(4 Pt 1):686–691.
16. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007;**50**:2156–2161.
17. Lip GY, Frison L, Grind M, SPORTIF Investigators. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med* 2008;**264**:50–61.
18. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ, Euro Heart Survey Investigators. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?. *Eur Heart J* 2008;**29**:915–922.
19. Ruigomez A, Johansson S, Wallander MA, Edvardsson N, Garcia Rodriguez LA. Risk of cardiovascular and cerebrovascular events after atrial fibrillation diagnosis. *Int J Cardiol* 2009;**136**:186–192.
20. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010;**31**:967–975.
21. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M, Steg PG. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol* 2012;**5**:632–639.
22. Flaker G, Ezekowitz M, Yusuf S, Wallentin L, Noack H, Brueckmann M, Reilly P, Hohnloser SH, Connolly S. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. *J Am Coll Cardiol* 2012;**59**:854–855.
23. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;**34**:2464–2471.
24. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. *Int J Cardiol* 2013;**167**:2682–2687.
25. Disertori M, Franzosi MG, Barlera S, Cosmi F, Quintarelli S, Favero C, Cappellini G, Fabbri G, Maggioni AP, Staszewsky L, Moroni LA, Latini R, investigators G-A. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSI-AF trial. *BMC Cardiovasc Disord* 2013;**13**:28.
26. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–1511.
27. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.

28. Connolly S, Yusuf S, Budaj A, Camm J, Chrolavicius S, Commerford PJ, Flather M, Fox KA, Hart R, Hohnloser S, Joyner C, Pfeffer M, Anand I, Arthur H, Avezum A, Bethala-Sithya M, Blumenthal M, Ceremuzynski L, De Caterina R, Diaz R, Flaker G, Frangin G, Franzosi MG, Gaudin C, Golitsyn S, Goldhaber S, Granger C, Halon D, Hermosillo A, Hunt D, Jansky P, Karatzas N, Keltai M, Lanas F, Lau CP, Le Heuzey JY, Lewis BS, Morais J, Morillo C, Oto A, Paolasso E, Peters RJ, Pfisterer M, Piegas L, Pipillis T, Proste C, Sitkei E, Swedberg K, Synhorst D, Talajic M, Tregou V, Valentin V, van Mieghem W, Weintraub W, Varigos J. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. *Am Heart J* 2006;**151**:1187–1193.
29. Eikelboom JW, O'Donnell M, Yusuf S, Diaz R, Flaker G, Hart R, Hohnloser S, Joyner C, Lawrence J, Pais P, Pogue J, Synhorst D, Connolly SJ. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J* 2010;**159**:348–353 e1.
30. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
31. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;**306**:1018–1022.
32. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994;**23**:961–969.
33. Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT, Deenadayalu N, Hoffman E, Patel I, Shi M, Mercuri M, Mitrovic V, Braunwald E, Solomon SD. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J* 2014;**35**:1457–1465.
34. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol* 2011;**58**:2225–2232.
35. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation* 2012;**125**:1605–1616.
36. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J* 2013;**34**:1475–1480.
37. Lip GY, Lowe GD, Rumley A, Dunn FG. Fibrinogen and fibrin D-dimer levels in paroxysmal atrial fibrillation: evidence for intermediate elevated levels of intravascular thrombogenesis. *Am Heart J* 1996;**131**:724–730.
38. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;**55**:725–731.
39. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
40. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
41. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
42. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GY, Mantovani LG, Turpie AG, van Eickels M, Misselwitz F, Rushton-Smith S, Kayani G, Wilkinson P, Verheugt FW. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS ONE* 2013;**8**:e63479.