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ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Guideline-directed medical therapies for comorbidities among patients with atrial fibrillation: results from GARFIELD-AF

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Aims

This study aimed to identify relationships in recently diagnosed atrial fibrillation (AF) patients with respect to anticoagulation status, use of guideline-directed medical therapy (GDMT) for comorbid cardiovascular conditions (co-GDMT), and clinical outcomes. The Global Anticoagulant Registry in the FIELD (GARFIELD)-AF is a prospective, international registry of patients with recently diagnosed non-valvular AF at risk of stroke (NCT01090362).

Methods and results

Guideline-directed medical therapy was defined according to the European Society of Cardiology guidelines. This study explored co-GDMT use in patients enrolled in GARFIELD-AF (March 2013–August 2016) with CHA_2DS_2-VASc ≥ 2 (excluding sex) and ≥1 of five comorbidities—coronary artery disease, diabetes mellitus, heart failure, hypertension, and peripheral vascular disease ($n = 23\,165$). Association between co-GDMT and outcome events was evaluated with Cox proportional hazards models, with stratification by all possible combinations of the five comorbidities. Most patients (73.8%) received oral anticoagulants (OACs) as recommended; 15.0% received no recommended co-GDMT, 40.4% received some, and 44.5% received all co-GDMT. At 2 years, comprehensive co-GDMT was associated with a lower risk of all-cause mortality [hazard ratio (HR) 0.89 (0.81–0.99)] and non-cardiovascular mortality [HR 0.85 (0.73–0.99)] compared with inadequate/no GDMT, but cardiovascular mortality was not significantly reduced. Treatment with OACs was beneficial for all-cause mortality and non-cardiovascular mortality, irrespective of co-GDMT use; only in patients receiving all co-GDMT was OAC associated with a lower risk of non-haemorrhagic stroke/systemic embolism.

Conclusion

In this large prospective, international registry on AF, comprehensive co-GDMT was associated with a lower risk of mortality in patients with AF and CHA_2DS_2-VASc ≥ 2 (excluding sex); OAC therapy was associated with reduced all-cause mortality and non-cardiovascular mortality, irrespective of co-GDMT use.

Clinical Trial Registration

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

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Graphical Abstract

Key questions

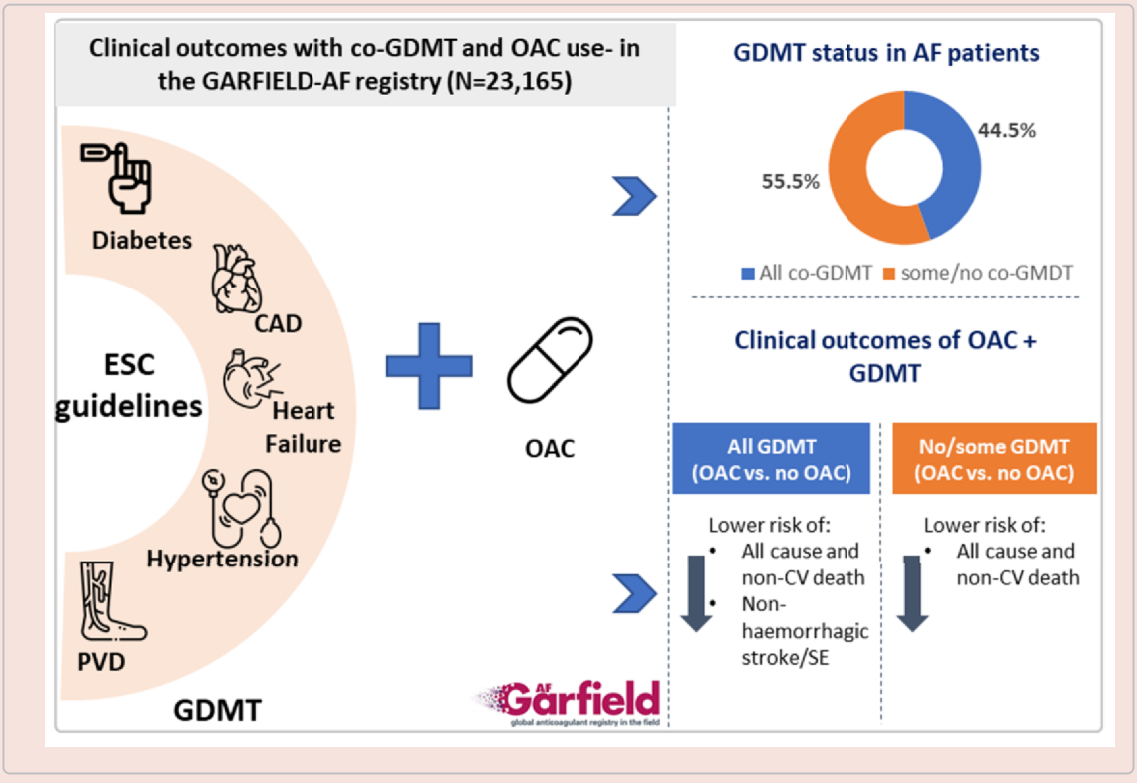
- Are AF patients receiving appropriate guideline directed medical therapy (GDMT) for their cardiovascular comorbidities?
- What is the relationship between anticoagulation status (OAC), GDMT, and clinical outcomes?

