

Title page

Why do Analyses of Prospectively and Retrospectively Enrolled Patients Yield Different Results? Insights from the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF)

Short title:

Fox Prospective and Retrospective Analyses

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Why do Analyses of Prospectively and Retrospectively Enrolled Patients Yield Different Results? Insights from the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF)

Short title: **Fox Prospective and Retrospective Analyses**

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Abstract

Background: Retrospective and prospective observational studies are designed to reflect real-world evidence on clinical practice, but can yield conflicting results. The GARFIELD-AF Registry includes both methods of enrolment and allows analysis of differences in patient characteristics and outcomes that may result.

Methods and Results: Patients with atrial fibrillation (AF) and ≥ 1 risk factor for stroke at diagnosis of AF were recruited either retrospectively (n=5069) or prospectively (n=5501) from 19 countries and then followed prospectively. The retrospectively enrolled cohort comprised patients with established AF (for a least 6, and up to 24 months before enrolment), who were identified retrospectively (and baseline and partial follow-up data were collected from the emedical records) and then followed prospectively between 0-18 months (such that the total time of follow-up was 24 months; data collection Dec-2009 and Oct-2010). In the prospectively enrolled cohort, patients with newly diagnosed AF (≤ 6 weeks after diagnosis) were recruited between Mar-2010 and Oct-2011 and were followed for 24 months after enrolment. Differences between the cohorts were observed in clinical characteristics, including type of AF, stroke prevention strategies, and event rates. More patients in the retrospectively identified cohort received vitamin K antagonists (62.1% vs. 53.2%) and fewer received non-vitamin K oral anticoagulants (1.8% vs. 4.2%). All-cause mortality rates per 100 person-years during the prospective follow-up (starting the first study visit up to 1 year) were significantly lower in the retrospective than prospectively identified cohort (3.04 [95% CI 2.51 to 3.67] vs. 4.05 [95% CI 3.53 to 4.63]; p=0.016).

Conclusions: Interpretations of data from registries that aim to evaluate the characteristics and outcomes of patients with AF must take account of differences in registry design and the impact of recall bias and survivorship bias that is incurred with retrospective enrolment.

Clinical Trial Registration — URL: <http://www.clinicaltrials.gov>. Unique identifier for GARFIELD-AF (NCT01090362)

Keywords: Registries, Atrial Fibrillation, Anticoagulation, Retrospective, Prospective

INTRODUCTION

Observational studies are designed to reflect real-world evidence on clinical practice, but they can yield conflicting results. This report aims to determine some of the reasons for these apparent differences.

The number of scientific publications indexed by MEDLINE that include ‘real-world’ in the title has increased by four-fold in the last decade. This increase is being driven by the needs of clinicians, regulators, and payers for data in unselected populations.¹ Data from observational studies are also needed to meet regulatory expectations for labeling, pricing and reimbursement. Combined with evidence from RCTs, real-world data has the potential to influence decision makers on the care of individual patients.²⁻⁶

Observational studies, including cohort studies, are longitudinal studies that aim to collect data on both the exposure(s) to therapy and the outcome(s) of interest but they are dependent on the accuracy and completeness of collected clinical data. The most common source of real-world evidence is based on observational studies using routinely collected data e.g., cancer records, hospital episode statistics, death records. In contrast, a patient registry is an ‘organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population or cohort defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purpose’. For this reason, registries may collect patient characteristics and outcomes that may not be available from routine data collection systems.⁷ However, registries differ in their design and quality assurance, their recruitment strategies and care settings, and their geographic distribution and follow-up.⁸⁻¹²

Another important consideration is whether the study is prospective or retrospective. We use the timing of subject identification to distinguish between prospective and retrospective cohort studies. Studies carried out forward into the future are denoted prospective studies, while studies carried out looking backward into the past are denoted retrospective cohort studies. The most common design of registries is retrospective, where both the identification and outcomes of patients with AF are recorded retrospectively. Such studies can be quick and relatively inexpensive and involve fewer resources and less study time than prospective studies, but are more susceptible to bias in both data collection and analysis and the influence of unidentified confounders

Prospective studies provide a more robust model for collecting data because patients with predefined characteristics are recruited and then their outcomes are recorded as and when they occur over the study.^{11, 13, 14} Generally, prospective studies require patient recruitment and informed consent (which may introduce a level of bias). Overall, however, prospective studies are associated with less bias in reporting and analyses because the study design generally is informed by a protocol including predefined statistical analyses plans and outcome measures.

The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) is a prospective non-interventional study.³ It is designed to reflect patient management according to local practices. Treatment is neither mandated nor paid for by a sponsor and no additional visits, tests or procedures are required by the protocol. To mitigate against selection bias in the recruitment of patients into GARFIELD-AF and to ensure an accurate representation of current practice, a number of steps were taken in the design of the registry.³ One such step

was the analyses of data from two cohorts of patients during the first cycle of recruitment: firstly, a retrospective enrolment cohort of patients with “established AF” (for a least 6, and up to 24 months before enrolment) akin to many of the ongoing registries in AF which were recruiting patients within 3 to 12 months of diagnosis.^{2, 14-16} Secondly, a prospective enrolment cohort of patients with “newly diagnosed AF” (enrolled within 6 weeks of diagnosis). Hence we were able to compare data from the first prospective cycle of recruitment with data from subsequent cycles, as well as with the data from patients enrolled retrospectively and followed prospectively.

The aim of this paper is to describe the demographics, clinical characteristics, and treatment patterns of newly diagnosed patients who were enrolled prospectively and compare these with retrospectively identified patients with “established AF” (for a least 6, and up to 24 months before enrolment). Differences in the burden of disease and outcome events were recorded with prospective follow-up of both cohorts.

