ESC HEART FAILURE
ESC Heart Failure (2021)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13156

ORIGINAL RESEARCH ARTICLE

Characteristics, treatment, and outcomes of newly diagnosed atrial fibrillation patients with heart failure: GARFIELD-AF

Giuseppe Ambrosio[1]*, A. John Camm[2], Jean-Pierre Bassand[3,4], Ramon Corbalan[5], Gloria Kayani[3], Erberto Carluccio[1], Lorenzo G. Mantovani[6,7], Saverio Virdone[3], Ajay K. Kakkar[3,8] for the GARFIELD-AF Investigators†

[1]*Division of Cardiology, University of Perugia School of Medicine, Ospedale S. Maria della Misericordia, Via S. Andrea delle Fratte, Perugia, 06156, Italy;* [2]*Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's, University of London and St George's University Hospitals NHS Foundation Trust, London, UK;* [3]*Thrombosis Research Institute, London, UK;* [4]*University of Besançon, Besançon, France;* [5]*Catholic University School of Medicine, Santiago, Chile;* [6]*Center for Public Health Research (CESP), Postgraduate School of Hygiene and Preventive Medicine, University of Milan-Bicocca, Monza, Italy;* [7]*Value-based Healthcare Unit, IRCCS Multimedica Research Hospital, Sesto San Giovanni, Italy;* [8]*University College London, London, UK*

Abstract

Aims Heart failure (HF) and atrial fibrillation (AF) may coexist and influence each other. However, characteristics, anticoagulant treatment, and outcomes of contemporary AF patients with concurrent HF are ill-defined. This study analyses characteristics, treatment, and 2 year outcomes in newly diagnosed Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) patients with vs. without HF.

Methods and results GARFIELD-AF is the world's largest observational AF patient study. At enrolment, 11 758 of 52 072 patients (22.6%) had HF; 76.3% were New York Heart Association class II–III. Patients with HF had comparable demographics, blood pressure, and heart rate but more likely had permanent (15.6% vs. 11.9%) or persistent AF (18.9% vs. 13.8%), acute coronary syndromes (16.7% vs. 8.9%), vascular disease (40.8% vs. 20.2%), and moderate-to-severe chronic kidney disease (14.6% vs. 9.0%) than those without. Anticoagulant prescription was similar between the two groups. At 2 year follow-up, patients with HF showed a greater risk of all-cause mortality [hazard ratio (HR), 2.06; 95% confidence interval (CI), 1.91–2.21; $P < 0.0001$], cardiovascular mortality (HR, 2.91; 95% CI, 2.58–3.29; $P < 0.0001$), acute coronary syndromes (HR, 1.25; 95% CI, 1.02–1.52; $P = 0.03$), and stroke/systemic embolism (HR, 1.24; 95% CI, 1.07–1.43; $P = 0.0044$). Major bleeding rate was comparable (adjusted HR, 1.00; 95% CI, 0.84–1.18; $P = 0.968$). Among patients without HF at baseline, incidence of new HF was low [0.69 (95% CI, 0.63–0.75) per 100 person-years], whereas propensity to develop worsening HF was higher in those with HF [1.62 (95% CI, 1.45–1.80) per 100 person-years].

Conclusions Patients with AF and HF have a high risk of all-cause and cardiovascular mortality and stroke/systemic embolism and may develop worsening HF.

Keywords Atrial fibrillation; Heart failure; Anticoagulant; GARFIELD-AF; Stroke

Received: 27 August 2020; Revised: 4 November 2020; Accepted: 15 November 2020
**Correspondence to: Prof. Giuseppe Ambrosio, MD, Division of Cardiology, University of Perugia School of Medicine, Ospedale S. Maria della Misericordia, Via S. Andrea delle Fratte, 06156 Perugia, Italy. Tel: +39 0755271509. Email: giuseppe.ambrosio@ospedale.perugia.it*
† The full list of GARFIELD-AF investigators is provided in the Supporting Information.
[Correction added on 25 January 2021, after first online publication: The order of the authors has been corrected in this version.]

Introduction

Atrial fibrillation (AF) and heart failure (HF) may coexist and interact with each other in many patients.[1] Considerable evidence points to a high risk for incident AF in HF patients, which may confer a negative prognostic impact.[2–8] However, most knowledge of HF in AF has been obtained by focusing on HF patients who have developed AF during the course of their index disease through retrospective analyses of historical randomized clinical trials or registries.[3,4,9] Therefore, there are inherent limitations

due to the use of strict inclusion criteria in clinical studies and outdated management practices with respect to both HF (drugs and device implant) and AF [new oral anticoagulant (NOAC)]. Furthermore, knowledge about AF patients who develop HF is limited, as recently reviewed by Ling *et al.*[10]

To gain further insights into the impact of HF on AF patients, we leveraged the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF). This registry is a large, prospective, multinational registry of over 50 000 AF patients followed for at least 2 years, designed to reflect contemporary clinical practice in a global population. As studies regarding the association of AF and HF have typically focused upon patients with a primary diagnosis of HF, the key interests of this study were to evaluate the clinical characteristics and antithrombotic treatment patterns of patients specifically with newly diagnosed AF who present with or without co-morbid HF. Using this large registry, we aim to establish the impact of concomitant HF upon long-term outcomes in AF patients, particularly all-cause mortality, stroke, and bleeding in AF, in a real-world population.

Methods

Study design

The design of the GARFIELD-AF registry was reported previously.[11,12] Briefly, men and women aged over 18 years with AF were diagnosed according to standard local procedures within the previous 6 weeks, with at least one non-prespecified risk factor for stroke as judged by the local investigator, and no valvular diseases were eligible for inclusion.[12] Patients were enrolled prospectively and consecutively at 1317 sites in 35 countries. If random site selection did not generate the required number of sites in a given country, the national lead investigator recommended additional sites (18 of 1317 sites). The sites represent different care settings in each participating country.