Key findings

- 45% of AF patients received comprehensive GDMT
- Comprehensive GDMT was associated with lower all-cause and non-CV mortality
- Patients on OAC therapy experienced lower risk of all-cause and non-CV mortality, whether receiving comprehensive GDMT or not

Take-home message

- In patients at high risk of stroke, OAC therapy is effective in reducing all-cause mortality and non-CV mortality, irrespective of GDMT use
- The beneficial effects of OAC appear to extend beyond stroke reduction



Keywords Atrial fibrillation • Comorbidity • GARFIELD-AF • Guideline-directed medical therapy • Mortality • Oral anticoagulant

Introduction

Atrial fibrillation (AF) is associated with an increased risk of all-cause mortality and increased cardiovascular morbidity, such as heart failure and stroke.[1] While the risk of death due to stroke can be reduced by anticoagulation, other cardiovascular deaths remain common, even in patients with AF treated according to current best practice.[1] Clinical outcomes in patients with AF are likely to be influenced by comorbid conditions, which are common in these patients. Cardiovascular comorbidities independently associated with AF include hypertension, congestive heart failure (CHF), myocardial infarction (MI), peripheral vascular disease (PVD), and diabetes mellitus (DM).[1,2] In community cohorts and registries, patients with AF have higher rates of comorbidities than controls.[3–5] For example, in a Swedish registry study of 272 186 patients with AF and 544 344 matched controls, 69.5 vs. 27.2% had any concomitant disease, with rates of 26.0 vs. 8.0% for ischaemic heart disease, 12.2 vs. 3.6% for MI, 24.8 vs. 2.9% for CHF, 25.4 vs. 6.8% for hypertension, and 13.4 vs. 6.2% for DM.[4] Similarly, in a US population-based study, comorbidities occurring at significantly higher rates than controls included hypertension (71.1 vs. 57.2%), CHF (18.2 vs. 4.9%), coronary artery disease (CAD) (39.0 vs. 21.0%), and DM (30.6 vs. 26.7%).[3] This study explored whether treatment of these comorbidities, using guideline-directed medical therapies (GDMT), optimizes management of AF patients.[1]

The Global Anticoagulant Registry in the FIELD (GARFIELD)-AF registry (ClinicalTrials.gov Identifier: NCT01090362) is a prospective, international, multicentre, observational study of adults with recently diagnosed non-valvular AF and at least one risk factor for stroke.[6] The GARFIELD-AF registry captures information on the management of unselected patients in everyday clinical practice, providing the opportunity to assess treatment patterns and explore relationships between management and outcomes. Oral anticoagulant (OAC) therapy is GDMT for stroke prevention in patients with AF with a CHA_2DS_2-VASc score of ≥2.[1] This study investigated the use of GDMT in patients in GARFIELD-AF with a CHA_2DS_2-VASc score of ≥2 (excluding sex) and one or more of five comorbidities—CAD, DM, CHF, hypertension, and PVD. The objectives are to explore whether appropriate use of GDMT for comorbidities (co-GDMT) is associated with increased use of anticoagulation for AF and whether the association between OACs and clinical outcomes differs according to appropriate GDMT use.

Methods

Study design and participants

The GARFIELD-AF registry recruited patients from a range of representative care settings in each country.[6,7] Investigator sites were selected randomly (apart from 18 sites, out of >1000). The study is non-interventional in nature, and treatment decisions were solely at the discretion of treating physicians, with no specific treatments, tests, or procedures mandated by the study protocol. Recruitment took place in five independent sequential cohorts.[6] Cohorts 3–5, prospectively recruited during April 2013–August 2016, were included in this analysis: the method of reporting concomitant medication (β-blockers and calcium channel blockers) changed between Cohorts 2 and 3 such that data on co-GDMT from Cohorts 3–5 are not comparable with data from Cohorts 1 and 2; in addition, the use of non-vitamin K oral anticoagulants (NOACs) was not common during the period when Cohorts 1 and 2 were recruited (December 2009–April 2013).[8]

Men and women aged ≥18 years with non-valvular AF diagnosed according to standard local procedures within the previous 6 weeks and with at least one risk factor for stroke as judged by the investigator were eligible for inclusion in GARFIELD-AF; patients with a transient reversible cause of AF and those for whom follow-up was not envisaged or possible were excluded.[6] This study includes patients who had at least one of five comorbidities—CAD, DM, CHF, hypertension, and PVD—and CHA_2DS_2-VASc ≥ 2 (excluding sex).[9] Patients with none of the selected comorbidities or with unavailable follow-up information were excluded (see Supplementary material online, *Figure S1*).

Definitions of GDMT were based on the published European Society of Cardiology (ESC) guidelines operative between 2013 and 2016 (*Table 1*; see Supplementary material online, *Table S1*). The study population was analysed in terms of those receiving none of the co-GDMT for which they were eligible, those receiving some of the co-GDMT, and those receiving all of the co-GDMT for which they were eligible. Statistical comparisons were made between patients receiving all the recommended co-GDMT and patients receiving no, or some, co-GDMT.

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. Additional approvals were obtained from individual study sites. GARFIELD-AF is conducted in accordance with the principles of the Declaration of Helsinki, the

Table 1 Criteria used to define GDMT for selected comorbidities in patients with AF and a CHA_2DS_2-VASc score of ≥2

Comorbidity	Eligible for
CAD	Statin
	β-Blocker
	AP agent only if the patient is not on anticoagulants or has a history of MI or stent or CABG
DM	ACEI or ARB only if the patient has CHF, CAD or hypertension, and CKD Stage <4
	Statin only if the patient has CAD, prior stroke, or PVD
	Insulin or oral antidiabetic drugs
CHF	ACEI or ARB only if CKD Stage <4
	β-Blocker only if the non-permanent type of AF
	Aldosterone blockade only if symptomatic (NYHA Class II–IV), the patient is taking ACEI/ARB and β-blockers, and CKD <4
Hypertension	Antihypertensive therapy (≥2 of the following):[a]
	ACEI or ARB only if CKD Stage <4
	Calcium channel blocker
	β-Blocker
	Diuretics
	Clonidine
	α-Blocker
PVD	Statin
	AP agent only if the patient is not on anticoagulants or has a history of MI or stent or CABG

See Supplementary material online, *Table S1* for details and references.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AP, antiplatelet; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, and sex category (female); CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease.
[a]ESC hypertension guidelines indicate that the blood pressure target is achieved with monotherapy in only a limited number of patients; more than one antihypertensive therapy is needed to achieve target blood pressure in most patients.[14]

local regulatory requirements, and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants.

