The association between patterns of atrial fibrillation, anticoagulation, and cardiovascular events

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Aims
Guidelines do not recommend to take pattern of atrial fibrillation (AF) into account for the indication of anticoagulation (AC). We assessed AF pattern and the risk of cardiovascular events during 2-years of follow-up.

Methods
We categorized AF as paroxysmal, persistent, or permanent in 29 181 patients enrolled (2010–15) in the Global Anticoagulant Registry In the FIELD of AF (GARFIELD-AF). We used multivariable Cox regression to assess the risks of stroke/systemic embolism (SE) and death across patterns of AF, and whether this changed with AC on outcomes. Atrial fibrillation pattern was paroxysmal in 14 344 (49.2%), persistent in 8064 (27.6%), and permanent 6773 (23.2%) patients. Median CHA 2DS2-VASc, GARFIELD-AF, and HAS-BLED scores assessing the risk of stroke/SE and/or bleeding were similar across AF patterns, but the risk of death, as assessed by the GARFIELD-AF risk calculator, was higher in non-paroxysmal than in paroxysmal AF patterns. During 2-year follow-up, after adjustment, non-paroxysmal AF patterns were associated with significantly higher rates of all-cause death, stroke/SE, and new/worsening congestive heart failure (CHF) than paroxysmal AF in non-anticoagulated patients only. In anticoagulated patients, a significantly higher risk of death but not of stroke/SE and new/worsening HF persisted in non-paroxysmal compared with paroxysmal AF patterns.

Conclusion
In non-anticoagulated patients, non-paroxysmal AF patterns were associated with higher risks of stroke/SE, new/worsening HF and death than paroxysmal AF. In anticoagulated patients, the risk of stroke/SE and new/worsening HF was similar across all AF patterns. Thus AF pattern is no longer prognostic for stroke/SE when patients are treated with anticoagulants.

Clinical Trial Registration
URL: http://www.clinicaltrials.gov. Unique identifier: NCT01090362.

Keywords
Atrial fibrillation • Atrial fibrillation type • Stroke prevention • Anticoagulation • Cardiovascular outcome • Registry

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What’s new?
• The relationship between atrial fibrillation (AF) pattern and the risk of cardiovascular events is based on the real-world prospective data collected during 2-years of follow-up in newly diagnosed AF patients from the Global Anticoagulant Registry In the FIELD of AF (GARFIELD-AF) registry.
• The GARFIELD-AF risk calculator showed a continuum of risk for death as evidenced by a gradual increase in the risk score across all three AF patterns.
• The novelty is that in anticoagulated patients, the risk of stroke/systemic embolism was similar across AF patterns.

Introduction
Patient characteristics included in the CHA2DS2-VASc score are important for risk stratification. Current guidelines in atrial fibrillation (AF) recommend this score when deciding whether anticoagulant therapy should be given for stroke prevention in patients with AF.1,2 The temporal pattern of AF, expressed as type of AF, has shown conflicting results with regard to its impact of stroke risk.3–5

The Global Anticoagulant Registry in the FIELD of AF (GARFIELD-AF) is a multinational prospective registry of more than 50,000 patients with newly diagnosed AF and at least one additional risk factor for stroke.6,7 We used data from GARFIELD-AF to compare the risk of stroke or death in patients with different types of AF, particularly to assess the risk conferred by paroxysmal vs. other patterns, and to evaluate whether the risk differed with the use of anticoagulation (AC). In this report, the patients with at least 2-year follow-up from the first four cohorts of GARFIELD-AF were evaluated.

Methods
GARFIELD-AF is a multinational registry of adults aged 18 years or more with non-valvular AF and with at least one additional risk factor for stroke, as judged by the investigator. Atrial fibrillation was diagnosed (according to standard local procedures) within 6 weeks before enrollment. Risk factors were not pre-specified in the protocol and were not limited to the components of existing risk stratification schemes. Patients with a transient and reversible cause of non-valvular AF and those for whom follow-up was not possible were excluded. To minimize recruitment bias, investigator sites were selected randomly from representative care settings in each participating country, and consecutive eligible consenting patients were enrolled.6,7 Informed consent was obtained from all study participants, and the study was approved by research Ethics Committees and Institutional Review Boards.

