CLINICAL RESEARCH STUDY

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Outcomes of Oral Anticoagulation in Atrial Fibrillation Patients With or Without Comorbid Vascular Disease: Insights From the GARFIELD-AF Registry

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ABSTRACT

BACKGROUND: Many patients with atrial fibrillation suffer from comorbid vascular disease. The comparative efficacy and safety of different types of oral anticoagulation (OAC) in this patient group have not been widely studied.
METHODS: Adults with newly diagnosed atrial fibrillation were recruited into the prospective observational registry, GARFIELD-AF, and followed for 24 months. Associations of vascular disease with clinical outcomes were analyzed using adjusted hazard ratios (HR) obtained via Cox proportional-hazard modeling. Outcomes of OAC vs no OAC, and of non-vitamin K antagonist OAC (NOAC) vs vitamin K antagonist (VKA) treatment, were compared by overlap propensity-weighted Cox proportional-hazard models.
RESULTS: Of 51,574 atrial fibrillation patients, 25.9% had vascular disease. Among eligible atrial fibrillation patients, those with vascular disease received OAC less frequently than those without (63% vs 73%). Over 2-year follow-up, patients with vascular disease showed a higher risk of all-cause mortality (HR 1.30; 95% confidence interval [CI], 1.16-1.47) and cardiovascular mortality (HR 1.59; 95% CI, 1.28-1.97). OAC was associated with a significant decrease in all-cause mortality and non-hemorrhagic stroke, and increased risk of major bleeding in non-vascular disease. In vascular disease, similar but non-significant trends existed for stroke and major bleeding. A significantly lower risk of all-cause mortality (HR 0.74; 95% CI, 0.61-0.90) and major bleeding (HR 0.45; 95% CI, 0.29-0.70) was observed in vascular disease patients treated with NOACs, compared with VKAs.
CONCLUSIONS: Atrial fibrillation patients with a history of vascular disease have worse long-term outcomes than those without. The association of NOACs vs VKA with clinical outcomes was more evident in atrial fibrillation patients with vascular disease.
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KEYWORDS: Anti-coagulation; Atrial fibrillation; Bleeding; Stroke; Vascular disease

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INTRODUCTION

Many patients with atrial fibrillation suffer from comorbid vascular disease. In recently published large prospective registries, patients who suffered from one or more comorbidities included 20% showing coronary artery disease,[1,2] 16% showing prior myocardial infarction,[3] and 13% showing peripheral artery disease.[3] These atrial fibrillation patients may need additional drug treatment such as antiplatelet therapy,[4] and many of them may have undergone revascularization procedures. Antiplatelet monotherapy treatment for stroke prevention has become obsolete[5,6] and thus, is not a recommended option for atrial fibrillation patients with comorbid vascular disease. Patients treated with dual antithrombotic therapy run a risk of excess bleeding. Lipid-modifying strategies are the standard of care in vascular disease, which contributes to polypharmacy with its inherent risk of poor adherence.[7] Insufficient data are available on the long-term outcomes of these patients.

CLINICAL SIGNIFICANCE

- One of 4 patients with newly diagnosed atrial fibrillation had a history of vascular disease.
- Atrial fibrillation patients with vascular disease had a higher risk of cardiovascular outcomes.
- Atrial fibrillation patients with vascular disease were less frequently anticoagulated.
- Atrial fibrillation patients with vascular disease had better outcomes from non-vitamin K oral anticoagulants compared with vitamin K oral anticoagulants.

In this analysis we studied the outcomes in atrial fibrillation patients with comorbid vascular disease compared with those without vascular disease by anticoagulation treatment. We used data from GARFIELD-AF (Global Anticoagulant Registry in the FIELD − Atrial Fibrillation), a prospective non-interventional registry of more than 50,000 consecutively enrolled patients with newly diagnosed atrial fibrillation and one or more investigator-determined defined risk factors for stroke.[8]

METHODS

Study Design and Participants

GARFIELD-AF is the largest fully recruited multinational prospective registry in atrial fibrillation.[8] Patients were prospectively recruited between March 2010 and August 2016 in over 1000 investigational sites (identified nationally as representative) in 35 countries. Adults ≥18 years were eligible for inclusion if they were diagnosed with atrial fibrillation within 6 weeks of study entry. Identification of patients was according to standard local practice, and patients were required to have at least one unspecified investigator-defined risk factor for stroke. Patients were enrolled prospectively and consecutively at sites that reflected the diversity of 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). They were included in 5 consecutive cohorts of about 10,000 patients each.

All patients who reported coronary artery disease, aortic or peripheral artery disease, acute coronary syndromes, myocardial infarction, stenting, or coronary artery bypass graft were classified as having vascular disease. For the purpose of these analyses, patients for whom follow-up or vascular disease information was unavailable were excluded from the analysis.

Ethics Statement

Independent ethics committee and hospital-based institutional review board approvals were obtained. The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation − Good Pharmacoepidemiologic and Clinical Practice guidelines. Written informed consent was obtained from all study participants.

Clinical Characteristics and Follow-Up

Baseline characteristics collected at study entry included: medical history, care setting, type of atrial fibrillation, date and method of diagnosis of atrial fibrillation, symptoms, antithrombotic treatment (vitamin K antagonist [VKA], non-vitamin K antagonist oral anticoagulant [NOAC], antiplatelet treatment), and cardiovascular drugs. The risk profiles for death, non-hemorrhagic stroke/systemic embolism, and bleeding were assessed with the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism − Vascular disease, Age 65-74 years, Sex category), the HAS-BLED (Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drug/alcohol usage)[6] and the GARFIELD-AF risk calculator.[9]

Collection of follow-up data using an electronic case report form occurred at 4-month intervals up to 24 months or until death or loss to follow-up, whichever occurred first. Submitted data were examined for completeness and accuracy by the coordinating center (Thrombosis Research Institute, London, UK), and data queries were sent to study sites. In accordance with the study protocol, 20% of all electronic case report forms were monitored against source documentation.[10]

Outcomes

The primary clinical outcomes in this study were all-cause mortality, non-hemorrhagic stroke/systemic embolism, and

major bleeding. Major bleeding was defined as clinically overt bleeding associated with a critical site, a fall in hemoglobin (≥2 g/dL), transfusion of packed red blood cells (≥2 units), hemorrhagic stroke, or fatal outcome (International Society on Thrombosis and Haemostasis definition).

Statistical Analysis

The distribution of variables collected at baseline is reported according to the presence of vascular disease. Continuous variables are reported using medians and interquartile range, and categorical variables are presented as percentages and frequency counts. As studies with large sample sizes tend to produce statistically significant findings in the presence of clinically irrelevant differences, no formal statistical tests were performed for the baseline tables. Data for components of the CHA_2DS_2-VASc and HAS-BLED risk stratification scores were collected; the latter was calculated excluding labile international normalized ratios, as this was not recorded at baseline.

Our first aim was to identify associations between baseline vascular disease and selected clinical endpoints: all-cause, cardiovascular, and non-cardiovascular mortality, non-hemorrhagic stroke/systemic embolism, major bleeding, myocardial infarction/acute coronary syndromes, and new/worsening heart failure. The follow-up period was calculated from the date of enrollment and truncated at the occurrence of the first event of interest, death, loss to follow-up, or 2 years after enrollment, whichever occurred first. The occurrence of clinical outcomes is described using the number of events, event rate per 100 person-years, and 95% confidence intervals (CI). Person-year rates were estimated using a Poisson model. The hazard ratio (HR) for the selected clinical outcomes was estimated using Cox proportional-hazards models adjusted for the confounding factors (see Supplementary Material text information, available online). A robust covariance estimate was included to account for correlation within countries.

Secondly, we examined the comparative effectiveness of OAC (NOAC + VKA) vs no OAC and NOAC vs VKA among anticoagulated patients according to vascular disease at baseline. Comparative effectiveness analyses were restricted to patients enrolled from April 2013-September 2016 (when NOACs became widely available) and who were eligible for anticoagulation (CHA_2DS_2-VASc score ≥2, excluding sex). Treatment comparisons were performed within each group by means of Cox proportional-hazards models using a propensity method of overlap weighting to balance covariates in the population. This applied method overlaps weights and optimizes the efficiency of comparisons by defining the population with the most overlap in the covariates between treatment groups. This scheme eliminates the potential for outlier weights by avoiding a weight based on a ratio calculation using values bounded by 0 and 1. Thus, when using overlap weights, many of the concerns about the assessment and the trimming of the weights were eliminated. Covariates evaluated in the weighting scheme included demographic characteristics and medical history. To determine whether the effect of baseline treatment differed between vascular disease groups, we reported *P* values for interaction between vascular disease and baseline treatment. The interaction term was added to Cox proportional-hazards models, with the same covariates included in the weighting scheme. Treatment was defined as the first treatment received at the time of enrollment, approximating "intention-to-treat".