Data collection and quality control

GARFIELD-AF data were captured using an electronic case report form (eCRF).[6] Oversight of operations and data management were performed by the coordinating centre, the Thrombosis Research Institute (TRI) (London, UK), with support from Quintiles (IQVIA) (Durham, NC, USA), the University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), the Thrombosis Research Group–Brigham and Women's Hospital (Boston, MA, USA), and AIXIAL (Paris, France). Submitted data were examined for completeness and accuracy by the co-ordinating centre, the TRI, and data queries were sent to study sites. The GARFIELD-AF protocol requires that 20% of all eCRFs are monitored against source documentation, that there is an electronic audit trail for all data modifications, and that critical variables are subjected to additional audit.[6,10]

Baseline characteristics collected at study entry included medical history, care setting, type of AF, date and method of diagnosis of AF, symptoms, antithrombotic treatment [vitamin K antagonists (VKAs), NOACs, and antiplatelet (AP)], and all cardiovascular drugs. Race was classified by the investigator in agreement with the patient.[6] Chronic kidney disease (CKD) was classified according to the National Kidney Foundation guidelines into moderate-to-severe (Stages 3–5), mild (Stages 1 and 2), or none. Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were collected and calculated retrospectively.[9,11] HAS-BLED scores were calculated excluding fluctuations in international normalized ratios. Collection of follow-up data occurred at 4-month intervals up to 24 months. Data for this report were extracted from the study database on 30 June 2019.

Statistical analysis

Our first aim was to compare the effects of receiving all recommended co-GDMT vs. receiving no, or some, co-GDMT for selected clinical endpoints: all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, unknown-cause mortality, non-haemorrhagic stroke/systemic embolism (SE), and major bleeding. Some- and no-GDMT groups were combined, as the number of patients with no GDMT was relatively small (see Supplementary material online, *Table S2*). Sensitivity analyses comparing the occurrence of clinical outcomes between the no- and some-GDMT groups were also performed. Only the first occurrence of each event was considered. The follow-up period was from the date of enrolment, truncated at the first event occurrence, death, loss to follow-up, or 2 years after enrolment, whichever occurred first. The relative risk for the selected clinical outcomes was estimated using stratified Cox proportional hazards models, adjusted for the following confounding factors: age, sex, ethnicity, type of AF, prior stroke/transient ischaemic attack (TIA)/SE, history of bleeding, moderate-to-severe CKD, anticoagulation at baseline, smoking status, and heavy alcohol consumption. The factors included for adjustment were previously applied based on clinician input, literature review, and important associations identified in the data. None of the five comorbidities were included in the model as single covariates. Variables used to directly define GDMT eligibility were also excluded. A robust covariance estimate was included to account for correlation within countries; the models included stratification by all possible combinations of the five comorbidities used to define GDMT eligibility. This approach allows to identify the associations within the strata, i.e. within subjects with identical sets of comorbidities.

Further, the comparative effectiveness of OAC vs. no OAC according to co-GDMT use was examined. Hazard ratios (HRs) for OAC vs. no OAC in two different co-GDMT groups (no/some co-GDMT and all co-GDMT) were obtained using a Cox proportional hazards model 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 concerns regarding the assessment and the trimming of the weights are eliminated. Covariates evaluated in the weighting scheme included country and year of enrolment, vitals, care setting, demographic characteristics, medical history, and lifestyle factors (see Supplementary material online, *Table S3*). Treatment was defined as the first treatment received at the time of enrolment, approximating 'intention-to-treat'.

Only complete cases are presented in descriptive tables. Multiple imputation was applied in the derivation for the modelling process for the estimation of the co-GDMT effect. Coefficients and standard errors for the risk models were obtained by combining estimates across five imputed databases. Single imputation was applied for the OAC vs. no-OAC analysis. Statistical analyses were carried out using SAS (version 9.4).

Results

Of 34 903 patients in GARFIELD-AF Cohorts 3–5, 5183 (14.8%) did not have any of the specified comorbidities and were excluded; a further 6536 were excluded as they had a CHA_2DS_2-VASc score of <2 (excluding sex) and a further 19 due to unavailability of follow-up information, leaving a study population of 23 165 (see Supplementary material online, *Figure S1*). Baseline characteristics of these patients by co-GDMT use are shown in *Table 2*; 9759 (42.1%) had one of the selected comorbidities, 8725 (37.7%) had two, 3659 (15.8%) had three, 924 (4.0%) had four, and 98 (0.4%) had all five comorbid conditions (see Supplementary material online, *Table S4*). The proportion of appropriate GDMT use has remained relatively stable (44–46%) across GARFIELD-AF cohorts (data not shown).

