Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF

Jean-Pierre Bassand1,2*, Gabriele Accetta2, Alan John Camm3, Frank Cools4, David A. Fitzmaurice5, Keith A.A. Fox6, Samuel Z. Goldhaber7, Shinya Goto8, Sylvia Haas9, Werner Hacke10, Gloria Kayani2, Lorenzo G. Mantovani11, Frank Misselwitz12, Hugo ten Cate13, Alexander G.G. Turpie14, Freek W.A. Verheugt15,16, and Ajay K. Kakkar2,17, for the GARFIELD-AF Investigators†

GARFIELD-AF is an ongoing, global observational study of adults with newly diagnosed NVAF. Two-year outcomes of 17 162 patients prospectively enrolled in GARFIELD-AF were analysed in light of baseline characteristics, risk profiles for stroke/systemic embolism (SE), and antithrombotic therapy. The mean (standard deviation) age was 69.8 (11.4) years, 43.8% were women, and the mean CHA2DS2-VASc score was 3.3 (1.6); 60.8% of patients were prescribed anticoagulant therapy with/without antiplatelet (AP) therapy, 27.4% AP monotherapy, and 11.8% no antithrombotic therapy. At 2-year follow-up, all-cause mortality, stroke/SE, and major bleeding had occurred at a rate (95% confidence interval) of 3.83 (3.62; 4.05), 1.25 (1.13; 1.38), and 0.70 (0.62; 0.81) per 100 person-years, respectively. Rates for all three major events were highest during the first 4 months. Congestive heart failure, acute coronary syndromes, sudden/unwitnessed death, malignancy, respiratory failure, and infection/sepsis accounted for 65% of all known causes of death and strokes for <10%. Anticoagulant treatment was associated with a 35% lower risk of death.

The relationship between outcomes and time after diagnosis for patients with non-valvular atrial fibrillation (NVAF) is poorly defined, especially beyond the first year.

Aims

Methods and results

Conclusion

Clinical Trial Registration

Keywords

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* Corresponding author. Tel.: +33 647827750, Email: jpbassand@tri-london.ac.uk; jpbassand@orange.fr
† A complete list of investigators is given in Appendix.
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Introduction

Atrial fibrillation (AF), the most frequent of all cardiac arrhythmias, is associated with an increased risk of stroke, systemic embolism (SE), and heart failure. Patients with AF have a two-fold increased risk of death compared with those without AF.1–3 Anticoagulation reduces the risk of stroke/SE and of death at the cost of an increased risk of bleeding. Anticoagulation with vitamin K antagonists (VKAs) or with the newer non-vitamin K antagonist oral anticoagulants (NOACs) is recommended for patients with AF and at least one additional risk factor for stroke, whereas antiplatelet (AP) therapy, either as monotherapy or with concomitant anticoagulation, is indicated in a specific subset of patients.1,4 Currently, there are very limited data on the extended time course of events after diagnosis of non-valvular atrial fibrillation (NVAF) in large multinational populations.

The Global Anticoagulant Registry in the FIELD—Atrial Fibrillation (GARFIELD-AF) is an ongoing, observational, worldwide study of adults with newly diagnosed NVAF, which is governed by the highest academic and ethical standards in the generation, dissemination, and communication of its research findings.5 The registry plans to prospectively recruit ~52 000 patients (representing all ethnicities and care settings) in five consecutive cohorts from randomly selected centres in 35 countries.

Here, we report 2-year event rates for all-cause mortality, stroke/SE, and major bleeding for the first two cohorts (in 17 162 patients) and the factors that have contributed to these events, namely baseline characteristics and treatment.

Methods

Study design and participants

Men and women aged ≥18 years with NVAF diagnosed according to standard local procedures within the previous 6 weeks, and with at least one additional risk factor for stroke as judged by the investigator, are eligible for inclusion. Risk factors are not prespecified in the protocol nor are they limited to the components of existing risk stratification schemes. The study excludes patients with a transient reversible cause of NVAF and those for whom follow-up is not envisaged or possible.6

Consecutive patients are enrolled prospectively into five sequential cohorts, with the aim of recruiting up to 52 000 patients. Investigator sites have been selected randomly and represent the different care settings in each participating country (office-based practice; hospital departments—neurology, cardiology, geriatrics, internal medicine, and emergency; anticoagulation clinics; and general or family practice).5,6

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained. 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. Written informed consent is obtained from all study participants. Confidentiality and anonymity of all patients recruited into this registry are maintained.