Collection of follow-up data occurred at 4-month intervals up to 24 months. Outcome measures included clinical events, therapy persistence, and healthcare utilization. The incidences of stroke/systemic embolism (SE), death (cardiovascular and non-cardiovascular), heart failure (HF) (occurrence or worsening), and bleeding (severity and location) were recorded. Data for this report were extracted from the study database in October 2017.

At baseline, investigators collected data on patient demographics, medical history, care setting, type of AF (also collected during follow-up), and antithrombotic treatment (vitamin K antagonists (VKA), non-vitamin K antagonist oral anticoagulants, and antiplatelet (AP) treatment). Data on components of the CHA2DS2-VASc and HAS-BLED risk stratification schemes were used to assess the risks of stroke and bleeding, retrospectively. HAS-BLED scores were calculated excluding fluctuations in the International Normalized Ratio. In addition, the risks of death, stroke/systemic embolism (SE), and major bleeding were estimated at baseline with the recently described GARFIELD-AF risk calculator.6

For patients with new (unclassified) AF at baseline, the type of AF was assessed by the investigator within 150 days of enrolment. If the AF type could not be assessed at 5 months, the patient was not included in the analysis. The definition of AF types are according to the European Society of Cardiology guidelines.1 Paroxysmal AF lasts for more than 7 days and is self-terminating or is cardioverted within the 7-day window. Persistent AF lasts longer than 7 days and includes episodes that are terminated by drug or direct current cardioversion after 7 days. When no rhythm control strategies are pursued and AF is a continuing condition, the AF is permanent.

Study outcomes and definitions
Clinical endpoints of the study were: (i) stroke/SE, (ii) major bleeding, (iii) all-cause mortality, (iv) cardiovascular mortality, (v) non-cardiovascular mortality, (vi) new acute coronary syndromes (ACS), and (vii) new or worsening HF at 2-year follow-up.

Oral anticoagulants (OAC) included VKAs, direct factor Xa inhibitors, and direct thrombin inhibitors. Antiplatelet therapy included: aspirin, adenosine diphosphate receptor antagonists (P2Y12 inhibitors) or both.

Vascular disease included peripheral artery disease or coronary artery disease with ACS. Chronic kidney disease was classified according to National Kidney Foundation guidelines into two groups: moderate-to-severe (stages 3–5), or mild (stages 1 and 2) or none.9 Heart failure at baseline was defined as current/prior history of congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) of <40%.

Data were collected using an electronic case report form and were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK). In accordance with the study protocol, 20% of all data submitted electronically were monitored against source documentation.

Ethics
The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation–Good Pharmacoepidemiological and Clinical Practice guidelines.

Statistical analysis
Baseline patient characteristics were presented for the three AF categories (paroxysmal, persistent, or permanent), classified by the investigators within the first 150 days of enrolment. Continuous variables were expressed as median [interquartile range (IQR)] or mean [standard deviation (SD)] and compared across the three AF categories using the Kruskall–Wallis test. Categorical variables were presented as frequencies (percentages) and were compared using the Pearson χ² test or exact test when appropriate.

Clinical outcomes were compared between patients with each type of AF. Occurrence of major clinical outcomes was expressed as person-time event rates (per 100 person-years) and 95% confidence intervals (CIs). Person-year rates were estimated using a Poisson model with the number of events as the dependent variable and the log of time as an offset, i.e., a covariate with a known coefficient of 1. Only the first occurrence of events was taken into account. Hazard ratios (HRs) were estimated using a proportional hazards Cox model. The proportional
hazard assumption was assessed visually using plots of the cumulative hazard function. The following variables were included in the Cox model: age groups (<65, 65–69, 70–74, ≥75 years), gender, race (Caucasian/Hispanic/Latino, Asian, other race—including Afro-Caribbean, mixed/other, and unwilling to declare/not recorded), smoking (no, ex-smoker, current), diabetes mellitus, hypertension, previous stroke/transient ischaemic attack/SE, history of bleeding, HF, vascular disease, moderate-to-severe renal disease, anticoagulant treatment, and heavy alcohol consumption (only in the model for bleeding). Data analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 39 871 patients included in GARFIELD-AF, 22 805 patients had a known type of AF, and 17 786 patients had new AF of unclassified type (Supplementary material online, Figure S1). Of the 17 786 patients with AF of unknown type, 7096 were classified by the investigator within the first 150 days of enrolment (median 35 days, interquartile range 8–90 days), bringing the total number of patients with a known type of AF to 29 181. Of these patients, 14 344 (49.2%) had paroxysmal, 8064 (27.6%) persistent, and 6773 (23.2%) permanent AF.

