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ORIGINAL ARTICLE

Oral anticoagulation across diabetic subtypes in patients with newly diagnosed atrial fibrillation: A report from the GARFIELD-AF registry

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Abstract

Aims: This study aims to describe both management and prognosis of patients with diabetes mellitus (DM) and newly diagnosed atrial fibrillation (AF), overall as well as by antidiabetic treatment, and to assess the influence of oral anticoagulation (OAC) on outcomes by DM status.

Methods: The study population comprised 52 010 newly diagnosed patients with AF, 11 542 DM and 40 468 non-DM, enrolled in the GARFIELD-AF registry. Follow-up was truncated at 2 years after enrolment. Comparative effectiveness of OAC versus no OAC was assessed by DM status using a propensity score overlap weighting scheme and weights were applied to Cox models.

Results: Patients with DM [39.3% oral antidiabetic drug (OAD), 13.4% insulin ± OAD, 47.2% on no antidiabetic drug] had higher risk profile, OAC use, and rates of clinical outcomes compared with patients without DM. OAC use was associated in patients without DM and patients with DM with lower risk of all-cause mortality [hazard ratio 0.75 (0.69-0.83), 0.74 (0.64-0.86), respectively] and stroke/systemic embolism (SE) [0.69 (0.58-0.83), 0.70 (0.53-0.93), respectively]. The risk of major bleeding with OAC was similarly increased in patients without DM and those with DM [1.40 (1.14-1.71), 1.37 (0.99-1.89), respectively]. Patients with insulin-requiring DM had a higher risk of all-cause mortality and stroke/SE [1.91 (1.63-2.24)], [1.57 (1.06-2.35), respectively] compared with patients without DM, and experienced significant risk reductions of all-cause mortality and stroke/SE with OAC [0.73 (0.53-0.99); 0.50 (0.26-0.97), respectively].

Conclusions: In both patients with DM and patients without DM with AF, OAC was associated with lower risk of all-cause mortality and stroke/SE. Patients with insulin-requiring DM derived significant benefit from OAC.

KEYWORDS
atrial fibrillation, cardiovascular disease, cohort study, observational study, oral anticoagulants, type 2 diabetes

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a global prevalence that is expected to rise in the coming decades.[1,2] AF is associated with higher risks of non-haemorrhagic stroke/stroke/systemic embolism (SE), all cause death, and bleeding incurred by antithrombotic therapy.[3] Diabetes mellitus (DM), particularly type 2 DM (T2DM), is a growing worldwide epidemic.[2] In the United States, 13.0% of all US adults are affected by T2DM.[4] DM prevalence increases in tandem with the income level of a given country.[5] The DM impact on outcomes depends on the duration and glycaemic burden.[6,7] DM is associated with an increased risk of death, cardiovascular (CV) outcomes, macro- and microvascular obstructive disease, and chronic kidney disease (CKD).[6] Insulin-requiring DM (IRD) and non-insulin-requiring DM (NIRD) may have a different impact on outcomes.[8–10]

Further, DM is associated with a high prevalence and incidence of AF through mechanisms common to both forms of diabetes: structural, electromechanical and autonomic atrial remodelling, as well as oxidative stress and inflammation.[11–13] DM is also an independent predictor of non-haemorrhagic stroke/SE in patients with AF.[14–16] DM is one of the most common comorbidities associated with AF, and the interplay of these two conditions has the potential of worsening the outcome. In this context, depending on the risk profile, oral anticoagulation (OAC) is indicated in addition to specific therapies targeting glycaemic balance and comorbidities.[17] OAC reduces the risk of non-haemorrhagic stroke/SE and of death in AF.[3] As non-vitamin K oral anticoagulants (NOAC) were introduced in therapeutics, few reports have explored the impact of NOAC and vitamin K antagonists (VKA) on the outcome of patients with AF and diabetes.[18,19]

The aims of our study were (a) to describe the management and prognosis of newly diagnosed patients with AF with DM, overall as well as by DM subtype, defined according to antidiabetic treatment, insulin or oral antidiabetic drugs (OAD) or lifestyle counselling only, and (b) to assess the association between OAC and clinical outcomes by DM status and by DM subtype, along with the relative effectiveness of NOAC versus VKA among those anticoagulated.

2 | METHODS

2.1 | Study design

GARFIELD-AF is the largest fully recruited multinational prospective registry in newly diagnosed patients with AF.[20] Patients were prospectively recruited between March 2010 and August 2016 in more than 1000 investigational sites in 35 countries. Adults ≥18 years were

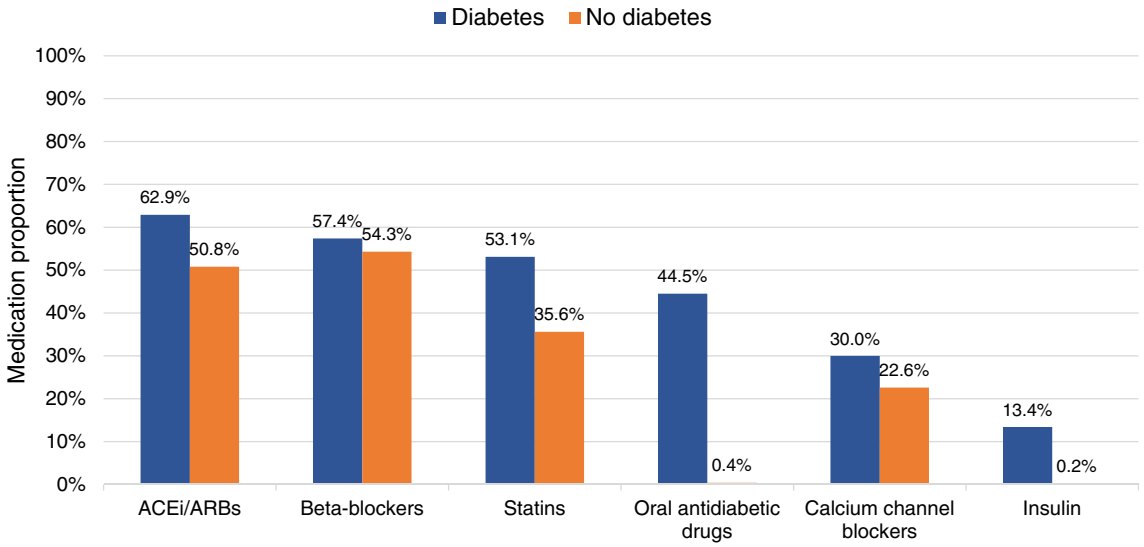

FIGURE 1 Additional medication by baseline diabetes in patients with atrial fibrillation enrolled in the GARFIELD-AF registry (Cohorts 1-5). ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers.