A sensitivity analysis was performed by adding carotid occlusive disease to the vascular disease definition. The associations between vascular disease and clinical outcomes, as well as the comparative effectiveness analyses by vascular disease group, were repeated using this definition.

Only complete cases were presented in descriptive tables. Multiple imputation was applied for the estimation of the vascular disease association coefficients and in the comparative effectiveness analyses. Standard errors were obtained by combining estimates across 5 imputed databases. Statistical analyses were carried out using SAS Enterprise Guide (version 8.1; SAS, Cary, NC).

RESULTS

Vascular disease and follow-up information was available for 51,574 of 52,057 patients in GARFIELD-AF (Supplementary Figure 1, available online). After excluding cohorts 1-2 and patients who were ineligible for OAC treatment, not receiving treatment or with missing treatment information, 18,351 patients remained. Of these, 25.9% had vascular disease. Significant differences existed between the vascular and non-vascular groups: vascular patients were older in comparison with non-vascular patients (Age, median [Q1; Q3]: 72 years [65; 79] vs 70 years [62; 78]) and, as expected, had more comorbidities such as heart failure (37% vs 18%), hypertension (83% vs 74%), hypercholesterolemia (58% vs 36%), and diabetes mellitus (29% vs 20%) (Table).

Among atrial fibrillation patients eligible for oral anticoagulation (ie, CHA_2DS_2-VASc ≥2), vascular patients were less likely than non-vascular patients to receive OAC (63% vs 73%), and more likely to be given antiplatelet agents (59% vs 26%), including antiplatelet monotherapy (31 vs 16%, respectively, Figure 1). Patients with vascular disease less frequently received NOACs (24% vs 30%) and VKAs (39% vs 43%) compared with those without. No antithrombotic drug was used in 6% of eligible vascular patients vs 11% in patients without vascular disease.

In NOAC-treated patients with available dosing information enrolled in cohorts 3-5 (the period when NOACs were available), the proportion of patients who received a non-recommended low NOAC dose was higher among patients with vascular disease than among patients without vascular disease (25% vs 23%, respectively). In patients with vascular disease receiving non-recommended low NOAC dose, 40% received concomitant antiplatelet therapy. The corresponding proportion using antiplatelet therapy among non-

Table Baseline Characteristics of Patients by Vascular Disease

Baseline Characteristics	Without Vascular Disease (n = 38,209)	With Vascular Disease (n = 13,365)
Sex, n (%)		
Male	20,497 (53.6)	8291 (62.0)
Female	17,711 (46.4)	5074 (38.0)
Age, years: median (Q1; Q3)	70.0 (62.0; 78.0)	72.0 (65.0; 79.0)
Ethnicity, n (%)		
Caucasian	22,430 (60.3)	9323 (71.0)
Hispanic/Latino	2754 (7.4)	625 (4.8)
Asian	11,248 (30.2)	2907 (22.1)
Afro-Caribbean/Mixed/Other	775 (2.1)	282 (2.1)
Body mass index, kg/m^2: median (Q1; Q3)	26.7 (23.8; 30.5)	27.4 (24.4; 31.2)
Systolic blood pressure, mm Hg: median (Q1; Q3)	131.0 (120.0; 145.0)	130.0 (120.0; 144.0)
Diastolic blood pressure, mm Hg: median (Q1; Q3)	80.0 (70.0; 89.0)	80.0 (70.0; 86.0)
Pulse, beats per minute: median (Q1; Q3)	85.0 (71.0; 107.0)	81.0 (70.0; 100.0)
Type of atrial fibrillation, n (%)		
Permanent	4778 (12.5)	1802 (13.5)
Persistent	5940 (15.5)	1779 (13.3)
Paroxysmal	10,816 (28.3)	3407 (25.5)
New onset (unclassified)	16,675 (43.6)	6377 (47.7)
Care setting specialty at diagnosis, n (%)		
Internal medicine/Neurology/Geriatrics	7931 (20.8)	2425 (18.1)
Cardiology	24,503 (64.1)	9365 (70.1)
Primary care/general practice	5775 (15.1)	1575 (11.8)
Care setting location at diagnosis, n (%)		
Hospital	21,429 (56.1)	8631 (64.6)
Office/Anticoagulation clinic/Thrombosis center	12,433 (32.5)	3385 (25.3)
Emergency department	4347 (11.4)	1349 (10.1)
Medical history, n (%)		
Heart failure	6734 (17.6)	4909 (36.7)
Carotid occlusive disease	631 (1.7)	892 (6.8)
Venous thrombo-embolism	953 (2.5)	390 (2.9)
Prior stroke/transient ischemic attack/systemic embolism	3962 (10.4)	1826 (13.8)
Prior bleeding	826 (2.2)	480 (3.6)
Hypertension	28,231 (74.1)	11,052 (82.8)
Hypercholesterolemia	13,305 (35.9)	7275 (58.1)
Diabetes	7527 (19.7)	3925 (29.4)
Cirrhosis	234 (0.6)	57 (0.4)
Moderate to severe chronic kidney disease	3416 (9.2)	1905 (14.9)
Dementia	530 (1.4)	222 (1.7)
Heavy alcohol consumption, n (%)	834 (2.6)	188 (1.7)
Current smoker, n (%)	3795 (10.9)	1365 (11.1)
Antithrombotic treatment, n (%)		
NOAC only	9634 (25.5)	1838 (14.0)
NOAC + AP	1218 (3.2)	1282 (9.8)
VKA only	12,556 (33.3)	2695 (20.5)
VKA + AP	2379 (6.3)	2421 (18.4)
AP only	6608 (17.5)	4075 (31.0)
None	5352 (14.2)	813 (6.2)
AP treatment, n (%)	10,205 (27.0)	7778 (59.3)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0; 4.0)	4.0 (3.0; 5.0)
HAS-BLED score,* median (Q1; Q3)	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)
GARFIELD-AF death score,† median (Q1; Q3)	3.9 (2.2; 7.0)	7.6 (4.6; 13.0)
GARFIELD-AF stroke score,‡ median (Q1; Q3)	1.4 (1.0; 2.1)	2.1 (1.5; 3.1)
GARFIELD-AF bleeding score,§ median (Q1; Q3)	1.5 (0.9; 2.2)	2.1 (1.4; 3.1)

AP = antiplatelet; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease; HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drug/alcohol usage; NOAC = non-VKA oral anticoagulant; Q1, Q3 = first and third quartile; VKA = vitamin K antagonist.

*The risk factor 'labile international normalized ratios' is not included in the HAS-BLED score as it was not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).

†Represents the expected probability of death within 2-year follow-up.

‡Represents the expected probability of non-hemorrhagic stroke/SE within 2-year follow-up.

§Represents the expected probability of major bleeding within 2-year follow-up.

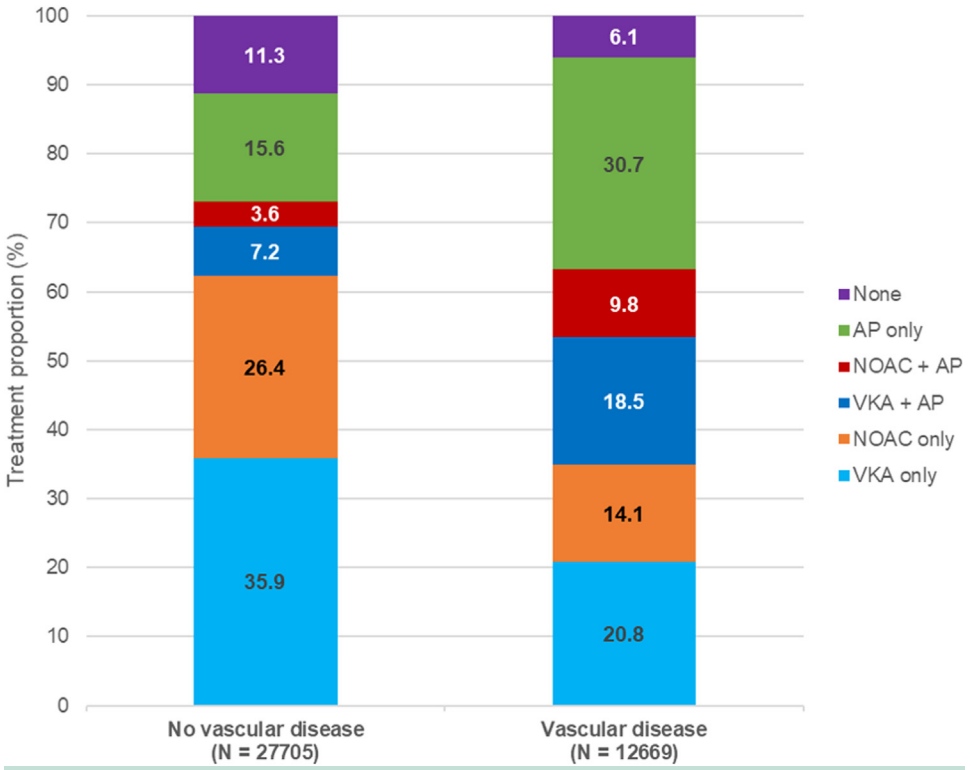

Figure 1 Distribution of baseline antithrombotic treatment* by vascular disease among patients with CHA_2DS_2-VASc ≥2 (excluding sex).
*Patients with unavailable antithrombotic treatment information were excluded from this analysis (n = 591). AP = antiplatelet; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease score; NOAC = non-VKA oral anticoagulant; VKA = vitamin K antagonist.

vascular patients treated with non-recommended low doses was 11% (Supplementary text information).