Procedures and outcome measures

Baseline data collected at inclusion included patient characteristics, medical history, care setting, type of AF, date and method of diagnosis, symptoms, and anticoagulant (AC) treatment (VKAs, factor Xa inhibitors [FXas], and direct thrombin inhibitors [DTIs], as well as AP treatment). Ethnicity was classified by the investigator in agreement with the patient.5

Data on all components of the CHA2DS2-VASc and HAS-BLED risk stratification schemes were collected to assess the risks of stroke and bleeding retrospectively. Vascular disease was defined as peripheral artery disease and/or coronary artery disease (CAD) with a history of acute coronary syndromes (ACS). Hypertension was defined as a documented history of hypertension or blood pressure >140/90 mmHg at rest.

Collection of follow-up data occurred at 4-month intervals up to 24 months. Outcome measures included clinical events, therapy persistence, and healthcare utilization.1,5,6 The incidences of stroke/SE, pulmonary embolism, ACS, hospitalization, death (cardiovascular and non-cardiovascular), heart failure (occurrence or worsening), and bleeding (severity and location) were recorded. Submitted data were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute [TRI], London, UK), and data queries were sent to study sites.

Data collection/quality control/auditing

GARFIELD-AF data are captured using an electronic case report form (eCRF) designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK). Oversight of operations and data management are managed by the sponsor and coordinating centre (TRI), with support from Quintiles (Durham, NC, USA), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group—Brigham and Women’s Hospital (Boston, MA, USA), and AIXIAL (Paris, France). The GARFIELD-AF protocol requires that 20% of all eCRFs are monitored against source documentation, that there is an electronic audit trail for all data modifications, and that critical variables are subjected to additional audit.5 Data for the analysis in this report were extracted from the study database on 3 August 2015.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as frequency and percentage. Use of antithrombotic therapy at baseline was analysed by CHA2DS2-VASc and ‘modified’ HAS-BLED (excluding fluctuations in the international normalized ratio) scores, calculated retrospectively from the data collected. Patients with missing values were not removed from the study.

Occurrence of major clinical outcomes is described using the number of events, the proportion of patients with the event divided by the population at risk at the beginning of the follow-up period, person-time event rate (per 100 person-years), and 95% confidence interval (CI). We estimated person-year rates 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 each event was taken into account. The 4-monthly event rates were compared with the overall rates using the ratio between the observed and expected numbers of events (applying the overall rate to assess expected rates for that period). The Poisson trend statistic was used to assess the trends over time. Hazard ratios (HRs) were estimated using a proportional hazards Cox model after multiple imputation by the Multiple Imputation by Chained Equations (MICE) algorithm.7,8 We used the MICE algorithm to fill in missing values, creating five complete datasets. Data analysis was performed at the TRI with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata Statistical Software: Release 13 (StataCorp, College Station, TX, USA).
Results

Study population

A total of 17,162 patients with NVAF were prospectively enrolled in the first and second GARFIELD-AF cohorts between March 2010 and June 2013 and are included in this analysis. Patients in these cohorts were recruited from 858 randomly selected study sites representative of routine practice in each of 30 countries. Two-year follow-up was achieved in 97% of patients.

At baseline, mean (SD) age was 69.8 (11.4) years, and 43.8% of patients were female. The mean (SD) CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were 3.3 (1.6) and 1.5 (0.9), respectively. Other baseline characteristics are shown in Table 1. At diagnosis of AF, 60.8% of patients were prescribed AC therapy (50.0% VKAs...
and 10.8% NOACs, with or without AP), 27.4% received AP monotherapy, and 11.8% received no AC or AP therapy. The proportion of patients receiving AC therapy (with or without AP) increased with CHA2DS2-VASc score, being lowest for patients with a score of 0 (41.6%) and highest for patients with a score of 5 (67.5%: Cuzick test, \( P < 0.001 \); Figure 1A). The use of AC (with or without AP) decreased with increasing HAS-BLED score, from 76.5 to 49.8% for patients with scores of 0 and \( \geq 4 \), respectively (Cuzick test, \( P < 0.001 \); Figure 1B). Anticoagulant therapy was not prescribed in 36.9% of patients with CHA2DS2-VASc \( \geq 2 \). Patients not receiving AC therapy tended to be younger (mean [SD] age 68.6 [12.3] vs. 70.6 [10.8] years; \( P < 0.001 \)), were more likely to have paroxysmal AF (29.6 vs. 22.3%; \( P < 0.001 \)), and had a lower mean (SD) CHA2DS2-VASc score (3.0 [1.6] vs. 3.4 [1.6]; \( P < 0.001 \)) but a higher mean (SD) HAS-BLED score (1.7 [0.9] vs. 1.5 [1.0]; \( P < 0.001 \)) than patients receiving AC therapy.

