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FULL RESEARCH PAPER
Cardiovascular disease

Heart failure in patients with recently diagnosed atrial fibrillation: findings from the GLORIA-AF Registry Phase III

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Aims Congestive heart failure (CHF) is often coexisting in patients with atrial fibrillation (AF), but the clinical epidemiology of this association is still uncertain. We aimed to analyse characteristics, management, and outcomes of patients with and without CHF, in a real-world cohort of patients with AF.

Methods and results From the GLORIA-AF Registry Phase III, which enrolled adults with a recent diagnosis of AF and a CHA_2DS_2-VASc ≥ 1, we analysed factors associated with CHF at baseline, the association of CHF with use of oral anticoagulants (OAC) and other treatments, and the risk of adverse outcomes during a 3-year follow-up. The primary outcome was a composite of all-cause death and major adverse cardiovascular events (MACE). Among 21,125 patients included (mean age: 70.2 ± 10.3 years, 44.9% females), 4632 (21.9%) had CHF. Patients with CHF and left ventricular ejection fraction (LVEF) ≤ 40% had higher odds of receiving OAC [odds ratio 1.47, 95% confidence interval (CI): 1.27–1.71], while no significant differences were found for CHF with LVEF > 40%. Compared with vitamin K antagonist, non-vitamin K oral anticoagulants were less used in patients with CHF, irrespective of LVEF. On multivariable Cox regression analysis, CHF was associated with an increased hazard of the primary outcome (hazard ratio: 2.04, 95% CI: 1.87–2.23). Similar results were observed for other secondary outcomes, including thromboembolism and major bleeding. Risk increases were higher in patients with LVEF ≤ 40%.

Conclusion Congestive heart failure is common in real-world patients with AF and is associated with a more complex clinical phenotype, different management, and worse prognosis. Additional interventions are needed to improve prognosis of AF-CHF patients.

Lay summary In this study, we investigated the characteristics, management, and outcomes of patients with and without congestive heart failure (CHF), in a real-world cohort of patients with a recent diagnosis of atrial fibrillation (AF).

- Using the data of the GLORIA-AF Registry Phase III, we found that CHF was present in one out five patients with a recent diagnosis of AF. Patients with AF and CHF received different treatments compared with non-CHF patients, and left ventricular ejection fraction (LVEF) influences the choices of oral anticoagulation.
- During the 3 years of follow-up, the coexistence of AF and CHF was associated with a higher risk of a composite outcome of all-cause death and major adverse cardiovascular events, as well as with higher risk of other secondary exploratory outcomes, with higher magnitude for CHF patients with LVEF ≤ 40%.

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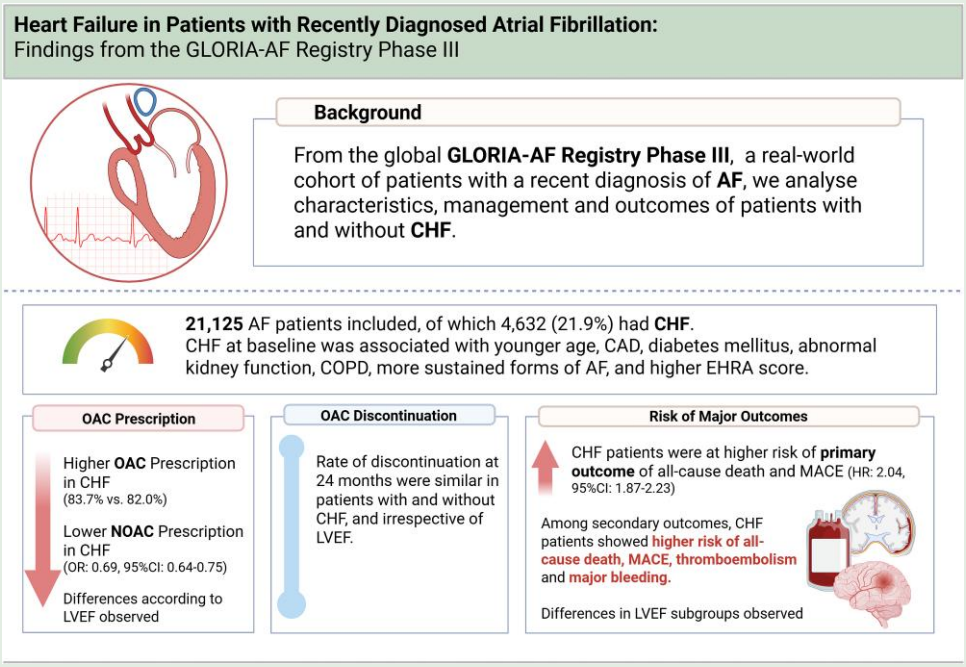
Graphical Abstract



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Keywords Atrial fibrillation • Heart failure • Epidemiology • Mortality • Outcomes

Introduction

Congestive heart failure (CHF) and atrial fibrillation (AF) are two of the most common non-communicable chronic diseases and are both emerging global epidemics.[1,2] The prevalence of CHF ranges from 1 to 12% of the global population,[3] with approximately 64 million of people that were living with heart failure (HF) in 2017.[4] These figures are expected to rise due to the longer life expectancy of the general population and the availability of treatments that are able to modify the trajectory of CHF.[5] Similarly, the ageing of the population has been linked to the increased prevalence and incidence of AF; in 2019, the Global Burden of the Disease estimated that 59.7 million people had AF or atrial flutter worldwide.[6]