Of the 23 165 patients in the study, 3481 (15.0%) received none of the co-GDMT for which they were eligible, 9369 (40.4%) received some, and 10 315 (44.5%) received all co-GDMT for which they were eligible (*Table 2*). There were no apparent relationships between baseline characteristics and patterns of co-GDMT use apart from ethnicity/geography. Patients who received all co-GDMT were less likely to be Asian, compared with patients receiving some/none of the co-GDMT; 22.8% of patients who received all co-GDMT were Asians, compared with 32.2% among patients who received some/none of the co-GDMT for which they were eligible (*Table 2*). In most Western European countries, Canada, Singapore, Australia, Argentina, and Chile, ≥50% of patients were prescribed all recommended co-GDMT; <30% of patients were receiving all co-GDMT in India, Turkey, Russia, and Ukraine (see Supplementary material online, *Figure S2*). The study population of this analysis had a low proportion (<3%) of missing data for most baseline characteristics, with the exception of lifestyle information (i.e. smoking and alcohol use; 8 and 15%, respectively) and vital signs (systolic blood pressure, diastolic blood pressure, and heart rate; 5–6%) (see Supplementary material online, *Table S5*).

The distribution of co-GDMT use overall, by individual comorbidity and by baseline OAC treatment, is shown in *Table 3*. The highest rate of 'all co-GDMT' was seen in hypertension (79.0%) and the lowest rate in CHF (30.7%). The majority of patients (73.8%) was treated with OACs as recommended. Among patients treated with OACs, 46.4% received all co-GDMT in comparison with 39.4% of those not treated with OACs (*Table 3*, *Figure 1*). Patients receiving neither OAC nor AP treatment were the most likely to be receiving no co-GDMT and the least likely to be receiving all co-GDMT (*Figure 1*). Sensitivity analyses comparing the occurrence of clinical outcomes between no and some GDMT are reported in Supplementary material online, *Table S6*.

At 2-year follow-up, patients treated with OACs at baseline had lower event rates for all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and non-haemorrhagic stroke/SE than patients not treated with OACs but higher rates of major bleeding (*Table 4*). The reduction in all-cause mortality associated with OAC treatment (4.2 vs. 5.4 per 100 person-years) was greater, in absolute

Table 2 Baseline characteristics of the study population by co-GDMT use

Variable	Comorbidity GDMT use		
	All (*N* = 10 315)	Some (*N* = 9369)	None (*N* = 3481)
Sex, *n* (%)			
Male	5142 (49.8)	5334 (56.9)	1880 (54.0)
Female	5173 (50.2)	4035 (43.1)	1601 (46.0)
Age, median (Q1; Q3), years	73.0 (67.0; 79.0)	72.0 (65.0; 79.0)	74.0 (69.0; 80.0)
Age, *n* (%), years			
<65	1355 (13.1)	2315 (24.7)	305 (8.8)
65–69	2109 (20.4)	1506 (16.1)	688 (19.8)
70–74	2250 (21.8)	1654 (17.7)	759 (21.8)
≥75	4601 (44.6)	3894 (41.6)	1729 (49.7)
Ethnicity, *n* (%)			
Caucasian	6920 (68.5)	6016 (65.2)	1509 (44.2)
Hispanic/Latino	676 (6.7)	488 (5.3)	259 (7.6)
Asian	2300 (22.8)	2541 (27.5)	1597 (46.8)
Afro-Caribbean/mixed/other	209 (2.1)	181 (2.0)	50 (1.5)
Body mass index, median (Q1; Q3), kg/m^2	27.4 (24.4; 31.2)	27.5 (24.3; 31.6)	25.1 (22.6; 28.4)
Systolic blood pressure, median (Q1; Q3), mmHg	135.0 (121.0; 148.0)	131.0 (120.0; 145.0)	132.0 (120.0; 144.0)
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (70.0; 90.0)	80.0 (70.0; 89.0)	80.0 (70.0; 86.0)
Pulse, median (IQR), b.p.m.	85.0 (71.0; 108.0)	84.0 (71.0; 105.0)	81.0 (70.0; 100.0)
Type of AF, *n* (%)			
Permanent	1457 (14.1)	1229 (13.1)	549 (15.8)
Persistent	1410 (13.7)	1496 (16.0)	536 (15.4)
Paroxysmal	2773 (26.9)	2406 (25.7)	1191 (34.2)
New onset (unclassified)	4675 (45.3)	4238 (45.2)	1205 (34.6)
Care setting specialty at diagnosis, *n* (%)			
Internal medicine/neurology/geriatrics	2075 (20.1)	1798 (19.2)	654 (18.8)
Cardiology	6602 (64.0)	6551 (69.9)	2338 (67.2)
Primary care/general practice	1638 (15.9)	1020 (10.9)	489 (14.0)
Care setting location at diagnosis, *n* (%)			
Hospital	5569 (54.0)	5705 (60.9)	1726 (49.6)
Office/anticoagulation clinic/thrombosis centre	3534 (34.3)	2779 (29.7)	1468 (42.2)
Emergency room	1212 (11.7)	885 (9.4)	287 (8.2)
Medical history, *n* (%)			
Heart failure	1332 (12.9)	4661 (49.7)	585 (16.8)
CAD	1688 (16.4)	4780 (51.0)	193 (5.5)
Acute coronary syndromes	881 (8.5)	2509 (26.8)	60 (1.7)
PVD	391 (3.8)	1024 (10.9)	124 (3.6)
Carotid occlusive disease	345 (3.4)	405 (4.4)	78 (2.3)
Venous thrombo-embolism	278 (2.7)	247 (2.6)	64 (1.8)
Prior stroke/TIA/SE	1239 (12.0)	1140 (12.2)	483 (13.9)
Prior bleeding	267 (2.6)	259 (2.8)	85 (2.4)
Hypertension	9700 (94.0)	8098 (86.4)	2938 (84.4)
Hypercholesterolaemia	4846 (48.8)	4644 (51.5)	1099 (32.5)
Diabetes	2030 (19.7)	4230 (45.1)	598 (17.2)
Cirrhosis	45 (0.4)	63 (0.7)	20 (0.6)
Moderate-to-severe CKD	1352 (13.1)	1365 (14.6)	360 (10.3)
Dementia	133 (1.3)	167 (1.8)	93 (2.7)
Heavy alcohol user, *n* (%)	173 (2.0)	136 (1.7)	64 (2.2)
Current smoker, *n* (%)	785 (8.2)	882 (10.1)	237 (7.5)
Antithrombotic treatment, *n* (%)			
NOAC ± AP	4007 (38.8)	3258 (34.8)	1350 (38.8)

