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Impact of heart failure on the clinical profile and outcomes in patients with atrial fibrillation treated with rivaroxaban. Data from the EMIR study

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Abstract

Background: *The aim of this study was to analyze the impact of the presence of heart failure (HF) on the clinical profile and outcomes in patients with atrial fibrillation (AF) anticoagulated with rivaroxaban.*

Methods: *Observational and non-interventional study that included AF adults recruited from 79 Spanish centers, anticoagulated with rivaroxaban ≥ 6 months before inclusion. Data were analyzed according to baseline HF status.*

Results: *Out of 1,433 patients, 326 (22.7%) had HF at baseline. Compared to patients without HF, HF patients were older (75.3 ± 9.9 vs. 73.8 ± 9.6 years; p = 0.01), had more diabetes (36.5% vs. 24.3%; p < 0.01), coronary artery disease (28.2% vs. 12.9%; p < 0.01), renal insufficiency (31.7% vs. 22.6%;*

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p = 0.01), higher CHA_2DS_2-VASc (4.5 ± 1.6 vs. 3.2 ± 1.4; p < 0.01) and HAS-BLED (1.8 ± 1.1 vs. 1.5 ± 1.0; p < 0.01). After a median follow-up of 2.5 years, among HF patients, annual rates of stroke/ /systemic embolism/transient ischemic attack, major adverse cardiovascular events (MACE) (non-fatal myocardial infarction, revascularization and cardiovascular death), cardiovascular death, and major bleeding were 1.2%, 3.0%, 2.0%, and 1.4%, respectively. Compared to those patients without HF, HF patients had greater annual rates of MACE (3.0% vs. 0.5%; p < 0.01) and cardiovascular death (2.0% vs. 0.2%; p < 0.01), without significant differences regarding other outcomes, including thromboembolic or bleeding events. Previous HF was an independent predictor of MACE (odds ratio 3.4; 95% confidence interval 1.6–7.3; p = 0.002) but not for thromboembolic events or major bleeding.

Conclusions: *Among AF patients anticoagulated with rivaroxaban, HF patients had a worse clinical profile and a higher MACE risk and cardiovascular mortality. HF was independently associated with the development of MACE, but not with thromboembolic events or major bleeding.* (Cardiol J 2022; 29, 6: 936–947)

Key words: atrial fibrillation, bleeding, EMIR, heart failure, MACE, rivaroxaban, stroke

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults worldwide, and it is expected to increase, mainly due to the extended longevity in the overall population as well as the increasing burden of other comorbidities such as hypertension, diabetes, or heart failure (HF) [1–3]. Despite anticoagulation markedly decreasing the risk of stroke, patients remain at risk of cardiovascular disease, including coronary artery disease, HF and cardiovascular death [4, 5].

Heart failure and AF are two common conditions that frequently coexist. In fact, the presence of one entity may precipitate/exacerbate the other [5–7]. Remarkably, the increased risk of AF occurs in both, HF with reduced left ventricular ejection fraction (LVEF) (HFrEF) and HF with preserved LVEF (HFpEF) [8]. This is not surprising, as AF and HF share common risk factors and comorbidities. In addition, dilatation of left atrium, left atrial and ventricular fibrosis, chronic inflammation, neurohormonal hyperactivation, and electrophysiologic remodeling also play a relevant role [9, 10]. The concomitance of both conditions translates into higher morbidity and mortality rates, including a greater risk of thromboembolic events, and consequently, anticoagulation is recommended [6, 11–13]. Although a number of studies have analyzed the impact of HF on patients with AF taking vitamin K antagonists, the information currently available among patients treated with direct oral anticoagulants, particularly in clinical practice remains scarce [14–18].

In ROCKET-AF, rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolic events and significantly reduced intracranial hemorrhage in patients with AF at high thromboembolic risk [19]. In a specific analysis of the ROCKET-AF trial, the relative efficacy and safety of rivaroxaban versus warfarin was independent of HF status [20]. However, data about the role of rivaroxaban among patients with HF and AF in clinical practice are warranted [21].

The EMIR (Estudio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares mayores en pacientes con fibrilación auricular no valvular tratados con un anticoagulante oral directo [Rivaroxaban] ["Observational study to identify risk factors associated with major cardiovascular events in patients with nonvalvular atrial fibrillation treated with a direct oral anticoagulant [rivaroxaban]") study [22, 23] was aimed to evaluate the performance of the cardiovascular risk 2MACE score in AF patients treated with rivaroxaban. In this study, the impact of the presence of HF at baseline on the clinical profile and outcomes in AF patients anticoagulated with rivaroxaban was analyzed.

Methods

The design and methods of the EMIR study have been extensively described in previous publications [22, 23]. Briefly, EMIR was a non-interventional and observational study that included patients 18 years or older, with an established diagnosis of AF (either paroxysmal, persistent or permanent), anticoagulated with rivaroxaban according to clinical practice ≥ 6 months before being enrolled and they provided written informed consent. Patients were recruited from 79 Spanish

centers (hospitals and private clinics). By contrast, patients with prosthetic heart valves, any severe valvopathy, severe cognitive impairment, chronic infections or systemic autoimmune diseases, active cancer or severe liver insufficiency were excluded from the study. The study was approved by each participating Institutional Review Board.

Patients were followed-up during 2.5 years with 4 visits (baseline, 12 months, 24 months, and study end) that should coincide with any of the patients' routine visits for HF management. No additional visits, laboratory tests, other diagnostic tests or treatments were specifically performed or prescribed for being included in the EMIR study. All data were recorded using an electronic case report form specifically created for the EMIR study.