METHODS

Registry design

The principal aim of the GARFIELD-AF registry is to define the management strategies for patients with newly diagnosed AF and one or more risk factors for stroke, and relate these to the primary outcomes (stroke/systemic embolism [SE], major bleeding, all-cause mortality).¹⁷ Data were captured from the time of enrolment and over 2 years of follow-up (data extraction date: Jul-2016).

Participating sites

Investigator sites in GARFIELD-AF are representative of the distribution of care settings and locations (rural or urban) in each participating country. Sufficient sites, both globally and on a national level, were identified from hospital, community, and anticoagulation clinic settings with the aim of achieving appropriate representation of AF-treating care settings in participating countries. The final national selection of representative sites in 19 countries was based on National Coordinating Investigator recommendations and sites were selected at random.³ A summary of the geographic location of study centres, baseline characteristics, and a full disclosure of the antithrombotic treatment of all patients enrolled into cohort 1 are given in a previously published paper.¹⁸ The paper included 44 patients who were excluded from the current analyses on account of subsequently identified audit violations.

Data collection and statistical analyses

Two cohorts of patients from 19 countries were evaluated during the first cycle of recruitment: data were collected on a retrospectively identified cohort from December 2009 to October 2010 and the prospectively identified cohort between March 2010 and October 2011. The retrospective cohort comprised patients with “established AF” (for at least 6, and up to 24 months before enrolment), who were identified retrospectively and then followed prospectively for 0-18 months (such that the total time of follow-up was 24 months from the day of diagnosis) (Figure 1). As mortality risk is higher in the early period after AF diagnosis,¹⁹ differences in the interval between AF onset and inclusion in a registry are likely to impact observed outcome rates (Figure 2).

In the prospectively identified cohort, patients with “newly diagnosed AF” (enrolled within 6 weeks of diagnosis) were followed prospectively until 24 months after the “first study visit”.

The term “first study visit” is the date that the patient was enrolled in GARFIELD-AF. Events recorded included stroke/SE, all-cause mortality, and bleeding (severity and location). Submitted data were audited for completeness and accuracy by the coordinating centre (Thrombosis Research Institute [TRI], London, UK). The GARFIELD-AF protocol requires that 20% of all electronic case report forms 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.³

Continuous variables are expressed as mean \pm standard deviation (SD) or median (25th, 75th percentiles) and categorical variables as frequency and percentage. Only the first occurrence of each event was analysed. Occurrence of major clinical outcomes is described using the number of events, person-time event rate (per 100 person-years), and 95% confidence interval (CI). The Poisson model was used to estimate person-year rates, 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.

Comparisons were made between the cohorts identified either retrospectively or prospectively and then followed prospectively from the date of first study visit. For the comparison of event rates between the two cohorts, we used the Mantel-Haenszel method to calculate the ratios and p values were derived by the Chi-square test.

A landmark analysis of the prospectively collected patients was also generated, starting follow-up at 6 months after enrolment in the study. This mortality rate illustrated the expected survival in patients who experienced AF for 6 months, making it more similar in

this respect to the retrospectively collected population. The rates of stroke/SE as well as the major bleed are recalculated in the subset of patients who survived to 6 months to simulate the retrospectively collected patients. In this landmark analysis, follow-up for events is from the time of AF onset as in the retrospectively collected group.

RESULTS

Data were collected from December 2009 on 5069 patients who were retrospectively identified and 5501 from March 2010 who were prospectively identified. The mean (\pm SD) time from diagnosis to the first study visit was 60.6 (\pm 23.6) weeks in the retrospectively identified cohort and 1.8 (\pm 1.8) weeks in the prospectively identified cohort. The mean (\pm SD) follow-up after the first study visit was 42.0 (\pm 23.9) weeks and 97.1 (\pm 40.8) weeks for each cohort, respectively. The mean (\pm SD) total duration from AF diagnosis to end of follow-up was 102.4 (\pm 24.4) weeks and 98.9 (\pm 40.8) weeks for the retrospectively identified and prospectively identified patients, respectively. The number of patients lost to prospective follow-up was 210 (2.4%) and 321 (5.8%) in each cohort, respectively.

Baseline demographic and clinical characteristics

The baseline characteristics recorded during the first study visit are summarized in Table 1. Although some demographic features (age, sex, geographic distribution, and care setting) were similar for both cohorts, other features differed substantially. At the time of the first study visit, a greater proportion of patients from the retrospectively identified cohort with “established AF” had a confirmed diagnosis of permanent AF (36.3% vs. 14.1% of prospective patients); there was a great proportion with identified paroxysmal AF (30.9% vs. 24.5% of prospective patients) and fewer had unclassified AF (13.3% vs. 44.8% of

prospective patients) (Fig. 3). The retrospectively identified cohort also had a lower proportion with New York Heart Association (NYHA) class III-IV congestive heart failure (27.5% vs. 32.9%), but a higher proportion with a history of stroke (10.9% vs. 8.6%) or history of bleeding (3.8% vs. 3.1%) than the prospectively identified cohort with “newly diagnosed AF”. Despite these differences, the median (interquartile range) CHA₂DS₂-VASc score did not differ: 3.0 (2.0 to 4.0) and 3.0 (2.0 to 4.0), respectively for retro- and prospectively identified cohorts.

Treatment patterns

As shown in Fig. 4., antithrombotic therapies prescribed were broadly similar in both cohorts, with a slightly greater proportion of patients in the retrospectively identified cohort treated with oral anticoagulants (OACs) ± antiplatelet (AP) therapy (63.9% vs. 57.4%) and fewer receiving either AP lone therapy (26.9% vs. 30.2%) or no stroke prevention therapy (9.2% vs. 12.4%). Analysis of patients with moderate-high risk of stroke (CHA₂DS₂-VASc score ≥2) found that patients refusal to take OACs was more likely in the retro- than the prospectively identified cohort: 9.8% vs. 6.0% (analyses based based on those who received no stroke prevention therapy, i.e. 768 patients in the retro- and 893 patients in prospectively identified cohorts).

