European Heart Journal (2010) **31**, 908–910
doi:10.1093/eurheartj/ehq074

EDITORIAL

Stroke risk in AF: do AF patterns matter?

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Online publish-ahead-of-print 18 March 2010

This editorial refers to 'Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation'†, by L. Friberg *et al.* on page 967

Atrial fibrillation (AF) is accompanied by substantial morbidity[1] and is increasing in both incidence and prevalence.[2,3] Stroke is the chief hazard from AF, and is five times more likely among individuals with AF than among those without the condition.[4] Moreover, AF-related strokes are associated with an ~50% increased odds of disability and a 60% increased odds of death at 3 months compared with strokes of other aetiologies.[5] The need for effective therapies that reduce morbidity from AF is underscored by the presence of an increasingly ageing population, particularly because the elderly are at increased risk for AF-related complications such as stroke.[6]

Although several stroke risk stratification schemes exist, which facilitate personalized thrombo-embolism prophylaxis for individuals with AF,[1] the underprescription of thrombo-embolism prophylaxis represents an established barrier to care.[7–9] The current AF classification scheme endorsed by the American College of Cardiology, American Heart Association, and European Society of Cardiology does not explicitly take stroke risk into account.[1] Rather, the AF classification scheme emphasizes rhythm-based patterns of disease. AF is classified as paroxysmal if it self-terminates within 1 week, persistent if it continues beyond this period and is not self-terminating, or permanent if attempts to terminate the rhythm fail or no attempts are made.

Friberg *et al.* have now attempted to discern whether the incidence of stroke in AF differs according to AF pattern.[10] The investigators performed a retrospective, observational analysis among patients diagnosed with AF at a single hospital or primary care centre in the vicinity of Stockholm, Sweden. AF status was ascertained by chart review and patterns were classified in accordance with existing consensus guidelines, although definitions were altered so that subjects who were cardioverted were not included among those classified as having paroxysmal disease. AF classifications were based on review of medical records from subjects' encounters at the hospital and primary care centre. Those with persistent AF were excluded from the analysis. Stroke was ascertained by the National Register of Hospital Discharges, and medication administration was based on the last recorded follow-up.

The study sample consisted of 855 subjects with paroxysmal AF and 1126 with permanent AF. After a follow-up of ~3 years, 77 strokes occurred among those with paroxysmal AF, and 116 among those with permanent AF. The primary finding was that the incidence of ischaemic stroke was similar between those with paroxysmal AF and those with permanent AF (incidence rate 26 vs. 29 per 1000 patient-years, $P = 0.54$). The hazard ratio (HR) for ischaemic stroke was similar for paroxysmal and permanent AF, even after adjusting for established stroke risk factors and warfarin use [HR 1.1, 95% confidence interval (CI) 0.78–1.56]. Moreover, the investigators observed an ~2-fold increase in the standardized incidence of ischaemic stroke for both paroxysmal and permanent AF as compared with the general population. Although the authors also assessed the incidence and hazard of haemorrhagic stroke, the analysis was underpowered to detect true differences, as only 23 subjects experienced a haemorrhagic stroke in the entire sample. As expected, warfarin use at last follow-up was associated with a substantially diminished incidence of stroke (HR 0.44, 95% CI 0.30–0.65) relative to those who were not taking warfarin.

As acknowledged by the authors, retrospective analyses have limitations. Among the drawbacks of such a study design is the potential for misclassification of the pattern of AF or the type of stroke. For example, in the study of Friberg *et al.*, many of those classified as having paroxysmal AF on the basis of medical encounters actually may have had more chronic forms of AF, particularly if they were asymptomatic with AF and did not seek medical attention, or if they sought medical care at other facilities. This misclassification would be likely to mask a true difference in stroke rates between paroxysmal and permanent AF. Another important limitation of this retrospective analysis is that treatments and other confounders that affect stroke risk were not randomly allocated between the paroxysmal and permanent AF groups. Although adjustment for thrombo-embolism prophylaxis may minimize the impact of such confounding, other unmeasured confounders similarly may be imbalanced and therefore can substantially bias the results.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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† doi:10.1093/eurheartj/ehn599

Table 1 Association between AF rhythm-based pattern and stroke

Study	No. with AF	AF types	Stroke risk	Adjustment for stroke risk factors?
Sage *et al.*[16]	140	Intermittent, chronic	NS	No
Roy *et al.*[17]	254	Paroxysmal, chronic	NS	No
Petersen and Godtfredsen[18]	426	Paroxysmal, chronic	Chronic >paroxysmal	Yes
Treseder *et al.*[19]	414	Transient, constant	Constant >transient	No
Kopecky *et al.*[20]	97	Isolated, recurrent, chronic	NS	No
Cabin *et al.*[21]	272	Paroxysmal, chronic	NS	No
Moulton *et al.*[22]	265	Paroxysmal, sustained	NS	No
Atrial Fibrillation Investigators[6]	3706	Paroxysmal, constant	NS	No
Levy *et al.*[23]	756	Paroxysmal, recent onset, chronic	NS	Yes
Hart *et al.*[24]	2012	Intermittent, sustained	NS	Yes
Hohnloser *et al.*[25]	6706	Paroxysmal, sustained	NS	Yes
Friberg *et al.*[10]	1981	Paroxysmal, permanent	NS	Yes

NS, not significant.