At baseline, biodemographic data (age, sex, permanent AF, body mass index), risk stratification (CHA_2DS_2-VASc, HAS-BLED, and 2MACE score), cardiovascular risk factors (hypertension, diabetes), vascular disease (previous coronary artery disease, prior cerebrovascular disease, peripheral artery disease) and renal insufficiency were recorded. Data were collected from the clinical history of the patients and during the interview with the patient during the patients' routine visit. The presence of HF was considered when it was reflected in the clinical history of the patient. Data were analyzed according to the presence of previous HF and the HF subtypes. HFrEF was defined as HF with a LVEF < 40%, HF with mildly reduced LVEF (HFmrEF) as HF with LVEF 40 – < 50% and HFpEF as HF with LVEF ≥ 50%. Renal insufficiency was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 by the MDRD-4 formula.

Events (major adverse cardiovascular events [MACE], thromboembolic events, myocardial infarction [MI], revascularization, cardiovascular death, death from any cause and major bleeding) during the study were evaluated. MACE events were defined as a combination of non-fatal MI, revascularization and cardiovascular death (death for coronary events, progressive HF death and sudden cardiac death). Thromboembolic events included stroke, systemic embolism and transient ischemic attack. Major bleedings were defined following the International Society of Thrombosis and Hemostasis definition [24]. The information source was in all cases the medical record and the patient. The investigator collected the study data from medical records or from personal interviews performed during the study follow-up. Before the present study started at the sites, all investigators were sufficiently trained on the background and objectives of the study. All outcome variables and covariates were recorded in a standardized electronic case report form. Medical review of the data was performed according to the medical review plan. A scientific committee independently evaluated and classified the events. Events were analyzed according to HF status and the HF subtypes. In addition, predictors of MACE, ischemic stroke and major bleeding in the EMIR population were analyzed.

Statement of ethics

This study protocol was reviewed and approved firstly by CAEIG (Comité Autonómico de Etica de Galicia) on July 14th, 2016, approval number 2016/348.

Patients were recruited from 79 Spanish centers (hospitals and private clinics). The study was approved by each participating Institutional Review Board.

Patients provided written informed consent.

Statistical methods

Qualitative variables were presented as absolute and relative frequencies and quantitative variables were described with measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range). Qualitative variables were compared using the χ^2 test or the Fisher exact test, as required. When 2 means were compared, the t test or the Mann-Whitney test was used, when appropriate and 3 means (HF subtypes) by the Kruskal-Wallis test. Annual event rates were calculated. To assess predictors of MACE, thromboembolic events and major bleeding (dependent variables), multivariate analyzes were performed. The multivariate models began to be constructed by introducing those factors with a significance of $p < 0.15$ in the bivariates by the automatic variable selection method by steps forward and backward. Only the significant factors ($p < 0.05$) were finally considered to build the model. Odd ratios (OR) along with the 95% confidence interval (CI) were calculated. The following independent variables were considered: age (continuous variable), sex (female vs. male), body mass index (continuous variable), previous bleeding, diabetes, permanent AF, ischemic heart disease, coronary revascularization, antiplatelet agents, previous cerebrovascular disease, dependence level (dependent vs. autonomous), hypertension, hyperlipidemia, smoking, pulmonary disease, renal insufficiency, liver dysfunction, cancer, peripheral

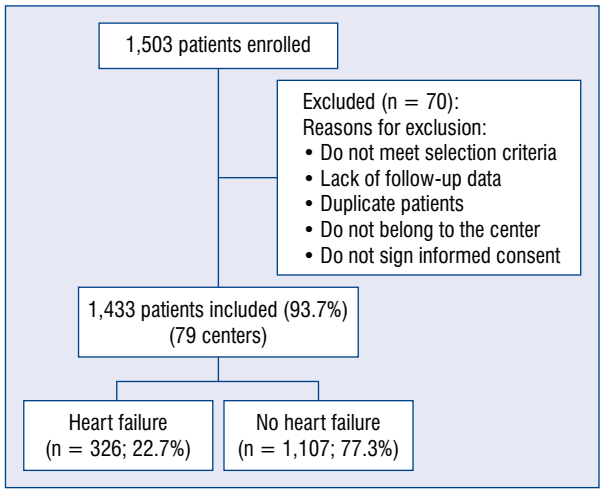

Figure 1. Flow chart of the study population.

artery disease, alcohol use, non-severe dementia, HF, CHA_2DS_2-VASc (continuous variable), HAS-BLED (continuous variable) and 2MACE ≥ 3. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

A total of 1,503 patients were initially enrolled. After the exclusion of 70 patients, 1,433 (93.7%) patients from 79 Spanish centers, were included for the final analysis, of whom 326 (22.7%) had HF at baseline (Fig. 1).

The baseline clinical characteristics of the overall study population and according to HF status are presented in Table 1A. Overall, mean age was 74.2 ± 9.7 years, 55.5% of patients were men, 37.5% had permanent AF, mean CHA_2DS_2-VASc score was 3.5 ± 1.5, mean HAS-BLED was 1.6 ± 1.0 and 26.9% had a 2MACE score ≥ 3. In addition, 79.3% of patients had hypertension, 27.1% diabetes, 28.3% vascular disease, 24.7% renal insufficiency (defined by MDRD-4 < 60 mL/min/1.73 m^2), 16.4% ischemic heart disease and 12.5% prior cerebrovascular disease.