Some differences in the prescribing of OACs were also observed between the cohorts, with more patients in the retrospectively identified cohort receiving vitamin K antagonist (62.1% vs. 53.2%) and fewer receiving non-vitamin K antagonist anticoagulants (NOACs) (1.8% vs. 4.2%).

Stroke and bleeding event rates

Stroke/SE rates per 100 person-years (recorded from the date of the first study visit up to 1 year) were numerically higher in the retro- than the prospectively identified cohort (1.34 [95% CI 1.00 to 1.79] vs. 1.07 [95% CI 0.82 to 1.39]), and the rate of major bleeding per 100 person-years was similar in both cohorts (0.72 [95% CI 0.49 to 1.07] vs. 0.82 [95% CI 0.60 to 1.10]). These differences were not statistically significant: $p=0.257$ and $p=0.624$, respectively (Fig. 4.). When evaluating event rates per 100 person-years up to 2 years, non-significant differences between the retro- and prospectively identified cohorts were also observed for stroke/SE (1.21 [95% CI 0.91 to 1.60] vs. 1.03 [95% CI 0.85 to 1.25], respectively; $p=0.362$) and for major bleeding (0.65 [95% CI 0.44 to 0.95] vs. 0.72 [95% CI 0.57 to 0.91], respectively; $p=0.662$).

All-cause mortality

All-cause mortality rates per 100 person-years during the prospective follow-up (starting from the date of the first study visit up to 1 year) were significantly lower in patients retrospectively identified compared with prospectively identified: 3.04 (95% CI 2.51 to 3.67) vs. 4.05 (95% CI 3.53 to 4.63); $p=0.016$ (Fig. 5.). These differences were also observed for all-cause mortality rates per 100 person-years evaluated up to 2 years: 2.95 (95% CI 2.46 to 3.53) vs. 3.67 (95% CI 3.30 to 4.07); $p=0.039$ in the retro- and prospectively identified cohorts, respectively.

In order to take account of the higher mortality rate over the first 6 months after diagnosis, a further analysis was conducted to compare the cohort identified retrospectively (and followed prospectively from the date of first study visit) with the cohort identified prospectively but excluding all patients who died within 6 months; thus follow-up started at 6 months (Fig.

5b). These analyses found that all-cause mortality rates per 100 person-years between the cohorts were similar: 3.04 (95% CI 2.51 to 3.67) vs. 3.54 (95% CI 2.9 to 4.37) for the retrospective cohort vs. the prospectively identified cohort, excluding patients who died within 6 months of the first visit (Fig. 5b)

DISCUSSION

Interpretations of data from registries that aim to evaluate the characteristics and outcomes of patients with AF need to account for differences in registry design, and in particular, the survivorship bias that is incurred with retrospective enrolment. The timing of the analysis in relation to the natural history of the disease and also the extent of exposure to stroke prevention therapies (such as antithrombotics) and adherence to these therapies are critical to the interpretation of outcomes.

These analyses demonstrate differences in outcome between retrospectively versus prospectively identified patients with AF and the findings are relevant to the interpretation of other registries where the methods of data collection are retrospective (such as the DANISH national registry²⁰), or those that identify patients with established AF (PREFER, EORP)^{11, 21}, versus prospective studies on newly identified AF (GARFIELD, GLORIA, ORBIT, RECORD)^{3, 14, 15, 22}. The significant decrease in events from retrospectively compared with the prospective cohort may be due in part to survivor bias. We have seen from our own analyses and also from the Framingham Heart study that there is an increased hazard for dying soon after the onset of AF.^{19, 23} These patients did not survive to enter the retrospectively identified cohort but were in the prospective identified cohort (Fig. 2.). As a consequence, the data show that the retrospectively identified cohort of patients had different characteristics compared to the prospective identified cohort patients. For example, patients

with more severe comorbid conditions (NYHA class III-IV congestive heart failure) at the time of diagnosis, who died before the study start date, were not included in the analyses of patients who were retrospectively identified (see Fig. 2.), with a consequent under-representation of these comorbidities at baseline.

The study also found a trend (not statistically significant) for differences in the unadjusted stroke rates in the prospectively identified cohort with “newly diagnosed AF” compared with retrospectively identified cohort with “established AF”. This may reflect the natural history of the disease. For example, patients in the retrospectively identified cohort were more likely to have permanent or persistent AF (in greater than half of the patients); they also showed a greater prevalence of prior stroke, moderate-to-severe chronic kidney disease, and prior major bleed than prospectively identified cohort (in whom the median time since diagnosis of AF was 1.8 weeks). It is likely that the progressive nature of cardiovascular disease increases the stroke risk over time after the diagnosis of AF.²⁴⁻²⁷ Other factors, such as non-adherence to OAC, tend to increase over time after the initial critical period at the diagnosis of AF (when patients are most compliant).²⁸ Thus, the time period of evaluation of AF, in relation to its onset, may be of key importance in the interpretations of these findings.

The introduction of NOACs in Europe in 2010 was associated with a change in prescribing practice.^{29, 30} We observed a slight shift in treatment patterns between prospectively identified patients enrolled between March 2010 and October 2011 and those from the retrospectively identified patients (evaluated between December 2009 and October 2011). Overall, prospectively identified patients with a new diagnosis of AF (including a greater proportion with paroxysmal AF) were more likely to receive either AP therapy alone or no antithrombotic therapy. There was a small increment in NOAC prescribing. Fewer patients

with a moderate-to-high risk of stroke refused OAC treatment with the recruitment of patients into the prospective cohort (compared with the retrospectively identified cohort).