Continued

Table 2 *Continued*

Variable	Comorbidity GDMT use		
	All (*N* = 10 315)	Some (*N* = 9369)	None (*N* = 3481)
VKA ± AP	3918 (38.0)	3442 (36.7)	1118 (32.1)
AP only	1617 (15.7)	1879 (20.1)	458 (13.2)
No OAC or AP	773 (7.5)	790 (8.4)	555 (15.9)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (3.0; 4.0)	4.0 (3.0; 5.0)	3.0 (3.0; 4.0)
HAS-BLED score, median (Q1; Q3)[a]	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)	1.0 (1.0; 2.0)

AF, atrial fibrillation; AP, antiplatelet; CAD, coronary artery disease; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, and sex category (female); CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratios, 2 elderly (>65 years), drugs/alcohol concomitantly (1 point each); IQR, interquartile range; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; PVD, peripheral vascular disease; VKA, vitamin K antagonist; SE, systemic embolism; TIA, transient ischaemic attack.
[a]The labile international normalized ratio risk factor 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).

Table 3 Distribution of co-GDMT use overall, by individual comorbidity, and by baseline OAC treatment

Eligible co-GDMT use[a]	Overall (*N* = 23 165)	Baseline treatment	
		OAC (*N* = 17 093)	No OAC (*N* = 6072)
Overall			
None of eligible co-GDMT	3481 (15.0)	2468 (14.4)	1013 (16.7)
Some of eligible co-GDMT	9369 (40.4)	6700 (39.2)	2669 (44.0)
All of eligible co-GDMT	10 315 (44.5)	7925 (46.4)	2390 (39.4)
CAD	***n* = 6661**	***n* = 4340**	***n* = 2321**
Statin	4736 (71.1)	3134 (72.2)	1602 (69.0)
β-Blocker	4844 (72.7)	3203 (73.8)	1641 (70.7)
AP agent	3412 (67.7)	1463 (53.9)	1949 (84.0)
Taking all of eligible co-GDMT	2681 (40.2)	1628 (37.5)	1053 (45.4)
DM	***n* = 6858**	***n* = 5134**	***n* = 1724**
ACEI or ARB	4224 (67.8)	3294 (69.9)	930 (61.1)
Statin	1838 (70.1)	1284 (70.4)	554 (69.3)
Insulin or oral antidiabetics	3985 (58.1)	3056 (59.5)	929 (53.9)
Taking all of eligible co-GDMT	2783 (40.6)	2180 (42.5)	603 (35.0)
CHF	***n* = 6578**	***n* = 4693**	***n* = 1885**
ACEI or ARB	4239 (66.5)	3125 (68.3)	1114 (61.7)
β-Blocker	4039 (73.2)	2895 (75.4)	1144 (68.1)
Aldosterone blockade	577 (26.9)	407 (26.2)	170 (28.7)
Taking all of eligible co-GDMT	2020 (30.7)	1536 (32.7)	484 (25.7)
Hypertension	***n* = 20 736**	***n* = 15 433**	***n* = 5303**
Antihypertensive therapy	16 374 (79.0)	12 451 (80.7)	3923 (74.0)
Taking all of eligible co-GDMT	16 374 (79.0)	12 451 (80.7)	3923 (74.0)
PVD	***n* = 1539**	***n* = 1154**	***n* = 385**
Statin	910 (59.1)	674 (58.4)	236 (61.3)
AP agent	544 (63.8)	258 (55.1)	286 (74.3)
Taking all of eligible co-GDMT	723 (47.0)	533 (46.2)	190 (49.4)

ACEI, angiotensin-converting enzyme inhibitor; AP, antiplatelet; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; co-GDMT, comorbidity guideline-directed medical therapy; DM, diabetes mellitus; OAC, oral anticoagulant; PVD, peripheral vascular disease.
[a]As defined in *Table 2*.