Atrial fibrillation and HF are intimately associated with several shared risk factors [e.g. arterial hypertension, coronary artery disease (CAD), diabetes mellitus, and obesity] that explain the tight relationship between these two diseases.[7,8] Indeed, the onset of AF or HF increases the probability that the other will develop as part of a vicious cycle.[9] From an epidemiological point of view, the prevalence of AF in patients with pre-existing HF ranges from <5 to 50%, depending on the severity of the HF[3]; also, left ventricular ejection fraction (LVEF) is a key feature, with HF usually categorized as with reduced ejection fraction (LVEF ≤ 40%), mid-range ejection fraction (LVEF 41–49%), and preserved ejection fraction (LVEF ≥ 50%).[10] These phenotypes of HF show differences in the management and prognosis,[10] as well as heterogeneous associations with AF.[11,12] However, CHF is regarded as a stroke risk factor in patients with AF, and one point is assigned for the presence of CHF when calculating the CHA_2DS_2-VASc score.[13] The age threshold for starting oral anticoagulation (OAC) in AF patients with CHF as a single risk factor may be as low as 35 years.[14]

Notwithstanding previous evidence and considering the evolving nature of the AF and CHF landscape, there is still need for data from real-world cohorts on the association of CHF and AF and on the impact of HF on the management of AF—including use of OAC—and the risk of major outcomes. In this analysis from the *Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial* Fibrillation (GLORIA-AF) Registry Phase III, we explore the impact of CHF on the outcomes of patients with a recent diagnosis of AF.

Methods

The GLORIA-AF Registry is a global, multicentre, prospective registry structured in three phases that investigated the long-term safety and effectiveness of dabigatran etexilate in patients with AF. Further details of the study design and primary analyses comparing dabigatran with vitamin K antagonist have been previously published.[15–17] Briefly, between November 2011 and December 2014 for the Phase II and between January 2014 and December 2016 for Phase III, the GLORIA-AF Registry enrolled consecutive patients with recent diagnosis of non-valvular AF and a CHA_2DS_2-VASc score ≥ 1. All subjects who received dabigatran during Phase II were followed for 2 years, while all subjects enrolled during the Phase III were followed up for 3 years, regardless of antithrombotic treatment received. For this analysis, we focused on patients recruited in Phase III of the registry.

Inclusion/exclusion criteria

Detailed inclusion and exclusion criteria have been published elsewhere.[16] Eligible patients were adults (≥18 years) with a recent diagnosis of AF (<3 months before enrolment, or <4.5 months in Latin America) and a CHA_2DS_2-VASc score ≥ 1. All the participants provided written informed consent. Main exclusion criteria were AF due to a reversible cause, presence of mechanical heart valve (or expected valve replacement), having received >60 days of vitamin K antagonist (VKA) treatment in the lifetime, having other medical indication for OAC treatment, or having a life

expectancy < 1 year. The study was conducted following the principles of Good Clinical Practice and the Declaration of Helsinki. Local institutional review boards at each participating site gave ethical approval. Data regarding comorbidities, drugs prescribed, and interventions received at baseline were obtained from standardized electronic case report forms (eCRFs).

For this analysis, we considered 'congestive heart failure' (CHF) as collected by the study investigators in the eCRF (i.e. 'congestive heart failure/left ventricular dysfunction'). Additionally, when patients were flagged as having CHF, investigators were able to specify current NYHA class and LVEF at the latest examination (either ≤40% or >40%). For both NYHA class and LVEF, investigators were able to select 'unknown' in the eCRF; we considered data as originally collected.

Follow-up and outcomes

Detailed descriptions of follow-up and outcomes for GLORIA-AF Registry Phase III have been reported elsewhere.[16,17] For this analysis, we considered the following outcomes: (i) all-cause mortality; (ii) major adverse cardiovascular events [MACE, which included cardiovascular (CV) death, stroke, and myocardial infarction]; (iii) thromboembolism [as the composite of stroke, transient ischaemic attack (TIA), and other non-central nervous system thromboembolism]; and (iv) major bleeding.

We defined the primary outcome for this analysis as the composite of all-cause death and MACE. Additionally, we assessed the following secondary exploratory outcomes: all-cause death, CV death, MACE, stroke (including haemorrhagic and ischaemic stroke, as well as strokes of uncertain classification), thromboembolism (as the composite of stroke, TIA, and other non-central nervous system thromboembolism), and major bleeding (defined as a life-threatening or fatal bleeding, symptomatic bleeding in a critical organ, or a bleeding associated with a haemoglobin reduction of ≥20 g/L or leading to ≥2 units of blood transfusion).

Statistical analysis

Normal and non-normal distributed continuous variables were reported according to mean and standard deviation (SD) or median and interquartile range [IQR] and were compared with appropriate parametric and non-parametric tests. Categorical variables, reported as frequencies and percentages, were compared using χ^2 test.

Multivariable logistic regression analyses were performed to analyse the association of baseline comorbidities and other clinical characteristics with odds of presenting with CHF at baseline; results were presented as odds ratio (OR) and 95% confidence intervals (CIs). Similarly, the association of CHF with key treatments received at baseline [i.e. OAC, beta-blockers, ACE inhibitors/angiotensin receptor blockers (ARBs), diuretics, digoxin, amiodarone, dronedarone, propafenone, flecainide, and ablation/cardioversion] was analysed through multivariable logistic regression model, and results were reported as OR and 95% CI. Models were adjusted for age class (<65, 65–75, ≥75 years old), sex, type of AF, body mass index (BMI), history of previous bleeding, and comorbidities included in the CHA_2DS_2-VASc [arterial hypertension, diabetes mellitus, history of stroke/TIA, peripheral artery disease [PAD], and CAD], with listwise deletion for missing data.