Among patients with HF (n = 326), 94 had HFrEF, 59 HFmrEF and 173 HFpEF. In patients with HF, mean LVEF was 48.0 ± 14.3%. Baseline clinical characteristics were analyzed according to HF status (Table 1A). Compared to patients without HF, patients with HF were older (75.3 ± 9.9 vs. 73.8 ± 9.6 years; p = 0.01), had more diabetes (36.5% vs. 24.3%; p < 0.01), permanent AF (50.9% vs. 33.3%; p < 0.01), previous coronary artery disease (28.2% vs. 12.9%; p < 0.01), renal insufficiency (MDRD-4: 31.7% vs. 22.6%; p = 0.001), as well as higher CHA_2DS_2-VASc score (4.5 ± 1.6 vs. 3.2 ± 1.4; p < 0.01), HAS-BLED score (1.8 ± ± 1.1 vs. 1.5 ± 1.0; p < 0.01) and more patients had a 2MACE score ≥ 3 (46.0% vs. 21.2%; p < 0.01). With regard to the baseline clinical characteristics according to HF subtype, patients with HFpEF were older, more commonly women, had a higher CHA_2DS_2-VASc score and more hypertension. By contrast, patients with HFrEF were more commonly men, had a higher 2MACE score ≥ 3 and more previous MI (Table 1B).

The mean follow-up was 2.2 ± 0.6 years (median 2.5 years, interquartile range 2.2–2.6 years). The annual rates of relevant events were calculated over 1,425 patients (323 out of 326 patients with HF and 1,102 out of 1,107 patients without HF) (Table 2A). Overall, 87 (6.1%) patients died during the study period, of whom 20 (1.4%) had a cardiovascular origin, where 13 (0.9%) were due to progressive chronic HF. As a result, 70.0% of cardiovascular deaths were caused by progressive HF. Among patients with baseline HF, annual rates of (stroke + systemic embolism + transient ischemic attack), MACE, cardiovascular death, death from any cause and major bleeding were 1.2%, 3.0%, 2.0%, 5.5% and 1.4%, respectively. Compared to those patients without HF at baseline, those patients with HF had greater annual rates of MACE (3.0% vs. 0.5%; p < 0.01), cardiovascular death (2.0% vs. 0.2%; p < 0.01) and death from any cause (5.5% vs. 2.0%; p < 0.01), without significant differences regarding other outcomes, including thromboembolic or bleeding events. With regard to events during the follow-up according to HF subtype, patients with HFpEF had more thromboembolic events and patients with HFrEF more MACE, MI and cardiovascular death (Table 2B).

A multivariate logistic regression analysis was performed to study the potential predictors of MACE events, thromboembolic events and major bleeding (Table 3). The presence of ischemic heart disease, renal insufficiency and HF were independent predictive factors associated to MACE in the global population. Type of AF did not have an impact on MACE risk (p = 0.662). On the other hand, the use of antiplatelet agents, non-severe dementia and CHA_2DS_2-VASc score were independently associated with the development of thromboembolic events and a score 2MACE ≥ 3, dependency and HAS-BLED score with major bleeding. The main results of the study are presented in Figure 2.

Table 1A. Clinical characteristics of the study population at baseline according to heart failure (HF) status.

	Total population (n = 1,433; 100%)	HF population (n = 326; 22.7%)	No HF population (n = 1,107;77.3%)	P
Biodemographic data				
Age [years]	74.2 ± 9.7	75.3 ± 9.9	73.8 ± 9.6	0.01
≥ 75 years	691 (48.2%)	173 (53.1%)	518 (46.8%)	0.05
Sex (men)	795 (55.5%)	193 (59.2%)	602 (54.4%)	0.12
Permanent atrial fibrillation	535 (37.5%)	166 (50.9%)	369 (33.3%)	< 0.01
Body mass index [kg/m^2]	29.1 ± 4.9	29.8 ± 5.3	28.9 ± 4.8	0.03
Risk stratification				
CHA_2DS_2-VASc score	3.5 ± 1.5	4.5 ± 1.6	3.2 ± 1.4	< 0.01
2MACE score ≥ 3	385 (26.9%)	150 (46.0%)	235 (21.2%)	< 0.01
HAS-BLED score	1.6 ± 1.0	1.8 ± 1.1	1.5 ± 1.0	< 0.01
Cardiovascular risk factors				
Hypertension	1,137 (79.3%)	261 (80.1%)	876 (79.1%)	0.72
Diabetes	388 (27.1%)	119 (36.5%)	269 (24.3%)	< 0.01
Vascular disease				
Vascular disease	406 (28.3%)	127 (39.0%)	279 (25.2%)	< 0.01
Previous coronary disease	235 (16.4%)	92 (28.2%)	143 (12.9%)	< 0.01
Prior cerebrovascular disease	179 (12.5%)	42 (12.9%)	137(12.4%)	0.81
Peripheral artery disease and/or aortic plaque	96 (6.7%)	33 (10.1%)	63 (5.7%)	0.005
Peripheral artery disease	58 (4.0%)	22 (6.7%)	36 (3.3%)	0.005
Other conditions/comorbidities				
Renal insufficiency (MDRD-4: < 60 mL/min/1.73 m^2)	350 (24.7%)	103 (31.7%)	247 (22.6%)	0.01
Renal insufficiency (Cockcroft-Gault: < 60 mL/min/1.73 m^2)	498 (35.1%)	133 (40.8%)	365 (33.0%)	0.01

Discussion

The present study showed that in a wide sample of real-life patients with AF anticoagulated with rivaroxaban compared to those patients without HF at baseline, individuals with previous HF have a worse clinical profile and a higher risk of MACE (cardiac mortality, coronary revascularization, non-fatal MI) and cardiovascular mortality. In addition, the history of HF is independently associated with the development of MACE, but not with stroke or major bleeding. Despite that, rates of MACE and death remained low in HF patients, indicating that anticoagulation with rivaroxaban may be a good choice in this population. This information is relevant, as although previous studies have analyzed the impact of HF on outcomes in anticoagulated AF patients, very scarce information is available in those patients taken rivaroxaban [21].