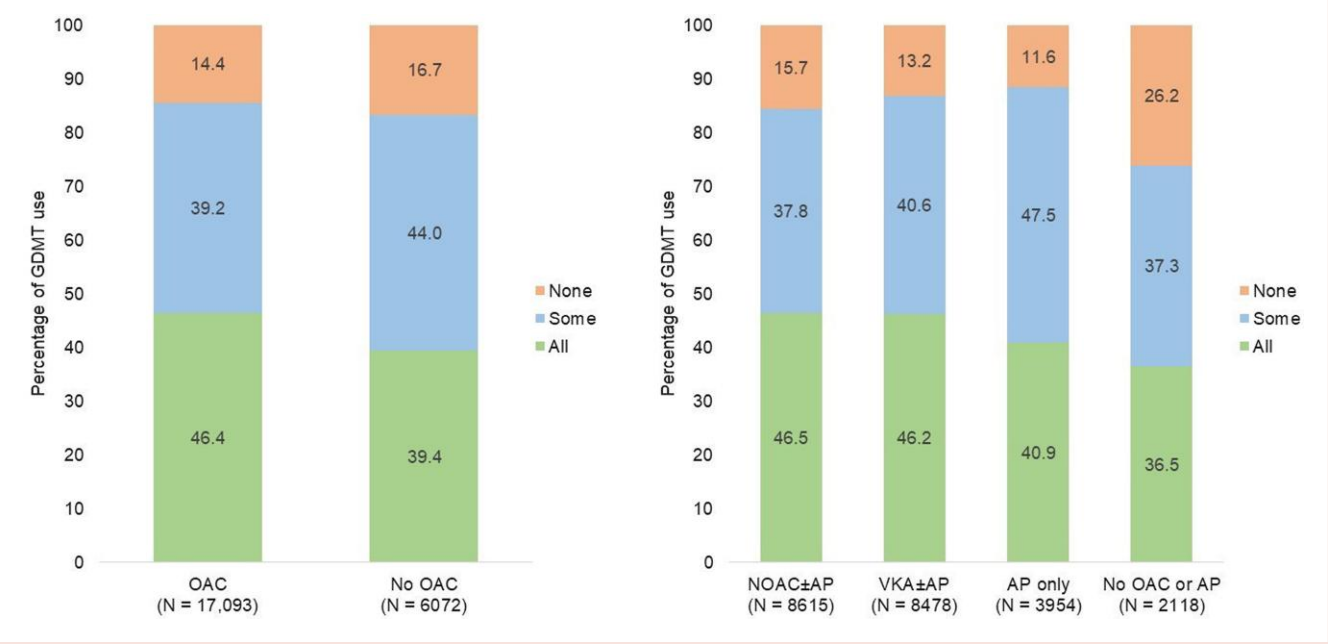


Figure 1 Distribution of guideline-directed medical therapy use for comorbid conditions in patients with atrial fibrillation and a CHA_2DS_2-VASc score of ≥2 by antithrombotic treatment. AF, atrial fibrillation; AP, antiplatelet; GDMT, guideline-directed medical therapy; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist.

Table 4 Event rates per 100 person-years for 2 years of follow-up by baseline OAC treatment

Outcome	Baseline treatment			
	No OAC		OAC	
	Events	Rate per 100 person-years (95% CI)	Events	Rate per 100 person-years (95% CI)
All-cause mortality	606	5.4 (5.0–5.9)	1344	4.2 (4.0–4.4)
Cardiovascular mortality	211	1.9 (1.7–2.2)	463	1.4 (1.3–1.6)
Non-cardiovascular mortality	249	2.2 (2.0–2.5)	505	1.6 (1.4–1.7)
Unknown-cause mortality	146	1.3 (1.1–1.5)	376	1.2 (1.1–1.3)
Cardiovascular/unknown-cause mortality	357	3.2 (2.9–3.5)	839	2.6 (2.4–2.8)
Non-haemorrhagic stroke/SE	157	1.4 (1.2–1.7)	329	1.0 (0.9–1.2)
Major bleeding	148	1.3 (1.1–1.6)	288	0.9 (0.8–1.0)

CI, confidence interval; OAC, oral anticoagulant; SE, systemic embolism.

terms, than the reduction in non-haemorrhagic stroke/SE risk (0.9 vs. 1.3 per 100 person-years) (*Table 4*).

At 2-year follow-up, HRs from models using stratification for co-GDMT categories and covariate adjustment (alpha HR [aHR]) as well as HRs from models that were both unstratified and unadjusted favoured all co-GMDT vs. no/some co-GMDT for all-cause mortality and non-cardiovascular mortality. An 11% reduction in all-cause mortality [aHR = 0.89, 95% confidence interval (CI) 0.81–0.99] and a 15% reduction in non-cardiovascular mortality (aHR = 0.85, 95% CI 0.73–0.99) were observed. The risk of cardiovascular mortality was not affected by co-GDMT use (*Figure 2*; see Supplementary material online, *Table S7*). (Results from analysis of GARFIELD-AF Cohorts 1–5 are shown in Supplementary material online, *Table S8*; no statistically significant effects of co-GDMT on outcomes were evident.) With respect to individual comorbidities, benefits of all vs. no/some co-GDMT were seen in terms of all-cause mortality in CAD and in non-cardiovascular mortality in CHF (see Supplementary material online, *Figure S3*). When data were analysed separately according to baseline OAC treatment, no effects of co-GDMT on mortality endpoints were evident in either the OAC group or the no-OAC group. Among patients not receiving OAC therapy, all vs. no/some co-GDMT was associated with an increased risk of non-haemorrhagic stroke/SE and major bleeding (aHR = 1.51, 95% CI 1.07–2.11, aHR = 1.81, 95% CI 1.03–3.19, respectively: *Figure 2*; see Supplementary material online, *Table S9*). Oral anticoagulant therapy was associated with lower all-cause mortality and non-cardiovascular mortality in