Both the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) and GARFIELD-AF focus on newly diagnosed patients (within 12 and 6 weeks of diagnosis, respectively), and both evaluate treatment during the period in which patients are at the highest risk of stroke. However, GLORIA excludes those who have a life expectancy of <1 year at the time of enrolment as well as patients with a medical condition other than AF for which chronic use of VKAs is indicated.²² By contrast, GARFIELD-AF is without exclusions due to comorbidities or treatments.¹⁷ Only a small proportion of patients in GARFIELD-AF (~5.0%) were lost to the prospective follow-up over 2 years.

In conclusion, interpretations of data from AF registries and observational cohorts need to take account of potential sources of bias relating to survivorship and recall, as well as the collection of data in relation to the time from the onset of AF. The analysis of retrospective and prospectively identified data from GARFIELD-AF reveals the potential differences in characteristics and outcomes where the patient enrolment begins retrospectively. For these reasons, a prospective study design was selected for successive cohorts of GARFIELD-AF as the most reliable way of capturing the burden of disease from an unselected population shortly after the diagnosis of AF.

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Declaration of interests

KAAF reports grants and personal fees from Bayer AG, Johnson and Johnson, personal fees from Lilly, grants and personal fees from AstraZeneca, personal fees from Sanofi/Regeneron outside the submitted work. GA reports none. KSP reports having provided statistical support and thought leadership for the Thrombosis Research Institute, during the conduct of the study and KSP has received personal fees from Bayer AG, outside the submitted work. J-PB reports personal fees from Aspen outside the submitted work. AJC is an advisor to Bayer AG, Boehringer Ingelheim, Pfizer/BMS, and Daiichi Sankyo. DAF reports personal fees from Bayer AG outside the submitted work. GK reports grants from Bayer AG during the conduct of the study. AKK reports grants from Bayer AG and personal fees from Bayer AG, Boehringer-Ingelheim Pharma, Daiichi Sankyo Europe, Sanofi SA, and Janssen Pharma outside the submitted work.

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[Table]

Table 1. Baseline characteristics of patients enrolled retrospectively and prospectively from cohort 1 of the GARFIELD-AF registry

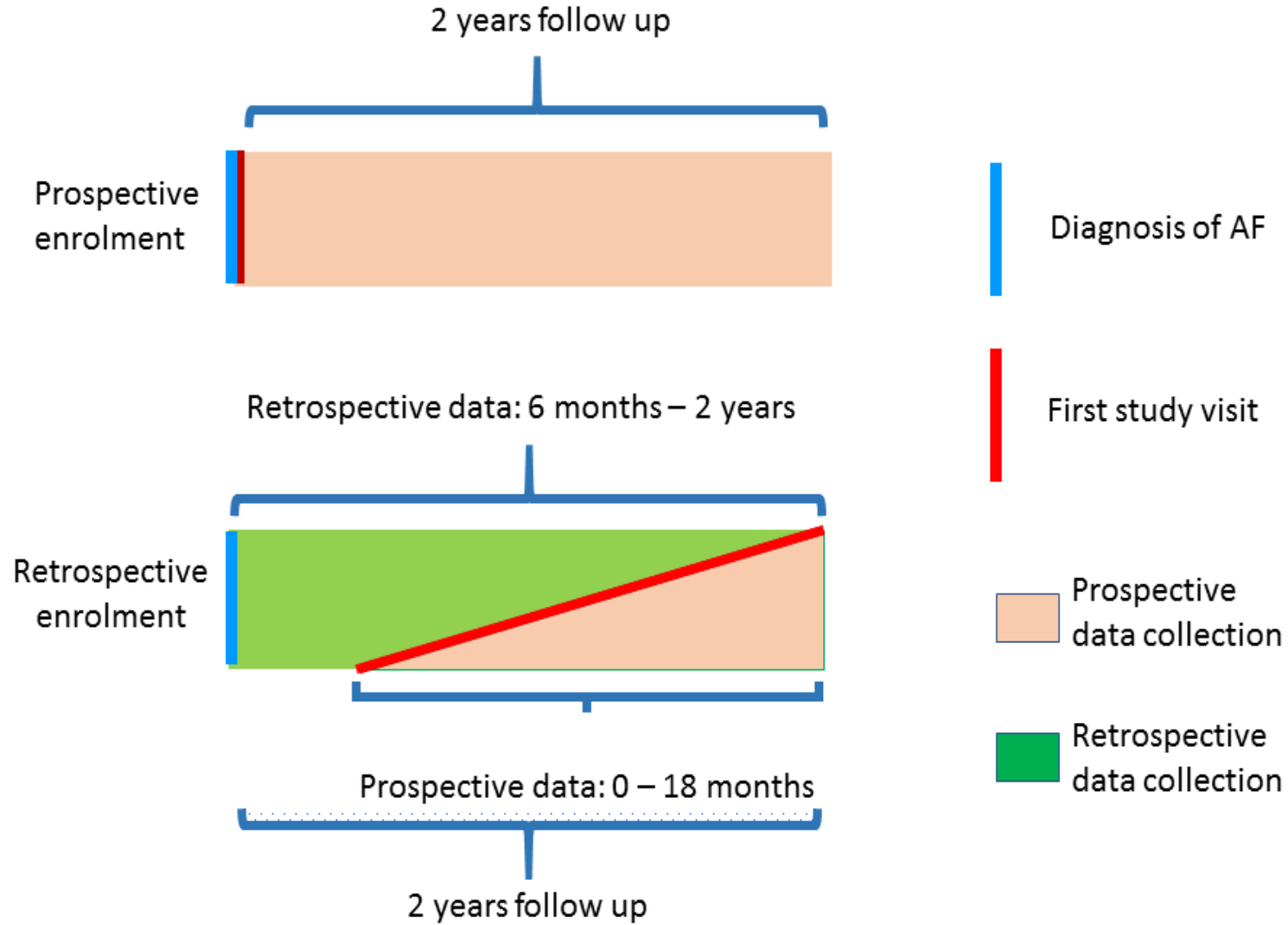
	Retrospectively enrolled cohort (N=5069)	Prospectively enrolled cohort (N=5501)
Female, n/N (%)	2159/5069 (42.6)	2402/5501 (43.7)
Age at diagnosis (years), median (IQR)	71.0 (63.0 to 77.0)	71.0 (63.0 to 78.0)
Time since AF diagnosis (weeks), median (IQR)	57.1 (39.2 to 80.5)	1.8 (0.7 to 3.7)
Systolic BP (mm Hg), median (IQR)	132.0 (120.0 to 145.0)	130.0 (120.0 to 145.0)
LVEF <40%, n/N (%)	277/2837 (9.8)	304/3314 (9.2)
Type of AF diagnosed at start of study, n/N (%)		
Unclassified	676/5065 (13.3)	2465/5499 (44.8)
Paroxysmal	1567/5065 (30.9)	1347/5499 (24.5)
Persistent	982/5065 (19.4)	909/5499 (16.5)
Permanent	1840/5065 (36.3)	778/5499 (14.1)
Congestive heart failure NYHA class, n/N (%)		
I	167/910 (18.4)	183/993 (18.4)
II	493/910 (54.2)	483/993 (48.6)
III	211/910 (23.2)	271/993 (27.3)
IV	39/910 (4.3)	56/993 (5.6)