### Clinical outcomes

During the 2-year follow-up, the rates (95% CI) of all-cause mortality, stroke/SE, and major bleeding (first occurrences) were 3.83 (3.62; 4.05), 1.25 (1.13; 1.38), and 0.70 (0.62; 0.81) per 100 person-years, respectively (Table 2). The rates of all three major events were significantly higher during the first 4 months of follow-up (mortality +29%; stroke/SE +35%; major bleeding +56%) compared with the overall event rates (Figure 2 and see Supplementary material online, Table S1). Beyond the first 4 months, the rates of events were lower and modestly declined over the course of follow-up (\( \chi^2 \) test for trend, \( P < 0.001 \) for mortality and stroke/SE, \( P = 0.001 \) for major bleeding). The early higher risk of death was observed irrespective of AF pattern, but was higher with new (newly diagnosed/new onset) AF than with other patterns of AF (standardized mortality rate 1.41 [95% CI 1.19; 1.66] vs. 1.19 [1.00; 1.41], respectively). The same was also true for major bleeding, with standardized incidence rates of 1.70 (95% CI 1.19; 2.44) vs. 1.43 (1.01; 2.03), respectively, for new AF compared with other AF patterns. No difference in early excess of risk was observed for stroke/SE.

The rate of death due to cardiovascular causes including fatal bleeds was 1.55 (1.42; 1.70) per 100 person-years (Table 2). The most frequent causes of cardiovascular death were congestive heart failure (CHF), sudden or unwitnessed death, ACS, and ischaemic stroke (Table 3). The rate of non-cardiovascular causes of death was lower (1.37 [1.25; 1.51] per 100 person-years) and mainly due to malignancy, respiratory failure, and infection/sepsis (Table 3). The primary cause of death could not be identified in 280 of 1181 deaths. By multivariate analysis, the baseline variables significantly associated with a higher risk of death were older age, diabetes mellitus, CHF, vascular disease, history of stroke/SE, history of bleeding, chronic kidney disease (CKD), smoking, and non-paroxysmal forms of AF. Anticoagulation was associated with a significantly lower risk of death (Figure 3).

### Table 2  Event rates (per 100 person-years) for selected clinical outcomes at 2 years of follow-up\(^a\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.83 (3.62; 4.05)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.55 (1.42; 1.70)</td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>1.37 (1.25; 1.51)</td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>0.91 (0.81; 1.02)</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>1.25 (1.13; 1.38)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.70 (0.62; 0.81)</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>0.63 (0.55; 0.73)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.41 (2.24; 2.59)</td>
</tr>
</tbody>
</table>

CI, confidence interval; SE, systemic embolism.

\(^a\)Only the first occurrence of each event was taken into account.

\(^b\)Occurrence of new CHF or worsening of pre-existing CHF.
The rates of different types of stroke are detailed in Table 3, along with the rates of bleeding events of different severity. Strokes were predominantly ischaemic, and primary haemorrhagic strokes were very uncommon. Sixty patients died from ischaemic stroke, 5 from haemorrhagic stroke, and 89 patients who survived a stroke died over the course of follow-up. The most frequent site for bleeding events was the gastrointestinal tract (occurring in 1.47% of the total population). Bleeds in a critical organ (intra-ocular/retinal, intra-splinal, haemo-pericardium, haemothorax, retroperitoneal) and intracranial bleeding (epidural/subdural haematomas) each occurred in 0.22% of the population.

At 2-year follow-up, the rates of ACS and CHF were 0.63 (95% CI 0.55; 0.73) and 2.41 (2.24; 2.59) per 100 person-years, respectively (Table 2).

The rates of death, stroke/SE, and major bleeding increased progressively with increasing grades of the CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED scoring schemes (Cuzick test, \( P < 0.001 \); see Supplementary material online, Figure S1) and correspondingly, the HRs for death, stroke/SE, and major bleeding correlated with the CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED scores (Figure 4).