Long-Term Outcomes of History of Vascular Disease vs no History of Vascular Disease

Vascular patients experienced a significantly higher risk of all-cause (HR 1.30; 95% CI, 1.16-1.47) and cardiovascular mortality (HR 1.59; 95% CI, 1.28-1.97), as well as new acute coronary syndromes (HR 2.62; 95% CI, 2.08-3.29). In addition, trends existed toward more frequent non-hemorrhagic stroke/systemic embolism (HR 1.16; 95% CI, 0.99-1.37), major bleeding (HR 1.17; 95% CI, 0.98-1.39), and new/worsening heart failure (HR 1.17; 95% CI, 0.98-1.39) (Figure 2 and Supplementary Table 1, available online).

Outcomes With or Without Oral Anticoagulation Related to History of Vascular Disease

Figure 3A and Supplementary Tables 2–4 (available online) show the 2-year outcomes in relation to the use of oral anticoagulation in patients with history of vascular disease vs those without.

OAC use in patients without a history of vascular disease significantly lowered the risks of all-cause mortality (HR 0.72; 95% CI, 0.63-0.82) and non-hemorrhagic stroke/systemic embolism (HR 0.64; 95% CI, 0.49-0.84), but at the cost of significantly more major bleeding (HR 1.40; 95% CI, 1.03-1.90) compared with no anticoagulation. Patients with a history of vascular disease showed only a trend toward less all-cause death (HR 0.94; 95% CI, 0.81-1.11) and non-hemorrhagic stroke/systemic embolism (HR 0.84; 95% CI, 0.59-1.21), and a trend toward more major bleeding (HR 1.32; 95% CI, 0.90-1.93) with the use of oral anticoagulants vs none. *P* values for the interactions between vascular disease and treatment are given in Supplementary Table 5 (available online). For the OAC vs no OAC, there was borderline significance for the endpoint of mortality but not for the other endpoints.

Outcomes With Type of Oral Anticoagulation Related to History of Vascular Disease

Supplementary Tables 6–8 (available online) and Figure 3B show the 2-year outcomes comparing VKA with NOACs in patients with a history of vascular disease vs those without. After applying comparative effectiveness models to patients with a history of vascular disease, a

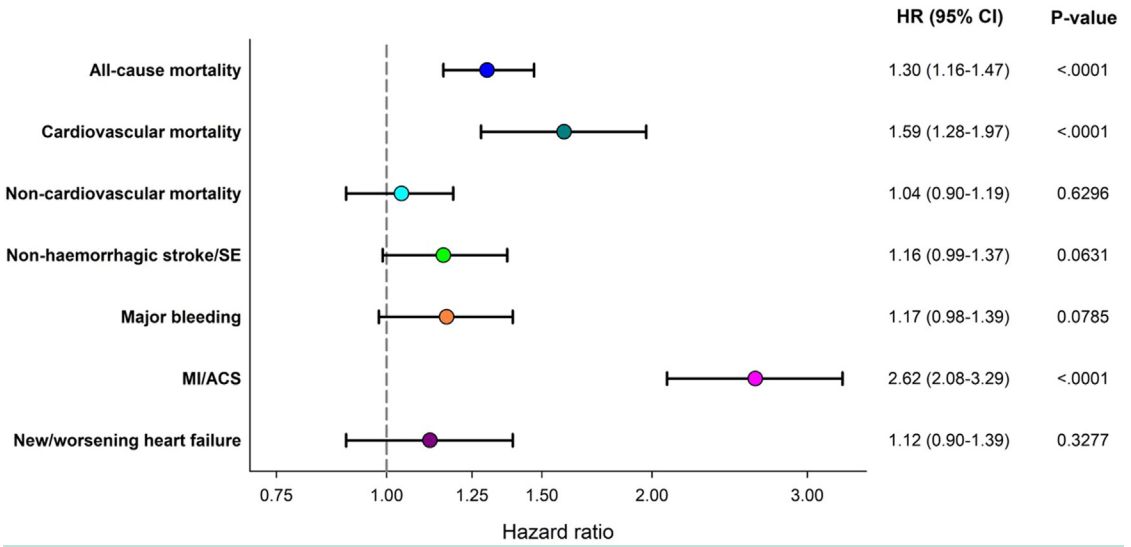

Figure 2 Adjusted* hazard ratios for selected outcomes of vascular disease vs no vascular disease (reference) within 2-year follow-up.
*Adjusted by sex, age, ethnicity, type of atrial fibrillation, congestive heart failure, diabetes, hypertension, prior stroke/transient ischemic attack/systemic embolism, prior bleeding, moderate to severe, current smoking, heavy alcohol consumption, baseline anticoagulation. and antiplatelet therapy.
ACS = acute coronary syndrome; MI = myocardial infarction; SE = systemic embolism.

significant benefit of all-cause mortality (HR 0.74; 95% CI, 0.61-0.90), a trend toward less non-hemorrhagic stroke/systemic embolism (HR 0.81; 95% CI, 0.52-1.28), and a significant benefit of less major bleeding (HR 0.45; 95% CI, 0.29-0.70) with NOACs in comparison with the use of vitamin K antagonists was observed. Patients without a history of vascular disease showed only a trend toward less all-cause mortality (HR 0.86; 95% CI, 0.73-1.01). No evidence of a reduction in the risk of non-hemorrhagic stroke/systemic embolism (HR 0.99; 95% CI, 0.70-1.39) or major bleeding (HR 0.98; 95% CI, 0.73-1.30) were observed with the use of NOACs vs vitamin K-antagonists. *P* values for the interactions between OAC type and vascular disease status are given in Supplementary Table 9 (available online). A significantly different effect of NOAC vs VKA between vascular disease groups was observed for major bleeding. The use of NOACs was associated with a reduced risk of major bleeding (HR 0.45; 95% CI, 0.29-0.70) in patients with vascular disease. The same was not seen in those without vascular disease (HR 0.98; 95% CI, 0.73-1.30; interaction *P* value: 0.0294).

Sensitivity Analysis

A sensitivity analysis added carotid occlusive disease to the vascular disease definition. The number of patients with vascular disease at baseline in the sensitivity analysis was 13,996 (27.1%). The modification of the definition increased the overall prevalence of baseline vascular disease by approximately 1% (from 26% to 27%). The differences in clinical outcomes compared with the main analysis are negligible (Supplementary Table 10). Effects of treatment by vascular disease group also remain very similar between the 2 definitions (Supplementary Tables 11 and 12).

DISCUSSION

The prospective GARFIELD-AF registry clearly shows that patients with atrial fibrillation and a history of vascular disease have worse long-term outcomes than patients without such a history. They were less likely to receive anticoagulation, in particular, NOACs, and, as expected, more likely to receive antiplatelet agents. They also received antiplatelet monotherapy (in the absence of an anticoagulant) more often, but such therapy has not been shown to be effective in the prevention of atrial fibrillation-related stroke.[11,12] When anticoagulated, vascular patients appear to receive greater benefit from NOACs than from VKAs.

