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ORIGINAL ARTICLE

Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: Results from the GARFIELD-AF Registry

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Abstract

Background: Oral anticoagulation (OAC) in atrial fibrillation (AF) reduces the risk of stroke/systemic embolism (SE). The impact of OAC discontinuation is less well documented.

Objective: Investigate outcomes of patients prospectively enrolled in the Global Anticoagulant Registry in the Field-Atrial Fibrillation study who discontinued OAC.

A complete list of investigators is given in Appendix S1.

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

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Methods: Oral anticoagulation discontinuation was defined as cessation of treatment for ≥7 consecutive days. Adjusted outcome risks were assessed in 23 882 patients with 511 days of median follow-up after discontinuation.

Results: Patients who discontinued (n = 3114, 13.0%) had a higher risk (hazard ratio [95% CI]) of all-cause death (1.62 [1.25–2.09]), stroke/systemic embolism (SE) (2.21 [1.42–3.44]) and myocardial infarction (MI) (1.85 [1.09–3.13]) than patients who did not, whether OAC was restarted or not. This higher risk of outcomes after discontinuation was similar for patients treated with vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) (p for interactions range = 0.145–0.778). Bleeding history (1.43 [1.14–1.80]), paroxysmal vs. persistent AF (1.15 [1.02–1.29]), emergency room care setting vs. office (1.37 [1.18–1.59]), major, clinically relevant nonmajor, and minor bleeding (10.02 [7.19–13.98], 2.70 [2.24–3.25] and 1.90 [1.61–2.23]), stroke/SE (4.09 [2.55–6.56]), MI (2.74 [1.69–4.43]), and left atrial appendage procedures (4.99 [1.82–13.70]) were predictors of discontinuation. Age (0.84 [0.81–0.88], per 10-year increase), history of stroke/transient ischemic attack (0.81 [0.71–0.93]), diabetes (0.88 [0.80–0.97]), weeks from AF onset to treatment (0.96 [0.93–0.99] per week), and permanent vs. persistent AF (0.73 [0.63–0.86]) were predictors of lower discontinuation rates.

Conclusions: In GARFIELD-AF, the rate of discontinuation was 13.0%. Discontinuation for ≥7 consecutive days was associated with significantly higher all-cause mortality, stroke/SE, and MI risk. Caution should be exerted when considering any OAC discontinuation beyond 7 days.

KEYWORDS
anticoagulation, antiplatelet, atrial fibrillation, discontinuation, marginal structure models, outcomes

1 | INTRODUCTION

Oral anticoagulation (OAC) has a major impact on the outcomes of patients with atrial fibrillation (AF).[1] Both vitamin K antagonists (VKAs) and the newer direct oral anticoagulants (DOACs) are strongly recommended by stroke prevention guidelines for patients with high-risk AF.[2] Nevertheless, past studies suggest that anticoagulants are often underprescribed,[3,4] with high rates of discontinuation (ranging from 26% to 55% at 1 year),[5,6] due in part to the limitations associated with VKA treatment. More recently, substantial discontinuation rates ranging from 21% to 34%[7–10] during follow-up in clinical trials, and 16% to 53% in real-world studies[11–14] at 6 to 24 months, have also been recorded with DOAC usage, despite their ease of use and superior safety profile compared with VKAs such as warfarin.[15]

Few studies have explored the relationship between OAC discontinuation and clinical outcomes. In this report, the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) collects starting and finishing dates of treatment which, unlike other databases, gives precise data regarding timing of treatment relative to outcomes. We assessed risk factors for discontinuing oral anticoagulants and its impact on clinical outcomes among 23 882 AF patients who were prescribed either VKAs or DOACs for stroke prevention at the time of enrollment into GARFIELD-AF. All patients had a recent newly diagnosed AF and were followed prospectively for 2 years.

Essentials

- Atrial fibrillation (AF) patients exhibit a high rates of oral anticoagulation (OAC) discontinuation.
- GARFIELD-AF, a large, global prospective registry of atrial fibrillation patients.
- Discontinuation of OAC for ≥7 consecutive days is associated with higher risks of death, stroke/systemic embolism, or myocardial infarction.
- Oral anticoagulation discontinuation should be discouraged, even for periods as short as 7 days.

2 | METHODS

The design of the GARFIELD-AF registry has been reported previously.[16] In total, 52 014 patients of ≥18 years with nonvalvular AF (diagnosed within the previous 6 weeks), and at least one nonprespecified risk factor for stroke (judged by the local investigator) were eligible for inclusion.[16] Patients were enrolled prospectively from representative centers in 35 countries between May 2013 and August 2016. Intended minimum follow-up was 2 years.[16] All follow-up beyond 2 years was truncated at 24 months. Data for this report were extracted from the study database in June 2019. This analysis involved patients with OAC usage from cohorts 3–5 only, because the exact treatment start and stop dates were recorded from cohort 3 onwards.

2.1 | Ethics statement

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

2.2 | Procedures and outcome measures

Collection of follow-up data occurred at 4-monthly intervals up to 24 months.[16] In accordance with the study protocol, 20% of all electronic case report forms were monitored against source documentation.[17] Timing of treatment is based upon the date treatment was started and the date treatment was discontinued. Changes in treatment type were recorded. Defining discontinuation based solely on stopping and never restarting a drug in a study where patients die or stop follow-up at different points will likely produce biased results. For example, patient A stops drug and dies 2 days later. Patient B stops drug and restarts 3 days later. Patient A would be defined as discontinued and B would not. Yet at day 2, the day of the event, they were both off drug. Therefore, permanent discontinuation based on never restarting is not an appropriate approach—a defined time window for discontinuation is necessary. Discontinuation was defined as the cessation of OAC treatment for ≥7 consecutive days (whether or not OAC was restarted later), based on a consensus from the GARFIELD-AF Steering Committee, which considered that the duration of most nonpermanent treatment interruptions would continue for <1 week. OAC switching, without a ≥7 consecutive day suspension of treatment, was not considered OAC discontinuation. This prespecified criterion was applied to both those who survived and those who did not, to reduce bias in patient allocation to the discontinuation group. Thus, patients remained in the nondiscontinuation group until discontinuation had continued for ≥7 consecutive days, without patient mortality. As a sensitivity analysis, the interruption of OAC treatment for at least 30 days was also assessed.

Endpoints of interest were the occurrence of the following combined outcomes as well as their individual components: death/stroke/systemic embolism (SE)/acute myocardial infarction (MI), death/stroke/SE, and death, stroke/SE, and MI. All strokes included in this analysis were nonhemorrhagic. Hemorrhagic strokes were considered major bleeds.