In the EMIR study, nearly 23% of AF patients presented with HF at baseline. This is in line with previous studies performed in Spain that have shown that the concomitance of both conditions is very common in clinical practice. Thus, in the PAULA study, that included AF patients treated in a primary care setting and anticoagulated with vitamin K antagonists, approximately 24% of patients had HF [25]. More recently, in the FANTASIIA study that included AF patients in a specialized cardiology setting and anticoagulated with direct oral anticoagulants or vitamin K antagonists, nearly 30% of patients also had HF [26]. In the international GLORIA-AF registry, in which AF patients anticoagulated with a direct oral anticoagulant were enrolled, 24% of patients had HF at baseline [27]. Conversely, different studies have shown that approximately one third of patients with HF also have AF [28, 29]. As each entity enhances the development of the other one [5, 6], an active search should be promoted to rule out the concomitance of both conditions [1].

In the current study, more patients had HFpEF than HFrEF or HFmrEF. Although some authors

Table 1B. Clinical characteristics of the study population at baseline according to heart failure (HF) subtype.

	HFpEF	HFmrEF	HFrEF	P
Biodemographic data				
N	173	59	94	
Proportion in the overall population	12.1%	4.1%	6.6%	–
Proportion in the HF population	53.1%	18.1%	28.8%	
Age [years]	77.5 ± 9.3	73.3 ± 9.8	72.6 ± 10.2	< 0.001
≥ 75 years	111 (64.2%)	23 (39.0%)	39 (41.5%)	< 0.001
Sex (men)	79 (45.7%)	42 (71.2%)	72 (76.6%)	< 0.001
Permanent atrial fibrillation	79 (45.7%)	30 (50.8%)	51 (54.3%)	0.39
Body mass index [kg/m^2]	30.6 ± 5.5	29.0 ± 5.3	28.8 ± 4.7	0.016
Risk stratification				
CHA_2DS_2-VASc score	4.9 ± 1.4	4.0 ± 1.5	4.2 ± 1.8	< 0.001
2MACE score ≥ 3	71 (41.0%)	21 (35.6%)	58 (61.7%)	0.001
HAS-BLED score	1.9±1.0	1.7±1.1	1.6±1.2	0.15
Cardiovascular risk factors				
Arterial hypertension	149 (86.1%)	45 (76.3%)	67 (71.3%)	0.011
Diabetes	65 (37.6%)	21 (35.6%)	33 (35.1%)	0.91
Vascular disease				
Vascular disease	59 (34.1%)	24 (40.7%)	44 (46.8%)	0.12
Previous coronary disease	39 (22.5%)	20 (33.9%)	33 (35.1%)	0.053
Previous myocardial infarction	12 (6.9%)	10 (16.9%)	25 (26.6%)	< 0.001
Previous cerebrovascular disease	23 (13.3%)	5 (8.5%)	14 (14.9%)	0.50
Peripheral artery disease and/or aortic plaque	17 (9.8%)	8 (13.6%)	8 (8.5%)	0.59
Peripheral artery disease	9 (5.2%)	7 (11.9%)	6 (6.4%)	0.21
Other conditions/comorbidities				
Renal insufficiency (MDRD-4: < 60 mL/min/1.73 m^2)	51 (29.5%)	19 (32.2%)	33 (35.5%)	0.60
Renal insufficiency (Cockcroft-Gault: < 60 mL/min/1.73 m^2)	70 (40.5%)	24 (40.7%)	39 (41.9%)	0.97

HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction

have not shown significant differences in the strength of an association between AF and the type of HF [8], other authors have reported that among HF patients, AF is progressively more common with increasing LVEF [28, 30, 31]. Despite previous studies showing that HFpEF accounts for at least half of the cases of HF, it is very likely that due to the ageing of the population, this proportion will increase in the following years, as well as the number of patients with AF and HF concomitantly [32, 33]. Remarkably, the present study showed that there were relevant differences in the clinical profile of patients according to HF subtype, particularly related with age, sex and some comorbidities. These differences are in line with previous studies of HF population [34, 35].

Compared to patients without HF, patients with HF had a worse clinical profile, with more risk factors, and comorbidities, as well as a greater thromboembolic and bleeding risk. This high-risk profile in patients with HF has also been observed in previous studies [29]. As a result, to reduce the disease burden in this population, all patients with HF and AF should receive in addition to anticoagulation, guideline-adherent HF therapy [36].

Remarkably, different studies have shown that the superiority of direct oral anticoagulants over vitamin K antagonists remain in patients

Table 2A. Events during the follow-up according to heart failure (HF) status.