Atherosclerotic disease is commonly seen in patients with atrial fibrillation: up to 25% in atrial fibrillation registries and in at least 30% in the recent randomized trials on optimal oral anticoagulation.[1-3,13] The combination of these conditions complicates the medical management of each: antiplatelet therapy is recommended for vascular disease, and anticoagulation for atrial fibrillation. Also in consideration are the interventional strategies for vascular disease and invasive procedures for atrial fibrillation. Antiplatelet and oral anticoagulation combined continue to be prescribed as therapy for these patients, whether chosen as a medical approach or as a subsequent treatment after interventional therapy. Numerous randomized clinical trials have tested the optimal antithrombotic treatment of percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndromes,[14] and shown

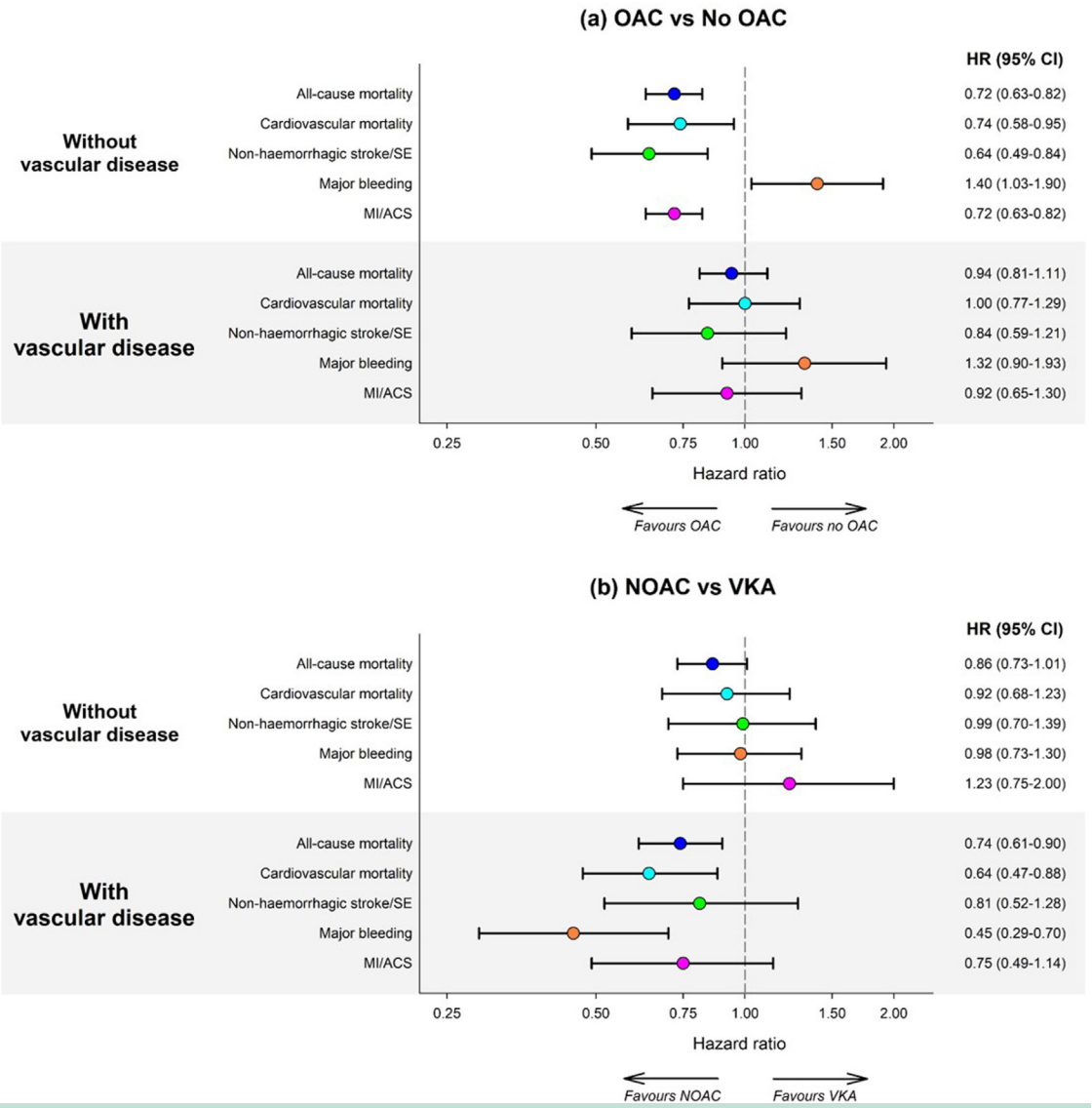

Figure 3 Adjusted* hazard ratios comparing (**A**) OAC vs No OAC (reference); (**B**) NOAC vs vitamin K antagonists (reference) baseline treatment through 2 years of follow-up by vascular disease presence at baseline.
*Adjusted using an overlap-weighted Cox model. Variables included in the weighting scheme: country and cohort of enrollment, sex, age, ethnicity, type of atrial fibrillation, care setting specialty and location, congestive heart failure, carotid occlusive disease, prior stroke/transient ischemic attack/systemic embolism, prior bleeding, venous thromboembolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyper- or hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet use.
NOAC = non-VKA OAC; OAC = Oral anticoagulant; VKA = vitamin K antagonist.

that modification of both antiplatelet (stopping use of aspirin) and anticoagulation (switching from VKA to NOACs) therapies improved outcomes with regards to bleeding without affecting ischemic events. A good example is the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) study; long-term rivaroxaban monotherapy was associated with a 38% lower risk of total cardiovascular and bleeding events in patients with atrial fibrillation and stable coronary artery disease compared with combination therapy.[15]

The benefit of OAC vs no OAC against ischemic stroke was significant in non-vascular, but not in vascular, patients. However, the difference in treatment effects between patients with and without vascular disease was not significant, as shown by the *P* value for interaction. Further studies in a larger patient population are required to confirm this result.

The benefits of NOACs compared with VKA were more evident in patients with vascular disease, especially with regard to major bleeding. One would expect the contrary

because vascular disease patients more often used antiplatelet agents, but in clinical practice, they tend to more often receive a non-recommended lower dose of a direct oral anticoagulant[16,17] or single or dual antiplatelet therapy.[18] However, a higher number of patients with vascular disease than without were under-dosed and on concomitant antiplatelet therapy. It is possible that these under-dosed patients had better outcomes with the use of more efficacious and safer anticoagulants. Interestingly, patients in the AFIRE trial with preserved renal function benefitted from physician-guided lower dosing of rivaroxaban, which was associated with a similar rate of thrombotic and decreased rate of hemorrhagic events compared with standard-dose therapy rivaroxaban. The difference was significant for patients treated with rivaroxaban and antiplatelet drugs in combination, although not for those on rivaroxaban monotherapy.[19]

Limitations

Although GARFIELD-AF is a very large global and well-validated registry,[10] it has limitations inherent to each registry due to selection bias. Only patients with newly diagnosed atrial fibrillation of <6 weeks duration and a perceived increased risk of stroke were included. These restrictions may have skewed the results on the history of vascular disease and on the use of antithrombotic therapies: Without these limitations, the number of patients with a history of vascular disease may have been higher. In addition, some changes in antithrombotic therapy during follow-up have not been recorded. Finally, the use of multivariate analysis with weighted overlap propensity scores may have confounded our results.

CONCLUSION

In the large global GARFIELD-AF registry, a history of vascular disease was associated with worse long-term outcomes of atrial fibrillation. Patients with vascular comorbidity received oral anticoagulation less frequently and, when given, were more likely to receive VKA than a NOAC. They also received antiplatelet agents more frequently, either alone or in combination with oral anticoagulants. When anticoagulated, these patients tended to have better outcomes with NOACs than when treated with VKA.

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SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2023.08.019.

SUPPLEMENTARY TEXT INFORMATION

Patient characteristics

- Of patients with vascular disease, 311 patients (2.3%) had vascular disease as the lone risk factor (i.e. males with CHA2DS2-VASc score of 1 or females with CHA2DS2-VASc score of 2). Among these 311 patients, we observed five deaths, five strokes, and no major bleeds.
- Proportion of AF patients with vascular disease at baseline by year of enrolment:
  - 2010: 24.6%
  - 2011: 25.1%
  - 2012: 25.6%
  - 2013: 26.9%
  - 2014: 24.4%
  - 2015: 25.7%
  - 2016: 28.3%

Note that patients from more countries were included in later years.

- Among patients enrolled in Egypt, 37% (192/525) had vascular disease at baseline. This makes Egypt the 6th country in terms of vascular disease prevalence in GARFIELD-AF, after Ukraine (67%), Russia (53%), China (42%), Turkey (39%) and the United Arab Emirates (37%).

Statistical analysis

Two different statistical methods were applied in these analyses to 1) quantify the associations of vascular disease with clinical endpoints and 2) to assess the effects of baseline treatment by vascular disease group. For analysis (1), **multivariable regression adjustment** was applied. For (2), one of the popular **propensity score** techniques (i.e., propensity score weighting) was performed.

In brief, propensity score analysis is a more favorable approach than multivariable adjustment when estimating causal effects using observational data. This is because a propensity score methodology is, under a series of assumptions, more closely mimicking what would be expected in a randomized controlled trial.