Ethics

Independent ethics committee and hospital-based institutional review boards approved the study. The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and International Conference on Harmonization–Good Pharmacoepidemiological and Clinical Practice guidelines. All patients provided written informed consent to participate, and their confidentiality and anonymity were maintained.

Procedures and outcome measures

Baseline characteristics were collected at inclusion in the registry.[11,12] Components of the CHA_2DS_2-VASc[13,14] and HAS-BLED[15] risk stratification schemes were documented; the latter score was calculated excluding fluctuations in international normalized ratio. Follow-up data on treatments and outcomes were captured on electronic case report forms (eCRFs) at four-monthly intervals up to 12 months. Submitted data were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute London, UK). One-fifth of eCRFs (20%) were monitored against source documentation.[12] Data for the present analysis were extracted from the study database in November 2018.

Definitions

Heart failure was defined as left ventricular ejection fraction (LVEF) $<40\%$, history of HF, or physician diagnosis of HF at baseline. Severity of HF was categorized according to the New York Heart Association (NYHA) functional classification. Worsening HF was defined as progressive or acute decompensation of previously stable HF or post-enrolment re-stratification into higher-severity NYHA functional classification, as determined by treating physicians. Vascular disease included coronary artery disease with or without history of acute coronary syndromes (ACS) and/or peripheral artery disease. Chronic kidney disease (CKD) was classified according to National Kidney Foundation guidelines[16] into moderate-to-severe (Stages 3–5), mild (Stages 1 and 2), or none.

Statistical analysis

Baseline characteristics are described with frequencies (percentage) for categorical variables and medians (interquartile range) for continuous variables. Incidence rates for the first occurrence of outcome events (per 100 person-years) were estimated by Poisson model with number of events as dependent variable and log of time as offset, that is, a covariate with known coefficient of 1. Hazard ratios (HRs) with 95% confidence intervals (CIs) for outcome events in HF vs. no-HF groups were calculated as unadjusted and adjusted results using Cox proportional hazards models. Adjustment factors were as follows: sex; race/ethnicity; age with spline knots at 48, 65, 79, and 88 years; body mass index (BMI); oral anticoagulant therapy at baseline; type of AF; hypertension; history of bleeding; vascular disease; prior stroke/transient ischaemic attack; moderate-to-severe CKD; diabetes; smoking status; and heavy alcohol intake. Five imputed datasets were used to account for missing data when calculating HRs.

Results

Baseline characteristics

A total of 52 072 AF patients (M/F, 55.8/44.2%; no-HF group, *n* = 40 314; mean age, 69.5 years; HF group, *n* = 11 758; mean age, 70.1 years) were followed prospectively for 2 years; their baseline characteristics and medications are summarized in *Table 1* and *Figure 1*. Approximately two-third of cases with and without HF had either paroxysmal or unclassified AF. Numerically, the link with HF was stronger for permanent/persistent than paroxysmal AF. In no-HF and HF groups, median CHA_2DS_2-VASc score (interquartile range) was 3.0 (2.0–4.0) and 4.0 (3.0–5.0), respectively; HAS-BLED score was 1.0 (1.0–2.0) in both groups. Prior stroke/transient ischaemic attack was documented in 11.6% and 10.9%, respectively; history of bleeding in 2.4% and 3.0%; and type 2 diabetes in 20.5% and 23.4%. Background therapy and implementation of guideline-recommended practice were consistent among all patients (*Table 1*). Most HF patients (76%) were categorized as NYHA class II–III.

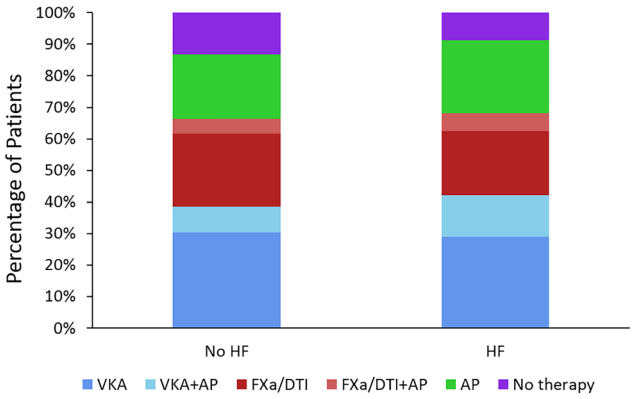
Table 1 Patient demographics and clinical characteristics

Parameter	No HF (*n* = 40 314)	HF (*n* = 11 758)	*P*-value[a]
Male, *n* (%)	22 344 (55.4)	6720 (57.2)	0.0009
Age (years), median (IQR)	71.0 (63.0–78.0)	71.0 (62.0–79.0)	0.0002
Ethnicity, *n* (%)			<0.0001
Afro-Caribbean	186 (0.5)	57 (0.5)	
Asian (not Chinese)	8926 (22.1)	2633 (22.4)	
Caucasian	24 692 (61.2)	7333 (62.4)	
Chinese	2138 (5.3)	605 (5.1)	
Hispanic/Latino	2689 (6.7)	707 (6.0)	
Other	594 (1.5)	233 (2.0)	
Unknown	1089 (2.7)	190 (1.6)	
BMI (kg/m^2), median (IQR)	27.0 (24.0–30.0)	27.0 (24.0–32.0)	<0.0001
SBP (mmHg), mean (SD)	133.9 (19.6)	132.0 (20.4)	<0.0001
DBP (mmHg), mean (SD)	79.6 (12.7)	80.1 (13.6)	0.0009
Heart rate (b.p.m.), mean (SD)	89.8 (26.7)	92.5 (26.8)	<0.0001
LVEF (%), median (IQR)	60.0 (55.0–65.0)	47.0 (35.0–58.0)	<0.0001
Type of AF, *n* (%)			<0.0001
Permanent	4798 (11.9)	1837 (15.6)	
Persistent	5549 (13.8)	2218 (18.9)	
Paroxysmal	11 894 (29.5)	2421 (20.6)	
New	18 073 (44.8)	5282 (44.9)	
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–5.0)	<0.0001
HAS-BLED score, median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	<0.0001
Medical history, *n* (%)			
ACS	3589 (8.9)	1956 (16.7)	<0.0001
Vascular disease	8072 (20.2)	4761 (40.8)	<0.0001
Moderate-to-severe CKD	3639 (9.0)	1721 (14.6)	<0.0001
Stroke/TIA	4680 (11.6)	1281 (10.9)	0.0388
Prior bleeding	965 (2.4)	353 (3.0)	0.0002
Diabetes (type 1 or 2)	8687 (21.5)	2868 (24.4)	<0.0001
Stroke prophylaxis			<0.0001
VKA	12 061 (30.3)	3318 (28.9)	
VKA + AP	3308 (8.3)	1519 (13.2)	
FXA	6851 (17.2)	1732 (15.1)	
FXA + AP	1400 (3.5)	496 (4.3)	
DTI	2410 (6.0)	612 (5.3)	
DTI + AP	465 (1.2)	162 (1.4)	
AP alone	8116 (20.4)	2655 (23.1)	
None	5241 (13.2)	1000 (8.7)	
Cardiac treatment[b]			
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	13 433 (50.6)	5144 (65.4)	<0.0001
Beta-blocker	14 680 (55.3)	5168 (65.7)	<0.0001
Diuretic agent	6864 (25.9)	4382 (55.7)	<0.0001
Digoxin/digitalis	1767 (6.7)	1381 (17.6)	<0.0001
Aldosterone antagonist	849 (3.2)	1463 (18.6)	<0.0001