	Total	HF (n = 326)	No HF (n = 1,107)	P
Stroke + SE + TIA:				
Number patients (%)	23 (1.6)	8 (2.5)	15 (1.4)	0.17
Annual rate events (%)*	0.7	1.2	0.6	0.22
Major bleeding:				
Number patients (%)	29 (2.0)	8 (2.5)	21 (1.9)	0.53
Annual rate events (%)*	1.0	1.4	0.9	0.33
MACE:				
Number patients (%)	30 (2.1)	17 (5.2)	13 (1.2)	< 0.01
Annual rate events (%)*	1.1	3.0	0.5	< 0.01
Myocardial infarction:				
Number patients (%)	5 (0.3)	3 (0.9)	2 (0.2)	0.08
Annual rate events (%)*	0.2	0.4	0.1	0.15
Revascularization:				
Number patients (%)	9 (0.6)	4 (1.2)	5 (0.5)	0.13
Annual rate events (%)*	0.3	0.6	0.2	0.22
Cardiovascular death:				
Number patients (%)	20 (1.4)	13 (4.0)	7 (0.6)	< 0.01
Annual rate events (%)*	0.6	2.0	0.2	< 0.01
Death from any cause:				
Number patients (%)	87 (6.1)	38 (11.7)	49 (4.4)	< 0.01
Annual rate events (%)*	2.7	5.5	2.0	< 0.01

*Event/100 patients/year; MACE — major adverse cardiovascular event; SE — systemic embolism; TIA — transient ischemic attack

with HF, in both, clinical trials and real-life studies [16–18]. In addition, it is more difficult to attain an adequate time in therapeutic range among patients taking vitamin K antagonists in patients with HF, leading to a lower protection [15]. In the current study, all patients were taking rivaroxaban. After a median follow-up of 2.5 years, among patients with previous HF, annual rates of thromboembolic events, cardiovascular death, death from any cause and major bleeding were 1.2%, 2.0%, 5.5%, and 1.4%, respectively. In the rivaroxaban arm of the ROCKET-AF trial, these numbers were 1.9%, 3.4%, 5.1%, and 14.2% for major or nonmajor clinically relevant bleeding, respectively [20]. A retrospective study performed in the United States that analyzed patients with HF and AF taking rivaroxaban between 2011 and 2016 showed that after a median follow-up of 1.4 years, rates of stroke or systemic embolism, ischemic stroke, major bleeding and intracranial hemorrhage were 1.0, 0.7, 3.9, and 0.3 events per 100 person-years, respectively [21]. As a result, in clinical practice, rates of outcomes in patients with HF and AF seem lower than those reported in the ROCKET-AF trial [20].

Although in non-anticoagulated patients the most devastating consequence related to AF is stroke and its associated complications (death and disability), anticoagulation changes mortality and outcome patterns in AF patients. Thus, in the anticoagulated AF population, most deaths are cardiac-related (cardiovascular death, MI and HF), and only a small proportion are associated with stroke and bleeding [37]. This has also been described in the AF population with HF, including those patients with HF enrolled in the ROCKET-AF trial [18, 20, 38]. Likewise, in the present study, compared to those patients without HF at baseline, those patients with HF had greater annual rates of MACE and cardiovascular death, but with similar rates of thromboembolic and bleeding events. In addition, the multivariate analyzes showed that previous HF was independently associated with the development of MACE, but not with thromboembolic events or major bleeding. Therefore, anticoagulation is not only important in AF patients with HF, but also choosing an oral anticoagulant that effectively reduces MACE events [1]. In this context, experimental and clinical studies have shown that

Table 2B. Events during the follow-up according to heart failure subtype.

	Type of heart failure			P
	HFpEF (n = 173) Annual rate of events (n = 171; accumulated time = 386.81 years)	HFmrEF (n = 59) Annual rate of events (n = 58; accumulated time = 128.29 years)	HFrEF (n = 94) Annual rate of events (n = 94; accumulated time = 179.80 years)	
Stroke + SE + TIA:				
Number patients (%)	8 (4.6)	0	0	0.036
Annual rate events (%)*	2.07	0	0	HFpEF vs. HFrEF: $p < 0.05$
Major bleeding:				
Number patients (%)	6 (3.5)	0	2 (2.1)	0.392
Annual rate events (%)*	1.81	0	1.67	No statistically significant difference
MACE:				< 0.001
Number patients (%)	2 (1.2)	1 (1.7)	14 (14.9)	HFpEF vs. HFrEF: $p < 0.001$
Annual rate events (%)*	0.78	0.78	9.45	HFmrEF vs. HFrEF: $p < 0.001$
Myocardial infarction:				
Number patients (%)	0	0	3 (3.2)	0.029
Annual rate events (%)*	0	0	1.67	HFpEF vs. HFrEF: $p < 0.05$
Revascularization:				
Number patients (%)	1 (0.6)	0	3 (3.2)	0.110
Annual rate events (%)*	0.26	0	1.67	No statistically significant difference
Cardiovascular death:				< 0.001
Number patients (%)	2 (1.2)	1 (1.7)	11 (11.7)	HFpEF vs. HFrEF: $p < 0.001$
Annual rate events (%)*	0.52	0.78	6.12	HFmrEF vs. HFrEF: $p < 0.05$
Death from any cause:				
Number patients (%)	14 (8.1)	6 (10.2)	18 (19.1)	0.025
Annual rate events (%)*	3.62	4.68	10.01	HFpEF vs. HFrEF: $p < 0.05$

*Event/100 patients/year; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; MACE — major adverse cardiovascular event; SE — systemic embolism; TIA — transient ischemic attack

Table 3. Predictors of MACE, ischemic stroke and major bleeding in the EMIR population.