Multivariable regression analysis limits the number of variables used to adjust for potential confounders when evaluating the relationship between the exposure (or treatment) and outcome. On the other hand, propensity score techniques reduce all confounding variables into a single number: the likelihood (or "propensity") of receiving one treatment as opposed to the other (e.g. of receiving OAC instead of no OAC). Thus, propensity score methods allow for the integration of large numbers of variables during the generation of the propensity scores, increasing the likelihood of achieving a balance in the measured covariates across the compared treatment groups.

This is also the reason why the two analyses consider a different number of factors. In multivariable adjustment (Table S1, Figure 3) we limit the confounding factors (sex, age, ethnicity, type of atrial fibrillation, congestive heart failure, diabetes, hypertension, prior stroke/Transient ischemic attack/systemic embolism, prior bleeding, moderate to severe, current smoking, heavy alcohol consumption, baseline anticoagulation and antiplatelet therapy) to avoid collinearity and reduce uncertainty around the final estimate (more adjustments increase width of confidence intervals). When applying propensity score techniques in Figures S2 and S3, we are able to account for more variables (country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting specialty and location, congestive heart failure, carotid occlusive disease, prior stroke/Transient ischemic attack/systemic embolism, prior bleeding, venous thromboembolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease , dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use) and thus achieve a greater reduction in confounding. If the propensity score assumptions are met (e.g. no unobserved confounding), we are increasing the probability of more valid estimates of the relationship between the exposure and outcome compared to multivariable regression adjustment.

Anti-platelet treatment in under-dosed patients

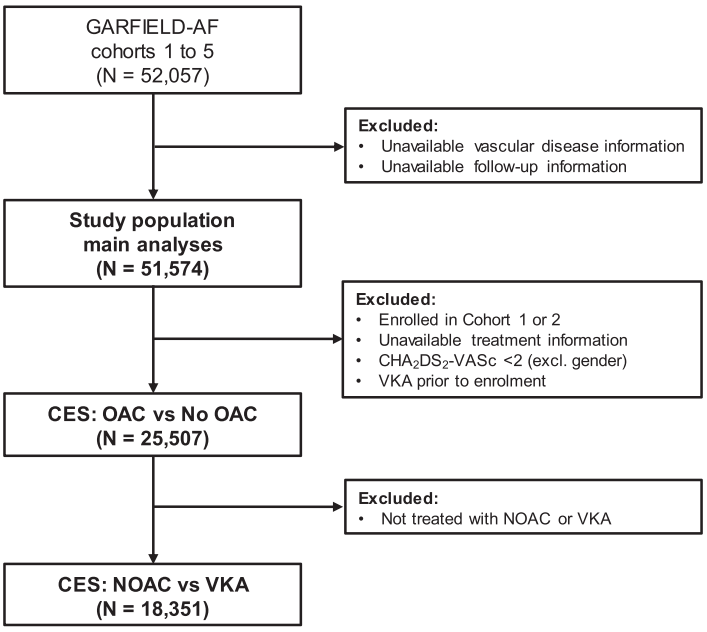
- Non-vitamin K antagonist oral anticoagulant (NOAC) dosing was estimated in a subgroup of NOAC-treated patients enrolled in cohorts 3-5, with available dosing and chronic kidney disease information (necessary to define recommended dosing).
- After applying these selections, out of the 2232 NOAC-treated patients with vascular disease, 562 (25.2%) received a non-recommended low NOAC dosing. Among the 7900 patients without vascular disease, 1794 (22.6%) received a non-recommended low NOAC dosing.
- Among patients with vascular disease who received a non-recommended low dose, 226 (40.2%) were on concomitant anti-platelet therapy. Among patients without vascular disease who received a non-recommended low dose, 187 (10.5%) were on concomitant anti-platelet therapy.

Sensitivity analysis

Adding carotid occlusive disease to the vascular disease definition. All patients who reported any of the following conditions or interventions were classified as having vascular disease at baseline:

- Coronary artery disease
- Aortic or peripheral artery disease
- Acute coronary syndrome/myocardial infarction or unstable angina
- Stenting (any type)
- Coronary artery bypass graft
- Carotid occlusive disease

The number of patients with vascular disease at baseline is **13,996 (27.1%)**



OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin-K antagonist; CES: comparative effectiveness study, CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease score

Figure S1 Flowchart for the selection of the study population.
OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin-K antagonist; CES: comparative effectiveness study, CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease score.

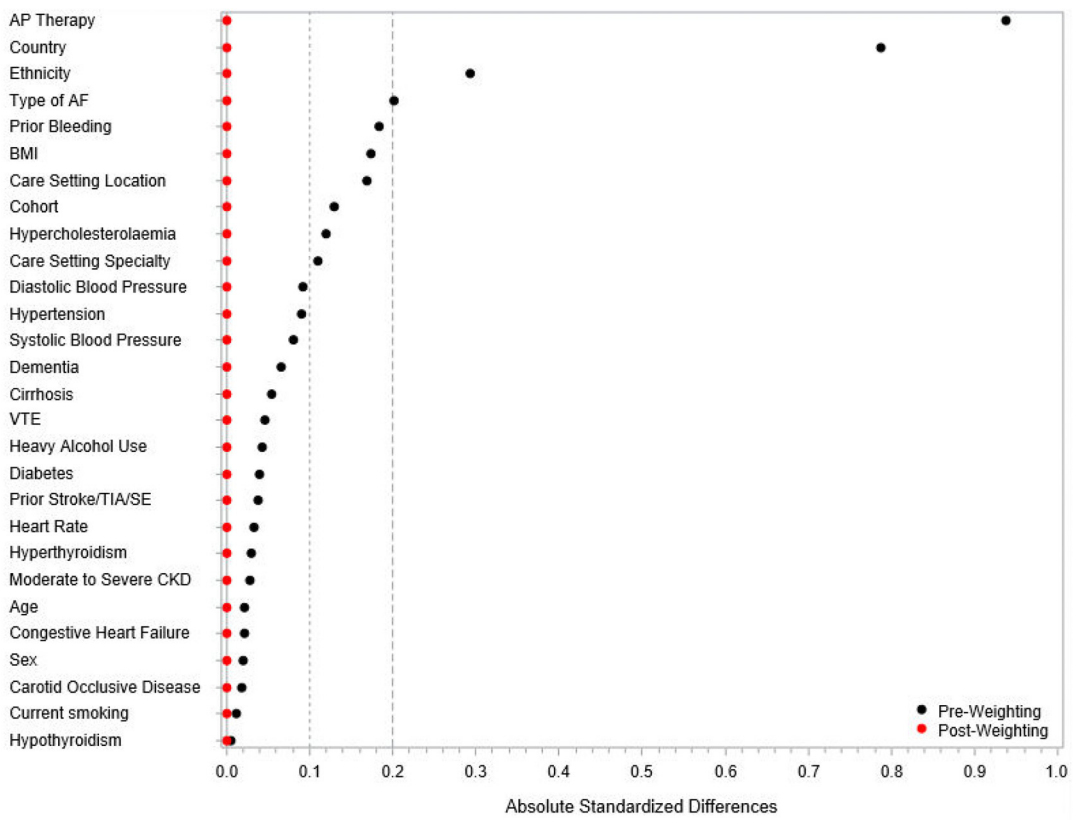


Figure S2. Absolute standardized difference of OAC vs No OAC baseline treatment among patients without vascular disease for the variables included in the weighting scheme before and after propensity score weighting.