2.3 | Statistical analysis

Descriptive analyses were conducted in patients stratified according to whether they discontinued OAC therapy over the 2-year follow-up period. Continuous variables were presented as the medians and 75th and 25th percentiles or means with standard deviations. Only the first occurrence of each event was taken into account. In patients who discontinued OAC therapy, Kaplan-Meier event-free survival curves displayed the time to the event (or censoring) from the date of discontinuation.

Because of the complex nature of discontinuation, a method was developed to appropriately account for the confounding of baseline factors and factors occurring close to the time of discontinuation, and, in the case of treatment comparisons, censoring with treatment changes. Treatment-specific marginal structural Cox proportional hazards models estimated the effect of discontinuation (hazard ratio) on death, nonhemorrhagic stroke and SE, MI, or combined endpoints. Adjustments were made for baseline characteristics and time-dependent variables, including bleeding left atrial appendage procedures, as well as MI and stroke (when not a component of the endpoint).[18] Baseline factors considered were type of AF, diabetes, history of stroke or transient ischemic attack (TIA), SE, bleeding, hypertension, vascular disease, acute coronary syndrome, moderate-to-severe kidney disease, dementia, alcohol use, smoking status, body mass index, sex, age, race, heart rate, baseline systolic and diastolic blood pressures, care setting location and type, and country. Subject-specific, time-dependent weights used in fitting the treatment-specific marginal structural Cox proportional hazards model controlled for three sources of potential bias: nonrandomized treatment, time-dependent confounding, and informative censoring (induced by censoring patients that either switch treatments or return to treatment after discontinuation). Figure S1 displays the time to discontinuation by treatment among patients who did not switch treatment before discontinuing. The interaction of OAC treatment type and discontinuation was nonsignificant for each endpoint considered, and thus was not included within the final model.

3 | RESULTS

Of 34 897 patients enrolled between May 2013 and July 2016, 8595 did not receive OAC or had missing information and 2420 started treatment during the follow-up period and were therefore excluded. The remaining 23 882 patients included 11 908 (49.9%) patients on VKAs and 11 974 (50.1%) on DOACs (factor Xa inhibitor [FXaI]: 9228 [38.6%] and direct thrombin inhibitor [DTI]: 2746 [11.5%]) as their first anticoagulant treatment following AF diagnosis. Follow-up after discontinuation (number of days to death or last follow-up) was 511 days (interquartile range [IQR]: 291–648). Overall, 3114 patients (13.0%) discontinued OAC for ≥7 consecutive days. Discontinuation for patients treated with VKA, FXaI, and DTI occurred in 12.7%, 12.8%, and 15.4% of cases, respectively (unadjusted). At least 95% of patients in both the discontinued and not-discontinued groups completed >700 days of follow-up.

Baseline characteristics are shown in Table 1. Patients who discontinued OAC tended to be younger, less likely to have diabetes, and more likely to have a history of bleeding and a history of stroke/

TABLE 1 Baseline characteristics of patients that discontinued OAC treatment vs. those that did not

Baseline Characteristics	Permanent Discontinuation (*n* = 3114)	No Discontinuation (*n* = 20 768)
Male, *n* (%)	1827 (58.7)	11 307 (54.4)
Age, median (IQR)	70 (61, 78)	72 (64, 79)
<65 y, *n* (%)	1032 (33.1)	5257 (25.3)
65–74 y, *n* (%)	984 (31.6)	7249 (34.9)
≥75 y, *n* (%)	1098 (35.3)	8262 (39.8)
Race, *n* (%)		
Caucasian	2235 (71.8)	13 221 (63.7)
Hispanic/Latino	120 (3.9)	1321 (6.4)
Afro-Caribbean	10 (0.3)	131 (0.6)
Asian (not Chinese)	553 (17.8)	4796 (23.1)
Chinese	51 (1.6)	504 (2.4)
Mixed/other/unspecified	145 (4.7)	795 (3.8)
Body mass index, median (IQR)	27 (24, 31)	27 (24, 31)
Hypertension, *n* (%)	2377 (76.7)	16 159 (77.1)
Hypercholesterolemia, *n* (%)	1635 (42.3)	9523 (42.5)
Diabetes, *n* (%)	649 (20.8)	4901 (23.6)
Smoking, *n* (%)		
Never smoked	1820 (63.3)	12 356 (65.2)
Ex-smoker	749 (26.1)	4675 (24.7)
Current smoker	305 (10.6)	1920 (10.1)
Alcohol consumption, *n* (%)		
Abstinent/light	2236 (85.8)	15 442 (88.4)
Moderate/heavy	370 (14.2)	2024 (11.6)
Type of atrial fibrillation, (%)		
Permanent	283 (9.1)	3004 (14.5)
Persistent	504 (16.2)	3507 (16.9)
Paroxysmal	879 (28.2)	5565 (26.8)
Unclassified	1448 (46.5)	8692 (41.9)
Care setting at diagnosis, *n* (%)		
Hospital	1719 (55.2)	10 935 (52.7)
Office	969 (31.2)	7582 (36.5)
AC clinic/thrombosis center	9 (0.3)	99 (0.5)
Emergency room	417 (13.4)	2152 (10.4)
Heart failure, *n* (%)	684 (22.0)	4650 (22.4)
Coronary artery disease, *n* (%)	672 (21.6)	4205 (20.3)
Vascular disease, *n* (%)	287 (9.2)	2485 (12.0)
Stroke/TIA, *n* (%)	1719 (55.2)	10 935 (52.7)
Systemic embolization, *n* (%)	16 (0.5)	174 (0.8)
Bleeding history, *n* (%)	88 (2.8)	338 (1.6)
Chronic kidney disease[a], *n* (%)	416 (13.8)	2198 (11.1)
CHA_2DS_2-VASc, mean (SD)	3.1 (1.7)	3.4 (1.5)
CHA_2DS_2-VASc, median (IQR)	3 (2.0–4.0)	3 (2.0–4.0)
HAS-BLED, mean (SD)	1.3 (0.9)	1.3 (0.9)
HAS-BLED, median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Baseline treatment, *n* (%)		
VKA	1123 (36.1)	7908 (38.1)
VKA+AP	388 (12.5)	2489 (12.0)
FXaI	959 (30.8)	6673 (32.1)
FXaI+AP	221 (7.1)	1375 (6.6)
DTI	348 (11.2)	1949 (9.4)
DTI+AP	75 (2.4)	374 (1.8)

Abbreviations: AC clinic, anticoagulation clinic; AP, antiplatelet; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, stroke, vascular disease, age 65-74 years, and sex category; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, and drugs or alcohol; IQR, interquartile range; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist

[a]Chronic kidney disease (stages 3–5)

(Continues)

TIA. A similar median congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, stroke, vascular disease, age 65-74 years, and sex category score and risk of bleeding according to the hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, and drugs or alcohol score was observed in both groups. Prescription of anticoagulants at baseline was balanced between the two groups, though numerically patients who discontinued were more frequently prescribed a DTI.