TABLE 1 Baseline characteristics of patients with AF by diabetes status at baseline in the GARFIELD-AF registry (Cohorts 1-5).

Baseline characteristics	No diabetes (N = 40 468)	All diabetic patients (N = 11 542)	No drug treatment for diabetes (N = 5452)	Oral antidiabetics only (N = 4540)	Insulin (w/wo oral antidiabetics) (N = 1550)
Sex, n (%)					
Male	22 509 (55.6)	6518 (56.5)	3116 (57.2)	2579 (56.8)	823 (53.1)
Female	17 958 (44.4)	5024 (43.5)	2336 (42.8)	1961 (43.2)	727 (46.9)
Age, median (Q1; Q3), years	71.0 (62.0; 78.0)	71.0 (64.0; 78.0)	71.0 (64.0; 78.0)	71.0 (64.0; 77.0)	71.0 (64.0; 78.0)
Ethnicity, n (%)					
Caucasian	25 017 (63.4)	6977 (61.8)	3119 (58.6)	2823 (63.4)	1035 (68.6)
Hispanic/Latino	2536 (6.4)	857 (7.6)	361 (6.8)	380 (8.5)	116 (7.7)
Asian	11 110 (28.2)	3166 (28.1)	1734 (32.6)	1139 (25.6)	293 (19.4)
Afro-Caribbean/mixed/other	786 (2.0)	285 (2.5)	107 (2.0)	114 (2.6)	64 (4.2)
Body mass index, median (Q1; Q3), kg/m^2	26.4 (23.6; 30.0)	28.7 (25.2; 33.1)	28.1 (24.8; 32.4)	29.0 (25.5; 33.3)	30.1 (26.2; 34.5)
Systolic blood pressure, median (Q1; Q3), mmHg	130.0 (120.0; 144.0)	133.0 (120.0; 146.0)	131.0 (120.0; 145.0)	135.0 (121.0; 148.0)	135.0 (120.0; 150.0)
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (70.0; 89.0)	80.0 (70.0; 88.0)	80.0 (70.0; 88.0)	80.0 (70.0; 88.0)	80.0 (70.0; 86.5)
Pulse, median (Q1; Q3), bpm	84.0 (70.0; 105.0)	85.0 (72.0; 105.0)	83.0 (72.0; 100.0)	86.0 (72.0; 109.0)	88.0 (73.0; 110.0)
Type of atrial fibrillation, n (%)					
Permanent	5117 (12.6)	1512 (13.1)	786 (14.4)	539 (11.9)	187 (12.1)
Persistent	6018 (14.9)	1735 (15.0)	845 (15.5)	702 (15.5)	188 (12.1)
Paroxysmal	11 361 (28.1)	2943 (25.5)	1402 (25.7)	1178 (25.9)	363 (23.4)
New onset (unclassified)	17 972 (44.4)	5352 (46.4)	2419 (44.4)	2121 (46.7)	812 (52.4)
Care setting specialty at diagnosis, n (%)					
Internal medicine/neurology/geriatric	7897 (19.5)	2545 (22.0)	1149 (21.1)	974 (21.5)	422 (27.2)
Cardiology	26 727 (66.0)	7445 (64.5)	3544 (65.0)	2959 (65.2)	942 (60.8)
Primary care/general practice	5844 (14.4)	1552 (13.4)	759 (13.9)	607 (13.4)	186 (12.0)
Care setting location at diagnosis, n (%)					
Hospital	23 651 (58.4)	6684 (57.9)	3199 (58.7)	2539 (55.9)	946 (61.0)
Office/anticoagulation clinic/thrombosis centre	12 339 (30.5)	3578 (31.0)	1765 (32.4)	1430 (31.5)	383 (24.7)
Emergency room	4478 (11.1)	1280 (11.1)	488 (9.0)	571 (12.6)	221 (14.3)
Medical history, n (%)					
Heart failure	8872 (21.9)	2867 (24.8)	1334 (24.5)	1038 (22.9)	495 (31.9)
Acute coronary syndromes	3710 (9.2)	1823 (15.9)	764 (14.1)	691 (15.3)	368 (23.9)
Vascular disease[a]	9074 (22.6)	3741 (32.6)	1691 (31.2)	1385 (30.7)	665 (43.3)
Carotid occlusive disease	1080 (2.7)	458 (4.0)	207 (3.9)	176 (3.9)	75 (4.9)
VTE	1052 (2.6)	303 (2.6)	129 (2.4)	129 (2.9)	45 (2.9)
Prior stroke/TIA/SE	4374 (10.9)	1465 (12.8)	705 (13.1)	532 (11.8)	228 (14.9)
Prior bleeding	1007 (2.5)	308 (2.7)	138 (2.5)	111 (2.5)	59 (3.8)
Hypertension	29 720 (73.7)	9884 (85.7)	4577 (84.0)	3960 (87.3)	1347 (87.0)
Hypercholesterolaemia	14 742 (37.7)	6213 (55.3)	2709 (51.0)	2566 (58.2)	938 (62.1)
Cirrhosis	194 (0.5)	99 (0.9)	48 (0.9)	31 (0.7)	20 (1.3)
Moderate to severe CKD	3751 (9.6)	1603 (14.4)	644 (12.3)	578 (13.2)	381 (25.5)
Dementia	551 (1.4)	213 (1.9)	109 (2.0)	68 (1.5)	36 (2.3)

(Continues)

TABLE 1 (Continued)

Baseline characteristics	No diabetes (N = 40 468)	All diabetic patients (N = 11 542)	No drug treatment for diabetes (N = 5452)	Oral antidiabetics only (N = 4540)	Insulin (w/wo oral antidiabetics) (N = 1550)
Heavy alcohol consumption, n (%)	844 (2.5)	184 (1.9)	84 (1.8)	80 (2.1)	20 (1.6)
Current smoker, n (%)	4215 (11.4)	987 (9.5)	473 (9.6)	397 (9.6)	117 (8.5)
Antithrombotic treatment, n (%)					
NOAC ± AP	11 093 (27.8)	3018 (26.5)	1231 (23.0)	1378 (30.8)	409 (26.8)
VKA ± AP	15 186 (38.0)	4997 (44.0)	2369 (44.2)	1984 (44.3)	644 (42.2)
AP only	8463 (21.2)	2298 (20.2)	1178 (22.0)	779 (17.4)	341 (22.3)
None	5177 (13.0)	1056 (9.3)	585 (10.9)	339 (7.6)	132 (8.7)
AP treatment ± OAC, n (%)	13 489 (33.8)	4614 (40.6)	2166 (40.4)	1733 (38.7)	715 (46.9)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0; 4.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)
HAS-BLED score[b], median (Q1; Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)
GARFIELD-AF death score[c], median (Q1; Q3)	4.3 (2.4; 8.0)	6.1 (3.4; 10.9)	6.1 (3.4; 10.6)	5.8 (3.3; 10.2)	7.3 (4.0; 12.9)
GARFIELD-AF stroke score[d], median (Q1; Q3)	1.5 (1.0; 2.2)	1.9 (1.3; 2.8)	1.9 (1.3; 2.8)	1.8 (1.3; 2.7)	2.1 (1.4; 3.2)
GARFIELD-AF bleeding score[e], median (Q1; Q3)	1.5 (0.9; 2.3)	1.9 (1.3; 2.9)	1.9 (1.3; 2.9)	1.9 (1.3; 2.9)	2.1 (1.5; 3.3)