ACS, acute coronary syndromes; AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; DTI, direct thrombin inhibitor; FXA, factor Xa antagonist; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; SBP/DBP, systolic/diastolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
[a]For categorical variables, *P*-values were obtained from a χ^2 test or Fisher's exact test, as appropriate. For continuous variables, *P*-values were obtained from a *t*-test or a Wilcoxon–Mann–Whitney test, as appropriate.
[b]Measured in GARFIELD-AF cohorts 3–5 (no HF, *n* = 26 526; HF, *n* = 7867).

DOI: 10.1002/ehf2.13156

Figure 1 Baseline therapy—heart failure vs. no heart failure: baseline treatment with anticoagulants/antiplatelet agents. AP, antiplatelet; DTI, direct thrombin inhibitor; FXa, factor Xa inhibitor; HF, heart failure; VKA, vitamin K antagonist.



Heart failure was defined according to LVEF, current HF, or a history of HF. Of patients with HF, 73.4% had recorded LVEF measurements, compared with 54.1% of patients without HF. To assess the potential reporting bias introduced by this difference, patients were also checked according to the presence of a new HF diagnosis at baseline or a history of HF only. Under these criteria, 10 347 patients had HF, of which 70% had an LVEF measurement, whereas the remaining no-HF patients had LVEF measure in 55.6% of cases. Although AF patients with and without concomitant HF were comparable in terms of sex, age, ethnicity, BMI, blood pressure, heart rate, and medical history, some of their clinical characteristics were significantly different: HF patients more frequently had history of ACS (16.7% vs. 8.9%), vascular disease (40.8% vs. 20.2%), and moderate-to-severe CKD (14.6% vs. 9.0%; all $P < 0.001$). Moreover, patients with HF were more likely to have permanent AF (15.6% vs. 11.9%) or persistent AF (18.9% vs. 13.8%).

Antithrombotic and heart failure therapies

A similar proportion of HF and no-HF patients received anticoagulation (68.2% vs. 66.5%; *Figure 1*). HF patients less frequently received no treatment (8.7% vs. 13.2%) and were more likely prescribed antiplatelet therapy, either alone (23.1% vs. 20.4%) or in combination with anticoagulant (18.9% vs. 13.0%). On the other hand, higher proportions of HF than no-HF patients received cardiovascular agents across all major drug classes (*Table 1*).

Clinical characteristics and treatment provided across the New York Heart Association functional categorizations

Clinical characteristics of patients stratified by the presence and severity of HF (NYHA I–II or III–IV) are displayed in *Table 2*. Within the HF group, most clinical characteristics were not markedly different across patients stratified by NYHA functional classification I–II or III–IV, although ACS, CKD, and vascular disease were more frequently observed in those with NYHA functional class III–IV.

Initial antithrombotic treatment provided to AF patients without HF and those with HF stratified according to NYHA functional class I–IV is shown in *Figure 2*. Although the number of patients categorized as NYHA functional class IV is rather small (n = 418), these individuals were clearly undertreated; they were less likely to receive anticoagulation and more likely to receive antiplatelet agents only or no antithrombotic treatment than AF patients with less severe or no HF.

Outcomes at 2 year follow-up

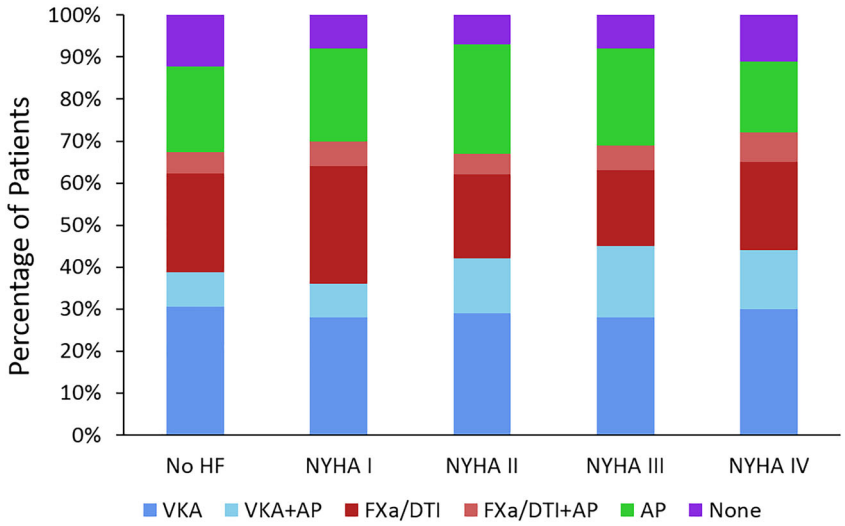
Among AF patients without HF at baseline, *de novo* HF developed in 517 individuals (1.3%) during 2 year follow-up,