Multivariable Cox regression analyses were performed to evaluate the association between CHF and OAC discontinuation (defined as a switching to another antithrombotic regimen, including different OAC, or an interruption longer than 30 days of the treatment received at baseline[18]) at 24 months, among patients prescribed with OAC at baseline; models were adjusted for age class, sex, type of AF, BMI, history of previous bleeding, and comorbidities included in the CHA_2DS_2-VASc, with listwise deletion for missing data. Results were reported as adjusted hazard ratio (aHR) and 95% CI.

Kaplan–Meier curves were used to represent survival probability for the primary outcome according to the presence of CHF; survival distributions were compared using log-rank test. The association of CHF with the risk of the primary and the exploratory secondary outcomes was evaluated through multivariable Cox regression models, adjusted for age class, sex, type of AF, BMI, history of previous bleeding, comorbidities included in the CHA_2DS_2-VASc, and the use of OAC, with listwise deletion for missing data. Additionally, for the primary outcome, we also evaluated the association of CHF and the primary composite outcome across key relevant subgroups (age class, sex, region of recruitment, type of AF, use of OAC, CHA_2DS_2-VASc score, history of stroke/TIA, PAD, CAD, and history of previous bleeding), through interaction analysis.

A two-sided $P < 0.05$ was regarded as statistically significant. All analyses were performed using R 4.3.1 (R Core Team, Vienna, Austria).

Results

Among the patients recruited in the GLORIA-AF Registry Phase III, we included 21 125 patients with available data on CHF in this analysis (mean age: 70.2 ± 10.3 years, 44.9% females). Of these, 4632 (21.9%) had CHF. Baseline characteristics and treatments according to the presence of CHF at baseline are reported in *Table 1*. Patients with CHF were less likely to be females and showed higher prevalences of CAD, diabetes mellitus, and PAD. On average, patients with CHF had higher mean CHA_2DS_2-VASc scores (3.9 ± 1.6 vs. 3.0 ± 1.4; $P < 0.001$). Data on NYHA class and LVEF were available for 4069 and 4004 patients with CHF, respectively; hence, 1289 (31.7%) had NYHA class III–IV, while 2175 (54.3%) had LVEF > 40%.

Factors associated with congestive heart failure at baseline

Results of the multivariable logistic regression on factors associated with CHF at baseline are reported in *Figure 1*. Compared with patients aged <65 years, age 65–75 years was associated with lower odds of having CHF (OR [95% CI]: 0.77 [0.70–0.84]), while no significant association was found for age ≥ 75 years; female sex was also associated with lower odds of having CHF (OR [95% CI]: 0.78 [0.72–0.84]). A more sustained form of AF, higher AF symptom burden (as encompassed by EHRA score), and being recruited in Asia and other regions were associated with higher odds of having CHF. Among comorbidities, diabetes mellitus (OR [95% CI]: 1.21 [1.11–1.32]), previous CAD (OR [95% CI]: 2.30 [2.11–2.51]), abnormal kidney function (OR [95% CI]: 2.98 [2.39–3.72]), and chronic obstructive pulmonary disease (OR [95% CI]: 1.84 [1.60–2.10]) were all associated with higher odds of presenting with CHF at baseline. On the other side, arterial hypertension, history of stroke/TIA, and history of previous bleeding were associated with lower likelihood of CHF (*Figure 1*).

In a sensitivity analysis in which age and BMI were fitted as restricted cubic splines with 3 knots placed at default position, both variables showed a non-linear relationship with odds of having CHF at baseline (P for non-linearity < 0.001 and 0.017 for age and BMI, respectively; Supplementary material online, *Figure S1*).

When evaluating separately CHF with LVEF ≤ 40% or >40%, older age and female sex were associated with higher odds of presenting with CHF and LVEF > 40%, but showed an opposite relation (i.e. lower odds) for CHF with LVEF ≤ 40% (see Supplementary material online, *Figure S2*). Similar results were observed for recruitment in Asia and arterial hypertension. Conversely, more sustained forms of AF and higher burden of AF symptoms were associated with higher odds of both CHF with LVEF ≤ 40% and >40%; similar results were observed for abnormal kidney function and chronic obstructive pulmonary disease. Finally, history of stroke/TIA was associated with similar lower odds of presenting with CHF (with LVEF ≤ 40% and >40%) (see Supplementary material online, *Figure S2*).

Table 1 Baseline characteristics and treatments according to the presence of CHF at baseline