[a]Defined as peripheral artery disease and/or coronary artery disease;
[b]Risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. Consequently, the maximum HAS-BLED score at baseline is 8 points (not 9).
[c]Represents the expected probability of death within 2 years of follow-up.
[d]Represents the expected probability of non-haemorrhagic stroke/SE within the 2-year follow-up.
[e]Represents the expected probability of major bleeding within 2-year follow-up.
Abbreviations: AP, antiplatelet; CKD, chronic kidney disease; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SE, stroke/systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K anticoagulant; VTE, venous thromboembolism.

eligible for inclusion if they were diagnosed with AF 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).[20,21] They were included in five consecutive cohorts of about 10 000 patients each. Cohorts 1 and 2 were enrolled between 2010 and 2013 and anticoagulated patients received primarily VKA. Cohorts 3-5 were enrolled between 2014 and 2016 and included patients on NOACs.[3,20]

2.2 | Procedures and outcome measures

Baseline characteristics collected at study entry included: medical history, care setting, type of AF, date and method of diagnosis of AF, symptoms, antithrombotic treatment [VKA, NOAC, antiplatelet (AP) treatment] and CV drugs. The risk profile for death, non-haemorrhagic stroke/SE and bleeding was assessed with the CHA_2DS_2-VASc, HAS-BLED[3,20,21] and GARFIELD-AF risk calculator.[22]

We used standardized definitions for clinical outcomes.[20,21] Diabetes status was indicated in the electronic case report form (eCRF) at the inclusion visit as type 1 diabetes (T1DM) or T2DM. For this analysis, patients with DM were further categorized according to antidiabetic therapy received, no antidiabetic drug (no-drug DM), OAD only, that is, NIRD, and insulin therapy ± OAD treatment, that is, IRD.

Collection of follow-up data using the eCRF occurred at 4-monthly intervals up to 24 months and yearly thereafter. In this analysis, the maximum follow-up considered was 24 months and outcome information beyond 24 months was censored. Submitted data were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK). In accordance with the study protocol, 20% of all eCRFs were monitored against source documentation.[23]

2.3 | Statistical analysis

Continuous variables were expressed as medians and interquartile ranges and categorical variables as frequencies and percentages. 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.

TABLE 2 Event rates (per 100 person-years), unadjusted and adjusted[a] HRs for selected outcomes within 2-year follow-up by baseline diabetes and diabetes treatment in patients with AF enrolled in the GARFIELD-AF registry (Cohorts 1-5)

Outcome	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
All-cause mortality				
No diabetes	2686	3.56 (3.42-3.69)	1 (ref.)	1 (ref.)
Diabetes	1022	4.79 (4.50-5.09)	1.35 (1.27-1.43)	1.28 (1.20-1.37)
No drug treatment	451	4.48 (4.08-4.91)	1.26 (1.15-1.37)	1.23 (1.11-1.38)
Oral antidiabetics only (NIRD)	335	3.94 (3.54-4.39)	1.11 (0.98-1.26)	1.11 (0.99-1.26)
Insulin w/wo oral antidiabetics (IRD)	236	8.54 (7.52-9.70)	2.39 (2.02-2.84)	1.91 (1.63-2.24)
Cardiovascular mortality				
No diabetes	941	1.25 (1.17-1.33)	1 (ref.)	1 (ref.)
Diabetes	379	1.78 (1.61-1.96)	1.42 (1.29-1.57)	1.25 (1.14-1.36)
No drug treatment	174	1.73 (1.49-2.00)	1.38 (1.18-1.62)	1.28 (1.06-1.55)
Oral antidiabetics only (NIRD)	115	1.35 (1.13-1.62)	1.09 (0.91-1.29)	1.05 (0.89-1.22)
Insulin w/wo oral antidiabetics (IRD)	90	3.26 (2.65-4.01)	2.60 (2.05-3.29)	1.73 (1.35-2.21)
Non-cardiovascular mortality				
No diabetes	1039	1.38 (1.29-1.46)	1 (ref.)	1 (ref.)
Diabetes	389	1.82 (1.65-2.01)	1.32 (1.15-1.52)	1.36 (1.17-1.57)
No drug treatment	162	1.61 (1.38-1.88)	1.17 (1.02-1.34)	1.21 (1.04-1.41)
Oral antidiabetics only (NIRD)	136	1.60 (1.35-1.89)	1.16 (0.93-1.46)	1.21 (0.95-1.54)
Insulin w/wo oral antidiabetics (IRD)	91	3.29 (2.68-4.04)	2.39 (1.90-3.00)	2.34 (1.85-2.96)
Non-haemorrhagic stroke/SE				
No diabetes	709	0.95 (0.88-1.02)	1 (ref.)	1 (ref.)
Diabetes	257	1.22 (1.08-1.37)	1.28 (1.09-1.52)	1.19 (1.01-1.41)
No drug treatment	103	1.03 (0.85-1.25)	1.09 (0.83-1.44)	1.07 (0.83-1.39)
Oral antidiabetics only (NIRD)	107	1.27 (1.05-1.54)	1.34 (1.09-1.66)	1.35 (1.09-1.67)
Insulin w/wo oral antidiabetics (IRD)	47	1.72 (1.29-2.28)	1.80 (1.31-2.49)	1.57 (1.06-2.35)
Major bleeding				
No diabetes	685	0.91 (0.85-0.99)	1 (ref.)	1 (ref.)
Diabetes	257	1.22 (1.08-1.38)	1.33 (1.10-1.61)	1.24 (1.02-1.50)
No drug treatment	104	1.04 (0.86-1.26)	1.14 (0.85-1.52)	1.15 (0.87-1.52)
Oral antidiabetics only (NIRD)	102	1.21 (1.00-1.47)	1.33 (1.04-1.70)	1.27 (0.96-1.68)
Insulin w/wo oral antidiabetics (IRD)	51	1.88 (1.43-2.47)	2.04 (1.39-2.99)	1.82 (1.16-2.87)
MI/ACS				
No diabetes	427	0.57 (0.52-0.62)	1 (ref.)	1 (ref.)
Diabetes	184	0.87 (0.75-1.00)	1.53 (1.28-1.82)	1.27 (1.07-1.52)
No drug treatment	81	0.81 (0.65-1.01)	1.42 (1.13-1.78)	1.22 (0.92-1.63)
Oral antidiabetics only (NIRD)	64	0.76 (0.59-0.97)	1.33 (0.98-1.81)	1.10 (0.81-1.49)
Insulin w/wo oral antidiabetics (IRD)	39	1.43 (1.04-1.95)	2.49 (1.87-3.32)	1.52 (1.14-2.02)
New/worsening heart failure				
No diabetes	592	0.79 (0.73-0.86)	1 (ref.)	1 (ref.)
Diabetes	232	1.10 (0.97-1.25)	1.39 (1.19-1.62)	1.31 (1.15-1.49)
No drug treatment	106	1.06 (0.88-1.29)	1.34 (1.12-1.61)	1.35 (1.10-1.65)
Oral antidiabetics only (NIRD)	93	1.11 (0.90-1.36)	1.40 (1.16-1.69)	1.57 (1.30-1.89)
Insulin w/wo oral antidiabetics (IRD)	33	1.21 (0.86-1.71)	1.52 (1.05-2.20)	1.25 (0.82-1.93)