Compared to patients with other AF types, those with paroxysmal AF had a slightly lower body mass index, were less likely to have HF or a LVEF <40%, but they were as likely to have history of stroke, transient ischaemic attack, carotid artery occlusive disease, or ACS. Median CHA2DS2-VASc and HAS-BLED scores were similar in all three AF categories, but patients with permanent AF were more likely to be ≥75 years of age (Table 1). The estimated risks of stroke/SE and major bleeding, as assessed with the GARFIELD-AF calculator, were similar in all three AF categories, but the estimated risk of death in patients with persistent and permanent AF patients was numerically higher than in patients with paroxysmal AF.

Antithrombotic therapy

Patients with paroxysmal AF were less likely to receive anticoagulant therapy (with or without AP agents) than those with persistent or permanent AF, and more likely to receive AP agents alone or no antithrombotic treatment (Figure 1). Patients with permanent AF were less likely to be treated by cardiologists and in a hospital than patients in the other two categories of AF.

Among patients without vascular disease, 7463 (29.9%) were prescribed with AP therapy. Among patients with vascular disease, 2462 (59.3%) were prescribed with AP therapy.

Cardiovascular outcomes

At 2-year follow-up, the rates of death (both cardiovascular and non-cardiovascular mortality), stroke/SE, stroke, and new or worsening HF were higher in patients with persistent and permanent AF than in patients with paroxysmal AF (Table 2). The rates of these endpoints were all significantly higher in patients with permanent AF compared with paroxysmal AF. The same was true for the comparison of persistent AF vs. paroxysmal AF, except for the risk of stroke/SE that was non-significantly higher in persistent AF. Finally, no significant differences were observed for the rates of major bleeding and myocardial infarction/ACS across patients with the different AF types (Table 2). After adjustment for age, gender, race, smoking, diabetes, hypertension, stroke/transient ischaemic attack, history of bleeding, cardiac failure, vascular disease, moderate-to-severe chronic kidney disease, and anticoagulant treatment at baseline, permanent AF was significantly associated with a higher risk of stroke/SE, ischaemic stroke, new or worsening HF, all-cause death, cardiovascular, and non-cardiovascular death compared with paroxysmal AF subgroup. Persistent AF was significantly associated with higher risk of new or worsening HF, all-cause death, cardiovascular, and non-cardiovascular death compared with paroxysmal AF subgroup (Figure 2). Full details of the crude and adjusted rates for all major events, and their components, are provided in Supplementary material online, Table S1.

With regard to HF, only few patients had undergone echocardiography. The available data show that 5.7% of the patients in paroxysmal AF had reduced LV function, patients in persistent AF: 12.4%, and patients in permanent AF: 13.1%.

Interactions between anticoagulant therapy and cardiovascular outcomes

The analysis was repeated to determine whether the observed risks were changed with anticoagulant treatment. There was a significant interaction between type of AF and anticoagulant therapy for the endpoints of stroke/SE, ischaemic stroke and new or worsening HF in the whole population, with higher risks in non-paroxysmal AF in non-anticoagulated patients only. The interaction for death was not statistically significant (Figure 3). In anticoagulated patients, there were no differences in the risks for any event between patients in the paroxysmal and persistent or permanent AF groups, except for the risk of death, which was significantly higher in non-paroxysmal compared with paroxysmal AF.

We also performed a sensitivity analysis of the interaction in the population of patients with a CHA2DS2-VASc score ≥2. This analysis confirmed the existence of a significant interaction for stroke/SE, ischaemic stroke and new/worsening HF, with higher risks in non-paroxysmal AF in non-anticoagulated patients only (Figure 4). The interaction for death was not statistically significant irrespective of stroke risk. In anticoagulated patients, there were no differences in the risks for any event between patients in the paroxysmal and persistent or permanent AF groups, except for the risk of death, which was significantly higher in non-paroxysmal compared with paroxysmal AF. In low-risk patients (CHA2DS2-VASc Score 0 or 1), the rate of events was too low to conduct meaningful sensitivity analyses.

