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How much does the presentation pattern of atrial fibrillation affect thrombo-embolic risk and mortality?

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Atrial fibrillation (AF) is associated with a substantial increase in mortality and morbidity. Systemic thrombo-embolism is the most serious complication associated with this arrhythmia. The use of anticoagulant drugs is the cornerstone of therapy for the prophylaxis of stroke and peripheral ischaemia in these patients. The current guidelines recommend the use of anticoagulant drugs based on the thrombo-embolic risk profile of each individual patient calculated by SCORE based on the presence or absence of clinical risk factors and regardless of the presentation pattern of AF. A review of literature data investigating the effect of AF presentation pattern on thrombo-embolic risk and mortality showed an increased risk of both thrombo-embolic events and death in patients with non-paroxysmal AF compared to patients with paroxysmal AF. Most of these studies, however, consist of post-hoc analyses of large trials or observational studies and meta-analyses derived from these, resulting in an important limitation in the interpretation of data derived from such studies. At the same time, these data suggest the need for both new therapies to prevent AF progression and for further studies to explore the integration of AF presentation pattern into models of thrombo-embolic risk.

Introduction

Atrial fibrillation (AF) represents the most commonly encountered and clinically relevant arrhythmia worldwide; the current estimated prevalence in adults is 2–4%.[1,2]

AF is an independent risk factor for stroke and all-cause mortality.[1,2]

Currently, the prevailing paradigm is that the risk of cerebral and systemic thrombo-embolism in AF patients is independent of the arrhythmia presentation pattern, whether paroxysmal or non-paroxysmal. This paradigm is based on historical evidence that has demonstrated the equivalence of the relative risk of stroke in patients with paroxysmal AF (PAF) and sustained forms of arrhythmia non-paroxysmal atrial fibrillation (NPAF), both persistent and permanent.[3]

Thrombo-embolic risk stratification is, therefore, guided by patient-intrinsic risk factors rather than by the type of AF. Based on these data, in recent decades the guidelines of the European Society of Cardiology for the management of AF have recommended the use or otherwise of oral anticoagulant therapy based on thrombo-embolic risk stratification systems (CHADS2 and subsequently CHA2DS2-VASc SCORE, CHADS2 score: congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke, or transient ischaemic attack (TIA)) in which assessment of the presentation pattern of AF is not contemplated.[1,2]

Recently, the number of articles exploring the impact of AF type on thrombo-embolic risk has increased with a number of studies on the topic.[4]

The aim of this work is to critically review the data in the literature, in the light of the most recent evidence, in order to understand the relationship between the presentation pattern of AF and the risk of thrombo-embolic events or death.

Classification of atrial fibrillation based on the pattern of presentation

Atrial fibrillation is a progressive heart rhythm disorder. The transition from intermittent to continuous forms of presenting arrhythmia can occur in 25% of patients.[5]

Based on the clinical presentation, available anamnestic data on the duration of AF, and spontaneous termination,

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different types of AF have been described, regardless of the presence/absence of symptoms (*Table 1*).[1,2]

Data from the international REALIZE-AF registry showed that, in the general population, permanent AF is the most frequent form of AF (49.6%), followed by PAF (26.5%) and persistent AF (23.8%).[6]

Role of the atrial fibrillation pattern on the risk of cerebral and systemic thrombo-embolism

Historically, the presentation pattern of AF has been considered a non-determinant factor in changes in the risk profile of thrombo-embolism.[3]

In fact, models for predicting thrombo-embolic risk in patients with AF do not include the pattern of AF as a variable; this could also be determined by the absence of data coded by type of AF in the databases used in the derivation and validation cohorts of the risk SCOREs.[4]

The relationship between AF pattern and stroke risk, regardless of CHADS2 and CHA2DS2-VASc scores, is currently a matter of intense debate.