[a]Adjusted by sex, age, ethnicity, type of AF, congestive heart failure, vascular disease, hypertension, previous stroke/transient ischaemic attack/SE, previous bleeding, moderate to severe, current smoking, heavy alcohol consumption, baseline anticoagulation and antiplatelet therapy.
Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CI, confidence interval; HRs, hazard ratios; IRD, insulin-requiring diabetes; MI, myocardial infarction; NIRD, non-insulin-requiring diabetes; SE, stroke/systemic embolism.

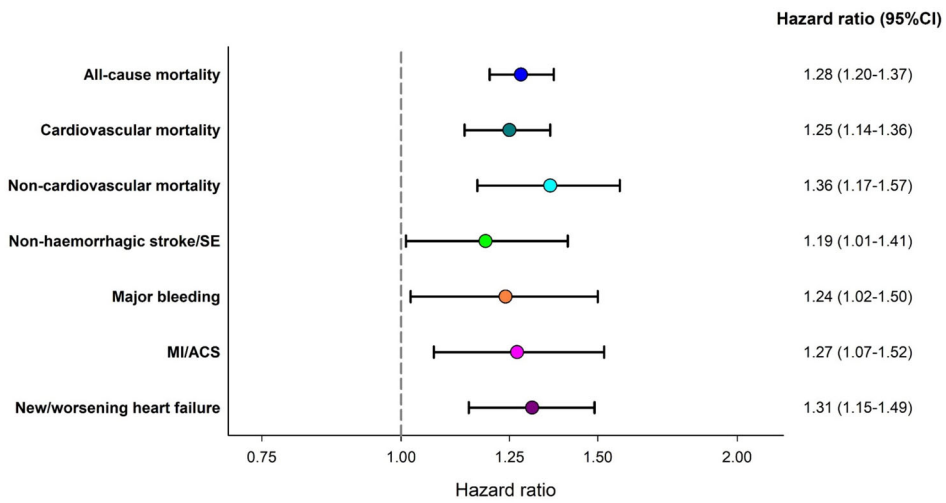

FIGURE 2 Adjusted[a] hazard ratios for selected outcomes of diabetes versus no diabetes (ref.) within 2-year follow-up by baseline diabetes in patients with atrial fibrillation (AF) enrolled in the GARFIELD-AF registry (Cohorts 1-5). [a]Adjusted by sex, age, ethnicity, type of AF, congestive heart failure, vascular disease, hypertension, previous stroke/transient ischaemic attack/SE, previous bleeding, moderate to severe, current smoking, heavy alcohol consumption, baseline anticoagulation and antiplatelet therapy. ACS, acute coronary syndrome; MI, myocardial infarction; SE, stroke/systemic embolism.

Rates were presented as person-years with 95% confidence intervals for the first occurrence of the clinical outcomes. Our first aim was to identify associations between the presence of DM at baseline and selected clinical endpoints: all-cause mortality, CV mortality, non-CV mortality, non-haemorrhagic stroke/SE, major bleeding, myocardial infarction/acute coronary syndromes (myocardial infarction/ACS) and new/worsening heart failure. Only the first occurrence of each event was considered. The follow-up period was from the date of enrolment, truncated at first event occurrence, death, loss to follow-up, or 2 years after enrolment, whichever occurred first. The hazard ratio (HR) for the selected clinical outcomes was estimated using Cox proportional hazards models adjusted for the confounding factors. A robust covariance estimate was included to account for correlation within countries.

Secondly, we examined the comparative effectiveness of OAC versus no OAC and NOAC versus VKA among anticoagulated patients according to DM at baseline. 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 regarding the assessment and the trimming of the weights were eliminated. Covariates included in the weighting scheme consisted of: country and cohort enrolment, sex, age, ethnicity, AF type, care setting speciality and location, congestive heart failure, previous stroke/transient ischaemic attack/SE, previous bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, cirrhosis, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline AP use. All recorded variables related to treatment assignment, the outcome of interest or both were included in the weighting scheme. The balance of the included covariates between treatment groups was quantified through absolute standardized differences (Figures S1 and S2). All covariate information was recorded at the time of enrolment, with no change during follow-up recorded. Treatment was defined as the first treatment received at the time of enrolment, approximating 'intention-to-treat'.

Only complete cases were presented in descriptive tables. Multiple imputation was applied for the estimation of the DM association coefficients and in the comparative effectiveness analyses.[24] Final estimates were obtained by combining results across five imputed datasets. Statistical analyses were carried out using SAS (version 9.4).

3 | RESULTS

3.1 | Whole group analysis

Overall, 52 057 patients were enrolled in GARFIELD-AF from 2010 to 2016 and followed up for a minimum of 2 years. The study population for this analysis comprised 52 010 patients with newly diagnosed AF: 40 468 (77.8%) patients without DM and 11 542 (22.2%) patients with DM (Figure S3). Diabetes prevalence in this registry varied from 12% in Norway to 45% in the United Arab Emirates (Figure S4).

Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, beta-blockers and calcium channel blockers were more frequently prescribed in DM than in patients without

TABLE 3 Unadjusted and adjusted[a] HRs comparing OAC versus no OAC (reference) baseline treatment at 2 years of follow-up by baseline diabetes status in patients with AF at high risk of stroke (i.e. CHA_2DS2-VASc ≥2, excluding sex) enrolled in the GARFIELD-AF registry (Cohorts 1-5)

	Treatment comparison OAC versus no OAC (ref.)			
	Unadjusted		Adjusted[a]	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Diabetes status outcome				
No diabetes				
All-cause mortality	0.86 (0.79-0.93)	.0002	0.75 (0.69-0.83)	<.0001
Non-haemorrhagic stroke/SE	0.69 (0.60-0.80)	<.0001	0.69 (0.58-0.83)	<.0001
Major bleeding	1.61 (1.35-1.93)	<.0001	1.40 (1.14-1.71)	.0013
Diabetes				
All-cause mortality	0.71 (0.63-0.81)	<.0001	0.74 (0.64-0.86)	<.0001
Non-haemorrhagic stroke/SE	0.65 (0.51-0.84)	.0010	0.70 (0.53-0.93)	.0152
Major bleeding	1.42 (1.06-1.91)	.0202	1.37 (0.99-1.89)	.0591
Diabetes subtypes				
No diabetes treatment				
All-cause mortality	0.67 (0.56-0.81)	<.0001	0.65 (0.52-0.81)	<.0001
Non-haemorrhagic stroke/SE	0.71 (0.48-1.05)	.0833	0.72 (0.46-1.12)	.1469
Major bleeding	2.39 (1.42-4.02)	.0010	2.28 (1.29-4.02)	.0045
Oral antidiabetics only				
All-cause mortality	0.85 (0.67-1.08)	.1851	0.94 (0.71-1.25)	.6814
Non-haemorrhagic stroke/SE	0.62 (0.41-0.93)	.0200	0.76 (0.48-1.22)	.2545
Major bleeding	0.98 (0.62-1.54)	.8311	0.98 (0.59-1.64)	.9482
Insulin (w/wo oral antidiabetics)				
All-cause mortality	0.68 (0.53-0.89)	.0049	0.73 (0.53-0.99)	.0435
Non-haemorrhagic stroke/SE	0.58 (0.33-1.03)	.0632	0.50 (0.26-0.97)	.0399
Major bleeding	1.08 (0.58-2.01)	.7981	1.08 (0.55-2.13)	.8286

[a]Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, previous stroke/transient ischaemic attack/SE, previous bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, 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.
Abbreviations: AF, atrial fibrillation; CI, confidence interval; HRs, hazard ratios; OAC, oral anticoagulant; SE, stroke/systemic embolism.

DM (Figure 1). The management strategy of AF was similar in both patients without DM and patients with DM with respect to rate or rhythm control and prescription of anti-arrhythmic drugs, although patients with DM received calcium antagonists more often than patients without DM (Table S1). Compared with patients without DM, patients with DM had higher median body mass index (28.7 vs. 26.4), more frequent history of heart failure (24.8% vs. 21.9%), acute coronary syndromes (15.9% vs. 9.2%), vascular disease (32.6% vs. 22.6%), previous stroke/transient ischaemic attack/SE (12.8% vs. 10.9%), hypertension (85.7% vs. 73.7%), hypercholesterolaemia (55.3% vs. 37.7%) and moderate to severe CKD (14.4% vs. 9.6%). Patients with DM received OAC more frequently (70.5% vs. 65.8%), particularly VKA (44.0% vs. 38.0%) and had a higher AP use (±OAC) (40.6% vs. 33.8%). In addition, patients with DM were at higher risk of death, non-haemorrhagic stroke/SE and major bleeding according to the GARFIELD-AF risk calculator and higher risk of stroke according to the CHA_2DS_2-VASc score (Table 1).

Overall, patients with DM had a higher 2-year risk of all-cause mortality, non-haemorrhagic stroke/SE, major bleeding, myocardial infarction/ACS and new/worsening heart failure than non-DM, even after adjustment for confounding factors (Table 2 and Figure 2). OAC was associated in both non-DM and DM populations with similar risk reduction for death [propensity score weighted HR (95% CI): 0.75 (0.69-0.83) and 0.74 (0.64-0.86), respectively], non-haemorrhagic stroke/SE [0.69 (0.58-0.83) and 0.70 (0.53-0.93), respectively], and similar increase in major bleeding risk [1.40 (1.14-1.71) and 1.37 (0.99-1.89), respectively], although the latter association was only statistically significant among patients without DM (Table 3).

For the comparative effectiveness of NOAC versus VKA by diabetes status, only patients enrolled in GARFIELD-AF Cohorts 3-5, when NOAC therapy became widely available, were included.

TABLE 4 Baseline characteristics by baseline AF treatment and diabetes status in patients with AF at high risk of stroke (i.e. CHA2DS2-VASc ≥2, excl. sex) enrolled in the GARFIELD-AF registry (Cohorts 3-5).

	No diabetes		Diabetes	
Baseline characteristics	**VKA (N = 6040)**	**NOAC (N = 7240)**	**VKA (N = 2561)**	**NOAC (N = 2532)**
Sex, n (%)				
Male	3065 (50.7)	3787 (52.3)	1435 (56.0)	1438 (56.8)
Female	2975 (49.3)	3453 (47.7)	1126 (44.0)	1094 (43.2)
Age, median (Q1; Q3), years	74.0 (68.0;80.0)	75.0 (69.0;81.0)	71.0 (64.0;77.0)	72.0 (65.0;78.0)
Ethnicity, n (%)				
Caucasian	4313 (72.8)	4644 (65.8)	1640 (65.1)	1630 (66.1)
Hispanic/Latino	495 (8.4)	313 (4.4)	237 (9.4)	129 (5.2)
Asian	1020 (17.2)	1963 (27.8)	567 (22.5)	636 (25.8)
Afro-Caribbean/mixed/other	93 (1.6)	136 (1.9)	74 (2.9)	71 (2.9)
Body mass index, median (Q1; Q3), kg/m^2	27.0 (24.1;30.8)	26.1 (23.4;29.4)	29.2 (25.5;33.6)	29.1 (25.3;33.5)
Systolic blood pressure, median (Q1; Q3), mmHg	134.0 (120.0;147.0)	132.0 (120.0;146.0)	134.0 (120.0;148.0)	134.0 (120.0;148.0)
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;87.0)
Pulse, median (Q1; Q3), bpm	85.0 (72.0;104.0)	84.0 (70.0;107.0)	86.0 (72.0;104.0)	85.0 (72.0;108.0)
Type of atrial fibrillation, n (%)				
Permanent	1135 (18.8)	902 (12.5)	406 (15.9)	308 (12.2)
Persistent	885 (14.7)	1234 (17.0)	439 (17.1)	369 (14.6)
Paroxysmal	1258 (20.8)	2321 (32.1)	521 (20.3)	816 (32.2)
New onset (unclassified)	2762 (45.7)	2783 (38.4)	1195 (46.7)	1039 (41.0)
Care setting specialty at diagnosis, n (%)				
Internal medicine/neurology/geriatrics	1233 (20.4)	1338 (18.5)	587 (22.9)	481 (19.0)
Cardiology	3675 (60.8)	5112 (70.6)	1548 (60.4)	1811 (71.5)
Primary care/general practice	1132 (18.7)	790 (10.9)	426 (16.6)	240 (9.5)
Care setting location at diagnosis, n (%)				
Hospital	3434 (56.9)	3525 (48.7)	1444 (56.4)	1277 (50.4)
Office/anticoagulation clinic/ thrombosis centre	1923 (31.8)	3046 (42.1)	786 (30.7)	1027 (40.6)
Emergency room	683 (11.3)	669 (9.2)	331 (12.9)	228 (9.0)
Medical history, n (%)				
Heart failure	1636 (27.1)	1804 (24.9)	588 (23.0)	599 (23.7)
Acute coronary syndromes	760 (12.6)	727 (10.1)	408 (16.0)	389 (15.4)
Vascular disease[a]	1768 (29.3)	1746 (24.1)	791 (30.9)	777 (30.7)
Carotid occlusive disease	200 (3.4)	265 (3.7)	94 (3.7)	95 (3.8)
VTE	178 (3.0)	165 (2.3)	58 (2.3)	63 (2.5)
Prior stroke/TIA/SE	862 (14.3)	958 (13.2)	309 (12.1)	337 (13.3)
Prior bleeding	100 (1.7)	145 (2.0)	46 (1.8)	55 (2.2)
Hypertension	4968 (82.3)	5821 (80.5)	2330 (91.0)	2221 (87.7)
Hypercholesterolaemia	2446 (42.5)	3006 (42.8)	1483 (60.2)	1457 (59.3)
Cirrhosis	30 (0.5)	21 (0.3)	19 (0.8)	11 (0.4)
Moderate to severe CKD	792 (13.8)	802 (11.5)	411 (16.9)	306 (12.4)
Dementia	65 (1.1)	144 (2.0)	28 (1.1)	54 (2.1)
Heavy alcohol consumption, n (%)	94 (1.8)	107 (1.8)	36 (1.7)	35 (1.7)
Current smoker, n (%)	474 (8.5)	563 (8.5)	208 (8.9)	219 (9.6)