Discussion

Our principal finding is that persistent and permanent AF are associated with a higher risk of stroke/SE, death, and new or worsening HF than paroxysmal AF, even after adjustment for a large variety of clinical features. The second important finding is that the increased risk of all major adverse events was only apparent in the subgroup of patients who was not prescribed anticoagulant therapy. In the anticoagulated subgroup, there was no difference in the risks of stroke/SE and new or worsening HF in paroxysmal compared with non-paroxysmal forms of AF. However, an excess risk of death persisted with AC in non-paroxysmal forms of AF, though at a lower level than observed in the non-anticoagulated subgroup of patients.

This is in line with the findings of most published reports derived from secondary analyses of large-scale clinical trials, registries or
Table 1  Baseline characteristics

|                          | Paroxysmal (N = 14 344) | Persistent (N = 8064) | Permanent (N = 6773) | P-value |
|--------------------------|--------------------------|-----------------------|----------------------|---------|
| Sex, n (%)               |                          |                       |                      | <0.0001 |
| Male                     | 7577 (52.8)              | 4796 (59.5)           | 3833 (56.6)          |         |
| Female                   | 6767 (47.2)              | 3268 (40.5)           | 2940 (43.4)          |         |
| Age, median (IQR), years| 70.0 (61.0; 77.0)        | 70.0 (62.0; 77.0)     | 74.0 (66.0; 80.0)    | <0.0001 |
| Age group, n (%)         |                          |                       |                      |         |
| <65 years                | 4770 (33.3)              | 2464 (30.6)           | 1438 (21.2)          | <0.0001 |
| 65–74 years              | 4747 (33.1)              | 2754 (34.2)           | 2110 (31.2)          |         |
| >75 years                | 4827 (33.7)              | 2846 (35.3)           | 3225 (47.6)          |         |
| Ethnicity, n (%)         |                          |                       |                      | <0.0001 |
| Caucasian                | 8375 (60.2)              | 4830 (61.0)           | 4854 (73.0)          |         |
| Hispanic/Latino          | 775 (5.6)                | 485 (6.1)             | 699 (10.5)           |         |
| Asian (not Chinese)      | 3835 (27.6)              | 2244 (28.4)           | 742 (11.2)           |         |
| Chinese                  | 693 (5.0)                | 237 (3.0)             | 221 (3.3)            |         |
| Afro-Caribbean/Mixed/Other| 240 (1.7)              | 117 (1.5)             | 130 (2.0)            |         |
| Vital measures           |                          |                       |                      |         |
| Body mass index, median (IQR), kg/m² | 26.0 (24.0–30.0) | 27.0 (24.0–31.0) | 28.0 (24.0–31.0) | <0.0001 |
| Pulse, median (IQR), b.p.m.| 80.0 (68.0–103.0) | 88.0 (74.0–105.0) | 84.0 (72.0–100.0) | <0.0001 |
| Systolic BP, median (IQR), mm Hg | 130.0 (120.0–145.0) | 130.0 (120.0–144.0) | 134.0 (120.0–145.0) | <0.0001 |
| Diastolic BP, median (IQR), mmHg | 80.0 (70.0–86.0) | 80.0 (70.0–90.0) | 80.0 (70.0–89.0) | <0.0001 |
| Left ventricular ejection fraction, n (%) | 498 (5.7) | 645 (12.4) | 445 (13.1) | <0.0001 |
| Care setting specialty at diagnosis, n (%) | 9945 (69.3) | 5516 (68.4) | 3521 (52.0) | <0.0001 |
| Cardiology               | 47 (0.3)                 | 29 (0.4)              | 37 (0.6)             |         |
| Geriatrics               | 2411 (16.8)              | 1389 (17.2)           | 1523 (22.5)          |         |
| Neurology                | 307 (2.1)                | 86 (1.1)              | 132 (2.0)            |         |
| Primary care/general practice | 1634 (11.4) | 1044 (13.0) | 1560 (23.0) | <0.0001 |
| Care setting location at diagnosis, n (%) | 68 (0.5) | 56 (0.7) | 96 (1.4) | <0.0001 |
| Anticoagulation clinic/thrombosis centre | 1681 (11.7) | 813 (10.1) | 548 (8.1) |         |
| Hospital                 | 8551 (59.6)              | 4843 (60.1)           | 3447 (50.9)          |         |
| Office                   | 1735 (12.2)              | 2352 (29.2)           | 2682 (39.6)          |         |
| Medical history, n (%)   |                          |                       |                      |         |
| Congestive heart failure | 2202 (15.4)              | 2033 (25.2)           | 1649 (24.4)          | <0.0001 |
| Coronary artery disease  | 2904 (20.3)              | 1514 (18.8)           | 1469 (21.7)          | <0.0001 |
| Acute coronary syndromes | 1328 (9.3)               | 669 (8.3)             | 663 (9.8)            | 0.0048  |
| Carotid occlusive disease| 450 (3.2)                | 216 (2.7)             | 255 (3.8)            | 0.0007  |
| Pulmonary embolism/deep vein thrombosis | 321 (2.2) | 193 (2.4) | 212 (3.1) | 0.0004  |
| Coronary artery bypass graft | 398 (2.8)     | 233 (2.9)             | 209 (3.1)            | 0.4266  |
| History of stroke        | 1182 (8.3)               | 581 (7.2)             | 572 (8.5)            | 0.0074  |
| History of transient ischaemic attack | 639 (4.5) | 312 (3.9) | 385 (5.7) | <0.0001 |
| History of systemic embolism | 87 (0.6) | 65 (0.8) | 53 (0.8) | 0.1506  |
| History of bleeding      | 363 (2.5)                | 204 (2.5)             | 211 (3.1)            | 0.0318  |
| History of hypertension  | 10 819 (75.5)            | 6157 (76.5)           | 5300 (78.4)          | <0.0001 |
| Hypercholesterolaemia    | 6019 (43.0)              | 3197 (40.9)           | 2760 (41.6)          | 0.0055  |
| Diabetes mellitus        | 2911 (20.3)              | 1797 (22.3)           | 1574 (23.2)          | <0.0001 |
| Hyperthyroidism          | 398 (2.8)                | 233 (2.9)             | 209 (3.1)            | 0.4266  |
| Hypothyroidism           | 856 (6.1)                | 366 (4.6)             | 443 (6.6)            | <0.0001 |
| Cirrhosis                | 59 (0.4)                 | 58 (0.7)              | 40 (0.6)             | 0.0081  |
| Vascular disease         | 2082 (14.5)              | 1058 (13.1)           | 1013 (15.0)          | 0.0022  |