The median time from initial anticoagulation to discontinuation was 182 days (IQR: 69–389). Many discontinuations occurred early after initiation of treatment: 38.2% within the first 4 months and 40.9% after 8 months (Figure 1). Of the patients who discontinued for ≥7 consecutive days, 77.9% remained off any OAC beyond 30 days. At the time of discontinuation, 93.9% of patients ($n = 2925$) had remained on the same OAC on which they were initiated on enrolment. In addition to OAC, antiplatelet therapy was used in 684 (22.0%) patients who discontinued treatment vs. 4238 (20.4%) of those that did not.

The reason for discontinuation was recorded in 2172 of cases. The decision to discontinue was most often made by the referring physician (51.0%) rather than the patient (18.5%). The decision for discontinuation was rarely end of planned treatment (6.2%), pregnancy or adverse events (3.5%), and cost of treatment or reimbursement (1.3%). In 35.4% of cases, "other" or no reason was given by the physician.

Rates of discontinuation differed by country. The lowest rates were observed in India (2.7%), Egypt (3.3%), and Thailand (4.2%) and the highest rates were in the United States (21.2%), South Africa (22.1%), and Australia (28.3%) (Figure 2).

3.1 | Predictors of discontinuation

As shown in Figure 3 and Table S1 of the propensity model for discontinuation, the adjusted likelihood of discontinuing was significantly higher in Caucasian patients vs. other races, patients with a history of bleeding, kidney disease, and/or coronary artery disease, paroxysmal (vs. persistent) AF, and in patients initiated by primary care physicians rather than cardiologists. Adjusted factors associated with a significantly lower risk of discontinuation were: increasing age, history of stroke or TIA, a history of acute coronary syndromes, diabetes mellitus, hypertension, and permanent AF (compared with persistent AF). The adjusted likelihood of treatment discontinuation also trended toward lower rates in patients recruited by neurologists vs. cardiologists.

Within the model, all post baseline factors such as bleeding (major, clinically relevant nonmajor bleed, and minor bleeding), left atrial appendage procedures, stroke/SE, and MI were associated with a higher risk of discontinuation (Figure 3).

3.2 | Restarting OAC after discontinuation

Of the 22 677 patients who survived to 1 year, 18 528 (81.7%) remained on their initial OAC. At 2 years' follow-up, 79.0% (14 516 of the 18 374 remaining patients) remained on their initial anticoagulant treatment. Overall, 1415 of 3114 patients (45.4%) who discontinued OAC therapy for ≥7 consecutive days restarted anticoagulation during follow-up. The median time to restarting antithrombotic therapy was 31 days (IQR: 12–158). The majority returned to the same OAC used at the time of discontinuation.