Analysis of the relationship between AF pattern and thrombo-embolic risk or mortality is complicated both by evidence that the profile of patients with PAF is different from other types. Patients with PAF are generally younger, with a lower prevalence of structural heart disease and other comorbidities (heart failure, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease), and consequently, a lower estimated thrombo-embolic risk.[5]

Other confounding factors, in addition to those considered above, in assessing the impact of the type of AF on thrombo-embolic risk are patient adherence to anticoagulant therapy and the intra-individual evolutionary nature of AF.

In fact, many patients can develop persistent or permanent AF, despite being classified as PAF at the time of diagnosis and vice versa; therefore a phenotype may not be representative of a specific patient.[6,7]

Literature data evaluating the effect of AF presentation pattern derived from post-hoc analyses of observational studies or randomized controlled intervention studies. In recent years, following the advent of the new oral anticoagulants and the respective large registration trials, the number of systematically enrolled patients with AF has grown exponentially, representing an excellent substrate for sub-analyses and in-depth studies.

Initially, the first sub-analyses in which the effect of the presentation pattern of AF was evaluated were performed on randomized controlled trials (RCTs) in which the effect of antiplatelet therapy in reducing the thrombo-embolic risk in patients with AF was tested. Notably, in a pooled analysis of the ACTIVE-A and AVERROES trials, which represent a population of 6563 aspirin-treated AF patients, the annual ischaemic stroke rates were 2.1%, 3.0%, and 4.0%. 0.2% in patients with PAF, persistent AF, and permanent AF, respectively, with a hazard ratio of 1.83 ($P < 0.001$) for permanent AF vs. PAF. Multivariate analysis identified: age? 75 years, gender, history of stroke or TIA, and AF pattern as independent predictors of stroke; permanent AF is also the second strongest predictor after a history of prior stroke/TIA.[8]

Other studies, also conducted to test the effect of antiplatelet therapy, have not confirmed this data. The SPAF study and similarly the ACTIVE-W study showed a comparable risk of developing ischaemic stroke in patients with PAF or non-steroid anti-inflammatory drugs (NSAID).[5]

Post-hoc analyses of the ROCKET-AF, ARISTOTLE, and ENGAGE-AF studies demonstrated significantly lower ischaemic stroke incidence rates in patients with PAF at the time of enrolment than in those with persistent AF, even after correction for baseline characteristics. population.[9-11]

In RE-LY, stroke rates were lower in patients with PAF than in patients with persistent AF (1.32% vs. 1.55%), but no formal comparisons were made after adjustment for the most common risk factors; indeed, patients with PAF tended to have lower CHADS2 scores.[12]

Figure 1 shows the annual rate of stroke or systemic embolism reported inRCTs performed on the role of antithrombotic and anticoagulant therapy in the different presentation patterns of AF.

At the same time, some studies performed on international observational registries have reported a comparable thrombo-embolic risk between patients with PAF and NSAIDs.

The data deriving from observational registries are, however, very heterogeneous and present numerous confounding variables such as, for example, the rate of adherence to anticoagulant therapy or the different intrinsic characteristics of patients affected by different AF patterns.

These factors, therefore, make it difficult to try to rigorously correct the data in such studies, so as to make the results derived from them less meaningful.[5]

These data along with others derived from previous RCTs and some observational studies were pooled by Ganesan *et al*. in a large meta-analysis consisting of 12 representative studies of 99 996 patients. The relative risk of uncorrected systemic thrombo-embolism was 1.355 for NPAF patients compared with PAF patients (95% CI: 1.169–1.571, *P*: 0.001). The rate of study heterogeneity was moderate (I2: 57.8%).[4] Multivariate-corrected HRs for thrombo-embolism were reported in 7 of 12 studies, representing 58 421 patients. Each of these studies provided data adjusted for major stroke risk factors including age, gender, hypertension, heart failure, prior thrombo-embolism, and diabetes mellitus. The HR for thrombo-embolism in patients with NPAF vs. PAF was 1.384 (95% CI: 1.191–1.608, *P*: 0.001, I2: 28.841%).[4]

In the same meta-analysis, the effect of the AF pattern on the bleeding risk of these patients was also tested. The results showed similar bleeding rates in the two groups (PAF and NPAF) both in the relative risk assessment and in the HR assessment by entering only the corrected data after multivariate analysis.[4]

The lack of association between AF pattern and bleeding risk could support the hypothesis that this factor represents, on the contrary, an independent variable for patients' thrombo-embolic risk.[5] However, this meta-analysis has a serious limitation determined by the inclusion of post-hoc analyses of studies carried out for different purposes and some observational studies.