Continued
meta-analyses, which consistently show that the risk of stroke/SE (and also death in a few studies) was higher in non-paroxysmal forms of AF compared with paroxysmal AF. The worse prognosis with non-paroxysmal AF is thought to be linked to the higher risk profile of these patients. In a few reports, the risk of stroke/SE was found to be similar across all patterns of AF, leading the authors to conclude that the decision to anticoagulate should be based on the risk factors rather than the type of AF. However, none of these reports analysed the impact of AC on the risk of major adverse events using a large prospective cohort, such as GARFIELD-AF.

This registry provides further confirmation that the AF pattern should not be taken into consideration when deciding on AC. Indeed, there is a continuum of risk for stroke/SE across the different patterns of AF. In patients with paroxysmal AF, the risk of stroke is twice as high as in the general population. In paroxysmal AF patients, the burden of AF (as defined by the percentage of time spent in AF during long-term monitoring) is significantly and independently associated with a higher risk of ischaemic stroke as shown by Go et al. In other words, what matters is not AF pattern, but the time spent in AF. The most recent Guidelines implicitly suggest that the decision to anticoagulate should be based on the clinical risk profile for stroke as assessed by various risk scoring systems/calculators, such as CHA2DS2-VASc, and not AF pattern. The differences in the risks of stroke/SE at 2-year follow-up, though substantial across the AF patterns, were not captured by the current scoring systems as in this population, the median values of CHA2DS2-VASc score (and also HAS-BLED score) were similar irrespective of AF patterns. As recently proposed, employing biomarker measurements, in addition to the clinical risk profile, may further refine the predictive value of such risk calculators.