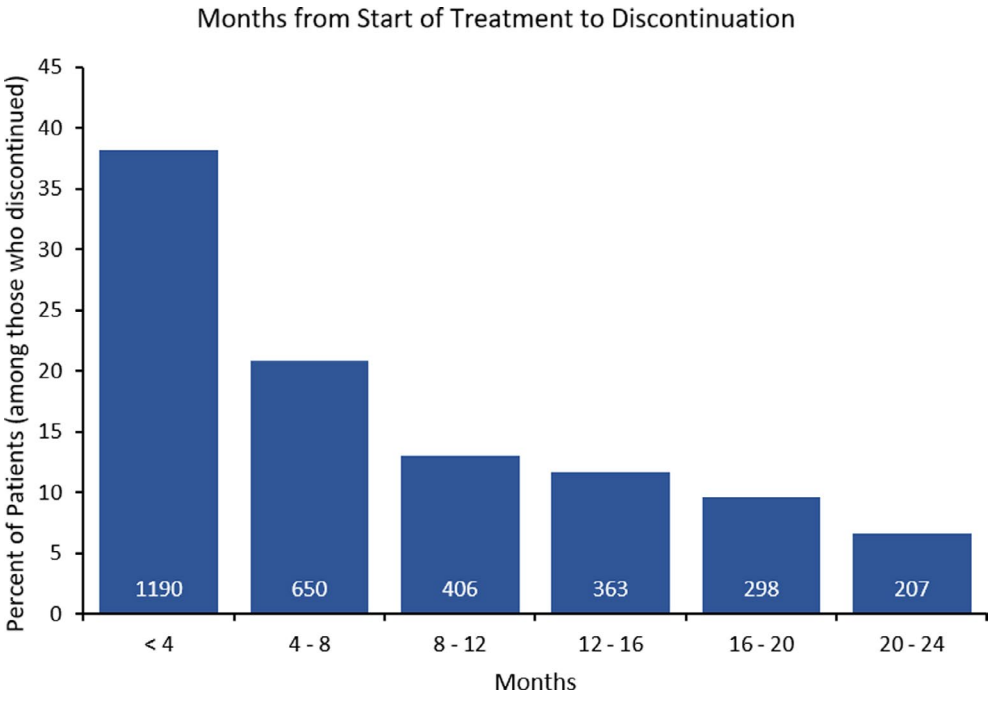

FIGURE 1 Months from start of treatment to discontinuation

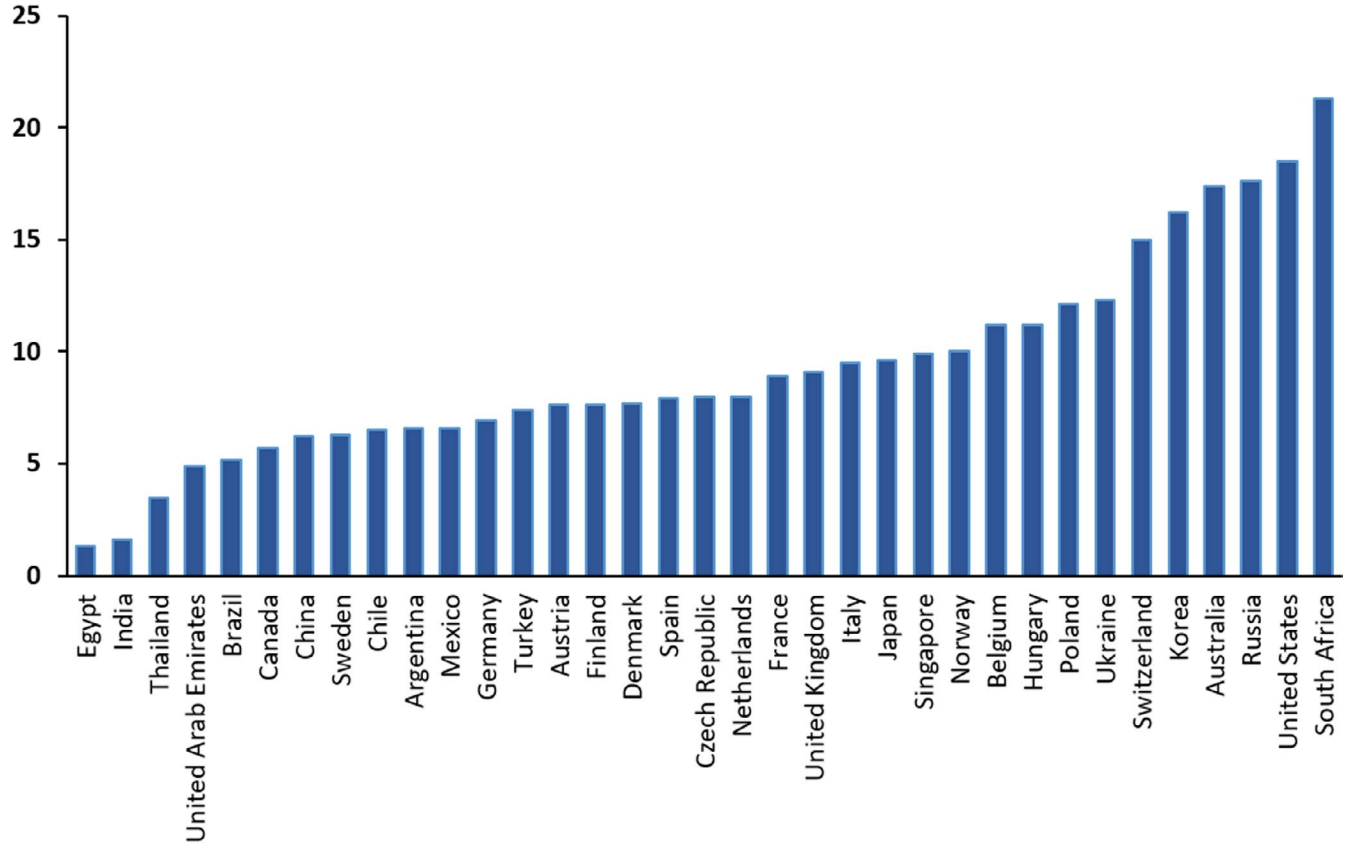

FIGURE 2 Percentages of discontinuation rates by country

Of 665 patients who discontinued VKA, 509 (76.5%) restarted on VKA and 156 (23.5%) switched to a DOAC: FXaI in 116 patients (17.4%) and DTI in 40 patients (6.0%). Of 561 patients who discontinued FXaI, 481 (85.7%) returned to a FXaI, 25 (4.5%) were given DTI, and 55 (9.8%) VKA. For the 189 patients who discontinued DTI, 116 (61.4%) restarted on DTI, 42 (22.2%) were given an FXaI, and 31 (16.4%) VKA. A total of 1160 (37%) of the 3114 patients who discontinued were given antiplatelet therapy only. Of these, 1020 (87.9%) were on antiplatelet and OAC therapy at the time of discontinuation.

3.3 | Outcome analysis

Among patients who discontinued OAC therapy, the majority of deaths was noncardiovascular (52%), with 44.5% and 15.1% of those being due to malignancy or respiratory failure, respectively (Table 2). Cardiovascular-related deaths accounted for 27.9% of mortality within the discontinuation group, of which chronic heart failure (34.4%) was most common. In contrast, patients who did not discontinue OAC had a comparable proportion of cardiovascular and noncardiovascular mortality (34.1% and 36.2%, respectively). Cumulative event-free survival for selected outcomes over 2 years in patients who either persisted or discontinued OAC is shown in Figure 4A,B. All event types occurred more in patients that discontinued (unadjusted). After discontinuation, the median time from discontinuation to death was 153 days (IQR: 50–348), to MI 174 days (IQR: 67–289), and to ischemic stroke 79 days (IQR: 32–220). The median time to stroke for those who discontinued VKAs or DOACs (censored for patients who switched drug before discontinuation) were similar (98 days [30–220] vs. 98 days [35–335], respectively).

Relative to patients who remained on OAC, patients who discontinued OAC for ≥7 consecutive days had a higher risk of all events ($p < .001$), with the exception of cardiovascular death (HR 1.37 [0.80–2.35]), including composite and individual endpoints: death/nonhemorrhagic stroke/SE/MI (HR 1.67 [1.35–2.08]), death/nonhemorrhagic stroke/SE (HR 1.66 [1.31–2.09]), death (HR 1.62 [1.25–2.09]), nonhemorrhagic stroke/SE (HR 2.21 [1.42–3.44]), and MI (HR 1.85 [1.09–3.13]) (Figure 5A). These results were confirmed by additional sensitivity analyses among patients who discontinued OAC ≥30 days (Figure 5B).

Figure 6 displays outcome data according to anticoagulation type (VKA vs. DOAC). The results, showing worse outcomes after OAC discontinuation, were consistent for both VKA- and DOAC-treated patients with no significant interactions (p for interactions range = 0.145–0.778).