Table 2 Baseline clinical characteristics in patients stratified by the presence and severity of heart failure

Parameter	No HF (n = 40 314)	NYHA class I–II (n = 6456)	NYHA class III–IV (n = 3057)	P-value[a]
Sex male, n (%)	22 344 (55.4)	3539 (54.8)	1682 (55.0)	0.6259
Age (years), median (IQR)	71.0 (63.0–78.0)	71.0 (62.0–79.0)	72.0 (63.0–80.0)	<0.0001
LVEF (%), median (IQR)	60.0 (55.0–65.0)	45.0 (43.0–61.0)	45.0 (35.0–55.0)	<0.0001
Medical history, n (%)				
Hypertension	30 519 (75.9)	5205 (80.7)	2366 (77.5)	<0.0001
ACS	3589 (8.9)	934 (14.6)	639 (21.0)	<0.0001
Vascular disease	8072 (20.2)	2543 (39.6)	1478 (48.7)	<0.0001
Moderate-to-severe CKD	3639 (9.0)	831 (12.9)	634 (20.7)	<0.0001
CHA_2DS_2-VASc, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	<0.0001
HAS-BLED, median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	<0.0001

ACS, acute coronary syndromes; CKD, chronic kidney disease; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]For categorical variables, P-values were obtained from a χ^2 test or Fisher's exact test, as appropriate. For continuous variables, P-values were obtained from a one-way ANOVA or a Kruskal–Wallis test, as appropriate.

Figure 2 Antithrombotic treatment patterns in patients stratified by the presence and severity of heart failure (HF). HF severity was categorized according to the New York Heart Association (NYHA) functional classification. AP, antiplatelet; DTI, direct thrombin inhibitor; FXa, factor Xa inhibitor; VKA, vitamin K antagonist.



corresponding to a rate of 0.69 (95% CI, 0.63–0.75) per 100 person-years. However, in the HF cohort, worsening HF was seen in 334 individuals (2.8%), corresponding to a rate of 1.62 (95% CI, 1.45–1.80) per 100 person-years.

In HF vs. no-HF patients, there were significantly (all $P < 0.0001$) higher incidence rates (95% CI; per 100 person-years) of all-cause death [6.93 (6.59–7.30) vs. 2.95 (2.83–3.08)], cardiovascular death [3.10 (2.87–3.34) vs. 0.87 (0.81–0.94)], non-cardiovascular death [2.08 (1.89–2.28) vs. 1.29 (1.21–1.37)], ACS [0.92 (0.80–1.06) vs. 0.54 (0.49–0.60)], and stroke/systemic embolism (SE) [1.43 (1.28–1.60) vs. 1.02 (0.95–1.09)]. Rates of major bleeding were similar in the two groups [1.03 (0.90–1.18) vs. 0.96 (0.89–1.03); $P = 0.4127$].

Kaplan–Meier curves depicting the probability of avoiding all-cause death, stroke/SE, and ACS in the HF and no-HF groups over 2 years are shown in *Figure 3*. In particular, survival curves for all-cause mortality in the two groups immediately began to diverge, with a significantly higher risk of this event noted in HF than no-HF patients throughout the study. Risk of stroke/SE and ACS was also higher in the HF group vs. the no-HF group, albeit delayed, reaching statistical significance after approximately 3 and 6 months, respectively.

Adjusted HRs for all outcome parameters are presented in *Figure 4*. Notably, risk of death by any cause was twice, and cardiovascular death thrice, as likely in HF vs. no-HF patients over 2 years.

Two-year outcomes in patients stratified by the presence of HF and NYHA functional class I–IV are shown in *Figure 5*. A clear correlation was noted between increasingly severe HF and progressively higher incidence rates of adverse outcomes. Especially, the rates of all-cause death, cardiovascular death, and non-cardiovascular death rose exponentially and were almost twice as high in each successive NYHA functional class from I to IV. In patients with no HF who died, cause of death was cardiovascular related in less than one-third of cases and non-cardiovascular in nearly half of cases (others unknown), whereas in patients with NYHA functional class III–IV who died, this trend was reversed (cardiovascular mortality, 47.8%; non-cardiovascular mortality, 27.7%).