Independent variables	Univariate analyzis			Multivariate analyzis		
	P	OR	95% CI	P	OR	95% CI
Dependent variable "MACE events"						
Antiplatelet agents	< 0.01	13.6	6.3–29.6			
Heart failure	**< 0.01**	**4.7**	**2.2–10.1**	**0.002**	**3.4**	**1.6–7.3**
Coronary revascularization	< 0.01	4.6	2.1–10.1			
Ischemic heart disease	< 0.01	4.6	2.2–9.8	0.002	3.4	1.6–7.3
2MACE ≥ 3	0.002	3.2	1.5–6.9			
Renal insufficiency	0.007	3.0	1.4–6.5	0.02	2.5	1.2–5.5
Peripheral artery disease	0.08	2.9	0.9–10.1			
Diabetes	0.15	1.8	0.8–3.8			
HAS-BLED (continuous variable)	0.02	1.5	1.1–2.1			
CHA_2DS_2-VASC (continuous variable)	0.05	1.3	1.0–1.6			
Sex (female vs. male)	0.02	0.3	0.1–0.8			
Dependent variable "Thromboembolic events"						
Antiplatelet agents	< 0.01	9.2	3.7–22.7	< 0.01	9.0	3.5–23.0
Non-severe dementia	0.002	7.7	2.2–27.5	0.02	5.5	1.3–22.7
2MACE ≥ 3	< 0.01	4.5	1.9–11.1			
Heart failure	**0.002**	**3.8**	**1.6–9.1**			
Previous bleeding	0.12	3.3	0.7–14.5			
Diabetes	0.01	3.0	1.3–7.2			
Previous stroke	0.03	2.8	1.1–7.4			
Coronary revascularization	0.04	2.8	1.1–7.3			
Ischemic heart disease	0.04	2.6	1.0–6.5			
CHA_2DS_2-VASc (continuous variable)	0.002	1.5	1.2–1.9	0.01	1.4	1.1–1.8
Age (continuous variable)	0.15	1.0	1.0–1.1			
Dependent variable "Major bleeding"						
Arterial hypertension	0.049	7.5	1.0–55.0			
Non-severe dementia	0.009	5.3	1.5–18.4			
Previous bleeding	0.003	5.2	1.7–15.6			
Patient autonomy (dependent vs. autonomous)	< 0.01	4.7	2.1–10.7	0.03	2.6	1.1–6.1
2MACE ≥ 3	< 0.01	4.6	2.2–9.9	0.02	2.6	1.1–6.1
Renal insufficiency	< 0.01	4.4	2.1–9.3			
Previous stroke	0.004	3.2	1.4–7.2			
Antiplatelet agents	0.03	3.0	1.1–8.0			
HAS-BLED (continuous variable)	< 0.01	2.2	1.6–3.0	0.01	1.9	1.3–2.7
Coronary revascularization	0.07	2.2	0.9–5.3			
Diabetes	0.08	1.9	0.9–4.1			
Hyperlipidemia	0.14	1.8	0.8–4.1			
CHA_2DS_2-VASc (continuous variable)	< 0.01	1.6	1.3–2.0			
Age (continuous variable)	< 0.01	1.1	1.0–1.1			

CI — confidence interval; MACE — major adverse cardiovascular event; OR — odds ratio

rivaroxaban decreases the progression of ischemic cardiomyopathy, as well as the risk of MI and cardiovascular death [39–42]. Of note, the use of antiplatelet agents was independently associated with the development of thromboembolic events. In the AFIRE trial, rivaroxaban monotherapy was

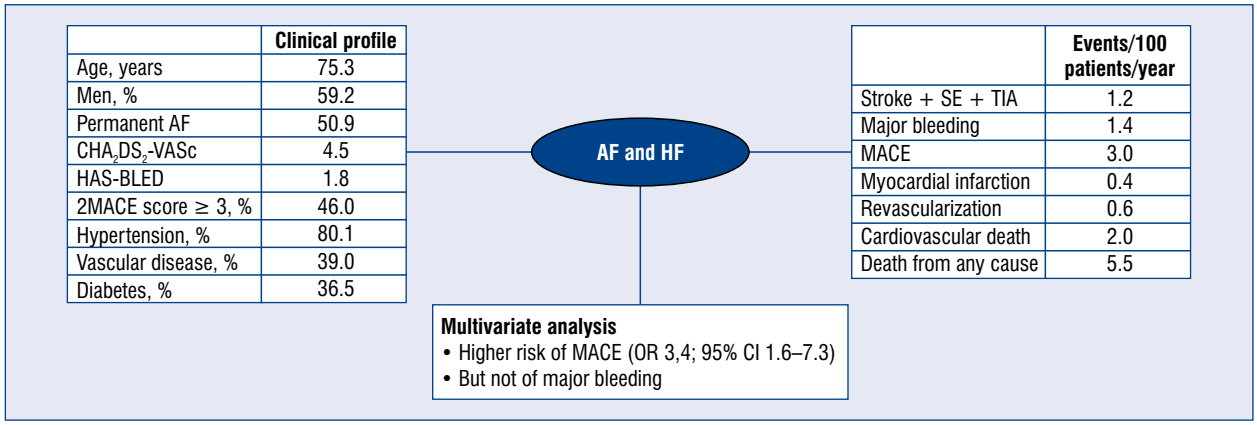

Figure 2. Graphical abstract; AF — atrial fibrillation; CI — confidence interval; HF — heart failure; MACE — major adverse cardiovascular events; OR — odds ratio; SE — systemic embolism; TIA — transient ischemic attack.

noninferior to a combination of rivaroxaban with an antiplatelet agent for thromboembolic events or death, and superior for major bleeding in AF patients with stable coronary artery disease, and this occurred irrespective of their risk for stroke and bleeding [43]. Therefore, all these data indicate that rivaroxaban in monotherapy should be considered in patients with HF and AF, not only to reduce the risk of thromboembolic events, but also the risk of MACE and cardiovascular mortality, leading to a comprehensive management of this population. On the other hand, despite the AMADEUS study, which showed that the risk of cardiovascular death, stroke, or systemic embolism increased among patients with permanent AF (vs. nonpermanent AF), regardless the presence of HF [44], in the present study the type of AF was not associated with an increased risk of outcomes. However, it should be noted that idraparinux and vitamin K antagonists were the anticoagulants used in AMADEUS, compared with rivaroxaban in the study herein. On the other hand, the current study showed that the risk of events varied according to HF subtype (thromboembolic events in HFpEF and MACE, MI and cardiovascular death in HFrEF). Other studies have also shown differences in outcomes according to HF subtype [45]. As a result, these particularities should be taken into account to provide a comprehensive approach in the management of patients with AF and HF.