4 | DISCUSSION

The main finding of this large prospective real-world cohort was that patients with newly diagnosed AF who discontinued OAC treatment

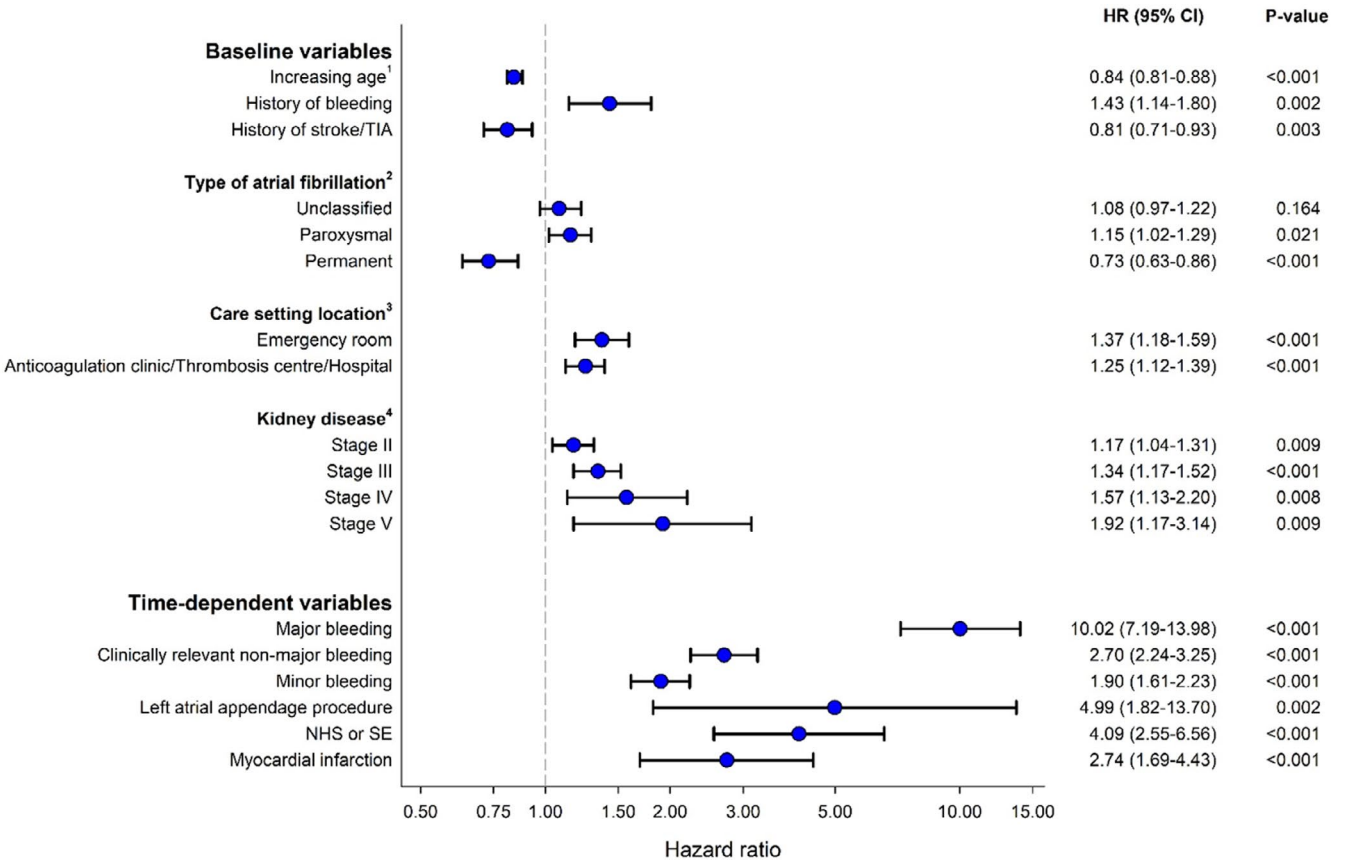

FIGURE 3 Adjusted hazard ratios for discontinuation with 95% CIs after atrial fibrillation (AF) diagnosis between patients who did and did not discontinue anticoagulation. Higher rates were seen in patients with a history of bleeding, all stages of kidney failure, as well as all postbaseline factors (all types of bleeding, stroke/systemic embolism, myocardial infarction, and left atrial appendage procedures). Lower discontinuation was seen with increasing age, when a history of stroke/transient ischemic accident and in permanent AF. [1]HR for age is for an increase of 10 years. HR relates to ages from 18-75 years. Risk is flat above 75. HR for weeks from AF onset to treatment is per unit 1 increase. [2]Reference: Persistent. [3]Reference: Office. [4]Reference: None/Stage I. CI: confidence interval, NHS: non-hemorraghic stroke, SE: systemic embolism.

for ≥7 consecutive days had worse clinical outcome, with a higher chance of stroke/SE and MI. These results were confirmed using a discontinuation window of 30 days, an important observation as 77.9% of patients who stopped the drug for 7 days remained off drug beyond 30 days. Although not statistically significant, a similar trend was also observed for cardiovascular-related mortality, whereby patients who discontinued OAC therapy were at a higher risk. The increased risk for MI supports the potential role of OAC in the prevention of acute coronary syndromes.[19] In agreement with our study, other studies evaluating the relationship between OAC persistence and clinical outcomes have also suggested worsening clinical outcomes with poor OAC adherence.[14,20–25] Many of these studies were retrospective in design, with small cohorts of patients, often from insurance or pharmacy databases.[20,21,23,24]

We found that the rate of OAC discontinuation (VKAs and DOACs) was 13.0%, with a median follow-up after discontinuation (number of days to death or last follow-up) of 511 days (IQR: 291–648). Treatment persistence was achieved in 82% of patients by 1 year of follow-up and 79% by 2 years. Patients who discontinued OAC had differing demographic, geographical, and clinical characteristics, and experienced adverse outcomes more frequently. Type of OAC did not impact patient outcomes.

Discontinuation rates of patients in GARFIELD-AF were lower compared with other registry studies and randomized trials,[5,11–13] although in line with rates found in the recent ORBIT II registry.[14] One possible reason for the lower discontinuation rate in GARFIELD-AF is that it includes only newly diagnosed AF patients (of whom 94.0% were OAC naïve), possibly leading to higher patient motivation and closer follow-up.[26] However, discontinuations occurred more frequently during the early months of follow-up, becoming less prevalent at subsequent time points, as in previous studies.[5,9,24] Although GARFIELD-AF is a noninterventional study, participation may have buttressed anticoagulation persistence.