**Discussion**

Analyses of event rates from the GARFIELD-AF registry have identified that death was the most frequent major adverse clinical event over 2 years of follow-up in patients with NVAF. The rate of death was three-fold higher than the rate of stroke/SE and more than five-fold higher than the rate of major bleeding. The highest frequency of events (for each major outcome measure) occurred during the first 4 months of follow-up. The early risks of death and major bleeding (but not stroke/SE) were higher with new (newly diagnosed/new onset) NVAF than with the other patterns of NVAF. These data suggest that incident NVAF may occur as a complication of a chronic or acute cardiovascular or non-cardiovascular underlying disease that impairs early evolution.\textsuperscript{10–13} In addition, fluctuations in AC control, which are commonly observed after the initiation of VKA therapy, may explain, at least in part, the early excess of

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**Table 3** Breakdown of primary outcomes by type of event at 2-year follow-up\textsuperscript{a}

<table>
<thead>
<tr>
<th>Event</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>1181</td>
<td>40.5</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>478</td>
<td>10.8</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>128</td>
<td>7.5</td>
</tr>
<tr>
<td>Sudden or unwitnessed death</td>
<td>95</td>
<td>5.9</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>70</td>
<td>5.1</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>60</td>
<td>5.1</td>
</tr>
<tr>
<td>Other\textsuperscript{b}</td>
<td>131</td>
<td>11.1</td>
</tr>
<tr>
<td>Non-cardiovascular causes</td>
<td>423</td>
<td>35.8</td>
</tr>
<tr>
<td>Malignancy</td>
<td>121</td>
<td>10.3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>95</td>
<td>8.0</td>
</tr>
<tr>
<td>Infection/sepsis</td>
<td>79</td>
<td>6.7</td>
</tr>
<tr>
<td>Other\textsuperscript{c}</td>
<td>128</td>
<td>10.8</td>
</tr>
<tr>
<td>Undetermined causes</td>
<td>280</td>
<td>23.7</td>
</tr>
</tbody>
</table>

| Stroke (not including systemic embolism) | 365 | 71.2 |
| Primary ischaemic | 260 | 4.1 |
| Secondary haemorrhagic ischaemic | 15 | 10.1 |
| Primary intracerebral haemorrhage | 37 | 5.5 |
| Intracerebral | 20 | 1.4 |
| Intraventricular | 3 | 0.8 |
| Subarachnoid | 5 | 2.5 |
| Undetermined\textsuperscript{d} | 68 | 18.6 |

| Bleeding events (not including minor bleeds) | 504 | 57.1 |
| Severity of bleed | 288 | 42.9 |
| Non-major, clinically relevant | 216 | 4.8 |
| Major | 24 | 18.6 |

\( ^{a}\)Only the first occurrence of each event was taken into account.

\( ^{b}\)Includes deaths due to intracranial haemorrhage, atherosclerotic vascular disease, dysrhythmia, pulmonary embolism, and haemorrhagic stroke.

\( ^{c}\)Includes deaths due to accidents/trauma, renal disease, and liver disease.

\( ^{d}\)Includes patients with unknown type of primary intracerebral haemorrhage and patients with combinations of types of stroke.

\( ^{e}\)Includes patients with unknown types of stroke and those with both primary ischaemic and primary intracerebral haemorrhagic strokes.

\( ^{f}\)All fatal bleeds are included in major bleeds and are also included in the mortality analysis.
Two-year outcomes of patients with newly diagnosed atrial fibrillation

Adjusted hazard ratios for 2-year all-cause mortality, Furthermore, higher rates of ischaemic events after 4 months (Table S1) may be related to better AC control and/or to a change in the CHA2DS2-VASc score was shown to be an equally good predictor of the risks of all three outcome measures (Figure 4). The CHA2DS2-VASc score is a risk stratification tool used in clinical practice to guide the initiation and optimization of anticoagulant therapy in patients with atrial fibrillation. It takes into account the presence of certain cardiac conditions and other risk factors. Despite the strong association between the CHA2DS2-VASc score and the risk of stroke, its predictive power for mortality is limited. However, it is worth noting that the CHA2DS2-VASc score is not the only tool used to assess the risk of stroke in patients with atrial fibrillation. Other tools, such as the HAS-BLED score, are also commonly used in clinical practice.

Study strengths

Several surveys, registries, and regional or national healthcare databases have reported outcomes for patients with NVAF but most studies had a limited duration of follow-up. Prior studies vary in terms of inclusion criteria, duration of follow-up, and care settings, and in the characterization of outcome events. In contrast, the design of the GARFIELD-AF registry is unique; it has a global reach and extended follow-up and incorporates patients with newly diagnosed NVAF from all care settings, making it representative of the overall AF population.
real-life management of NVAF worldwide. In addition, GARFIELD-AF audit and quality assurances exceed the standards of most large-scale registries and even some randomized trials.