Table I

| Risk factor                       | Paroxysmal (N = 14 344) | Persistent (N = 8064) | Permanent (N = 6773) | P-value |
|----------------------------------|--------------------------|-----------------------|----------------------|---------|
| Smoking status, n (%)            |                          |                       |                      |         |
| Never-smoker                     | 8742 (67.1)              | 4756 (64.2)           | 4066 (64.1)          | <0.0001 |
| Ex-smoker                        | 2864 (22.0)              | 1839 (24.8)           | 1727 (27.2)          | <0.0001 |
| Current smoker                   | 1429 (11.0)              | 815 (11.0)            | 548 (8.6)            | <0.0001 |
| Alcohol consumption, n (%)       |                          |                       |                      | <0.0001 |
| Abstinent                        | 6710 (55.3)              | 3687 (53.1)           | 3009 (51.2)          |         |
| Light                            | 3971 (32.7)              | 2311 (33.3)           | 2177 (37.0)          |         |
| Moderate                         | 1189 (9.8)               | 749 (10.8)            | 560 (9.5)            |         |
| Heavy                            | 260 (2.1)                | 194 (2.8)             | 131 (2.2)            |         |
| CHA2DS2-VASc score, median (IQR) | 3.0 (2.0; 4.0)           | 3.0 (2.0; 4.0)        | 3.0 (2.0; 4.0)       | <0.0001 |
| CHA2DS2-VASc score, mean (SD)    | 3.1 (1.6)                | 3.1 (1.6)             | 3.5 (1.5)            | <0.0001 |
| HAS-BLED score, median (IQR)*    | 1.0 (1.0; 2.0)           | 1.0 (1.0; 2.0)        | 1.0 (1.0; 2.0)       | <0.0001 |
| GARFIELD death score, median (IQR) | 1.4 (0.9)              | 1.4 (0.9)             | 1.5 (0.9)            |         |
| GARFIELD death score, mean (SD)  | 2.9 (3.6)                | 4.3 (5.1)             | 4.9 (5.1)            | <0.0001 |
| GARFIELD stroke score, median (IQR) | 0.9 (0.6; 1.4)          | 0.9 (0.6; 1.4)        | 1.0 (0.7; 1.6)       | <0.0001 |
| GARFIELD stroke score, mean (SD) | 1.2 (1.0)                | 1.2 (1.1)             | 1.4 (1.2)            |         |
| GARFIELD bleeding score, median (IQR) | 0.9 (0.6; 1.3)          | 0.9 (0.6; 1.3)        | 1.0 (0.8; 1.5)       | <0.0001 |
| GARFIELD bleeding score, mean (SD) | 1.0 (0.7)                | 1.1 (0.7)             | 1.2 (0.7)            |         |

BP, blood pressure; IQR, interquartile range; SD, standard deviation.

*The risk factor ‘labile INRs’ is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).
Figure 1  Antithrombotic therapy at diagnosis according to type of AF. AF, atrial fibrillation; AP, antiplatelet; DTI, direct thrombin inhibitor; FXa, factor Xa; VKA, vitamin K antagonist.

Table 2  Incidence event rates per 100 person-years and corresponding 95% confidence intervals during 2-year follow-up of patients with different types of AF

| Outcomes                          | Types of AF                      | Paroxysmal (N = 14,344) | Persistent (N = 8,064) | Permanent (N = 6,773) | Overall (N = 29,181) |
|-----------------------------------|----------------------------------|-------------------------|------------------------|-----------------------|----------------------|
|                                   | Events                           | Rates (95% CI)          | Events                 | Rates (95% CI)        | Events               | Rates (95% CI)       |
| Stroke/systemic embolism          | 301                              | 1.16 (1.03–1.29)        | 184                    | 1.29 (1.1–1.49)       | 194                  | 1.63 (1.42–1.88)     |
| Stroke without systemic embolism  | 275                              | 1.06 (0.94–1.19)        | 161                    | 1.12 (0.96–1.31)      | 167                  | 1.40 (1.20–1.63)     |
| Ischaemic stroke                  | 191                              | 0.73 (0.63–0.84)        | 120                    | 0.84 (0.70–1.00)      | 127                  | 1.06 (0.89–1.26)     |
| Ischaemic stroke or unknown type of stroke | 246                           | 0.94 (0.83–1.07)        | 148                    | 1.03 (0.88–1.21)      | 149                  | 1.25 (1.06–1.46)     |
| Major bleeding and its components | 190                              | 0.73 (0.63–0.84)        | 103                    | 0.72 (0.59–0.87)      | 116                  | 0.97 (0.81–1.16)     |
| Major bleeding                     | 177                              | 0.68 (0.58–0.79)        | 92                     | 0.64 (0.52–0.78)      | 100                  | 0.84 (0.69–1.02)     |
| Mortality and its components      |                                  |                         |                        |                       |                      |                      |
| All-cause mortality               | 716                              | 2.72 (2.53–2.93)        | 574                    | 3.97 (3.65–4.30)      | 713                  | 5.92 (5.50–6.37)     |
| Cardiovascular                    | 259                              | 0.99 (0.87–1.11)        | 214                    | 1.48 (1.29–1.69)      | 282                  | 2.34 (2.08–2.63)     |
| Non-cardiovascular mortality      | 292                              | 1.11 (0.99–1.25)        | 215                    | 1.49 (1.30–1.70)      | 275                  | 2.29 (2.03–2.57)     |
| Myocardial infarction or acute coronary syndrome | 193                           | 0.74 (0.64–0.85)        | 95                     | 0.66 (0.54–0.81)      | 97                   | 0.81 (0.66–0.99)     |
| Congestive heart failure          | 390                              | 1.51 (1.37–1.67)        | 331                    | 2.35 (2.11–2.62)      | 302                  | 2.58 (2.31–2.89)     |