Notably, patients who discontinued also more frequently had concomitant renal dysfunction, which itself increases the rate of major bleeding in response to OACs.[11,27,28] Also paroxysmal AF was associated with higher discontinuation rates.[29] In contrast, lower discontinuation was observed in patients with a higher thrombotic risk and those with a higher motivation to take OACs such as those with a prior stroke/TIA, permanent AF, a history of acute coronary

TABLE 2 Distribution of cause of death by discontinuation status

Cause of Death	Discontinued (229 Deaths) *N* (%)	Did not Discontinue (1424 Deaths) *N* (%)
Noncardiovascular death	119 (52.0)	515 (36.2)
Cardiovascular death	64 (27.9)	485 (34.1)
Other/unknown causes of death	46 (20.1)	424 (29.8)
Noncardiovascular causes[a]		
Malignancy	53 (44.5)	148 (28.7)
Respiratory failure	18 (15.1)	85 (16.5)
Sepsis	15 (12.6)	51 (9.9)
Infection	9 (7.6)	53 (10.3)
Renal disease	6 (5.0)	30 (5.8)
Accidental/trauma	1 (0.8)	21 (4.1)
Liver failure	3 (2.5)	8 (1.6)
Suicide	0 (0.0)	4 (0.8)
Other/Unknown noncardiovascular	14 (11.8)	115 (22.3)
Cardiovascular causes[b]		
Congestive heart failure	22 (34.4)	184 (37.9)
Sudden or unwitnessed death	12 (18.7)	71 (14.6)
Myocardial infarction	4 (6.3)	49 (10.1)
Nonhemorrhagic stroke	12 (18.7)	42 (8.7)
Intracranial hemorrhage	1 (1.6)	24 (5.0)
Pulmonary embolism	2 (3.1)	22 (4.5)
Atherosclerotic vascular disease	1 (1.6)	14 (2.9)
Dysrhythmia	2 (3.1)	12 (2.5)
Directly related to revascularization	0 (0.0)	2 (0.4)
Other/unknown cardiovascular	8 (12.5)	65 (13.4)

[a]Percentages calculates among patients deceased of noncardiovascular causes.

[b]Percentages calculates among patients deceased of cardiovascular causes.

syndrome, or increasing age. We also observed lower discontinuation when OAC was initiated by cardiologists compared with primary care.

Marked geographical differences in discontinuation rates were found whereby the highest rates of discontinuation were observed in the United States and South Africa. Studies investigating OAC discontinuation rates have collectively revealed varying rates of discontinuation across countries. Many of these studies, however, have been small in size, each reported data from single countries, used different definitions of discontinuation, were investigated over short time frames, or reported discontinuation rates differently.[6,11,30–34] Thus comparisons among countries are complex. Reports from the prospective GLORIA-AF registry provide discontinuation data for dabigatran by region but no country details: compared with Europe, discontinuation rates were higher in North America and Asia, whereas rates within Latin America and the Middle East were notably lower.[12] In GARFIELD-AF, insurance status and health care setting may have played a role. Indeed, socioeconomic factors and local health care related factors likely influence patient compliance.[35]

In patients for whom cause of discontinuation was provided (64%), cessation was mainly resulting from physician (51.1%) and patient decision (17.5%). Bleeding, including minor bleeding, was associated with an increased rate of discontinuation, especially during the week before discontinuation. In addition to bleeding episodes, new thrombotic events (stroke, MI) as well as left atrial appendage closure procedures were often associated with OAC discontinuation. The latter are commonly associated as they are performed most frequently in patients with contraindications to OACs.[36–39] Certainly, left atrial appendage closure procedures have been demonstrated as noninferior to OAC treatment for the prevention of stroke/SE, making it an attractive alternative for patients with OAC contraindications.[40] However, the absolute number of these procedures was low.

Discontinuation rates of VKAs are known to be high.[5,6,41] Several studies show that DOACs generally have lower discontinuation rates[11–13,41] compared with VKA, with DTI showing higher discontinuation rates than Xa inhibitors.[7,11] In GARFIELD-AF, we observed a higher rate of DTI discontinuation compared with Xa inhibitors or VKAs.

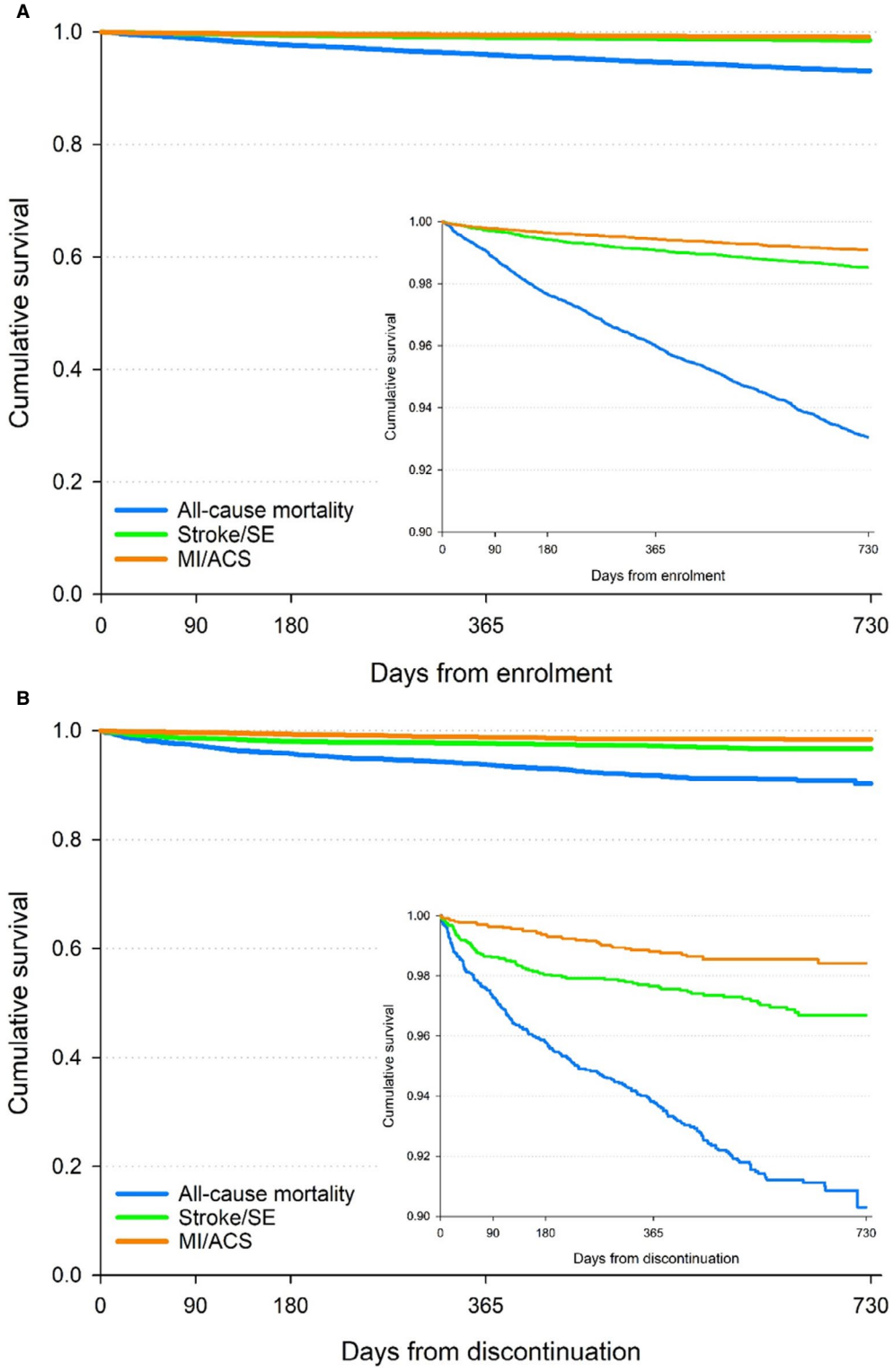

FIGURE 4 (A) Cumulative event-free survival for selected endpoints of patients who did not discontinue during follow-up. Follow-up starts at enrollment and is truncated at 2 years. (B) Cumulative event-free survival for selected endpoints of patients who discontinued during follow-up. Follow-up starts at the time of discontinuation and is truncated at 2 years