Conclusions

Death was the most frequent adverse outcome in NVAF. The highest event rates for death, stroke/SE, and major bleeding occurred during the first 4 months of follow-up, gradually diminishing over time. Stroke-related mortality was not the most frequent cause of death, suggesting that a more comprehensive approach to the management of patients with NVAF may be needed to improve outcome. This could include interventions targeting other modifiable, cause-specific risk factors for death (such as CHF, CAD, ACS, diabetes, and hypertension) in addition to anticoagulation. CHA²DS²-VASc and HAS-BLED scores were both predictive of all three major outcome measures, suggesting that a single integrated risk score derived from a large cohort of patients like the GARFIELD-AF registry, encompassing all three major outcome measures, may have an added value compared with existing risk scores.

Authors’ contributions

J.-P.B. drafted the report. All authors critically reviewed the report and approved the final manuscript. A.K.K. and G.K. handled funding and supervised the registry.

Supplementary material

Supplementary material is available at European Heart Journal online.

Acknowledgements

We thank the physicians, nurses, and patients involved in the GARFIELD-AF registry, Martin van Eickels (Bayer HealthCare Pharmaceuticals, Berlin, Germany) for his contribution to the study design, and Karen Chiswell and Karen S. Pieper (Duke Clinical Research Institute, Durham, NC, USA) for their statistical expertise. Editorial support was provided by Claire Aukim-Hastie, Emily Chu, Rae Hobbs, and Jane Tricker (TRI). SAS programming support was provided by Jagan Allu (TRI).

Funding

This work was supported by an unrestricted research grant from Bayer Pharma AG, Berlin, Germany, to TRI, London, UK, which sponsors the GARFIELD-AF registry.

Conflict of interest: J.-P.B. reports personal fees from Aspen outside the submitted work. G.A. reports grants from Bayer Pharma AG during the conduct of the study. A.J.C. is an advisor to Bayer, Boehringer Ingelheim, Pfizer/BMS, and Daiichi-Sankyo. F.C. reports consulting and speaker fees from Bayer, speaker fees from BMS and Boehringer Ingelheim. D.A.F. reports personal fees from Bayer outside the submitted work. K.A.A.F. reports grants and personal fees from Bayer, Johnson and Johnson, personal fees from Lilly, grants and personal fees from AstraZeneca, personal fees from Sanofi/Regeneron outside the submitted work. S.Z.G. reports grants from Bio2O Medical, grants from Boehringer Ingelheim, grants from Bristol Meyers Squibb, grants from BTG EKOS, grants from Daiichi-Sankyo, grants from National Heart Lung and Blood Institute of the National Institutes of Health, grants from Janssen, grants from Thrombosis Research Group, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Bristol Meyers Squibb, personal fees from Daiichi-Sankyo, personal fees from Janssen, personal fees from Portola outside the submitted work. S.G. reports personal fees from Bayer, grants from Sanofi, grants from Pfizer, personal fees from Daiichi-Sankyo, personal fees from AstraZeneca during the conduct of the study, and grants from Bayer outside the submitted work. S.H. reports personal fees from Aspen, personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Daiichi-Sankyo, personal fees from Pfizer, personal fees from Sanofi outside the submitted work. W.H. reports personal fees from Bayer during the conduct of the study. G.K. reports grants from Bayer during the conduct of the study. L.G.M. reports grants and personal fees from Bayer Healthcare during the conduct of the study, and grants from Boehringer Ingelheim, grants and personal fees from Pfizer, personal fees from Daiichi-Sankyo outside the submitted work. F.M. reports grants and other from Bayer Pharma AG during the conduct of the study, and other from Bayer Pharma AG outside the submitted work. H.T.C. reports personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Leo, personal fees from Roche, personal fees from Stago, personal fees from Philips, grants from Bayer, grants from Boehringer Ingelheim, grants from AstraZeneca outside the submitted work, and he is Chair of the board for the Dutch Federation of Anticoagulation Clinics. A.G.G.T. reports consultant fees from Bayer Pharma AG during the conduct of the study. F.W.A.V. reports personal fees from Boehringer Ingelheim, personal fees from Bayer Healthcare, personal fees from BMS/Pfizer, personal fees from Daiichi-Sankyo during the conduct of the study, and personal fees from AstraZeneca outside the submitted work. A.K.K. reports grants and personal fees from Bayer Healthcare, personal fees from Boehringer Ingelheim Pharma, personal fees from Daiichi-Sankyo Europe, personal fees from Sanofi SA, personal fees from Aspen Pharmacare, personal fees from Pfizer, personal fees from Amrarethon Inc. outside the submitted work.

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