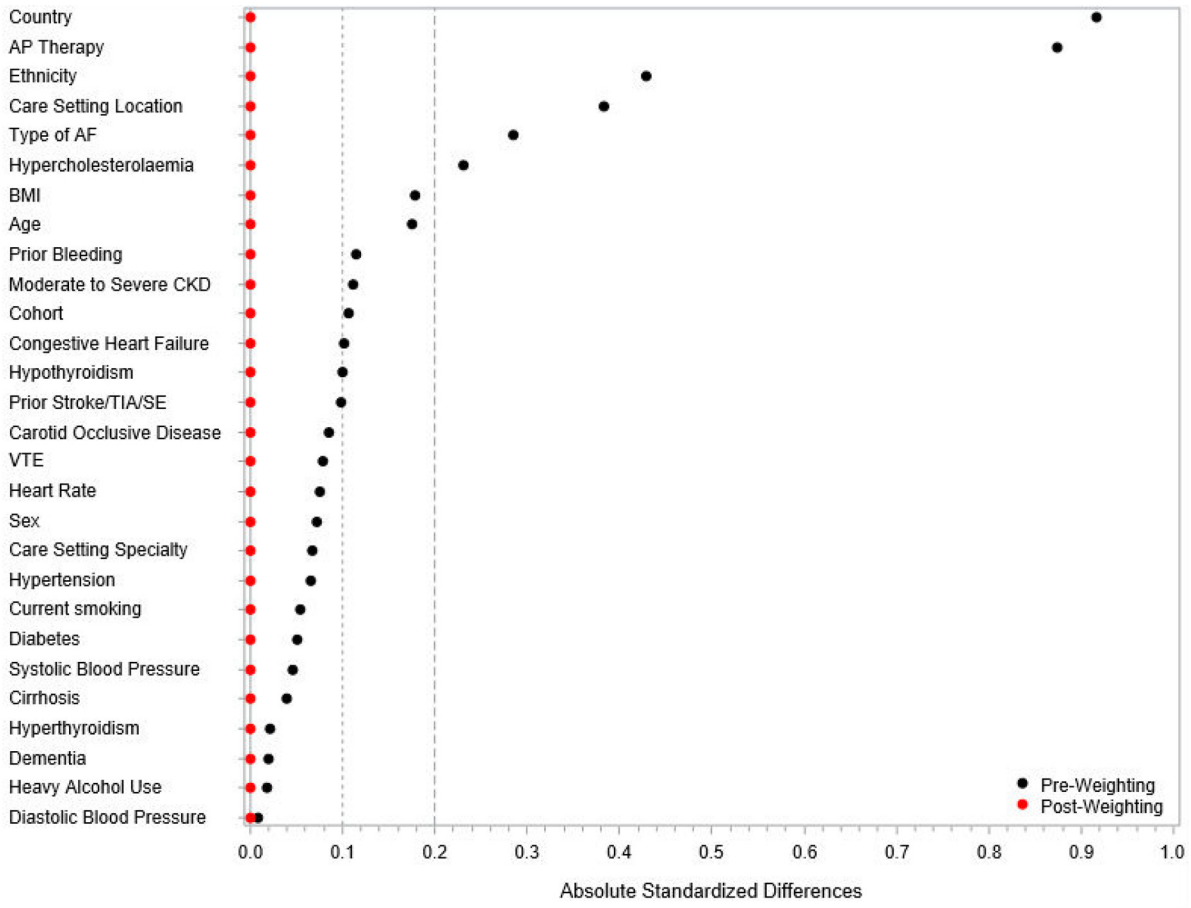


Figure S3 Absolute standardized difference of OAC vs No OAC baseline treatment among patients with vascular disease for the variables included in the weighting scheme before and after propensity score weighting.

Table S1 Event rates (per 100 person-years), unadjusted and adjusted[1] hazard ratios for selected outcomes within 2-year follow-up by baseline vascular disease

Outcome	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted [1] HR (95% CI)
All-cause mortality				
No vascular disease	2251	3.14 (3.02-3.28)	1 (ref.)	1 (ref.)
Vascular disease	1415	5.78 (5.48-6.09)	1.84 (1.59-2.11)	1.30 (1.16-1.47)
Cardiovascular mortality				
No vascular disease	718	1.00 (0.93-1.08)	1 (ref.)	1 (ref.)
Vascular disease	595	2.43 (2.24-2.63)	2.42 (1.88-3.11)	1.59 (1.28-1.97)
Non-cardiovascular mortality				
No vascular disease	961	1.34 (1.26-1.43)	1 (ref.)	1 (ref.)
Vascular disease	452	1.85 (1.68-2.02)	1.37 (1.13-1.67)	1.04 (0.90-1.19)
Non-haemorrhagic stroke/ systemic embolism				
No vascular disease	633	0.89 (0.82-0.96)	1 (ref.)	1 (ref.)
Vascular disease	325	1.34 (1.20-1.49)	1.50 (1.26-1.79)	1.16 (0.99-1.37)
Major bleeding				
No vascular disease	621	0.87 (0.81-0.95)	1 (ref.)	1 (ref.)
Vascular disease	313	1.29 (1.16-1.44)	1.47 (1.17-1.85)	1.17 (0.98-1.39)
Myocardial infarction/ Acute coronary syndrome				
No vascular disease	270	0.38 (0.34-0.43)	1 (ref.)	1 (ref.)
Vascular disease	338	1.40 (1.26-1.55)	3.67 (2.98-4.51)	2.62 (2.08-3.29)
New/ worsening heart failure				
No vascular disease	529	0.75 (0.68-0.81)	1 (ref.)	1 (ref.)
Vascular disease	291	1.20 (1.07-1.35)	1.61 (1.27-2.03)	1.12 (0.90-1.39)

CI: confidence interval; HR: hazard ratio

[1]Adjusted by sex, age, ethnicity, type of atrial fibrillation, congestive heart failure, diabetes, hypertension, prior stroke/transient ischemic attach/systemic embolism, prior bleeding, moderate to severe chronic kidney disease, current smoking, heavy alcohol consumption, and baseline anticoagulation.

Table S2 Baseline characteristics by baseline anticoagulant treatment and vascular disease

Baseline characteristics	Without vascular disease		With vascular disease	
	No OAC (N = 4272)	OAC (N = 13125)	No OAC (N = 2884)	OAC (N = 5226)
Sex, n (%)				
Male	2143 (50.2)	6449 (49.1)	1699 (58.9)	3262 (62.4)
Female	2129 (49.8)	6676 (50.9)	1185 (41.1)	1964 (37.6)
Age, median (Q1; Q3), years	74.0 (68.0;81.0)	74.0 (68.0;80.0)	71.0 (63.0;78.0)	73.0 (66.0;79.0)
Ethnicity, n (%)				
Caucasian	2107 (50.6)	8258 (64.5)	1721 (60.4)	3952 (77.0)
Hispanic/Latino	371 (8.9)	945 (7.4)	103 (3.6)	229 (4.5)
Asian	1619 (38.9)	3343 (26.1)	977 (34.3)	841 (16.4)
Afro-Caribbean/Mixed/Other	68 (1.6)	261 (2.0)	50 (1.8)	112 (2.2)
Body mass index, median (Q1;Q3), kg/m	26.2 (23.1;29.8)	26.8 (23.8;30.8)	26.8 (24.0;30.6)	27.7 (24.7;31.7)
Systolic blood pressure, median (Q1;Q3), mmHg	132.0 (120.0;146.0)	135.0 (121.0;148.0)	130.0 (120.0;142.0)	130.0 (120.0;145.0)
Diastolic blood pressure, median (Q1;Q3), mmHg	80.0 (70.0;88.0)	80.0 (70.0;90.0)	80.0 (70.0;87.0)	80.0 (70.0;87.0)
Pulse, median (Q1;Q3), bpm	86.0 (72.0;110.0)	85.0 (72.0;107.0)	80.0 (68.0;100.0)	84.0 (70.0;102.0)
Type of atrial fibrillation, n (%)				
Permanent	512 (12.0)	1901 (14.5)	277 (9.6)	844 (16.2)
Persistent	460 (10.8)	2179 (16.6)	237 (8.2)	746 (14.3)
Paroxysmal	1238 (29.0)	3669 (28.0)	838 (29.1)	1246 (23.8)
New onset (unclassified)	2062 (48.3)	5376 (41.0)	1532 (53.1)	2390 (45.7)
Care setting specialty at diagnosis, n (%)				
Internal medicine/Neurology/Geriatrics	1014 (23.7)	2680 (20.4)	474 (16.4)	955 (18.3)
Cardiology	2520 (59.0)	8456 (64.4)	2110 (73.2)	3680 (70.4)
Primary care/general practice	738 (17.3)	1989 (15.2)	300 (10.4)	591 (11.3)
Care setting location at diagnosis, n (%)				
Hospital	2452 (57.4)	6613 (50.4)	2129 (73.8)	3058 (58.5)
Office/Anticoagulation clinic/Thrombosis centre	1329 (31.1)	5117 (39.0)	467 (16.2)	1653 (31.6)
Emergency room	491 (11.5)	1395 (10.6)	288 (10.0)	515 (9.9)
Medical history, n (%)				
Heart failure	930 (21.8)	2743 (20.9)	1178 (40.8)	1877 (35.9)
Carotid occlusive disease	81 (1.9)	280 (2.1)	150 (5.3)	371 (7.3)
Venous thrombo-embolism	77 (1.8)	323 (2.5)	45 (1.6)	139 (2.7)
Prior stroke/Transient ischemic attack/ Systemic embolism	507 (11.9)	1724 (13.1)	310 (10.7)	732 (14.0)
Prior bleeding	208 (4.9)	214 (1.6)	134 (4.7)	132 (2.5)
Hypertension	3389 (79.4)	10879 (83.0)	2379 (82.5)	4440 (85.0)
Hypercholesterolaemia	1440 (35.7)	5194 (41.1)	1399 (51.5)	3187 (63.2)
Diabetes	1052 (24.6)	3458 (26.3)	831 (28.8)	1626 (31.1)
Cirrhosis	40 (1.0)	65 (0.5)	15 (0.5)	16 (0.3)
Moderate to severe chronic kidney disease	518 (12.9)	1503 (11.9)	332 (12.5)	805 (16.2)
Dementia	112 (2.6)	222 (1.7)	44 (1.5)	67 (1.3)
Heavy alcohol consumption, n (%)	94 (2.6)	201 (1.8)	32 (1.3)	71 (1.6)
Current smoker, n (%)	304 (7.8)	960 (8.0)	333 (12.5)	503 (10.5)
AP treatment, n (%)	2249 (52.6)	1679 (12.8)	2372 (82.2)	2275 (43.5)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (3.0;4.0)	3.0 (3.0;4.0)	4.0 (3.0;5.0)	4.0 (3.0;5.0)
HAS-BLED score[1], median (Q1; Q3)	2.0 (1.0;2.0)	1.0 (1.0;2.0)	2.0 (1.0;2.0)	2.0 (1.0;2.0)