Direct oral anticoagulants and VKA discontinuation have been previously associated with comparable rates of stroke and systemic embolism within 30 days of discontinuation.[42] Because the short half-life of DOACs, discontinuation could lead to a "rebound phenomenon," resulting in an increase in pro-coagulant markers and an early increase in stroke risk.[43] In GARFIELD-AF, the impact of type of OAC discontinuation upon outcomes did not differ between those who discontinued DOACs or VKAs. In a

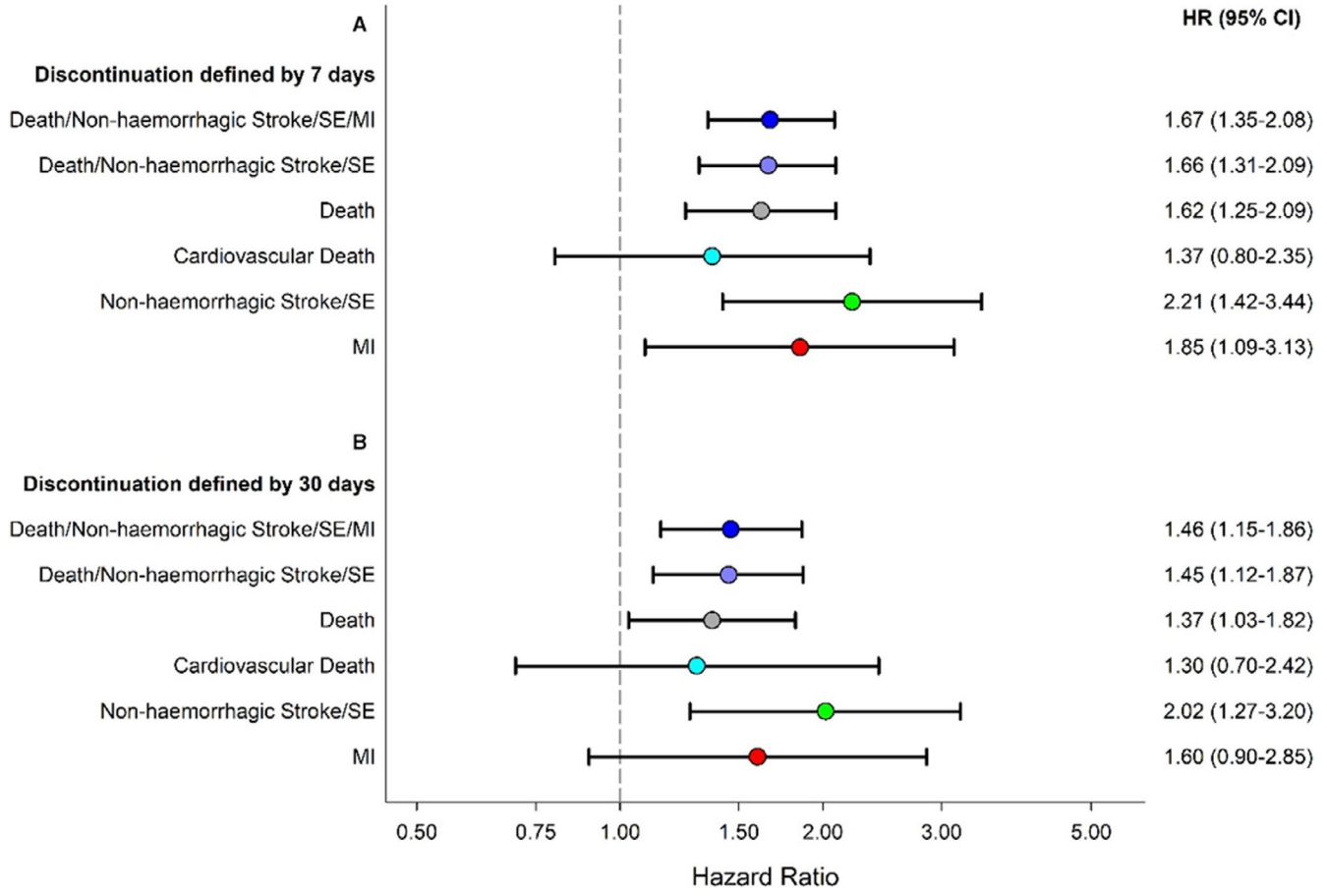

FIGURE 5 Adjusted hazard ratios for outcome events with 95% CIs over 2 years following AF diagnosis for patients who discontinued anticoagulation for (A) ≥7 consecutive days and (B) ≥30 consecutive days, vs those who did not discontinue anticoagulation (reference group). AF, atrial fibrillation; MI, myocardial infarction; SE, systemic embolism

study by Park *et al*., following abrupt DOAC discontinuation, the median time to stroke was reported to be 7 days (IQR: 4–15),[43] although the number of patients was limited. In GARFIELD-AF, the median time to ischemic stroke was 79 days (IQR: 32–220). The 2-year follow-up of GARFIELD-AF provides data regarding the long-term effects of OAC discontinuation and suggests that, over time, there is no significant difference between DOAC and VKA discontinuation.

Increased all-cause mortality following discontinuation is an important finding to consider. Noncardiovascular-related mortality accounted for a substantial proportion of deaths within the discontinuation group compared to the nondiscontinuation group. This likely reflects differences in the proportion of underlying or preexisting comorbidities. Indeed, newly diagnosed nonvalvular AF could itself represent a marker of worsening underlying conditions, both cardiovascular and noncardiovascular.[44–48] Within the discontinuation group, the majority of deaths was attributable to malignancy. Furthermore, new cancer itself likely leads to OAC discontinuation in favor of parenteral treatment.