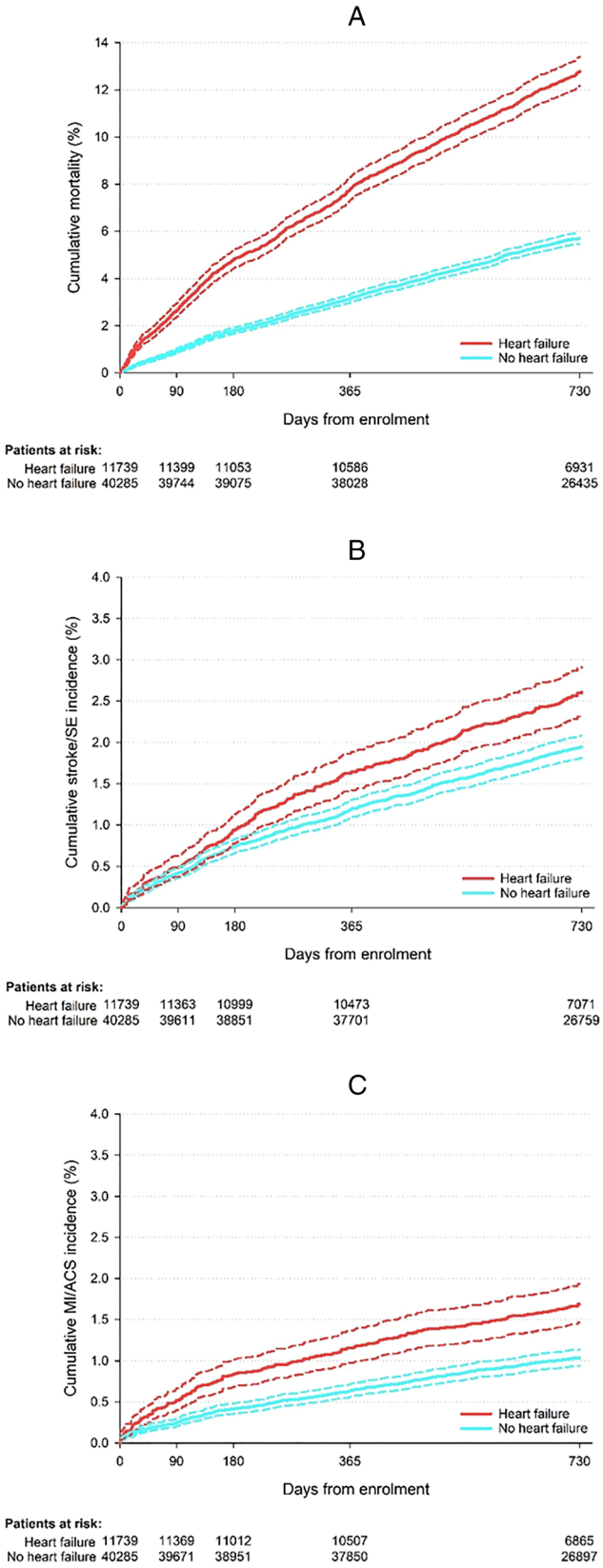
Patients with no HF at baseline were at a low risk of going on to develop HF [incidence rate, 0.69 (95% CI, 0.63–0.75)]; in those with HF, risk of worsening HF increased with higher NYHA functional class from I [rate of HF worsening, 1.16 (95% CI, 0.84–1.58)] to IV [HF worsening, 2.15 (95% CI, 1.27–3.63)].

New heart failure

Of the 40 314 patients with 'no HF', 517 (1.3%) developed new HF during the study compared with 39 797 (98.7%) who did not. Patients with new HF were less often male and slightly older than those without (49.5% and 75.0 years vs. 55.5% and 71.0 years). Paroxysmal and persistent AF were more common in patients with new HF than in those without (29.6%; 13.8% vs. 20.9%; 16.1%, respectively), whereas permanent AF was less common in new HF patients (16.1% vs. 11.9%, respectively). Of patients with new HF, 79.6% were Caucasian and 12.2% were Asian, compared with 62.7% and 28.4% of those without new HF. Clinical characteristics differed between these two groups. Patients who developed new HF more often had ACS, vascular disease, diabetes, and

DOI: 10.1002/ehf2.13156

Figure 3 Cumulative incidence rates of (A) all-cause mortality, (B) stroke/SE, and (C) ACS in atrial fibrillation patients. Rates are stratified by the presence and absence of heart failure at baseline over a 2 year observation period. ACS, acute coronary syndromes; MI, myocardial infarction; SE, systemic embolism.



DOI: 10.1002/ehf2.13156

Figure 4 Major adverse outcomes in atrial fibrillation patients with heart failure vs. without heart failure (reference): adjusted hazard ratios (HRs). This figure is the central illustration of the manuscript. ACS, acute coronary syndromes; CI, confidence interval; MI, myocardial infarction; SE, systemic embolism.

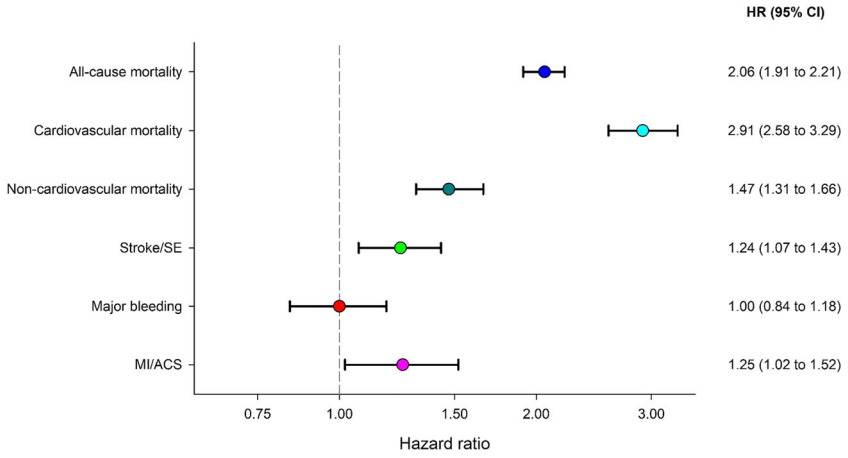
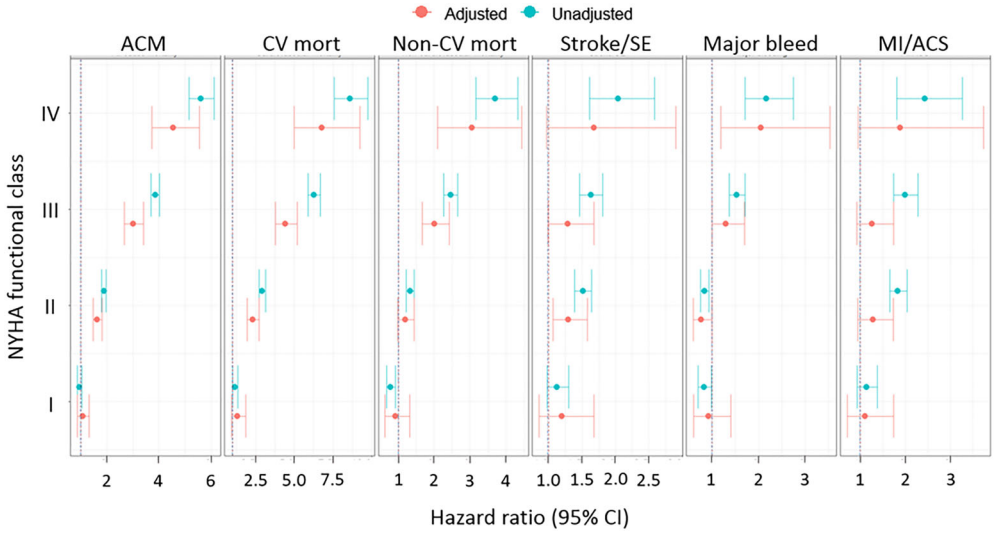