CI, confidence interval.
the prescription of anticoagulants and the optimal management of comorbidities that have a major impact on outcome, which is chiefly, but not limited to, HF. In evaluations of all patients, regardless of risk, AC was associated with a >30% risk reduction in death rates.23,24

Limitations
The current study has several limitations. The event rates are low in this study, both ischaemic stroke and major bleeding. This raises the concern that not all events have been identified.

The classification of AF at a single time point can be misleading as AF patterns often change over time. Hence the one-time rhythm assessment is a limitation. Furthermore, there was no type of AF determination during the 2-year follow-up period.

This is an observational database. Oral anticoagulant treatments were not randomized. Although adjustments were made for confounding, one cannot make conclusive statements about causation for AF type or treatment with outcomes.

The type of AF classification is a relatively poor surrogate measure for the burden of AF (proportion of time spent in AF). Another difficulty is that patients with paroxysmal AF, in general, are healthier than those with the non-self-limiting types of AF, although our statistical methods have attempted to correct for such differences. Finally, the reasons why individual patients/investigators choose not to use anticoagulants are complex and incompletely understood.24

A further limitation pertains to the question whether results from this registry are generalizable. Precautions have been made that patients opting to be included in the GARFIELD-AF registry are as representable as possible of a general AF population, yet there remains an underlying selection that might introduce a bias. For example, it is conceivable that patients agreeing to be followed

![Figure 2](image-url)
in a registry have a different level of interest in the disease studied, which in turn might lead to certain more conscientious treatment decisions.

In a sensitivity analysis comparing the excluded patients with unavailable (new/unclassified) type of AF and the selected patients with known type of AF, some differences emerged both in terms of baseline characteristics and with regard to the event rates (Supplementary material online, Tables S2 and S3).

Lastly, loss to follow-up could potentially be different across exposure groups, since permanent AF patients may be associated with a worse prognosis in general, irrespective of the outcomes investigated, which in turn may lead to a higher drop-out of the registry. Our analysis provided clear evidence that there was no significant difference in drop-out rates or lost-to-follow-up between the type of AF groups (data not shown).

**Conclusion**

In non-anticoagulated patients, non-paroxysmal AF patterns were associated with significantly higher risks of death, stroke/SE, and new/worsening CHF than paroxysmal AF pattern. In anticoagulated
patients, the risks of stroke/SE and new/worsening HF were similar across all AF patterns, but non-paroxysmal AF patterns remained associated with a significantly higher risk of death than paroxysmal AF pattern. A continuum in the risk of death across all AF patterns was shown by GARFIELD-AF risk score. Thus, AF pattern is no longer prognostic for stroke/SE when patients are treated with anticoagulants.’

Supplementary material

Supplementary material is available at Europace online.

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How to release PentaRay catheter entrapped in the hinge point of mechanical mitral valve?

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A 63-year-old woman with a mechanical bileaflet mitral valve (MV) (St. Jude Medical Heart Valve: St. Jude Medical and Abott, St. Paul, MN, USA) underwent catheter ablation for drug-refractory symptomatic atrial tachycardia. During left atrial mapping by PentaRay catheter on CARTO system (Biosense Webster, Inc., Diamond Bar, CA, USA), the catheter was suddenly entrapped in the mechanical MV with the fixation of the ipsilateral disc (Figure). Simple traction freed the catheter to leave the distal portion of two spine tips behind, which remained in the left inferior pulmonary vein and the right deep femoral artery. After non-restricted motion of mechanical MV was confirmed, catheter ablation was performed as scheduled.

In vitro verification, the entrapment of the spines in the hinge point was replicated only when the PentaRay catheter was pulled back at the timing of the disc closing. Furthermore, the entrapped spines were easily released by advancement of the catheter.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.

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