4.1 | Study strengths and limitations

In observational research there is always a risk of bias, such as confounding by indication. To minimize this risk, we used marginal structural models, analyzing baseline and time-dependent variables. This approach is considered more reliable than a time-dependent Cox proportional hazards model.[18]

Because of the time-dependent nature of this analysis, comparing event rates at a time point rather than overall hazard ratios between groups can only be descriptive. Uncaptured confounding factors may be present and the cause of missing data was not recorded. Additionally, a small proportion of 26 patients within the discontinuation group were initiated on heparin within at least 7 days of OAC discontinuation, although this small number of patients was negligible. Nevertheless, GARFIELD-AF is a global rigorously designed registry with a unique methodology and prospective follow-up of at least 2 years, with a significant rate of source data verification.[17] Therefore, significant underreporting is unlikely. The start and stop dates of treatment are exactly known, providing precise information on timing of treatment relative to outcomes. In addition, pharmacy data were not collected, and therefore treatment adherence could not be assessed.

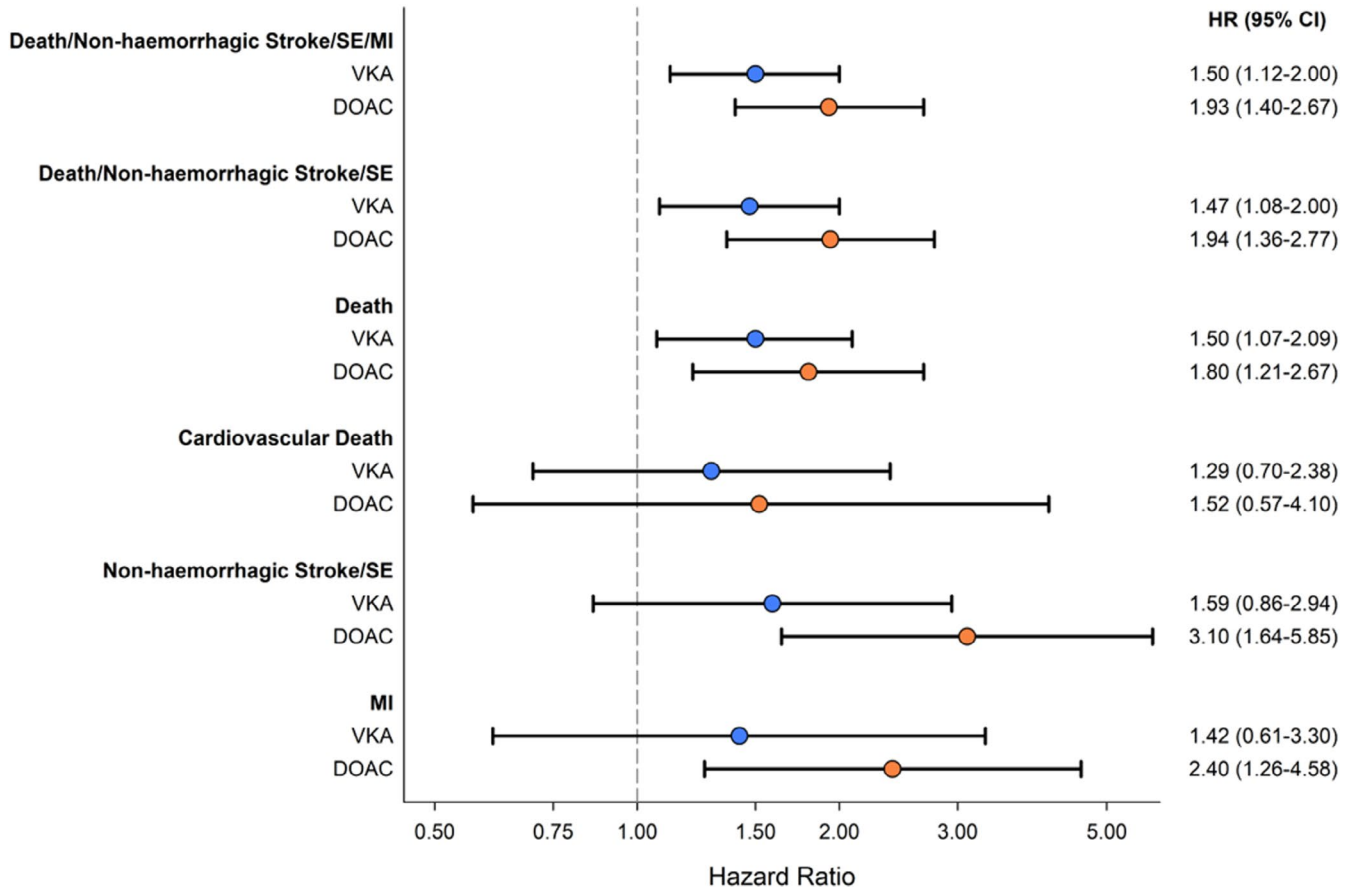

FIGURE 6 Adjusted hazard ratios for outcome events in patients treated with DOAC or VKA over 2 years following AF diagnosis who discontinued anticoagulation vs those who did not discontinue anticoagulation (reference group). There were no significant interactions between discontinuation and type of anticoagulant (all $p > .14$). AF, atrial fibrillation; DOAC, direct oral anticoagulation; VKA, vitamin K antagonist

4.2 | Clinical implications

In this large prospective registry, discontinuation rates are lower than historically reported. However, the outcome analysis suggests that discontinuation of OAC treatment in these patients should be discouraged, especially if the reasons for discontinuation do not relate to persistent hazards for the patients. Patients should be counselled that most adverse events, especially minor bleeds, should not lead to permanent OAC discontinuation. In cases of major gastrointestinal or intracranial bleeds, it is preferable to restart OAC therapy after resolution of the bleeding episode.[49,50] As recommended by the European Heart Rhythm Association, an integrated AF care program with active patient involvement should be implemented.[2] This need is especially important during the first year after treatment initiation when rates of discontinuation are highest.

5 | CONCLUSIONS

In GARFIELD-AF, the rate of discontinuation in this mixed VKA-DOAC population was 13.0%. Patients who discontinued their OAC for ≥7 consecutive days had a greater risk of a clinically relevant adverse outcome. These data suggest that discontinuation of OAC therapy in patients with AF at risk for stroke should be discouraged unless persistent patients' hazards are identified.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to the concept, design and conduct of the study. Frank Cools wrote the manuscript. Dana Johnson and Karen S. Pieper conducted the statistical analysis. All authors contributed to data interpretation, critically reviewed the manuscript, and approved the manuscript. Ajay K. Kakkar and Gloria Kayani handled funding and supervised the registry.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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