Coronary artery disease, n/N (%)	963/5065 (19.0)	1059/5499 (19.3)
Acute coronary syndromes, n/N (%)	487/5065 (9.6)	553/5499 (10.1)
Stroke, n/N (%)	550/5065 (10.9)	472/5499 (8.6)
History of bleeding, n/N (%)	195/5065 (3.8)	172/5499 (3.1)
History of hypertension, n/N (%)	3986/5065 (78.7)	4224/5499 (76.8)
Hypercholesterolaemia, n/N (%)	2114/5065 (41.7)	2027/5499 (36.9)
Diabetes, n/N (%)		
No	3959/5064 (78.2)	4284/5499 (77.9)
Type I	47/5064 (0.9)	57/5499 (1.0)
Type II	1058/5064 (20.9)	1158/5499 (21.1)
Chronic kidney disease – moderate-to-severe grade, n/N (%)	529/5065 (10.4)	495/5483 (9.0)
CHA ₂ DS ₂ -VASc score *		
Mean (SD)	3.2 (1.6)	3.2 (1.6)
Median (IQR)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)
HAS-BLED score [†]		
Mean (SD)	1.5 (1.0)	1.5 (0.9)
Median (IQR)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)

AF, atrial fibrillation; BP, blood pressure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation

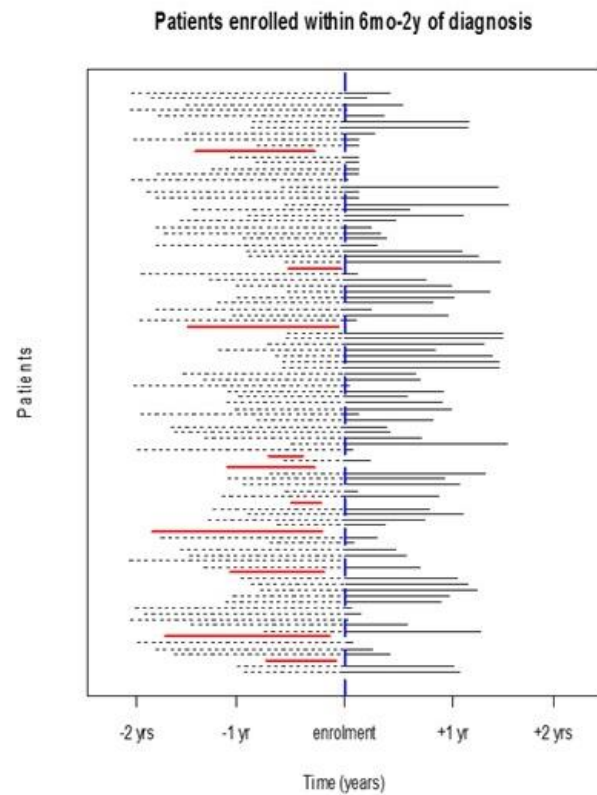
Missing from the analyses: * established AF (159); newly diagnosed AF (94); [†] established AF (2037); newly diagnosed AF (1961)

Figure 1



Retrospectively enrolled cohort

- Patients are enrolled within 6 months to 2 years of diagnosis (retrospective patients)
- Patients who die before enrolment (in red) cannot be included



Prospectively enrolled cohort

- Newly diagnosed patients are recruited to the study
- Patients with <2 year survival (in red) are now included