[1]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)OAC: oral anticoagulant; Q1, Q3: first and third quartile; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, HAS-BLED: Hypertension, Abnormal renal and liver function

Table S3 Event rates (per 100 person-years) for selected outcomes through 2-year follow-up by baseline vascular disease presence and baseline anticoagulant treatment outcome

Baseline treatment	Without vascular disease		With vascular disease	
	Events	Rate (95% CI)	Events	Rate (95% CI)
All-cause mortality				
No OAC	428	5.46 (4.97-6.01)	309	5.84 (5.23-6.53)
OAC	846	3.39 (3.17-3.62)	593	6.15 (5.67-6.66)
Non-haemorrhagic stroke/ Systemic embolism				
No OAC	105	1.36 (1.12-1.64)	66	1.26 (0.99-1.60)
OAC	195	0.79 (0.68-0.90)	105	1.10 (0.91-1.33)
Major bleeding				
No OAC	64	0.82 (0.64-1.05)	42	0.80 (0.59-1.08)
OAC	276	1.12 (0.99-1.26)	131	1.38 (1.16-1.63)

OAC: oral anticoagulant; CI: confidence interval

Table S4 Unadjusted and adjusted[1] hazard ratios comparing oral anticoagulation versus no oral anticoagulation (reference) baseline treatment through two years of follow-up by vascular disease presence at baseline

Vascular disease presence at baseline Outcome	Treatment comparison OAC vs No OAC (ref.)			
	Unadjusted		Adjusted[1]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Without vascular disease				
All-cause mortality	0.62 (0.55-0.70)	<.0001	0.72 (0.63-0.82)	<.0001
Non-haemorrhagic stroke/ Systemic embolism	0.58 (0.46-0.74)	<.0001	0.64 (0.49-0.84)	<.0001
Major bleeding	1.36 (1.04-1.79)	0.0253	1.40 (1.03-1.90)	0.0299
With vascular disease				
All-cause mortality	1.05 (0.92-1.21)	0.4735	0.94 (0.81-1.11)	0.4872
Non-haemorrhagic stroke/ Systemic embolism	0.87 (0.64-1.19)	0.3824	0.84 (0.59-1.21)	0.3430
Major bleeding	1.72 (1.22-2.43)	0.0022	1.32 (0.90-1.93)	0.1529

[1]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, congestive heart failure, carotid occlusive disease, prior stroke/transient ischemic attack/ systemic embolism, prior bleeding, venous thrombo-embolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.OAC: oral anticoagulant; HR: hazard ratio; CI: confidence interval

Table S5 P-values for interaction between baseline treatment and vascular disease

Outcome	OAC vs No OAC[1]	NOAC vs VKA[2]
All-cause mortality	0.0505	0.1131
Non-haemorrhagic stroke/Systemic embolism	0.1965	0.7393
Major bleeding	0.8194	0.0294

[1]Models 4a
[2]Models 4bOAC: Oral anticoagulant

Table S6 Baseline characteristics by baseline type of anticoagulant treatment and vascular disease

Baseline characteristics	Without vascular disease		With vascular disease	
	VKA (N = 5952)	NOAC (N = 7173)	VKA (N = 2638)	NOAC (N = 2588)
Sex, n (%)				
Male	2893 (48.6)	3556 (49.6)	1599 (60.6)	1663 (64.3)
Female	3059 (51.4)	3617 (50.4)	1039 (39.4)	925 (35.7)
Age, median (Q1; Q3), years	74.0 (67.0;80.0)	74.0 (68.0;80.0)	72.0 (65.0;78.0)	74.0 (67.0;80.0)
Ethnicity, n (%)				
Caucasian	3904 (66.9)	4354 (62.4)	2040 (78.6)	1912 (75.3)
Hispanic/Latino	590 (10.1)	355 (5.1)	142 (5.5)	87 (3.4)
Asian	1228 (21.0)	2115 (30.3)	357 (13.8)	484 (19.1)
Afro-Caribbean/Mixed/Other	112 (1.9)	149 (2.1)	55 (2.1)	57 (2.2)
Body mass index, median (Q1;Q3), kg/m	27.4 (24.2;31.5)	26.5 (23.5;30.4)	28.0 (24.9;32.0)	27.5 (24.5;31.5)
Systolic blood pressure, median (Q1;Q3), mmHg	135.0 (122.0;148.0)	134.0 (121.0;148.0)	130.0 (120.0;145.0)	130.0 (120.0;144.0)
Diastolic blood pressure, median (Q1;Q3), mmHg	80.0 (70.0;90.0)	80.0 (70.0;88.0)	80.0 (70.0;90.0)	80.0 (70.0;85.0)
Pulse, median (Q1;Q3), bpm	85.0 (72.0;105.0)	85.0 (70.0;109.0)	85.0 (72.0;102.0)	81.0 (69.0;103.0)
Type of atrial fibrillation, n (%)				
Permanent	985 (16.5)	916 (12.8)	551 (20.9)	293 (11.3)
Persistent	975 (16.4)	1204 (16.8)	348 (13.2)	398 (15.4)
Paroxysmal	1286 (21.6)	2383 (33.2)	493 (18.7)	753 (29.1)
New onset (unclassified)	2706 (45.5)	2670 (37.2)	1246 (47.2)	1144 (44.2)
Care setting specialty at diagnosis, n (%)				
Internal medicine/Neurology/Geriatrics	1314 (22.1)	1366 (19.0)	506 (19.2)	449 (17.3)
Cardiology	3425 (57.5)	5031 (70.1)	1792 (67.9)	1888 (73.0)
Primary care/general practice	1213 (20.4)	776 (10.8)	340 (12.9)	251 (9.7)
Care setting location at diagnosis, n (%)				
Hospital	3227 (54.2)	3386 (47.2)	1646 (62.4)	1412 (54.6)
Office/Anticoagulation clinic/Thrombosis centre	1985 (33.4)	3132 (43.7)	719 (27.3)	934 (36.1)
Emergency room	740 (12.4)	655 (9.1)	273 (10.3)	242 (9.4)
Medical history, n (%)				
Heart failure	1204 (20.2)	1539 (21.5)	1017 (38.6)	860 (33.2)
Carotid occlusive disease	123 (2.1)	157 (2.2)	169 (6.6)	202 (8.0)
Venous thrombo-embolism	164 (2.8)	159 (2.2)	71 (2.7)	68 (2.6)
Prior stroke/Transient ischemic attack/ Systemin embolism	783 (13.2)	941 (13.1)	384 (14.6)	348 (13.4)
Prior bleeding	83 (1.4)	131 (1.8)	63 (2.4)	69 (2.7)
Hypertension	5039 (84.7)	5840 (81.5)	2249 (85.3)	2191 (84.7)
Hypercholesterolaemia	2405 (42.3)	2789 (40.1)	1520 (60.3)	1667 (66.2)
Diabetes	1730 (29.1)	1728 (24.1)	827 (31.3)	799 (30.9)
Cirrhosis	37 (0.6)	28 (0.4)	12 (0.5)	4 (0.2)
Moderate to severe chromic kidney disease	795 (14.1)	708 (10.2)	406 (16.4)	399 (16.0)
Dementia	66 (1.1)	156 (2.2)	26 (1.0)	41 (1.6)
Heavy alcohol consumption, n (%)	92 (1.8)	109 (1.8)	38 (1.7)	33 (1.5)
Current smoker, n (%)	426 (7.8)	534 (8.2)	255 (10.4)	248 (10.7)
AP treatment, n (%)	896 (15.1)	783 (10.9)	1278 (48.4)	997 (38.5)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (3.0;4.0)	3.0 (3.0;4.0)	4.0 (3.0;5.0)	4.0 (3.0;5.0)
HAS-BLED score [1], median (Q1; Q3)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	2.0 (1.0;2.0)	2.0 (1.0;2.0)