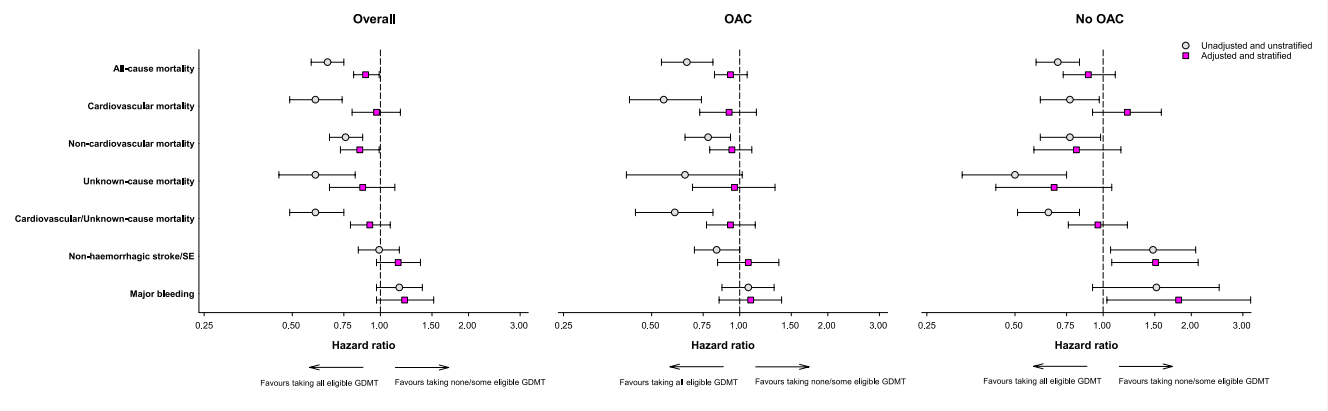


Figure 2 Hazard ratios with 95% confidence intervals (2-year follow-up) for all vs. no/some comorbidity guideline-directed medical therapy use at enrolment in the overall group, patients receiving oral anticoagulants, and patients not receiving oral anticoagulants. [1]Hazard ratios derived from univariable Cox models without stratification of possible comorbidity combinations. [2]Hazard ratios derived from univariable Cox models that include stratification by all possible combinations of the five comorbidities used to define guideline-directed medical therapy eligibility. [3]Hazard ratios are adjusted for age, sex, ethnicity, type of atrial fibrillation, prior stroke/transient ischaemic attack/systemic embolism, history of bleeding, moderate-to-severe chronic kidney disease, anticoagulation at baseline, smoking status, and heavy alcohol consumption. A robust covariance estimate is included in order to account for correlation within each country. Models include stratification by all possible combinations of the five comorbidities used to define guideline-directed medical therapy eligibility. GDMT, guideline-directed medical therapy; OAC, oral anticoagulant; SE, systemic embolism.

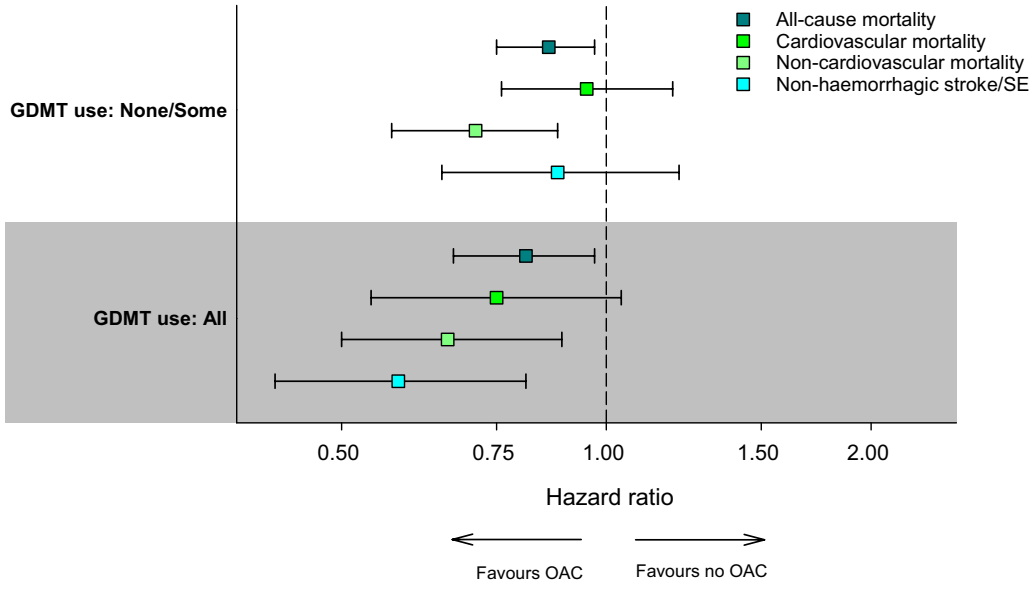


Figure 3 Hazard ratios (2-year follow-up) for baseline oral anticoagulant treatment by comorbidity GMDT use (see Supplementary material online, *Table S2* for covariates). Hazard ratios are obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are country and cohort enrolment, sex, age, ethnicity, type of atrial fibrillation, care setting speciality and location, acute coronary syndromes, carotid occlusive disease, prior stroke/transient ischaemic attack/systemic embolism, prior bleeding, venous thromboembolism (VTE), 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. A robust covariance estimate is included in order to account for correlation within each country. GDMT, guideline-directed medical therapy; OAC, oral anticoagulant; SE, systemic embolism.

comparison with no OAC, irrespective of co-GDMT use; in patients receiving all co-GDMT, OAC was additionally associated with a reduced risk of non-haemorrhagic stroke/SE (*Figure 3*; see Supplementary material online, *Table S10*).

Discussion

In our cohort of patients with AF and CHA_2DS_2-VASc ≥ 2 and at least one of the selected comorbid conditions, around 70% were treated with OAC therapy at baseline, as recommended by ESC guidelines. In these patients, OAC therapy was associated with a reduced risk of all-cause mortality to an extent that cannot be explained solely by the reduction in non-haemorrhagic stroke/SE risk. Just under half of the patients were prescribed with all appropriate GDMT for the specified comorbidities. Patients receiving OACs tended to receive all recommended co-GDMT more frequently than patients not treated with OACs, which may partly explain the unexpectedly large effect of OAC therapy on all-cause mortality.