Role of the atrial fibrillation pattern on the risk of death

AF is associated with an increased risk of death from all causes. It is also important to note that a higher AF burden is associated with higher mortality.[5] The association

Table 1 Presentation patterns of atrial fibrillation modified from Hindricks et al. (2020).[1]

Pattern of atrial fibrillation (AF)	Definition	Comments
First occurrence of AF	AF has never been diagnosed up to this point, regardless of the duration of the arrhythmia or the presence of associated symptoms	AF diagnosed for the first time, does not yet identify with any specific presenting pattern
Paroxysmal AF	AF that terminates spontaneously, in most cases within 48 hours. Some AF paroxysms can continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal	The classification extends the duration of the single AF episode up to 7 days, but the likelihood of spontaneous conversion with the restoration of sinus rhythm is reduced after 48 hours
Persistent AF	AF lasting more than 7 days, including episodes that are terminated by cardioversion, either pharmacologic or electrical, after 7 days or more	Form of AF that persists beyond 7 days or requires active interruption for restoration of sinus rhythm
Long-lasting persistent AF	Continuous AF episode of ≥1-year duration for which the decision to adopt the rhythm control strategy is decided	Form of AF lasting ≥12 months, for which rhythm control strategy is needed or preferred
Permanent AF	AF for which the rhythm control strategy is not attempted and the permanence of the arrhythmia is accepted by the patient (and the doctor)	Form of AF for which no attempt at cardioversion is performed; and the arrhythmia is accepted by the patient and the doctor. Permanent AF represents a therapeutic attitude rather than an intrinsic pathophysiological attribute of the arrhythmia. If a rhythm control strategy is adopted, the arrhythmia should be reclassified as "long-standing persistent AF"