TABLE 4 (Continued)

Baseline characteristics	No diabetes		Diabetes	
	VKA (N = 6040)	NOAC (N = 7240)	VKA (N = 2561)	NOAC (N = 2532)
AP treatment (±OAC), n (%)	1405 (23.3)	1146 (15.8)	770 (30.1)	636 (25.1)
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[b], median (Q1; Q3)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)

[a]Defined as peripheral artery disease and/or coronary artery disease;
[b]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).
Abbreviations: AF, atrial fibrillation; AP, antiplatelet; CKD, chronic kidney disease; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SE, stroke/systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K anticoagulant; VTE, venous thromboembolism.

Baseline antithrombotic other than NOAC or VKA, VKA before enrolment and CHA2DS2-VASc <2 (excluding sex) were additional exclusion criteria. The study population consisted of 18 373 patients (Figure S3).

In the non-DM subgroup, patients treated with VKA tended to have more frequent history of heart failure, ACS, vascular disease, hypertension, and moderate-to-severe CKD than NOAC-treated patients. They were also more often treated with AP. In the DM subgroup, patients treated with VKA tended to have a more frequent history of moderate-to-severe CKD and to be more often treated with AP than NOAC-treated patients (Table 4). Event rates by NOAC and VKA treatment in patients with DM and patients without DM are reported in Table 5. NOAC use was associated with a lower risk of all-cause mortality than VKA use [0.76 (0.66-0.88)] in patients without DM. The corresponding estimate in patients with DM was of similar magnitude but did not reach statistical significance [0.80 (0.64-1.01)]. Associations for major bleeding risk with NOAC versus VKA were not statistically significant in either patients without DM [0.77 (0.58-1.02)] or patients with DM [0.72 (0.46-1.12)]. The association for non-haemorrhagic stroke/SE risk with NOAC versus VKA in patients with DM was also not statistically significant [HR 1.37 (0.82-2.27)] (Table 5 and Figure 3).

In the population without DM at baseline, incident DM was reported in 169 (0.4%) patients during the 2-year follow-up; namely in 65 (0.5%) patients treated with no OAC, in 103 (0.4%) patients treated with OAC and one missing treatment information. In the OAC group, 35 (0.3%) in NOAC-treated patients and 68 (0.5%) in VKA-treated patients had incident DM (data not shown).

3.2 | Analysis by diabetes subtypes

Overall, 4540 of 11 542 (39.3%) patients with DM received only OAD, referred to as NIRD, 1550 of 11 542 (13.4%) received insulin ± OAD referred to as IRD, and 5452 of 11 542 (47.2%) received neither OAD nor insulin referred to as no-drug DM. All three DM subtypes had higher risk scores than patients without DM, but both patients with no-drug DM and patients with NIRD were at lower risk than patients with IRD (Table 1).

In the IRD subgroup, 599 of 1550 received OAD in addition to insulin. These patients tended to have a lower risk profile according to CHA_2DS_2-VASc score and/or GARFIELD-AF risk calculator than patients who received insulin only (Table S2). Patients with IRD had an almost two-fold higher event rate than patients without DM for all the studied clinical endpoints. Patients with no-drug DM had a significantly higher risk of all-cause, CV- and non-CV death, and new/worsening heart failure compared with the no-DM group. In the NIRD group compared with the no-DM group, only the outcomes of non-haemorrhagic stroke/SE and new/worsening heart failure showed significantly higher risk (Table 2).

OAC use was associated with a significant risk reduction of all-cause mortality in patients with no-drug DM and patients with IRD, and of non-haemorrhagic stroke/SE only in patients with IRD. No significant risk reduction of all-cause mortality and of non-haemorrhagic stroke/SE were observed in patients with NIRD. A significantly higher risk of major bleeding was observed in the no-drug DM group only (Table 3).

4 | DISCUSSION

Our study confirmed previous observations showing that patients with AF and DM had higher risk profiles for stroke or SE and had worse outcomes when compared with patients without DM. These patients with DM experienced increased rates of the key outcomes for AF in spite of higher rates of anticoagulation, lower rates of AP monotherapy or no antithrombotic therapy, and higher rates of prescription of CV drugs such as angiotensin-converting enzyme inhibitors/angiotensin receptors blockers, statins, betablockers, or calcium channel blockers compared with patients without DM. This study also confirmed that oral anticoagulation was associated with a risk reduction of similar magnitude in both patients with DM and patients without DM for all-cause mortality and non-haemorrhagic stroke/SE. Patients without DM experienced a significantly higher risk of major bleeding when treated with OAC. The estimated association was of similar magnitude for patients with DM, although it did not reach statistical significance mainly because of the lower number of patients in this group.[25–28]

NOAC use was associated with lower risk of all-cause mortality in patients without DM, confirming data from previous reports based on

TABLE 5 Event rates (per 100 person-years), unadjusted and adjusted[a] HRs comparing NOAC versus VKA (reference) baseline treatment at 2 years of follow-up by baseline diabetes.