[1]The risk factor 'Labile International Normalized Ratios' 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)VKA: vitamin K antagonist; NOAC: non-VKA oral anticoagulant; AP: anti-platelet; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, HAS-BLED: Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or alcohol; Q1, Q3: first and third quartile

Table S7 Event rates (per 100 person-years) for selected outcomes through 2-year follow-up by baseline vascular disease presence and baseline type of anticoagulant treatment

Outcome Baseline treatment	Without vascular disease		With vascular disease	
	Events	Rate (95% CI)	Events	Rate (95% CI)
All-cause mortality				
VKA	415	3.69 (3.35-4.06)	356	7.48 (6.75-8.30)
NOAC	431	3.14 (2.86-3.45)	237	4.85 (4.27-5.51)
Non-haemorrhagic stroke/Systemic embolism				
VKA	95	0.85 (0.70-1.04)	59	1.25 (0.97-1.62)
NOAC	100	0.73 (0.60-0.89)	46	0.95 (0.71-1.27)
Major bleeding				
VKA	141	1.27 (1.08-1.50)	86	1.84 (1.49-2.27)
NOAC	135	0.99 (0.84-1.17)	45	0.93 (0.69-1.25)

VKA: vitamin K antagonist; NOAC: non-VKA oral anticoagulant; CI: confidence interval

Table S8 Unadjusted and adjusted[1] hazard ratios comparing NOAC with vitamin-K antagonists (reference) baseline treatment through two years of follow-up by vascular disease presence at baseline

Outcome	Treatment comparison NOAC vs VKA (ref.)			
	Unadjusted		Adjusted [1]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Without vascular disease				
All-cause mortality	0.85 (0.74-0.98)	0.0196	0.86 (0.73-1.01)	0.0671
Non-haemorrhagic stroke/ Systemic embolism	0.86 (0.65-1.14)	0.3041	0.99 (0.70-1.39)	0.9486
Major bleeding	0.79 (0.62-0.99)	0.0448	0.98 (0.73-1.30)	0.8619
With vascular disease				
All-cause mortality	0.65 (0.55-0.77)	<.0001	0.74 (0.61-0.90)	0.0026
Non-haemorrhagic stroke/ Systemic embolism	0.76 (0.52-1.12)	0.1642	0.81 (0.52-1.28)	0.3756
Major bleeding	0.51 (0.36-0.73)	0.0003	0.45 (0.29-0.70)	0.0003

[1]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, congestive heart failure, carotid occlusive disease, prior stroke/transient ischemic attack/systemic embolism, prior bleeding, venous thrombo-embolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.NOAC: non-VKA oral anticoagulant; VKA: vitamin K antagonist; HR: hazard ratio; CI: confidence interval

Table S9 Adjusted [1] hazard ratios comparing NOAC vs No OAC (reference) and VKA vs No OAC (reference) baseline treatment through two years of follow-up by vascular disease presence at baseline

Vascular disease presence at baseline Outcome	Treatment comparison			
	NOAC vs No OAC (ref.)		VKA vs No OAC (ref.)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Without vascular disease				
All-cause mortality	0.67 (0.56-0.79)	<.0001	0.79 (0.67-0.92)	0.0034
Non-haemorrhagic stroke/ Systemic embolism	0.60 (0.43-0.84)	0.0028	0.71 (0.51-0.98)	0.0387
Major bleeding	1.27 (0.89-1.83)	0.1905	1.58 (1.11-2.24)	0.0105
With vascular disease				
All-cause mortality	0.69 (0.56-0.85)	0.0006	1.07 (0.90-1.28)	0.4383
Non-haemorrhagic stroke/ Systemic embolism	0.66 (0.42-1.06)	0.0844	0.93 (0.62-1.41)	0.9320
Major bleeding	0.67 (0.41-1.09)	0.1068	1.80 (1.19-2.71)	0.0055

[1]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, congestive heart failure, carotid occlusive disease, prior stroke/Transient ischemic attack/Systemic embolism, prior bleeding, venous thrombo-embolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.NOAC: non-VKA OAC; OAC: oral anticoagulant; VKA: vitamin K antagonist; HR: hazard ratio; CI: confidence interval

Table S10 Sensitivity analysis adding carotid occlusive disease to the vascular disease definition: Unadjusted and adjusted [1] hazard ratios for selected outcomes within 2-year follow-up by baseline vascular disease (2nd def).

Outcome	Unadjusted analysis		Adjusted [1] analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause mortality				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	1.85 (1.61-2.12)	<.0001	1.30 (1.16-1.47)	<.0001
Cardiovascular mortality				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	2.37 (1.86-3.01)	<.0001	1.54 (1.25-1.90)	<.0001
Non-cardiovascular mortality				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	1.40 (1.15-1.70)	0.0007	1.04 (0.91-1.20)	0.5529
Non-haemorrhagic stroke/Systemic embolism				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	1.50 (1.26-1.79)	<.0001	1.16 (0.99-1.36)	0.0668
Major bleeding				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	1.52 (1.21-1.91)	0.0004	1.19 (1.00-1.43)	0.0567
Myocardial infarction/ Acute coronary syndrome				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	3.54 (2.88-4.35)	<.0001	2.50 (1.98-3.16)	<.0001
New/worsening heart failure				
No vascular disease	1 (ref.)		1 (ref.)	
Vascular disease (2nd def)	1.61 (1.27-2.03)	<.0001	1.12 (0.90-1.40)	0.3190

[1]Adjusted by sex, age, ethnicity, type of atrial fibrillation, congestive heart failure, diabetes, hypertension, prior stroke/Transient ischemic attack/Systemic embolism, prior bleeding, moderate to severe chronic kidney disease, current smoking, heavy alcohol consumption, and baseline anticoagulation.
HR: hazard ratio; CI: confidence interval

Table S11 Sensitivity analysis adding carotid occlusive disease to the vascular disease definition: Unadjusted and adjusted [1] hazard ratios comparing OAC vs No OAC (reference) baseline treatment through two years of follow-up by vascular disease (2nd def) presence at baseline

Outcome	Treatment comparison OAC vs No OAC (ref.)			
	Unadjusted		Adjusted [1]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Without vascular disease				
All-cause mortality	0.62 (0.55-0.70)	<.0001	0.71 (0.62-0.82)	<.0001
Non-haemorrhagic stroke/Systemic embolism	0.58 (0.46-0.74)	<.0001	0.64 (0.49-0.85)	0.0018
Major bleeding	1.37 (1.04-1.81)	0.0278	1.43 (1.05-1.95)	0.0244
With vascular disease (2nd def)				
All-cause mortality	1.04 (0.91-1.19)	0.5889	0.94 (0.80-1.09)	0.4100
Non-haemorrhagic stroke/Systemic embolism	0.85 (0.63-1.15)	0.3003	0.81 (0.57-1.15)	0.2368
Major bleeding	1.72 (1.23-2.40)	0.0015	1.32 (0.91-1.90)	0.1431

[1]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, congestive heart failure, prior stroke/Transient ischemic attack/Systemic embolism, prior bleeding, venous thrombo-embolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.OAC: oral anticoagulant; HR: hazard ratio; CI: confidence interval

Table S12 Sensitivity analysis adding carotid occlusive disease to the vascular disease definition: Unadjusted and adjusted [1] hazard ratios comparing NOAC vs VKA (reference) baseline treatment through two years of follow-up by vascular disease (2nd def) presence at baseline

Outcome	Treatment comparison NOAC vs VKA (ref.)			
	Unadjusted		Adjusted [1]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Without vascular disease				
All-cause mortality	0.86 (0.75-0.98)	0.0275	0.87 (0.74-1.03)	0.0984
Non-haemorrhagic stroke/ Systemic embolism	0.82 (0.62-1.09)	0.1780	0.97 (0.69-1.37)	0.8655
Major bleeding	0.79 (0.62-1.01)	0.0579	0.99 (0.73-1.33)	0.9292
With vascular disease (2nd def)				
All-cause mortality	0.65 (0.56-0.77)	<.0001	0.74 (0.61-0.89)	0.0015
Non-haemorrhagic stroke/ Systemic embolism	0.83 (0.58-1.21)	03369	0.86 (0.56-1.33)	0.4952
Major bleeding	0.53 (0.38-0.74)	0.0002	0.51 (0.34-0.76)	0.0012

[1]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, congestive heart failure, carotid occlusive disease, prior stroke/Transient ischemic attack/Systemic embolism, prior bleeding, venous thrombo-embolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.NOAC: non-VKA OAC; OAC: oral anticoagulant; VKA: vitamin K antagonist; HR: hazard ratio; CI: confidence interval

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