Comprehensive co-GDMT was associated with reduced all-cause mortality by 11% in comparison with none/inadequate co-GDMT; the reduction in non-cardiovascular mortality (15%) was the major contributor to this reduction in all-cause mortality. In patients with AF and CHA_2DS_2-VASc ≥ 2 (excluding sex), guideline-directed OAC therapy was effective in reducing all-cause mortality and non-cardiovascular mortality, irrespective of co-GDMT. In patients taking all co-GDMT, benefits of OACs extended to reduced non-haemorrhagic stroke/SE risk.

The lack of lowering of cardiovascular mortality associated with GDMT for cardiovascular disease and the significant reduction in non-cardiovascular mortality associated with OACs are counterintuitive. Therapy with OACs may be associated with lower non-cardiovascular mortality by revealing cancer at an earlier stage or reducing venous thrombo-embolic disease.[12] Non-vitamin K oral anticoagulants in particular have a variety of heterogeneous effects that might have some unrecognized value in treatment of other non-cardiovascular conditions. Participants receiving good co-GDMT for cardiovascular comorbidities probably received similarly better therapy for non-cardiovascular disease, but these data were not captured by GARFIELD-AF. Furthermore, this may be explained on the basis that longer treatment duration may be necessary to uncover the long-term impact of GMDT on cardiovascular outcomes.

The higher risk of non-haemorrhagic stroke/SE associated with comprehensive co-GDMT in patients not receiving OAC was an unexpected finding, and the explanation for this outcome remains unclear.

Our results show some similarities to those from a study carried out by the US Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), which looked at associations between clinical outcomes in patients with AF and co-GDMT for the comorbid conditions investigated in our study, plus hyperlipidaemia and obstructive sleep apnoea.[13] Like our study, the ORBIT-AF study found underuse of co-GDMT, with only 33% of patients with AF receiving all recommended co-GDMT. The use of all co-GDMT was associated with a non-significant reduction in the rate of major adverse cardiac or neurovascular events and a trend towards a lower rate of all-cause mortality, which achieved statistical significance in CHF.

One limitation of our study is that medication use is based on baseline (intention-to-treat) data so that any changes in medication over the 2-year follow-up period were not taken into account. Moreover, due to the observational nature of this registry, only categories of medication used for the various comorbidities were assessed; medication dosing and guideline-directed titration of medication were not addressed but may have a relevant impact, particularly in heart failure, hypertension, and statin use. Further, only treatments available at the time of the study were included. Therefore, contemporary heart failure medications such as angiotensin receptor–neprilysin and sodium–glucose cotransporter-2 inhibitors were not included in this analysis. In addition, co-GDMT was not assessed for any non-cardiovascular comorbidities and for only five major cardiovascular comorbidities. The adequacy of co-GDMT for treating these comorbidities—in particular for hypertension—cannot be established with certainty. Under the definition used, compliance with GDMT for hypertension required at least two therapies, as guidelines state that blood pressure targets are achieved with monotherapy in only a limited number of patients and that use of more than one agent is necessary in the majority of patients.[14] This definition of GDMT excluded patients taking only one antihypertensive, even though this therapy may have been effective in some. However, changing the definition of co-GDMT to at least one antihypertensive reduced the proportion of patients considered to be receiving no/some co-GDMT but did not alter impacts on mortality endpoints [all co-GDMT remained associated with reduced all-cause mortality (HR = 0.89, 95% CI 0.79–0.99) and non-cardiovascular mortality (HR = 0.79, 95% CI 0.67–0.93); see Supplementary material online, *Tables S6*]. Although a comprehensive set of variables were used in the propensity score weighting scheme, it is not possible to exclude the potential influence of unmeasured confounders, such as frailty and malnutrition. Finally, there are some limitations in regard to the guidelines used to define co-GDMT. Only European (ESC) guidelines were used; these may have differed from US or other guidelines in use in other geographical areas. The study period covered ESC guidelines operative from 2013 to 2016. There were some updates to guidelines during this period, but changes were minor and were unlikely to impact the definitions of co-GDMT used in this study.

Conclusions

In conclusion, in this large prospective, international registry on AF, comprehensive co-GDMT was associated with reduced all-cause mortality and non-cardiovascular mortality in patients with AF and CHA_2DS_2-VASc ≥ 2 (excluding sex) but not with reduced cardiovascular mortality. Although not seen with comprehensive co-GDMT, the significant decrease in mortality with OAC use appears to extend beyond stroke reduction.

Lead author biography

John Camm is a professor of Clinical Cardiology (emeritus) at St George's University of London. His interests include cardiac arrhythmias, atrial fibrillation (AF), stroke prevention, anticoagulation, clinical cardiac electrophysiology, cardiac pacemakers, and risk stratification in post-myocardial infarction, heart failure, AF, and cardiomyopathy patients. Professor Camm is a fellow of the European Society of Cardiology (ESC) and the European Heart Rhythm Association (EHRA). He is the past president of the EHRA and the president of the Arrhythmia Alliance, a founder and trustee of the Atrial Fibrillation Association, and a trustee of the Drug Safety Research Unit. Professor Camm is the editor-in-chief of the *European Heart Journal - Case Reports*, an editor of the *European Heart Journal*, the immediate past editor-in-chief of *Europace*, and also an editor of the ESC Textbook of Cardiovascular Medicine and ESC CardioMed.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Data availability

Aggregated data can be shared upon reasonable request and analysis plan to Saverio Virdone (Svirdone@tri-london.ac.uk)

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