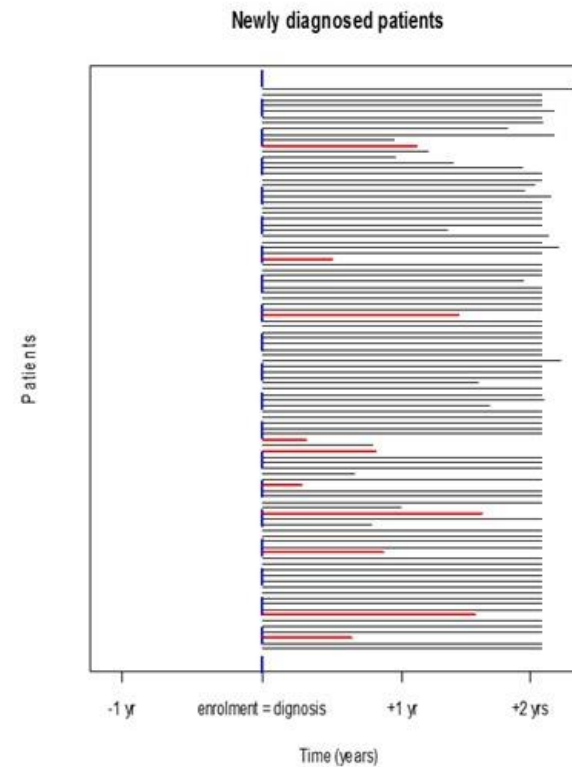


Figure 3

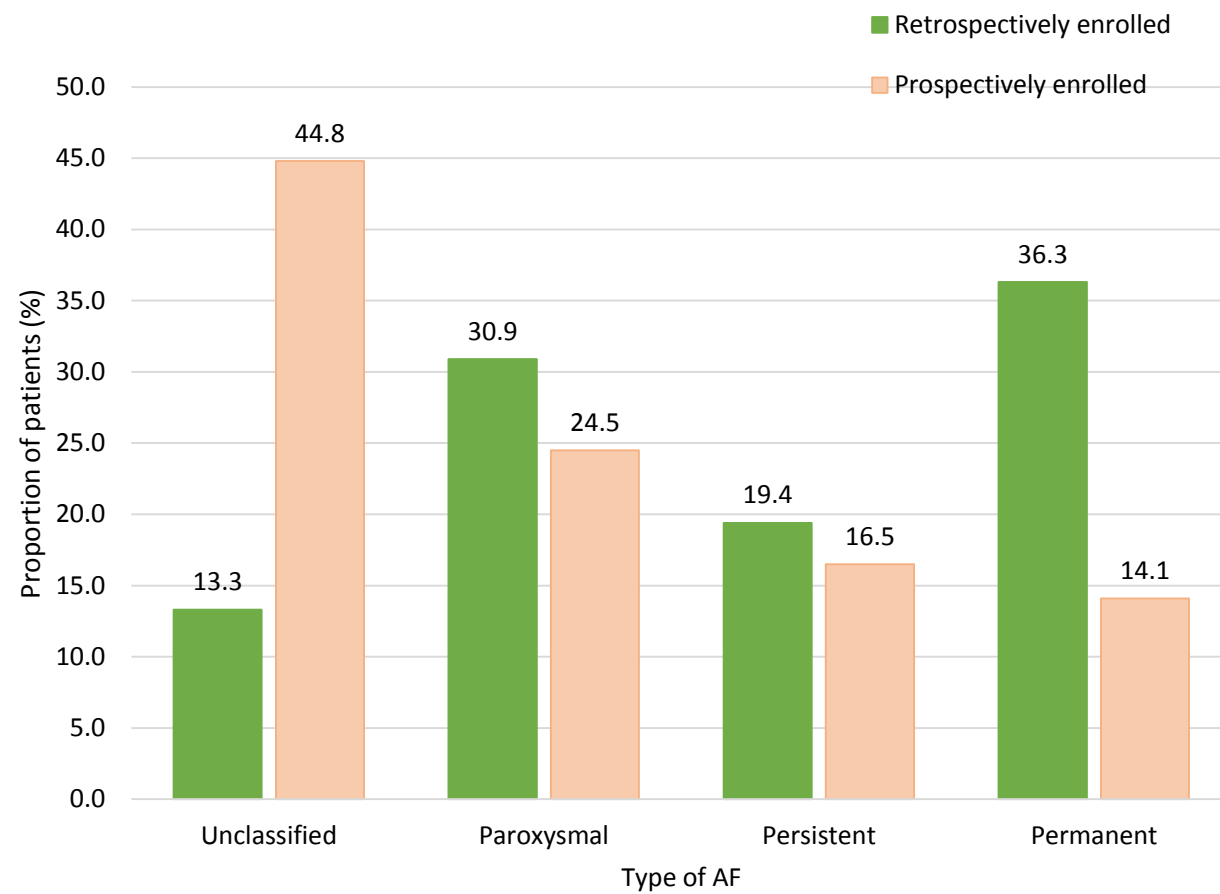


Figure 4