Variables	No CHF (*N* = 16 493)	CHF (*N* = 4632)	*P*
Age, mean (SD)	70.2 (10.1)	70.0 (11.0)	0.159
Age group, *n* (%)			**<0.001**
<65 years	4081/16 493 (24.7)	1308/4632 (28.2)	
65 to <75 years	6166/16 493 (37.4)	1480/4632 (32.0)	
≥75 years	6246/16 493 (37.9)	1844/4632 (39.8)	
Female sex, *n* (%)	7688/16 493 (46.6)	1797/4632 (38.8)	**<0.001**
BMI, median [IQR], kg/m^2	27.3 [24.4, 31.2]	27.8 [24.5, 32.1]	**<0.001**
SBP, median [IQR], mmHg	130 [120–143]	129 [115–140]	**<0.001**
DBP, median [IQR], mmHg	80 [70–85]	78 [70–85]	**<0.001**
HR, median [IQR], bpm	75 [65–88]	79 [68–93]	**<0.001**
Region, *n* (%)			**<0.001**
Europe	8103/16 493 (49.1)	2076/4632 (44.8)	
North America	4060/16 493 (24.6)	1043/4632 (22.5)	
Asia	3249/16 493 (19.7)	981/4632 (21.2)	
Other	1081/16 493 (6.6)	532/4632 (11.5)	
AF type, *n* (%)			**<0.001**
Paroxysmal AF	9955/16 493 (60.4)	1962/4632 (42.4)	
Persistent AF	5138/16 493 (31.2)	2068/4632 (44.6)	
Permanent AF	1400/16 493 (8.5)	602/4632 (13.0)	
EHRA III–IV, *n* (%)	4587/16 493 (27.8)	1980/4632 (42.7)	**<0.001**
LVEF (%) > 40%, *n* (%)	—	2175/4004 (54.3)	—
NYHA class III–IV, *n* (%)	—	1289/4069 (31.7)	—
Comorbidities, *n* (%)			
Hypertension	12 312/16 469 (74.8)	3442/4620 (74.5)	0.737
CAD	2601/16 196 (16.1)	1373/4471 (30.7)	**<0.001**
Diabetes mellitus	3605/16 493 (21.9)	1309/4632 (28.3)	**<0.001**
Previous stroke/TIA	2493/16 493 (15.1)	517/4631 (11.2)	**<0.001**
PAD	434/16 418 (2.6)	181/4563 (4.0)	**<0.001**
Previous bleeding	895/16 213 (5.5)	219/4555 (4.8)	0.065
Chronic obstructive pulmonary disease	841/16 349 (5.1)	440/4585 (9.6)	**<0.001**
Abnormal kidney function[a]	206/16 320 (1.3)	183/4569 (4.0)	**<0.001**
Dementia	83/16 343 (0.5)	40/4588 (0.9)	**0.006**
Neoplasia	1690/16 294 (10.4)	416/4560 (9.1)	**0.014**
Risk scores			
CHA2DS2-VASc [mean (SD)]	3.0 (1.4)	3.9 (1.6)	**<0.001**
HAS-BLED [mean (SD)]	1.4 (0.9)	1.4 (0.9)	0.441

AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; EHRA, European Heart Rhythm Association; HR, heart rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease; SBD, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack. Bold text indicates statistical significance at 0.05 level.
[a]Defined as chronic dialysis, renal transplantation, or serum creatinine ≥ 2.26 mg/dL.

Treatments according to congestive heart failure at baseline

Treatments prescribed in patients with and without CHF are reported in Supplementary material online, *Table S1*, and results of the multivariable logistic regression are shown in Supplementary material online, *Figure S3*. Patients with CHF were more treated with OAC (83.7% vs. 82.0%), although without statistically significant differences at multivariable logistic regression. Conversely, among patients who received OAC, patients with CHF were less likely to receive non-vitamin K oral anticoagulant (NOAC) vs. VKA (see Supplementary material online, *Figure S3*). Patients with CHF showed also higher likelihood of receiving beta-blockers, amiodarone, digoxin, ACE inhibitors/ARB, and diuretics. Ablation/cardioversion was also more likely reported in patients with CHF. On the other side, verapamil/diltiazem, dronedarone, and class IC antiarrhythmics were less used in patients with CHF (see Supplementary material online, *Figure S3*).

When restricting the analysis to patients with available values on LVEF and compared with patients without CHF (see Supplementary material online, *Figure S4*), we found that OACs were more likely used in patients with CHF and LVEF ≤40%, but not in CHF with LVEF >40%; conversely, NOACs were less likely used in CHF patients irrespective of LVEF. Similar results (although with different magnitude of association) were found for other drugs in patients with CHF and LVEF ≤ 40% and >40%, except for