Figure 5 Unadjusted and adjusted 2 year outcomes [hazard ratios vs. no heart failure (HF)] in patients stratified by severity of HF. Severity of HF is stratified via the New York Heart Association (NYHA) functional classes I–IV. ACM, all-cause mortality; ACS, acute coronary syndromes; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; SE, systemic embolism.



moderate-to-severe CKD (13.2%, 28.2%, 26.1%, and 20.7%, respectively), compared with those who did not develop HF (8.9%, 20.1%, 21.5%, and 10.1%, respectively) (*Table 3*).

Of patients with no HF, those who developed new HF during follow-up were less likely to receive vitamin K antagonists at baseline than those who did not develop new HF (19.0% vs. 28.0%). Conversely, those who developed new HF were slightly more likely to have received AP therapy alone (25.5% vs. 20.3%). NOAC usage was comparable (*Table 3*).

Discussion

This analysis of GARFIELD-AF registry on over 50 000 patients provides useful insights into the complex and often challenging condition of *de novo* AF with co-morbid HF at baseline. GARFIELD-AF is the largest registry to date investigating the impact of concurrent HF in AF patients, providing global observational data in a real-world clinical setting. Several important findings emerged. First, the present data extend previous observations to a more contemporary, multi-country,

Table 3 Baseline characteristics of atrial fibrillation patients who developed new heart failure vs. those who did not

Parameter	No new heart failure (n = 39 797)	New heart failure (n = 517)	P-value[a]
Male, n (%)	22 088 (55.5)	256 (49.5)	0.0065
Age (years), median (IQR)	71.0 (63.0–78.0)	75.0 (68.0–80.0)	<0.0001
Ethnicity, n (%)			<0.0001
Caucasian	24 301 (62.7)	391 (79.6)	
Hispanic/Latino	2660 (6.9)	29 (5.9)	
Asian	11 004 (28.4)	60 (12.2)	
Afro-Caribbean/mixed/other	769 (2.0)	11 (2.2)	
BMI (kg/m^2), median (IQR)	26.8 (23.9; 30.4)	28.4 (24.6; 32.9)	<0.0001
SBP (mmHg), mean (SD)	132.0 (120.0; 145.0)	135.0 (120.0; 145.0)	0.4284
DBP (mmHg), mean (SD)	80.0 (70.0; 88.0)	80.0 (70.0; 90.0)	0.8864
Heart rate (b.p.m.), mean (SD)	83.0 (70.0; 104.0)	88.0 (72.0; 112.0)	0.0024
Type of AF, n (%)			<0.0001
Permanent	4715 (11.9)	83 (16.1)	
Persistent	5492 (13.8)	57 (11.0)	
Paroxysmal	11 786 (29.6)	108 (20.9)	
New	17 804 (44.7)	269 (52.0)	
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–4.0)	<0.0001
HAS-BLED score, median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	<0.0001
Medical history, n (%)			
ACS	3521 (8.9)	68 (13.2)	0.0007
Vascular disease	7926 (20.1)	146 (28.2)	<0.0001
Carotid occlusive disease	1159 (3.0)	18 (3.5)	0.4537
VTE	1003 (2.5)	19 (3.7)	0.0966
Stroke/TIA/SE	4520 (11.4)	67 (13.1)	0.2525
Prior bleeding	942 (2.4)	23 (4.5)	0.0021
Hypertension	30 107 (75.9)	412 (79.8)	0.0361
Hypercholesterolaemia	15 937 (41.3)	200 (39.5)	0.4202
Diabetes	8552 (21.5)	135 (26.1)	0.0111
Cirrhosis	197 (0.5)	5 (1.0)	0.1375
Moderate-to-severe CKD	3547 (10.1)	92 (20.7)	<0.0001
Dementia	488 (1.2)	5 (1.2)	0.8938
Treatment			<0.0001
VKA ± AP	11 030 (28.0)	96 (19.0)	
NOAC ± AP	15 163 (38.5)	206 (40.7)	
AP alone	7987 (20.3)	129 (25.5)	
None	5166 (13.1)	75 (14.8)	

ACS, acute coronary syndromes; AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; IQR, interquartile range; NOAC, new oral anticoagulant; SBP/DBP, systolic/diastolic blood pressure; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]For categorical variables, P-values were obtained from a χ^2 test or Fisher's exact test, as appropriate. For continuous variables, P-values were obtained from a t-test or a Wilcoxon–Mann–Whitney test, as appropriate.

and multi-setting practice, showing that approximately one quarter of patients with newly diagnosed AF present with HF. Second, this study demonstrates that the rate of anticoagulation was similar, or higher, in AF patients with concurrent HF compared with those without HF and that prescription rates of NOACs were comparable. Third, although most demographics and baseline characteristics were similar in the two groups, classical risk factors were different between HF and no-HF patients. Those with HF had more ACS and CKD and were twice as likely to have history of vascular disease. Fourth, AF patients with HF experienced substantially higher rates of adverse outcomes than those without HF. It is noteworthy that although HF patients received more cardiovascular drugs than no-HF individuals, their prescription rates of beta-blockers and renin-angiotensin-aldosterone system inhibitors were suboptimal, and this may have contributed to worse outcomes. Finally, at odds with common beliefs, among patients with AF and no HF at baseline, incidence of new HF over 2 year follow-up was low. Worsening HF, on the other hand, was more often observed in AF patients in higher NYHA class.