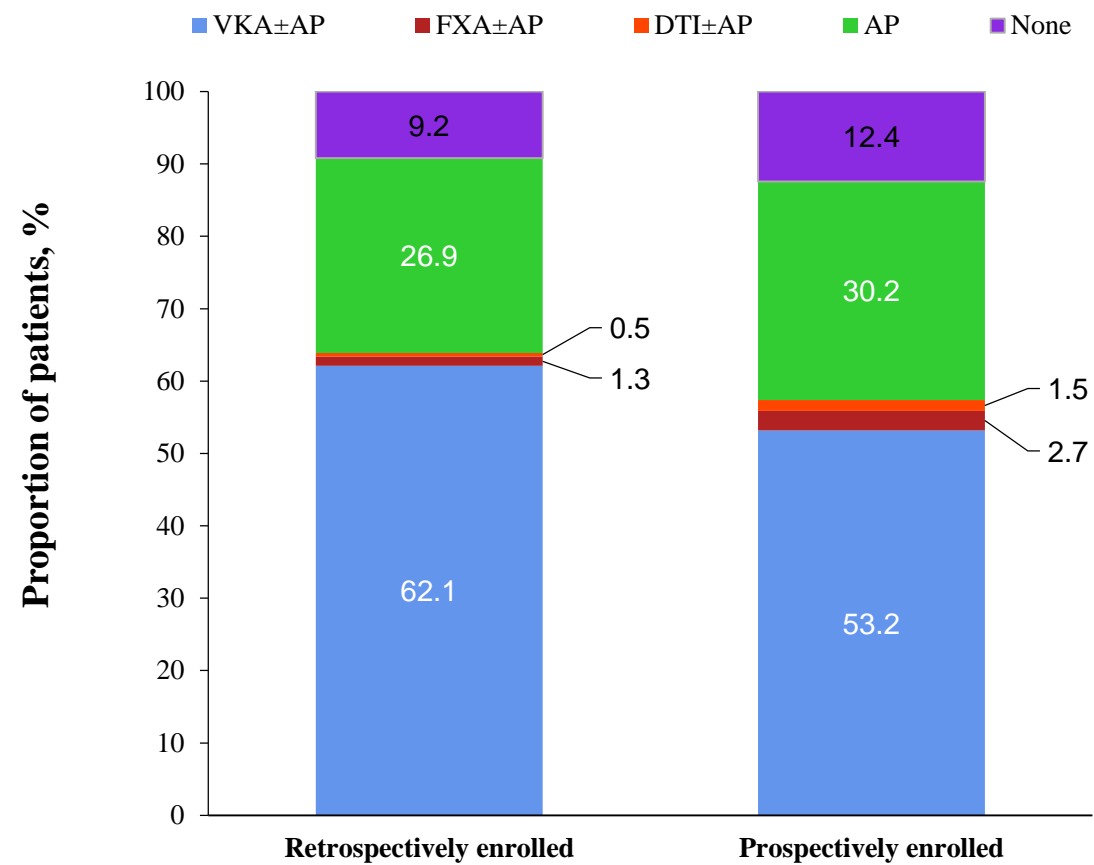
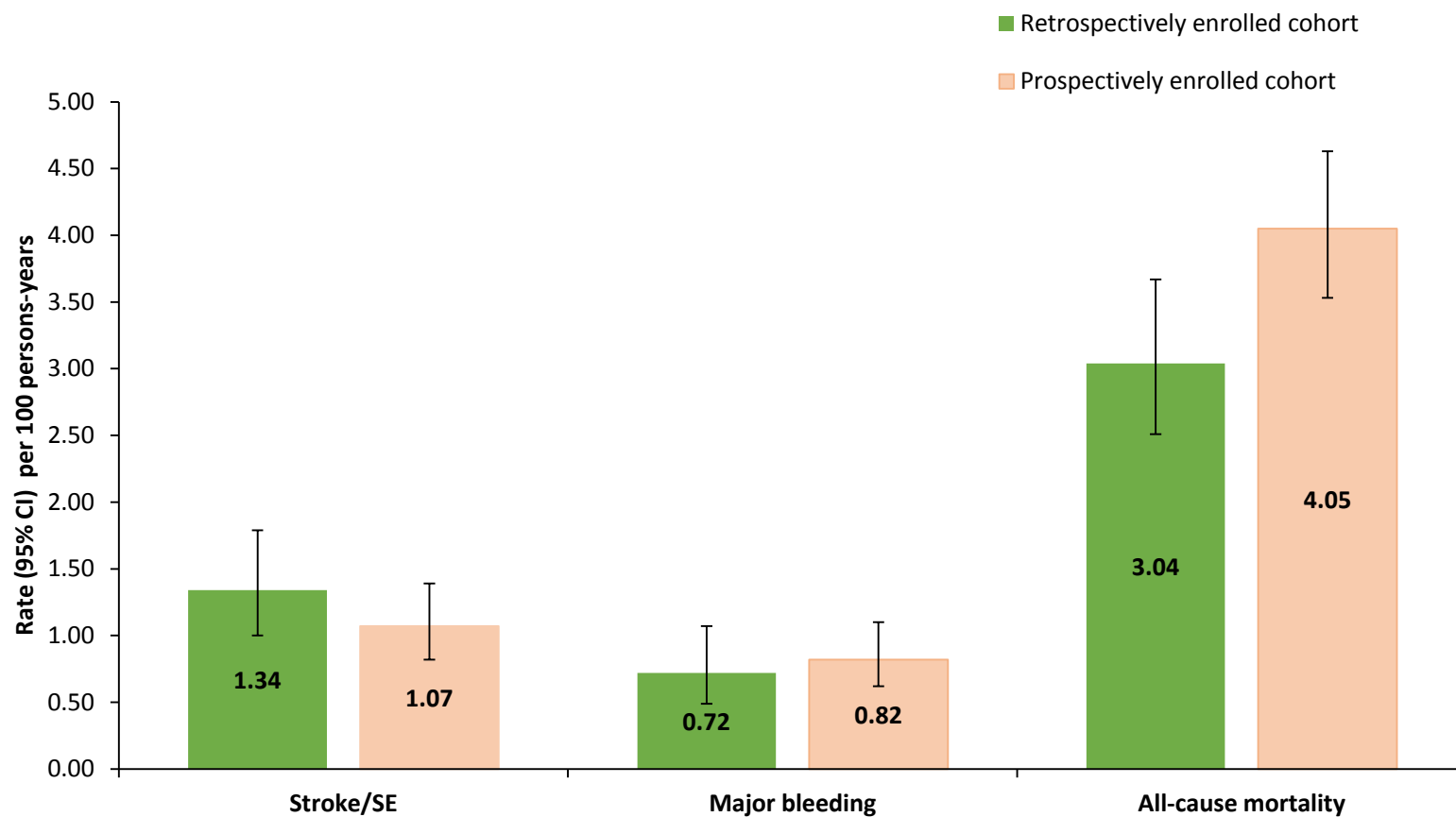
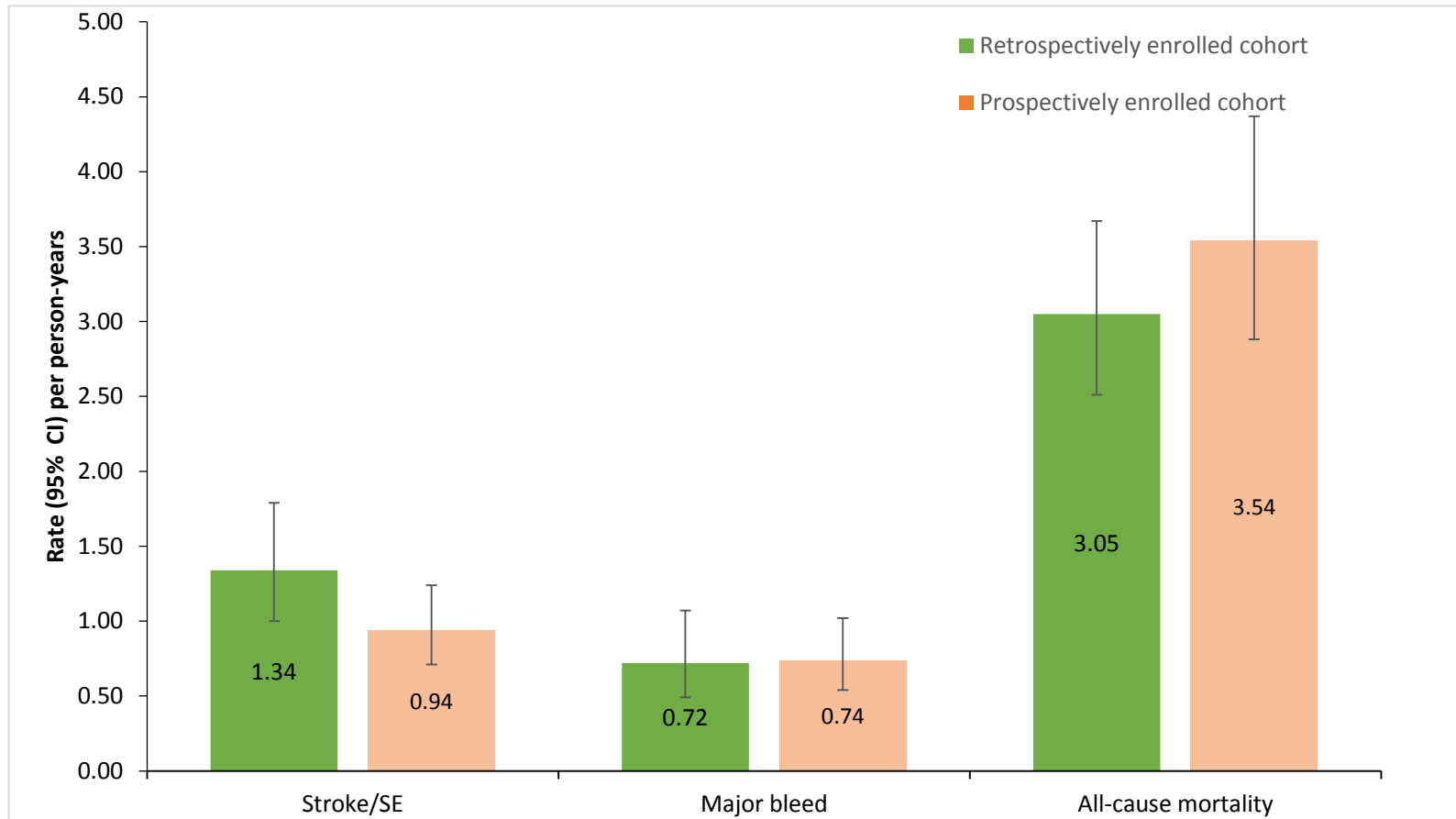