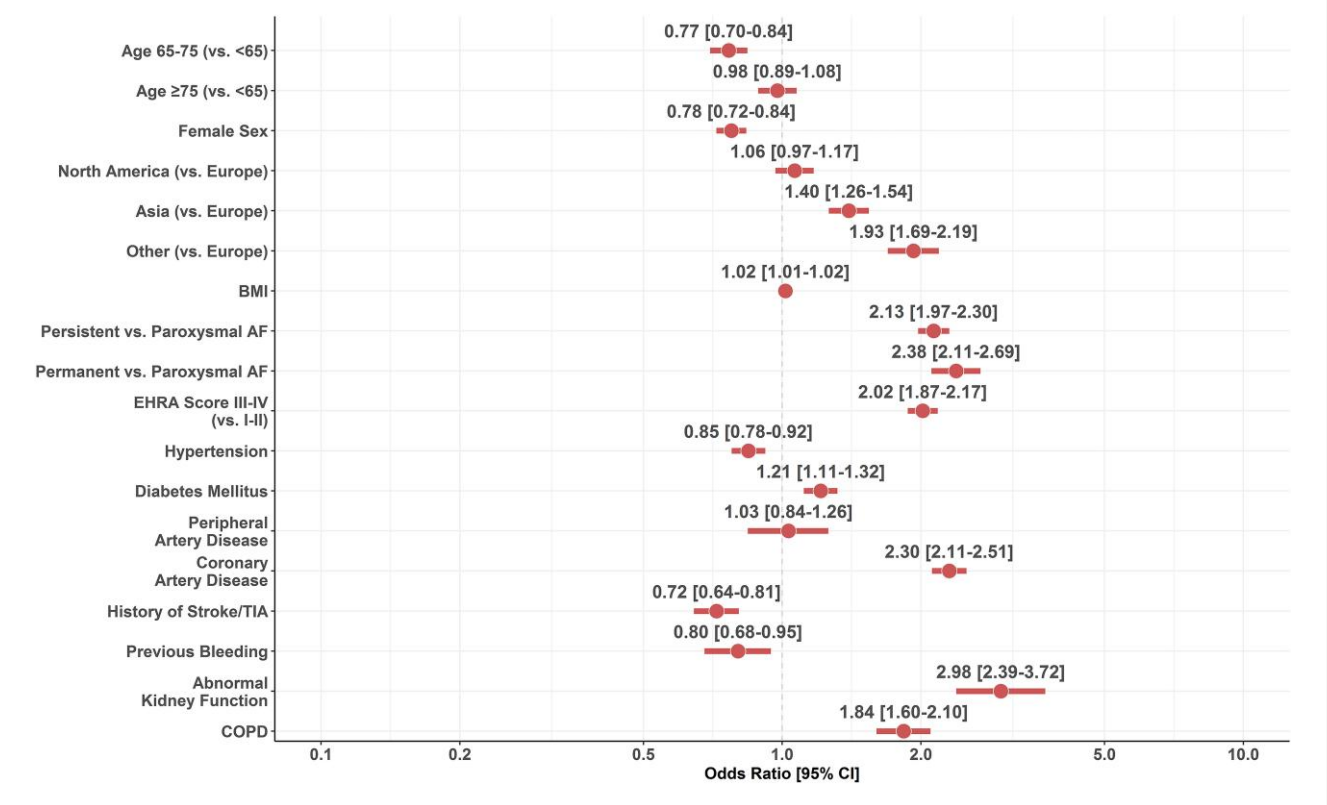

Figure 1 Multivariable logistic regression analysis on factors associated with congestive heart failure at baseline. AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EHRA, European Heart Rhythm Association; TIA, transient ischaemic attack.

verapamil/diltiazem, which use was lower only in patients with CHF and LVEF ≤ 40% (see Supplementary material online, *Figure S4*).

Rates of OAC discontinuation at 24 months were similar in patients with and without CHF and irrespective of LVEF (see Supplementary material online, *Figure S5*). Compared with patients without CHF, CHF was not associated with higher risk of OAC discontinuation at 24 months (HR [95% CI]: 1.01 [0.94–1.09]). Similar results were observed considering patients with CHF and LVEF ≤ 40% and CHF with LVEF > 40% (HR [95% CI]: 1.01 [0.91–1.12] and 0.99 [0.90–1.10], respectively).

Risk of adverse outcomes according to congestive heart failure

Of the patients included, 21 070 (99.7%; 4610 with CHF) had available data on the primary outcome and were included in the survival analysis. Over a median follow-up of 3.0 [IQR: 2.9–3.1] years, patients with CHF had a higher incidence of the primary composite outcome (*Figure 2*; log-rank $P < 0.001$). Patients with CHF and LVEF ≤ 40% had the highest incidence, compared with patients with CHF and LVEF > 40% and those without CHF (see Supplementary material online, *Figure S6*; log-rank $P < 0.001$). Moreover, patients with CHF had higher incidence of the primary composite outcome across all subtypes of AF (paroxysmal, persistent, and permanent; Supplementary material online, *Figure S7*; log-rank $P < 0.001$ for all).

Results of the multivariable Cox regression analyses for the risk of the primary and exploratory outcomes are reported in *Table 2* for CHF vs. no CHF and Supplementary material online, *Table S2* for CHF vs. no CHF according to LVEF. Patients with CHF had higher risk of the primary composite outcome of all-cause death and MACE (HR [95% CI]: 2.04 [1.87–2.23]); similar results were observed for all the other exploratory secondary outcomes, including all-cause death (HR [95% CI]: 2.36 [2.14–2.60]), MACE (HR [95% CI]: 1.95 [1.73–2.19]), thromboembolism (HR [95% CI]: 1.27 [1.06–1.51]), and major bleeding (HR [95% CI]: 1.31 [1.10–1.57]) (*Table 2*). Magnitude of risk increase was higher in patients with CHF and LVEF ≤ 40% for all outcomes except thromboembolism, for which a non-statistically significant association was found after adjustment (HR [95% CI]: 1.01 [0.75–1.36]) (see Supplementary material online, *Table S2*).

Results of the interaction analysis on the association of CHF with hazard of the primary outcome across key subgroup showed consistent association of CHF with primary outcome across most subgroup, except for age, for which a higher magnitude of risk increase was observed in patients <65 years, compared with 65–75 and ≥75 years ($P_{int} = 0.009$). Some evidence for potential heterogeneity of association was observed also for CHA_2DS_2-VASc score ≥ 4 vs. 4, with highest magnitude of risk increase in patients with CHA_2DS_2-VASc < 4 ($P_{int} = 0.051$) (*Figure 3*).

Discussion

In this analysis of the real-world GLORIA-AF Registry Phase III, our main results are as follows: (i) in patients with a recent diagnosis of AF, CHF is a common comorbidity, and its presence is associated with a specific clinical phenotype, associated with other CV risk factors such as CAD, diabetes mellitus, and obesity, a higher burden of symptoms, and more sustained forms of AF; (ii) patients with AF and CHF