	No diabetes				Diabetes			
Outcome baseline treatment	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality								
VKA	543	4.83 (4.44-5.25)	1 (ref.)	1 (ref.)	230	4.81 (4.23-5.47)	1 (ref.)	1 (ref.)
NOAC	482	3.49 (3.19-3.81)	0.72 (0.64-0.82)	0.76 (0.66-0.88)	187	3.88 (3.36-4.48)	0.81 (0.67-0.98)	0.80 (0.64-1.01)
Non-haemorrhagic stroke/SE								
VKA	110	0.99 (0.82-1.19)	1 (ref.)	1 (ref.)	44	0.93 (0.69-1.25)	1 (ref.)	1 (ref.)
NOAC	103	0.75 (0.62-0.91)	0.76 (0.58-1.00)	0.79 (0.58-1.09)	44	0.92 (0.68-1.24)	1.00 (0.66-1.51)	1.37 (0.82-2.27)
Major bleeding								
VKA	158	1.42 (1.22-1.66)	1 (ref.)	1 (ref.)	69	1.46 (1.16-1.85)	1 (ref.)	1 (ref.)
NOAC	130	0.95 (0.80-1.13)	0.67 (0.53-0.85)	0.77 (0.58-1.02)	50	1.05 (0.80-1.38)	0.72 (0.50-1.04)	0.72 (0.46-1.12)

[a]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, previous stroke/transient ischaemic attack/SE, previous bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, cirrhosis, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.

Abbreviations: CI, confidence interval; HRs, hazard ratios; NOAC, non-vitamin K oral anticoagulant; SE, stroke/systemic embolism; VKA, vitamin K anticoagulant.

large metanalyses of randomized trials and/or observational studies. Although the associations for non-haemorrhagic stroke/SE and major bleeding did not reach statistical significance, the estimates are in line with two meta-analyses comparing these endpoints between NOAC- and VKA-treated patients.[29,30]

Patients with NOAC-treated DM experienced a lower occurrence of all-cause mortality and major bleeding compared with patients with VKA-treated DM. Although these estimates were in line with the corresponding ones in the non-DM population, they did not reach statistical significance because of the lower sample size. In contrast, the occurrence of non-haemorrhagic stroke/SE was higher in patients with NOAC-treated DM than patients with VKA-treated DM. The proportion of NOAC non-recommended low dosing was similar in DM and non-DM populations (approximately 24%; data not shown). This association, although far from statistical significance, warrants further investigation.

It was recently shown that NOAC use was associated with lower risk of incident diabetes than VKA use in new onset AF, mostly in patients ≥65 years.[31] The authors suggest that through various mechanisms, vitamin K improved insulin sensitivity, glucose tolerance, prevented insulin resistance and reduced the risk of developing DM.[32–34] In the elderly, vitamin K deficiency is common and vitamin K supplementation has a favourable impact on glucose metabolism and reduces the risk of new-onset DM.[34] In this context, VKA use may be associated with deteriorating glucose metabolism leading to an increased risk of new-onset DM. This does not occur with NOAC agents, which are devoid of interaction with vitamin K-mediated metabolism. This early observation needs to be confirmed in future analyses. Although the rate of incident diabetes was very low in our no diabetes population at baseline, the same trend was observed, with lower rates of incident diabetes in NOAC-treated patients than in VKA-treated patients.

In the DM subtypes analysis, namely no-drug DM, NIRD and IRD, the outcome in all three subtypes was worse than in the non-DM group with a gradient in the risk of any outcome across subtypes, from NIRD, no-drug DM to IRD, confirming previous observations in a large study based on the retrospective analysis of Medicare and Medicaid data.[29] This is in keeping with the positive association between HbA1c level and outcome where, the higher the glycaemic burden, the higher the risk.[30] The no-drug DM subgroup was quite large, with 47.2% of patients declared as diabetics by the investigators, far more than in other reports, 40% in the ROCKET-AF trial and 27% in a retrospective health care database analysis.[35,36] The different rates of patients with no-drug DM across studies may be related to the nature of the GARFIELD-AF registry, which included patients from different health care systems and with wide variations in treatment strategies. Patients with no-drug DM may have had prediabetes, namely impaired fasting glucose or impaired glucose tolerance, condition where lifestyle counselling without OAD is recommended as first line.[37–40] Prediabetes is associated with an increased risk of macro- and microvascular complications.[40–42] In a population-based analysis involving 44 451 patients with AF and diabetes, the risk of non-haemorrhagic stroke compared with patients with normoglycaemia

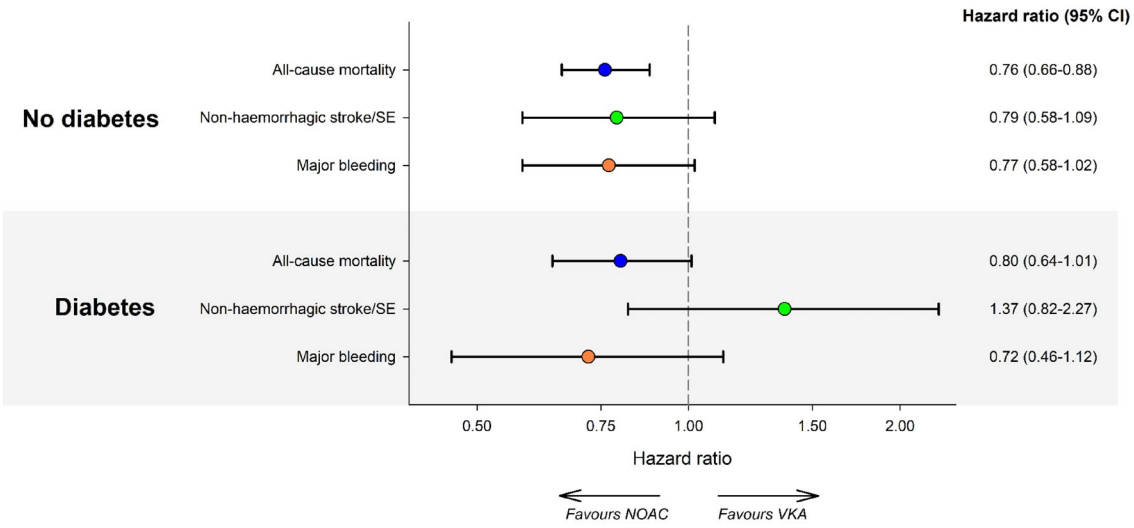

FIGURE 3 Propensity-weighted[a] hazard ratios comparing non-vitamin K oral anticoagulant (NOAC) versus vitamin K anticoagulant (VKA) (ref.) baseline treatment within 2-year of follow-up by baseline diabetes in patients with atrial fibrillation (AF) at high risk of stroke (i.e. CHA_2DS_2-VASc ≥2, excl. sex) enrolled in the GARFIELD-AF registry (Cohorts 3-5). [a]Propensity-weighting was obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, previous stroke/transient ischaemic attack/SE, previous bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, cirrhosis, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use. Acute coronary syndrome, vascular disease, carotid occlusive disease and moderate-to-severe chronic kidney disease being part of the diabetic spectrum, are not included in the weighting scheme. SE, stroke/systemic embolism.