Individually, AF and HF are the two biggest epidemics in cardiology.[17] In the USA, AF affects approximately 2% of the population aged under 65 years and 9% of those aged over 65.[10,18] The prevalence rates of these two conditions are expected to increase in future due to aging populations and higher survival rates among people with cardiovascular diseases as better therapies emerge. Importantly, AF and HF are linked aetiologically: many AF patients also have HF, and the likelihood of developing AF increases with severity of HF.[18] The Euro Heart Study on AF[9] estimated that one-third of AF patients also have HF, a slightly higher prevalence than that observed in the present contemporary patient cohort. In distinction to the important role of HF in AF, a range of further critical risk factors are independently responsible for triggering AF in the absence of HF. Non-exhaustively, examples include vascular disease such as hypertension, atherosclerosis, the presence of pulmonary vein foci, and

myocardial infarction. Diabetes, renal dysfunction, and demographic characteristics such as BMI, sex, and age are also closely linked to an increasing rate of incident AF.

Risk factors for AF and HF greatly overlap,[19] and AF-induced cardiomyopathy can lead to decline of left ventricular function leading to HF.[20] Given these common pathophysiological aspects, it has been postulated 'AF begets HF, and HF begets AF'.[21] Specific pathophysiological changes by which AF and HF contribute to their co-development are complex and not fully understood.[19] Cardiac remodelling, activation of neurohormonal compensatory mechanisms, and impairment of left ventricular function have been posited as possible reasons for how AF and HF can cause and exacerbate each other. In our registry, most patients with newly diagnosed AF and HF had preserved LVEF; increased heart rate and loss of atrial contraction in AF may have contributed to development of HF. It is clear, however, that patients with concurrent AF and HF have worse prognosis than those with either condition alone, as confirmed by the present analysis and in a previous report on GARFIELD-AF patients with HF associated with ischaemic cardiomyopathy.[22]

Both AF and HF are major causes of stroke.[23,24] Indeed, the widely accepted AF-related stroke risk index CHA_2DS_2-VASc includes 1 point for the presence of HF.[13,14] Subgroup analyses of the landmark trials of NOACs vs. warfarin revealed that these drugs work equally well at preventing stroke/SE in AF patients with and without HF, with similar rates of bleeding.[25–28] In the present study, patients with AF and co-morbid HF had an approximately 30% higher risk of stroke/SE compared with no-HF patients, a statistically significant difference ($P < 0.001$), despite their receiving equivalent anticoagulation regimens. This finding suggests that even in contemporary medicine and after the introduction of NOACs, HF in itself remains a major risk factor for stroke and that patients with concomitant AF and HF should be closely monitored to reduce risk and optimize treatment.

In this analysis, new HF arising during follow-up was seen in only 517 of the 40 314 AF patients (1.3%). This apparently contrasts with reports from the Framingham study, in which 16% of patients developed incident HF after AF diagnosis. It should be noted, however, that the Framingham study followed only 1737 AF patients with no HF at baseline, as opposed to the over 40 000 in GARFIELD-AF. More importantly, whereas GARFIELD-AF patients were followed over 2 years, the 277 cases of incident HF in the Framingham study were accrued over a much longer period of time: between 1980 and 2012. Therefore, incidence rate per person-year was actually quite small. In support of the present findings, similar results were reported by the US-based ORBIT-AF registry of AF patients, in whom *de novo* HF developed in only a few per cent over 2 years of observation.[29] Similar to the ORBIT-AF registry, new HF was associated with a slightly older cohort of patients and was more frequently linked to adverse clinical characteristics, including vascular disease and moderate-to-severe CKD. Age, vascular disease, and renal dysfunction are important independent risk factors for HF, possibly indicating the cause of incident HF in these 517 patients.

The present study also clearly shows that, for patients who already have HF, newly diagnosed AF is indeed an influencing factor associated with clinical deterioration of HF. These findings confirm and extend a recent report from a retrospective analysis of PARADIGM-HF and ATMOSPHERE databases, which shows that new-onset AF was associated with a significantly increased risk of HF rehospitalization.[30]

This study has limitations. The definition of HF adopted herein (i.e. LVEF $<$40% or history of HF as adjudged by signs and symptoms) was conceived when the GARFIELD-AF study was designed. However, it tallies well with those suggested by international medical societies; indeed, both the 2013 American College of Cardiology Foundation/American Heart Association guidelines[31] (most recently updated 2017[32]) and the 2016 European Society of Cardiology guidelines[33] broadly classify HF patients as having preserved or reduced ejection fraction with a cut-off value for the latter $\leq$40%, on the basis that this was selection criterion used in clinical trials demonstrating efficacy of drug therapies. Importantly, the proportion of patients with a recorded LVEF measurement was notably lower in those without concurrent HF. It is possible that this may introduce a potential reporting bias, whereby those without HF may have been incorrectly assigned to this group simply due to the lack of LVEF measurement. However, LVEF was not the only criterion to allocate patients to the 'no-HF' group, as we also recorded history of HF, or current diagnosis of HF: reassessing the assignment of patients into each group according to a history of HF or current HF only shows that a similar number of patients were characterized with HF. Additionally, the proportion of patients in the HF group who had measured LVEF remained substantially higher than in the no-HF patient group. It is therefore likely that the disparity in recorded LVEF measurements may have arisen as patients who presented with no history nor evidence for HF were not considered for measurement of LVEF. A further limitation of this study is that ventricular filling pressures were not collected for this cohort, and thus, we are unable to establish the role it may have played in the prognosis of GARFIELD-AF patients.

Another limitation is outcomes in HF patients with LVEF $<$40% and $\geq$40%, who were not analysed separately. This study stratified patients with HF by NYHA functional class I–IV. However, their European Heart Rhythm Association score of AF was not measured; hence, disabilities attributable to these two disease conditions were not differentiated. We were therefore unable to analyse this cohort according to a combination of NYHA and European Heart Rhythm Association scoring. As in all registries, patients were not randomly enrolled to treatments. Also, adverse event recognition was left at investigators' judgement, and not centrally

adjudicated—although to minimize errors, a sizable proportion (20%) of eCRFs were audited. Finally, it is possible that, in addition to the extensive collection of ancillary data, other variables that were not measured could have further refined interpretation of the findings.