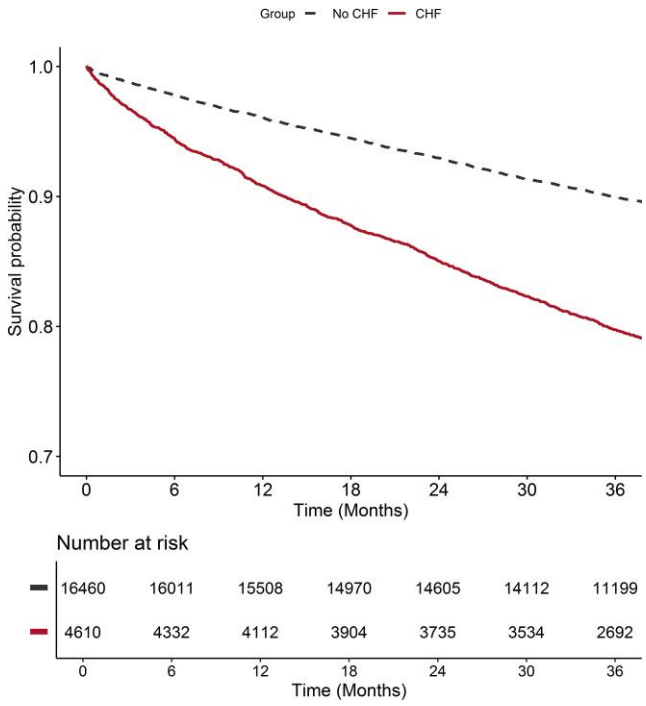

Figure 2 Survival curves for the primary composite outcome, according to congestive heart failure. Log-rank $P < 0.001$; CHF, congestive heart failure.

Table 2 Incidence rates and multivariable Cox regression models on the risk of major outcomes according to CHF

	IR [95% CI]	aHR [95% CI]	*P*
Composite of all-cause death or MACE			
No CHF	3.5 [3.4–3.7]	Ref.[a]	Ref.
CHF	7.7 [7.2–8.2]	**2.04 (1.87–2.23)**[a]	**<0.001**
Secondary outcomes			
All-cause death			
No CHF	2.5 [2.4–2.7]	Ref.[a]	Ref.
CHF	6.4 [5.9–6.9]	**2.36 (2.14–2.60)**[a]	**<0.001**
MACE			
No CHF	1.9 [1.8–2.0]	Ref.[a]	Ref.
CHF	4.0 [3.6–4.4]	**1.95 (1.73–2.19)**[a]	**<0.001**
Thromboembolism			
No CHF	1.3 [1.2–1.4]	Ref.[a]	Ref.
CHF	1.6 [1.4–1.8]	**1.27 (1.06–1.51)**[a]	**0.008**
Major bleeding			
No CHF	1.1 [1.0–1.2]	Ref.[a]	Ref.
CHF	1.6 [1.4–1.9]	**1.31 (1.10–1.57)**[a]	**0.002**

CI, confidence interval; CHF, congestive heart failure; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiovascular events. Bold text indicates statistical significance at 0.05 level.
[a]Adjusted for age class, sex, type of AF, previous bleeding, BMI, prior stroke/TIA, hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, and use of OAC.

receive different management, and LVEF influences treatment choices: OACs were more used in patients with CHF and LVEF ≤ 40%, while NOACs were consistently less used compared with VKA in patients with CHF. Also, the use of other CV drugs and interventions was influenced by the CHF phenotype; (iii) CHF has a detrimental effect on prognosis of patients with AF, with the magnitude of risk increase which was significantly influenced by LVEF ≤ 40% vs. >40%; and (iv) the relative contribution of CHF on prognosis appears higher in patients with lower baseline risk, as observed by subgroup analyses on younger patients and those with CHA_2DS_2-VASc scores < 4 (*Graphical Abstract*).