was 19% higher in prediabetes patients [HR 1.19 (1.01-1.4)] and 56% higher in patients with established T2DM [adjusted HR 1.56 (1.37-1.79)].[36] In our study, patients with no-drug DM had a substantially higher prevalence of comorbidities and higher risk profile than patients without DM, but lower rates of comorbidities and moderately higher baseline risk profile than patients with NIRD. Patients with no-drug DM had a higher risk for all-cause, CV and non-CV mortality compared with patients without DM, but not for non-haemorrhagic stroke/SE or major bleeding.

We found a high rate of patients with IRD (13.4%) not commensurate with the rate of T1DM in our study (4.5%). In a recent report based on a large cohort of subjects without AF, the rates of T1DM and T2DM were respectively 1.5% and 11.8%.[43] This observation is not uncommon as insulin was used in over 15% of patients with DM in the ROCKET-AF trial, and in over 20% in EORP-AF and PREFER registries, rates far exceeding the prevalence of T1DM in a DM population.[9,26,35,43] Patients with IRD had the worse outcome, as the risk of any outcome except new/worsening heart failure was higher than in any other subgroups, particularly with respect to all-cause mortality, and non-haemorrhagic stroke/SE. The risk of clinical outcomes, particularly, death and non-haemorrhagic stroke incurred by diabetes in AF remains controversial. Some reported that insulin-only treated DM was associated with a higher risk of stroke[9] or of non-haemorrhagic stroke and CV death[10,44]; whereas others reported a similar risk of non-haemorrhagic stroke/SE in both OAD and insulin-treated patients.[8] Other reports showed no excess of non-haemorrhagic stroke/SE compared with patients without DM, but a higher risk of death.[25,28] The discrepancies may exist because of differences in study populations. Meta-analyses of randomized clinical trials or registries and retrospective health care databases analyses may yield different outcome data as compared with prospective registries such as GARFIELD-AF.[45] The different nature of AF in various studies, prevalent versus newly diagnosed AF, may play a role. A substantial proportion of patients with IRD concomitantly receive OAD. According to the American and European diabetes management guidelines, adding insulin to OAD should be considered in patients with newly diagnosed T2DM who are not achieving glycaemic goals.[40,41] These patients tended to have a lower risk profile and lower rates of events than patients only treated with insulin. Presumably, they were patients with T2DM with uncontrolled glycaemic balance that had insulin added to their initial OAD therapy. They were profiled as at intermediate risk and having intermediate rates of events between NIRD and IRD.

The NIRD group had the lowest baseline risk profile and the lowest rates of events, not significantly different from the non-DM group, except for non-haemorrhagic stroke and new/worsening heart failure rates respectively 35% and 57% higher than in patients without DM. A better glycaemic balance achieved with OAD may have had a favourable impact on the outcome.

Importantly, OAC use was associated with a significant risk reduction in all-cause mortality in no-drug and IRD subtypes, and a significant risk reduction for non-haemorrhagic stroke/SE in the IRD subtype. This latter observation challenges reports in which OAC was shown to have less efficacy in patients with DM, particularly in IRD.[29]

As with all observational studies, unobserved confounding factors may be present in this registry. The analysis considered baseline treatment only. Major outcomes, death, stroke/SE and bleeding were documented by the investigators but not independently adjudicated. Only 306 patients (2.7% of the DM cohort) had diabetes as the lone risk factor for stroke. No meaningful assessment of their outcome could be undertaken. Diabetes subtypes were defined according to therapy prescribed by the investigators and not according to the glycaemic profile because of the non-interventional nature of the GARFIELD-AF registry. Consequently, no information about glycaemic balance was collected. Treatment changes such as discontinuation or persistence of therapy over the 2-year follow-up were not considered in this analysis. Furthermore, while we included a wide spectrum of recorded medical history information in the propensity score weighting scheme, we did not include CV drug information, nor did we evaluate drug-drug interactions.

5 | CONCLUSIONS

Patients with DM had a higher baseline risk profile, and a higher risk of all-cause, CV and non-CV death, non-haemorrhagic stroke/SE, and major bleeding than patients without DM. The risks of CV and non-CV endpoints were higher in patients with IRD.

In both patients with DM and patients without DM, OAC was associated with a significantly lower risk of all-cause mortality and non-haemorrhagic stroke/SE. Patients with IRD derived a substantial benefit from OAC treatment, with significant risk reductions in all-cause mortality and non-haemorrhagic stroke.

AUTHOR CONTRIBUTIONS

JPB and SV wrote the manuscript. KSP, JPB, JC and SV were the working group that conceptualized, analysed and oversaw the development of the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript. AKK and GK handled funding and supervised the registry.

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CONFLICT OF INTEREST STATEMENT

JPB reports personal fees from Thrombosis Research Institute, during the conduct of the study. AJC receives personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Pfizer/BMS, personal fees from Daiichi Sankyo. KAAF has received grants and personal fees from Bayer/Janssen and AstraZeneca. SZG has received research support from Bayer, BMS, Boston Scientific BTG EKOS, Janssen, NHLBI, Pfizer; has a consultancy with Pfizer. SG has received fees from the American Heart Association and received a Steering Committee fee from Duke University. SH has received personal fees from Bayer, BMS, Daiichi Sankyo, Pfizer and Sanofi, outside the submitted work. KP has a consultancy with Johnson & Johnson, Element Science, Artivion and Novartis. AGGT reports honoraria from Bayer Pharma AG, Janssen. FWAV has received grants from Bayer Healthcare and personal fees from Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo and Boehringer-Ingelheim. AKK has received research support and personal fees from Bayer AG, Sanofi and Anthos Therapeutics. Other authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15202.

DATA AVAILABILITY STATEMENT

The leading author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. Aggregated data can be shared upon reasonable request and analysis plan to Saverio Virdone (Svirdone@tri-london.ac.uk).

CLINICAL TRAIL REGISTRATION

NCT01090362 (https://clinicaltrials.gov/ct2/show/NCT01090362?term=GARFIELD-AF&draw=2&rank=1).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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