Conclusions

The present analysis of a very large, contemporary, multi-country registry shows that patients with HF and newly diagnosed AF are treated similarly to those with AF and no HF in terms of anticoagulation; yet they remain a higher-risk group with respect to stroke/SE, all-cause death, and cardiovascular death than no-HF patients. AF confers a relatively low risk of developing HF or worsening HF already present.

Acknowledgements

The authors thank the physicians, caregivers, and patients who participated in this research. Alex Kahney and Rebecca Watkin of Thrombosis Research Institute London, UK, provided editorial assistance.

Conflict of interest

GA has received personal fees from Merck, Menarini, Angelini, Novartis and Behring; AJ Camm has received institutional grants and personal fees from Bayer, Boehringer Ingelheim, Pfizer/BMS and Daiichi Sankyo. JPB has received personal fee from thrombosis research institute; LGM has received grants and personal fees from Bayer AG during the conduct of the study, and grants from Boehringer Ingelheim, grants and personal fees from Pfizer and personal fees from Daiichi Sankyo and has received support by Italian Ministry of Health Ricerca Corrente - IRCCS MultiMedica outside the submitted work; AKK has received grants and personal fees from Bayer AG and Sanofi; personal fees from Bayer AF, Janssen Pharma, Pfizer, Sanofi, Verseon and Anthos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. [Correction added on 25 January 2021, after first online publication: The Conflict of Interest has been updated in this version.]

Funding

This work was supported by an unrestricted grant awarded by Bayer Pharma AG (Berlin, Germany) to the Thrombosis Research Institute (London, UK).

Supporting information

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

Data S1. GARFIELD-AF Registry Investigators.

References

1. Hohendanner F, Heinzel FR, Blaschke F, Pieske BM, Haverkamp W, Boldt HL, Parwani AS. Pathophysiological and therapeutic implications in patients with atrial fibrillation and heart failure. *Heart Fail Rev* 2018; **23**: 27–36.
2. Campbell NG, Cantor EJ, Sawhney V, Duncan ER, DeMartini C, Baker V, Diab IG, Dhinoja M, Earley MJ, Sporton S, Davies LC, Schilling RJ. Predictors of new onset atrial fibrillation in patients with heart failure. *Int J Cardiol* 2014; **175**: 328–332.
3. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; **87**: VI102–VI110.
4. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail* 2014; **16**: 1317–1322.
5. Crijns HJ, Tjeerdsma G, de Kam PJ, Boomsma F, van Gelder IC, van den Berg MP, van Veldhuisen DJ. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J* 2000; **21**: 1238–1245.
6. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA, Investigators C. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; **47**: 1997–2004.
7. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005; **26**: 1303–1308.
8. van Veldhuisen DJ, Aass H, El Allaf D, Dunselman PH, Gullestad L, Halinen M, Kjekshus J, Ohlsson L, Wedel H, Wikstrand J, Group M-HS. Presence and development of atrial fibrillation in chronic heart failure. Experiences from the MERIT-HF Study. *Eur J Heart Fail* 2006; **8**: 539–546.
9. Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, Lopez-Sendon JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. *J Am Coll Cardiol* 2009; **53**: 1690–1698.
10. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial

fibrillation and heart failure. *Nat Rev Cardiol* 2016; **13**: 131–147.
11. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GY, Mantovani LG, Turpie AG, van Eickels M, Misselwitz F, Rushton-Smith S, Kayani G, Wilkinson P, Verheugt FW, Investigators GR. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS ONE* 2013; **8**: e63479.
12. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GY, Mantovani LG, Verheugt FW, Jamal W, Misselwitz F, Rushton-Smith S, Turpie AG. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J* 2012; **163**: 13–19 e1.
13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–2870.
14. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010; **137**: 263–272.
15. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138**: 1093–1100.
16. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014; **63**: 713–735.
17. Siller-Matula JM, Pecen L, Patti G, Lucerna M, Kirchhof P, Lesiak M, Huber K, Verheugt FWA, Lang IM, Renda G, Schnabel RB, Wachter R, Kotecha D, Sellal JM, Rohla M, Ricci F, De Caterina R, Group TiA. Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF-HF substudy. *Int J Cardiol* 2018; **265**: 141–147.
18. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**: 2D–8D.
19. Lee Park K, Anter E. Atrial fibrillation and heart failure: a review of the intersection of two cardiac epidemics. *J Atr Fibrillation* 2013; **6**: 751.
20. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-induced cardiomyopathies: mechanisms, recognition, and management. *J Am Coll Cardiol* 2015; **66**: 1714–1728.
21. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016; **133**: 484–492.
22. Corbalan R, Bassand JP, Illingworth L, Ambrosio G, Camm AJ, Fitzmaurice DA, Fox KAA, Goldhaber SZ, Goto S, Haas S, Kayani G, Mantovani LG, Misselwitz F, Pieper KS, Turpie AGG, Verheugt FWA, Kakkar AK, Investigators G-A. Analysis of outcomes in ischemic vs nonischemic cardiomyopathy in patients with atrial fibrillation: a report from the GARFIELD-AF registry. *JAMA Cardiol* 2019; **4**: 526–548.
23. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Group ESCSD. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893–2962.
24. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke* 2011; **42**: 2977–2982.
25. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–1151.
26. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093–2104.
27. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Committees A, Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981–992.
28. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883–891.
29. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC, Investigators O-A, Patients. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Heart Fail* 2017; **5**: 44–52.
30. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Kober L, McMurray JJV, Paradigm HF, Investigators A, Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017; **70**: 2490–2500.
31. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F, American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147–e239.
32. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; **136**: e137–e161.
33. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.