Figure 5a



	Stroke/SE		Major bleeding		All-cause mortality	
Enrolment	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Prospective
Person-years	3432.7	5144.1	3466.7	5146.3	3491.1	5166.1
Events	46	55	25	42	106	209

Figure 5b



	Stroke/SE		Major bleeding		All-cause mortality	
Enrolment	Retrospective	Prospective*	Retrospective	Prospective*	Retrospective	Prospective*
Person-years	3432.7	5117.1	3466.7	5119.4	3491.1	2509.3
Events	46	48	25	38	106	89

[Figure Legends]

Figure 1. Description of time-to-event analyses relative to enrolment and diagnosis of atrial fibrillation

AF, atrial fibrillation

Figure 2. Schematic representation of the study design. The figure illustrates patients enrolled either retrospectively or prospectively in relation to survival over the time period from diagnosis of atrial fibrillation. The red lines indicate the patients who died in our schema (not actual data). These patients would be missing from the data collected retrospectively, but included in the data from patients enrolled prospectively.

Figure 3. Type of AF at first study visit in patients with established AF enrolled retrospectively or newly diagnosed AF enrolled prospectively

Figure 4. Antithrombotic treatment for patients in the retrospectively enrolled cohort (n=5069) or the prospectively enrolled cohort (n=5501)

AP, antiplatelet; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; VKA, vitamin K antagonist.

Figure 5. Summary of event rates and 95% confidence intervals (per 100 person-years) for data collected prospectively a. starting from the date of the first study visit up to 1 year
b. Mortality is based on a landmark analysis, which excluded all patients who died within 6 months and follow-up starts at 6 months (day 183). Event rates for stroke/SE and for major bleed are in the subset of patients who survived to 6 months, but start follow-up at the time of AF onset.

SE, systemic embolism; AF, atrial fibrillation