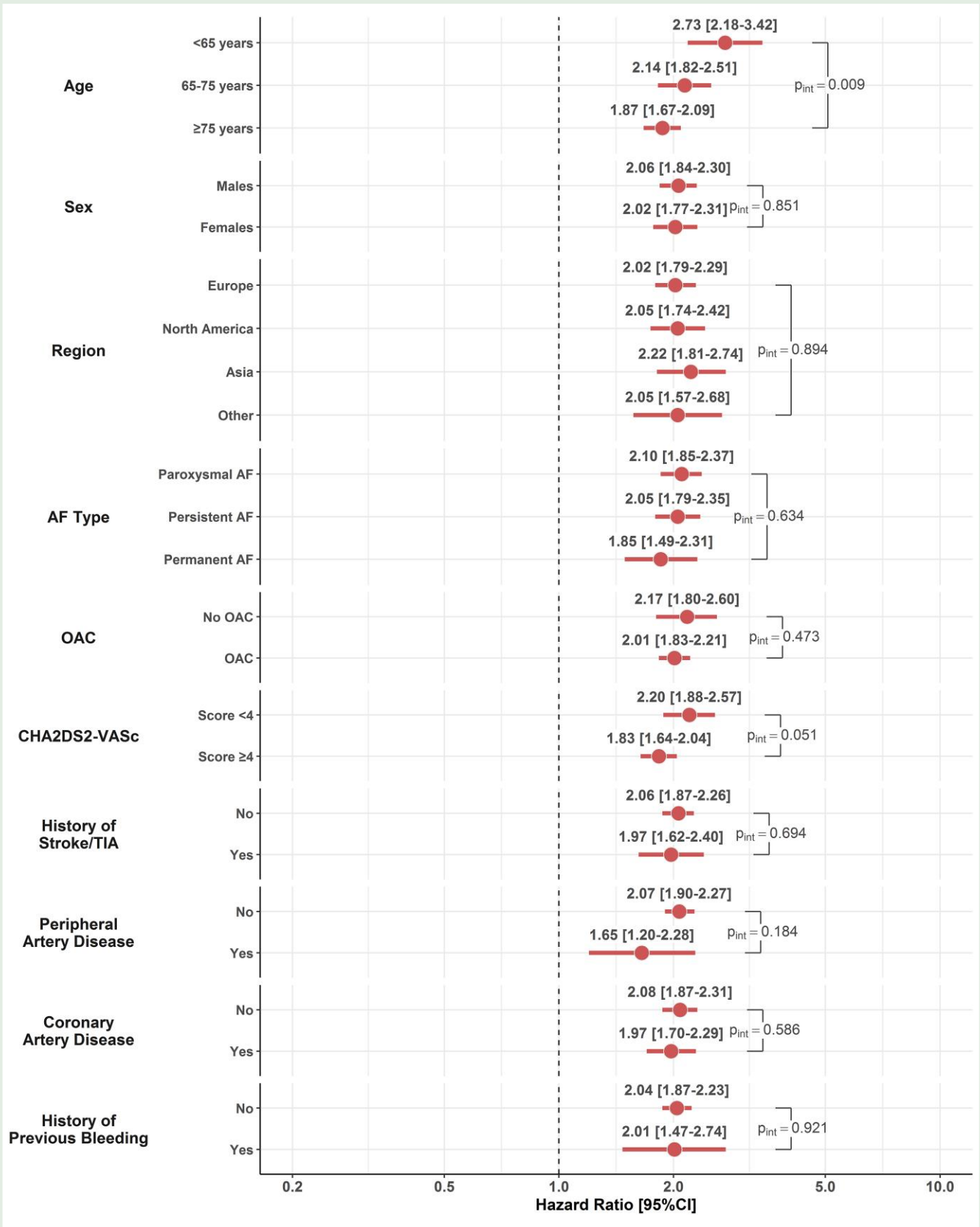

Figure 3 Interaction of congestive heart failure and clinical characteristics on the risk of the primary composite outcome. AF, atrial fibrillation; CI, confidence interval; OAC, oral anticoagulant; P_{int}, *P* for interaction; TIA, transient ischaemic attack.

Despite the well-known association of AF and CHF, epidemiological estimates on the actual prevalence of CHF in patients with AF are still uncertain. Our analysis showed that approximately one out of five patients with AF present with CHF; of those with data on LVEF available (86.4%), 54.3% had a LVEF > 40%. Our figures appear in line with previous estimates found in global registries of patients with recent diagnosis of AF, such as the GARFIELD-AF (which found a prevalence of HF of 22.6% at enrolment).[19] Notably, prevalence of HF varies across geographical regions: data from European cohorts, such as the EORP-AF Pilot and Long-Term registries, pointed out higher prevalences of HF in patients with AF (47.5 and 36.5%, respectively)[20,21]; similarly, higher prevalences of HF were found in a recent population study of more than 4 million US residents, with up to 46% of AF patients aged ≥65 years reported to have HF.[22] Consistently, we observed significant regional variation in our cohort, with lower odds of presenting with HF in patients recruited in Asia and higher odds when recruited in North America, compared with Europe. These results suggest that ethnic and geographical differences should be taken into account when considering the epidemiology of the AF–HF relationship and underline the importance of studying the AF–HF relationship in cohort with diversity and a global outlook.

We also found that presence of CHF at baseline was associated with more sustained form of AF (with 13% of patients with CHF presenting with permanent AF and 45% with persistent AF); this may reflect a more advanced stage of the arrhythmia, consistent with the detrimental and bidirectional effect of HF on the trajectory of AF.[12] Patients with CHF also had a higher burden of AF symptoms (as assessed by EHRA score) and a specific clinical phenotype, which was also influenced by LVEF. Specifically, CHF with LVEF > 40% was more common in elderly and females and in patients with arterial hypertension, diabetes mellitus, and other non-CV comorbidities (such as chronic obstructive pulmonary disease). On the other side, we found that a history of CAD was consistently associated with CHF (irrespective of LVEF), while a history of stroke/TIA was less common in patients with AF and CHF. These results reflect the pathogenesis and determinants of CHF[23] and suggest that in patients with AF and CHF, the combination of comorbidities is likely to have a critical role in influencing the phenotype of CHF and its clinical manifestation. Of note, the observation of a lower prevalence of previous stroke/TIA in patients with CHF may be explained by the inclusion criteria of the GLORIA-AF Registry (which require a recent diagnosis of AF and CHA_2DS_2-VASc ≥ 1 for inclusion). In the context of pre-existing CHF, the onset of AF may cause more symptoms and may lead to earlier diagnosis of AF and therefore a lower temporal exposure to stroke risk. Of note, our findings are in line with those observed in the GARFIELD-AF Registry, which included patients with newly diagnosed AF, and found lower prevalence of previous stroke/TIA in patients with HF (10.9% vs. 11.6%).[19] Similar considerations may apply to the heterogeneous association that we found between hypertension and CHF at baseline, which suggest that in our cohort, other CV risk factors could have a greater role in determining the presence of CHF—particularly CHF with LVEF ≤ 40%. Notwithstanding these caveats, our results highlight the complexity of patients with AF and CHF, who had more sustained form of AF, more symptoms, and an undebated more complex clinical risk phenotype.

The complexity of the AF–HF interplay is also reflected by the differences observed in the management of these patients, which underline the profound impact exerted by CHF on treatment choices in clinical practice. Indeed, we found that patients with CHF and LVEF ≤ 40% (but not those with LVEF >40%) were more likely to receive OAC, compared with patients without CHF; on the other side, CHF (irrespective of LVEF) was associated with a higher use of VKA, compared with NOAC, in anticoagulated patients. These results may reflect the evolving practices in the use of OAC during the study period, when there could be residual uncertainties on the benefits of NOAC vs. VKA in patients with CHF, and despite subsequent evidence reaffirming their risk/benefit profile in patients with AF and HF.[24]