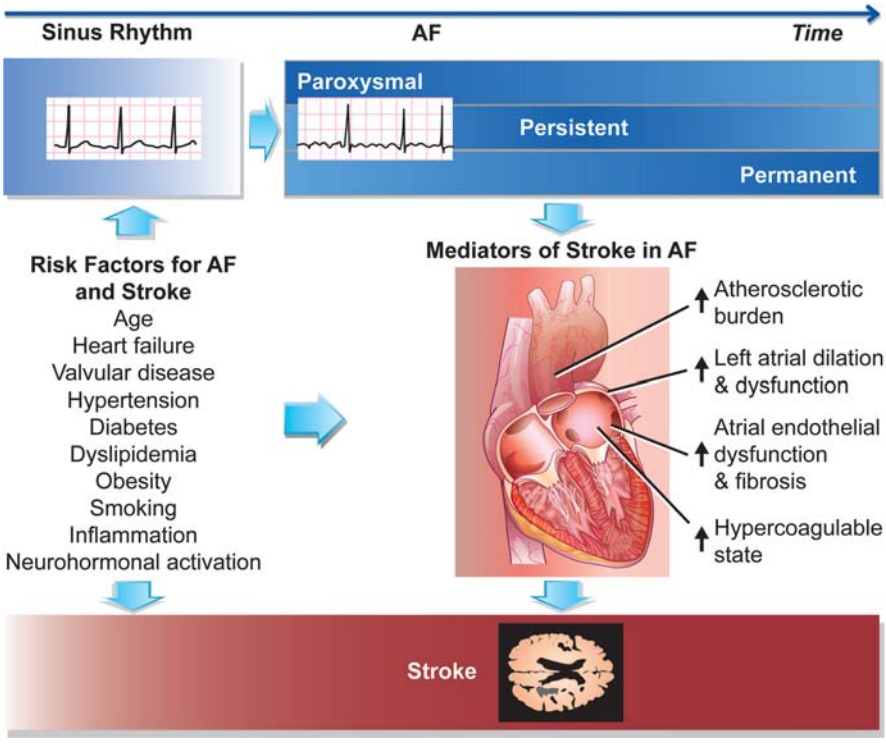

Figure 1 Risk of stroke in AF. Patterns of recurrent AF may be classified as paroxysmal, persistent, or permanent. A hypothetical paradigm is displayed in which the probability of a given pattern of AF varies over the lifecourse of AF, with darker blue shading indicating a higher probability corresponding to a given pattern. Shared risk factors for incident AF and stroke are indicated, as are several mediators of stroke once a patient develops AF. The risk of stroke, displayed in red at the bottom of the figure, is greater once in AF as compared with sinus rhythm, and is generally similar across paroxysmal, persistent, and permanent patterns of AF.

Nevertheless, this study is an important reminder of prior lessons learned. In 1994, a meta-analysis of randomized trials of antithrombotic therapy reported that stroke risk does not differ according to AF pattern (*Table 1*).[6] Unfortunately, this lesson has not been heeded. Rather, decisions to prescribe thrombo-embolism prophylaxis may be more influenced by perceived rhythm-based patterns of AF than by an individual's stroke risk.[7] The underestimation of stroke risk is one factor contributing to the underprescription of thrombo-embolism prophylaxis.[11] Friberg and colleagues as well as others previously have reported that individuals with paroxysmal AF are

less likely to receive thrombo-embolism prophylaxis than those with more chronic forms of AF regardless of stroke risk.[8,9] Similarly, data suggest that there remains a general misconception that pharmacological rhythm control reduces the risk of stroke in individuals with AF.[12] While not proven, the logic influencing these practice observations is probably predicated on the notion that individuals who experience less AF (i.e. those with paroxysmal AF) experience less atrial mechanical dysfunction, a factor commonly cited in the pathogenesis of AF-related stroke, and thus a reduced risk of stroke itself.

There are several pitfalls with this logic. First, prospective evidence from randomized controlled trials does not support the notion that rhythm control strategies reduce the risk of ischaemic stroke in AF.[13] Secondly, ambulatory monitoring reveals that asymptomatic sustained AF occurs more frequently than symptomatic AF among individuals with paroxysmal disease, suggesting that clinical classification of AF on the basis of clinical encounters and occasional electrocardiograms may drastically underestimate the true burden of AF.[14] Thirdly, approximately a quarter of strokes in AF are estimated to be non-cardioembolic.[15] Thus, the relative contribution of AF duration to stroke risk remains unclear. Currently defined rhythm-based patterns of AF do not distinguish stroke risk (*Figure 1*). At the present time, clinicians should rely on clinical guidelines that advocate antithrombotic therapy on the basis of established risk factors for stroke and bleeding.[1] Risk can be more accurately estimated using validated prediction algorithms.[1]

What then, is the value of the currently endorsed AF pattern-based classification scheme? In research, classification of individuals based on patterns of AF has been difficult. AF is characteristically transient, and therefore conventional methods for monitoring AF rhythm are bound to result in misclassification of the AF pattern. Clinically, these distinctions represent convenient proxies that identify the prevalence of co-morbidities commonly associated with each separate pattern of AF. However, the independent role of these patterns for distinguishing the response to various therapies, prediction of morbidity, and prediction of survival is uncertain. Moreover, it remains unclear whether these distinctions merely represent different stages of AF or separate biological subtypes of disease.

Our understanding of AF pathogenesis has grown substantially in the past several years, with new insights into the genetic, molecular, and electrophysiological mediators of this disease. This knowledge presents an opportunity to re-examine the classification of AF in order to determine whether convenient distinctions that effectively summarize both pathogenic and clinical factors are possible. In the meantime, clinicians should recognize that currently defined AF patterns are not useful for approximation of stroke risk.

Conflict of interest: none declared.

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