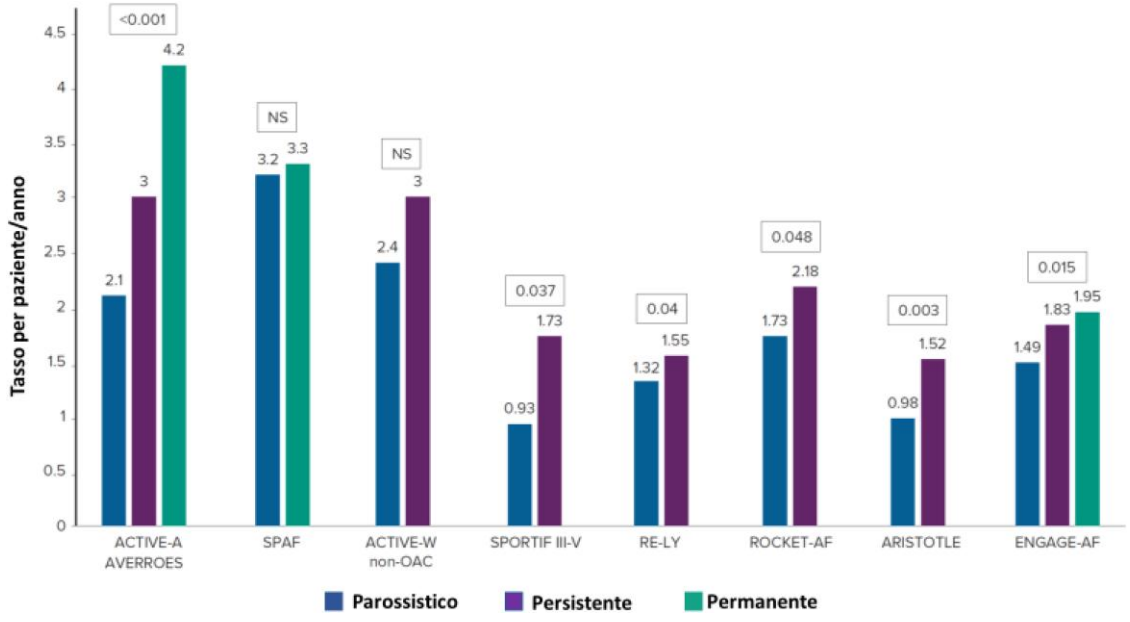

Figure 1 Rate per patient/year of stroke or systemic embolism in randomized controlled trials (RCTs) performed on the role of antithrombotic and anticoagulant therapy in different presentation patterns of AF. Used after permission of Arrhythmia and Electrophysiology Editor in Chief, published on the manuscript ***Impact of the Pattern of Atrial Fibrillation on Stroke Risk and Mortality***" in July 2021; vol 10 (2):68-76.

between AF presentation pattern and risk of death from all causes was investigated in two large meta-analyses.

In the meta-analysis by Zhang *et al.*, based solely on post-hoc analyses of RCTs in patients at risk of moderate to severe stroke receiving anticoagulant therapy, a reduction in all-cause mortality was demonstrated in patients with PAF compared with patients with NPAF [HR 0.72; 95% CI (0.66–0.79); $P < 0.00001$].[13]

The meta-analysis by Ganesan *et al.*, represents the largest pooled dataset of AF patients. In this meta-analysis, as already mentioned, both sub-analyses of RCTs and observational studies were included. Overall, all-cause mortality was higher in patients with NSAID than in those with PAF [HR 1.46; 95% CI (1.26–1.70); $P < 0.001$)] only after correction by multivariate analysis was a partial attenuation of this association observed [HR 1.22; 95% CI (1.09–1.37); $P < 0.001$].[4]

The mechanisms by which patients with NSAIDs experienced increased mortality may potentially have been worsening heart failure or more severe stroke episodes, or perhaps a higher prevalence of the serious underlying non-cardiovascular disease.[4]

Conclusions

AF is associated with a substantial increase in mortality and morbidity. The most serious representation of the latter is constituted by cerebral and systemic thrombo-embolism.

Risk stratification for stroke and systemic thrombo-embolism is a crucial cornerstone in the clinical management of patients with AF. Currently, the determination of the thrombo-embolic risk profile of each individual patient is based on the evaluation of a series of clinical factors included in the risk SCORE.

Current guidelines from major international cardiology societies recommend the use of anticoagulant therapy in patients with AF based on this risk stratification system and regardless of AF presentation pattern.[1,2]

In patients with a high thrombo-embolic risk spectrum calculated based on current risk scores (CHADS2 or CHA2DS2-VASc), clinical risk factors play a more important role than the AF pattern.[5]

Conversely, in deciding whether or not to initiate anticoagulant therapy in patients at low clinical risk of thrombo-embolism (CHA2DS2-VASc score =1), for whom the risk/benefit ratio of such therapy is less clear, it could be useful to consider the type of AF (PAF vs. NPAF). In this case, in fact, the presence of PAF would configure a lower risk profile than that with NPAF.[4,5]

However, it should be emphasized that the meta-analyses on which this evidence is based suffer from the limitation of having included post-hoc analyses of studies performed for purposes other than evaluating the pure role of the AF pattern in predicting main outcomes.[4]

The association of NSAIDs with increased mortality also suggests that prevention of AF progression may potentially impact not only AF symptoms or stroke risk, but could also potentially improve survival.[4]

These data, therefore, suggest the need for new therapies to prevent AF progression and at the same time the need for further studies to explore the integration of AF type into thrombo-embolic risk stratification models.

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Data availability

No new data were generated or analysed in support of this research.

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