Our findings corroborate previous studies conducted in the same years, which showed a higher use of VKA in patients with HF. For example, in a Canadian population-based study on more than 60.000 patients with a first diagnosis of AF from 2011 to 2014, those with CHF were less likely to initiate a NOAC compared with VKA (adjusted OR: 0.76, 95% CI: 0.70–0.82)[25]; similar results were found in a cohort study conducted in Netherlands from 2008 to 2017[26] and in other observational studies.[27] Consistently, the presence of CHF influenced use of other CV drugs, with highest odds of receiving beta-blockers, ACE inhibitors/ARB, diuretics and digoxin, and heterogeneous influence on other antiarrhythmic drugs. These results largely reflect current practices and guideline recommendations in patients with HF[28] and confirm that contemporary presence of CHF complicates management of AF. Of note, patients with CHF (irrespective of LVEF) were more likely to have undergone ablation or cardioversion, reflecting both the higher symptom burden of these patients, and the expected benefit of interventional procedures and rhythm control in patients with AF and HF.[29–31]

We finally observed an increased risk of the primary composite and all secondary exploratory outcomes in patients with CHF and AF, with approximately two-fold higher hazard of death and MACE and 30% higher hazard of thromboembolism and major bleeding. Interestingly, the risk of thromboembolism was increased in patients with CHF and LVEF > 40%, but not in those with reduced LVEF, while for the other outcomes, the relative increase was higher in magnitude in patients with CHF and LVEF ≤ 40%, similarly to other reports.[32–34] These results should be interpreted with caution, and in view of the higher use of OAC in patients with CHF and LVEF ≤ 40%, despite the adjustment made for OAC use in the multivariable regression. Indeed, these results suggest that even patients with CHF and LVEF > 40% have an increased risk of thromboembolic events, which need to be carefully evaluated and managed, to reduce the associated morbidity and mortality. Notably, we observed that CHF had a detrimental effect on the risk of the primary outcome across all subgroups of patients investigated, although with evidence of a greater relative effect in patients with lower baseline risks (such as younger patients and those with CHA_2DS_2-VASc < 4).

Taken together, these results underline the complex clinical risk profile of patients with AF and CHF. The higher risk observed in all subgroups confirms that CHF is a strong determinant of prognosis in patients with AF. Such complexity requires dedicated and multidisciplinary efforts to modify the disease trajectory,[12] even beyond anticoagulation. Indeed, previous studies showed how comprehensive approaches (encompassing optimal medical therapy for HF and an integrated management of AF) are able to improve prognosis in these patients.[21] Specifically, the Atrial fibrillation Better Care pathway was proposed to streamline an integrated approach to the management of AF along three pillars: avoid stroke through anticoagulation, better symptoms control, and management of comorbidities and CV risk factors[35,36]; such approach has been proven effective in improving prognosis of patients with AF in randomized trials[37,38] and also in the specific subgroup of patients with AF and HF.[21,39–41]

Within such framework, optimization of thromboembolic risk prevention and guideline-directed medical therapy for HF, appropriate decisions on rhythm vs. rate control (also considering the benefits of rhythm control on symptoms and prognosis in patients with

HF[29–31]), and active management of the complexity arising from CV and non-CV comorbidities appear as appropriate steps to undertake for improving prognosis of patients with AF and CHF.

Strengths and limitations

Our analysis is based on a large, global, and diverse cohort of patients with AF and provides outlook on the real-world epidemiology and management of AF and CHF; the large sample size and global representation of our cohort also increase the external validity and robustness of our estimates.

Nonetheless, we acknowledge some limitations. First, we had limited data on LVEF, which was also only available as a dichotomous variable (≤40% vs. >40%) and was missing for ∼14% of patients with CHF included, thus limiting our ability to further characterize CHF in this cohort. This is particularly in relation to distinguishing patients with HF and mid-range ejection fraction vs. patients with HF and preserved ejection fraction. Moreover, we cannot exclude that some misclassification could have occurred, particularly in patients with LVEF close to 40% at the time of the enrolment and that this could have contributed to our results observed. Also, no data on specific or reversible aetiology (e.g. tachycardia-induced cardiomyopathy) were available, and it was not possible to further characterize the cohort of patients with CHF. Second, treatment practices and recommendations have evolved over years, particularly for HF,[28] and the availability of newer drugs (which were not available during the GLORIA-AF study period) has likely changed the landscape. Therefore, it might be possible that more recent cohorts of patients with AF or CHF may demonstrate different associations; also, we did not analyse whether the attainments of treatment targets for other comorbidities and risk factors (e.g. arterial hypertension) modified the risk of major outcomes associated with CHF, and further studies are required to explore this. Third, the inclusion and exclusion criteria of the GLORIA-AF Registry, by enrolling patients with AF and at least one additional stroke risk factor, could have influenced some of the results that we observed (including the association with specific comorbidities and risk factors and the use of OAC), as explained before. Finally, although we adjusted our analysis for the most important factors that influence prognosis in patients with AF, we cannot exclude the contribution of unaccounted confounders, and therefore our results should be interpreted with caution.

Conclusion

Congestive heart failure is found in approximately one out of five patients with recent diagnosis of AF. Patients with CHF exhibit a specific clinical phenotype, which varies according to LVEF. Furthermore, the presence of CHF also influences management and has detrimental effects on prognosis of patients with AF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

B.C., G.F.R., and G.Y.H.L. conceived the study; B.C. and G.F.R. run the analyses, interpreted the results, and drafted the first version of the manuscript; M.P., G.B., B.O., M.V.H., and G.Y.H.L. reviewed the manuscript and provided important intellectual contributions. All authors approved the final version of the manuscript.

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Data availability

Data supporting this study were contributed by the data contributors from Boehringer Ingelheim and are available through Vivli, Inc. Access was provided after a proposal was approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement.

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