Limitations of the study

As this was an observational study, no control group was available, and the presence of some confounding factors could not be excluded. However, the high number of patients included, as well as that the recruitment was performed consecutively after office consultation, may reduce possible selection bias. On the other hand, it should be considered that the patients were recruited after at least 6 months under rivaroxaban treatment. Therefore, the results of this study can only be extended to a similar population.

Conclusions

Nearly 1 out of 4 patients with AF anticoagulated with rivaroxaban in clinical practice have HF concomitantly. After a median follow-up of 2.5 years, annual rates of thromboembolic events, MACE, cardiovascular death, and major bleeding in HF population are 1.2%, 3.0%, 2.0%, and 1.4%, respectively. Compared to patients without HF, HF patients are older, have a greater baseline risk profile, and a higher risk of developing MACE and cardiovascular mortality, but not thromboembolic or bleeding events. The management of patients with HF and AF requires a comprehensive approach, with the aim to reduce not only the stroke risk, but also cardiovascular-related complications. In this context, rivaroxaban should be considered as a first-line therapy in the treatment of patients with HF and AF in clinical practice.

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References

1. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
2. Virani SS, Alonso A, Aparicio HJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021; 143(8): e254–e743, doi: 10.1161/CIR.0000000000000950, indexed in Pubmed: 33501848.
3. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013; 34(35): 2746–2751, doi: 10.1093/eurheartj/eht280, indexed in Pubmed: 23900699.
4. Soliman EZ, Lopez F, O'Neal WT, et al. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2015; 131(21): 1843–1850, doi: 10.1161/CIRCULATIONAHA.114.014145, indexed in Pubmed: 25918127.
5. Ziff OJ, Carter PR, McGowan J, et al. The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: Insights from the, United Kingdom ACALM registry. Int J Cardiol. 2018; 252: 117–121, doi: 10.1016/j.ijcard.2017.06.033, indexed in Pubmed: 29249421.
6. Nji MAM, Solomon SD, Chen LY, et al. Association of heart failure subtypes and atrial fibrillation: Data from the Atherosclerosis Risk in Communities (ARIC) study. Int J Cardiol. 2021; 339: 47–53, doi: 10.1016/j.ijcard.2021.07.006, indexed in Pubmed: 34246724.
7. Ferreira JP, Cleland JG, Lam CSP, et al. New-onset atrial fibrillation in patients with worsening heart failure and coronary artery disease: an analysis from the COMMANDER-HF trial. Clin Res Cardiol. 2022; 111(1): 50–59, doi: 10.1007/s00392-021-01891-2, indexed in Pubmed: 34128083.
8. Nicoli CD, O'Neal WT, Levitan EB, et al. Atrial fibrillation and risk of incident heart failure with reduced versus preserved ejection fraction. Heart. 2022; 108(5): 353–359, doi: 10.1136/heartjnl-2021-319122, indexed in Pubmed: 34031160.
9. Taniguchi N, Miyasaka Y, Suwa Y, et al. Heart failure in atrial fibrillation: an update on clinical and echocardiographic implications. Circ J. 2020; 84(8): 1212–1217, doi: 10.1253/circj.CJ-20-0258, indexed in Pubmed: 32641592.
10. Tsigkas G, Apostolos A, Despotopoulos S, et al. Heart failure and atrial fibrillation: new concepts in pathophysiology, management, and future directions. Heart Fail Rev. 2022; 27(4): 1201–1210, doi: 10.1007/s10741-021-10133-6, indexed in Pubmed: 34218400.
11. Zafrir B, Lund LH, Laroche C, et al. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. Eur Heart J. 2018; 39(48): 4277–4284, doi: 10.1093/eurheartj/ehy626, indexed in Pubmed: 30325423.
12. Isnard R, Bauer F, Cohen-Solal A, et al. Non-vitamin K antagonist oral anticoagulants and heart failure. Arch Cardiovasc Dis. 2016; 109(11): 641–650, doi: 10.1016/j.acvd.2016.08.001, indexed in Pubmed: 27836786.
13. Zhao L, Wang WYS, Yang X. Anticoagulation in atrial fibrillation with heart failure. Heart Fail Rev. 2018; 23(4): 563–571, doi: 10.1007/s10741-018-9693-0, indexed in Pubmed: 29569146.
14. Thomas I, EncisoSilva J, Schlueter M, et al. Anticoagulation therapy and NOACs in heart failure. Handb Exp Pharmacol. 2017; 243: 515–535, doi: 10.1007/164_2016_126, indexed in Pubmed: 28233177.
15. Tsigkas G, Apostolos A, Despotopoulos S, et al. Anticoagulation for atrial fibrillation in heart failure patients: balancing between Scylla and Charybdis. J Geriatr Cardiol. 2021; 18(5): 352–361, doi: 10.11909/j.issn.1671-5411.2021.05.006, indexed in Pubmed: 34149824.
16. von Lueder TG, Atar D, Agewall S, et al. All-Cause mortality and cardiovascular outcomes with non-vitamin K oral anticoagulants versus warfarin in patients with heart failure in the food and drug administration adverse event reporting system. Am J Ther. 2019; 26(6): e671–e678, doi: 10.1097/MJT.0000000000000883, indexed in Pubmed: 31145139.
17. Amin A, Garcia Reeves AB, Li X, et al. Effectiveness and safety of oral anticoagulants in older adults with non-valvular atrial fibrillation and heart failure. PLoS One. 2019; 14(3): e0213614, doi: 10.1371/journal.pone.0213614, indexed in Pubmed: 30908512.
18. Savarese G, Giugliano RP, Rosano GMC, et al. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation

and heart failure: a meta-analysis. JACC Heart Fail. 2016; 4(11): 870–880, doi: 10.1016/j.jchf.2016.07.012, indexed in Pubmed: 27614940.
19. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/NEJMoa1009638, indexed in Pubmed: 21830957.
20. van Diepen S, Hellkamp AS, Patel MR, et al. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. Circ Heart Fail. 2013; 6(4): 740–747, doi: 10.1161/CIRCHEARTFAILURE.113.000212, indexed in Pubmed: 23723250.
21. Martinez BK, Bunz TJ, Eriksson D, et al. Effectiveness and safety of rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation and heart failure. ESC Heart Fail. 2019; 6(1): 10–15, doi: 10.1002/ehf2.12365, indexed in Pubmed: 30299591.
22. Fernández M, Marín F, Rafols C, et al. Thromboembolic and bleeding events with rivaroxaban in clinical practice in Spain: impact of inappropriate doses (the EMIR study). J Comp Eff Res. 2021; 10(7): 583–593, doi: 10.2217/cer-2020-0286.
23. Sanmartín Fernández M, Anguita Sánchez M, Arribas F, et al. Outcomes and predictive value of the 2MACE score in patients with atrial fibrillation treated with rivaroxaban in a prospective, multicenter observational study: The EMIR study. Cardiol J. 2022; 29(4): 601–609, doi: 10.5603/CJ.a2022.0044, indexed in Pubmed: 35621092.
24. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3(4): 692–694, doi: 10.1111/j.1538-7836.2005.01204.x, indexed in Pubmed: 15842354.
25. Barrios V, Escobar C, Prieto L, et al. Anticoagulation control in patients with nonvalvular atrial fibrillation attended at primary care centers in spain: the PAULA study. Rev Esp Cardiol (Engl Ed). 2015; 68(9): 769–776, doi: 10.1016/j.rec.2015.04.017, indexed in Pubmed: 26169326.
26. Anguita Sánchez M, Bertomeu Martínez V, Ruiz Ortiz M, et al. Direct oral anticoagulants versus vitamin K antagonists in real-world patients with nonvalvular atrial fibrillation. The FANTASIIA study. Rev Esp Cardiol (Engl Ed). 2020; 73(1): 14–20, doi: 10.1016/j.rec.2019.02.021, indexed in Pubmed: 31160265.
27. Dubner S, Teutsch C, Huisman M, et al. Characteristics and 2-year outcomes of dabigatran treatment in patients with heart failure and atrial fibrillation: GLORIA-AF. ESC Heart Failure. 2020; 7(5): 2679–2689, doi: 10.1002/ehf2.12857.
28. Escobar C, Varela L, Palacios B, et al. Características clínicas, manejo y riesgo de complicaciones a un año en pacientes con insuficiencia cardíaca con y sin diabetes tipo 2 en España. Rev Clin Esp. 2022; 222(4): 195–204, doi: 10.1016/j.rce.2021.04.008.
29. Sicras-Mainar A, Sicras-Navarro A, Palacios B, et al. Epidemiology and treatment of heart failure in Spain: the HF-PATHWAYS study. Rev Esp Cardiol (Engl Ed). 2022; 75(1): 31–38, doi: 10.1016/j.rec.2020.09.033, indexed in Pubmed: 33380382.
30. Sartipy U, Dahlström U, Fu M, et al. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail. 2017; 5(8): 565–574, doi: 10.1016/j.jchf.2017.05.001, indexed in Pubmed: 28711451.
31. Son MiK, Park JJ, Lim NK, et al. Impact of atrial fibrillation in patients with heart failure and reduced, mid-range or preserved ejection fraction. Heart. 2020; 106(15): 1160–1168, doi: 10.1136/heartjnl-2019-316219, indexed in Pubmed: 32341140.
32. Nagueh SF. Heart failure with preserved ejection fraction: insights into diagnosis and pathophysiology. Cardiovasc Res. 2021; 117(4): 999–1014, doi: 10.1093/cvr/cvaa228, indexed in Pubmed: 32717061.
33. Kapłon-Cieślicka A, Kupczyńska K, Dobrowolski P, et al. On the search for the right definition of heart failure with preserved ejection fraction. Cardiol J. 2020; 27(5): 449–468, doi: 10.5603/CJ.a2020.0124, indexed in Pubmed: 32986238.
34. Hamada T, Kubo T, Kawai K, et al. Clinical characteristics and frailty status in heart failure with preserved vs. reduced ejection fraction. ESC Heart Fail. 2022; 9(3): 1853–1863, doi: 10.1002/ehf2.13885, indexed in Pubmed: 35355441.
35. Rywik TM, Doryńska A, Wiśniewska A, et al. Epidemiology and clinical characteristics of hospitalized patients with heart failure with reduced, mildly reduced, and preserved ejection fraction. Pol Arch Intern Med. 2022; 132(5), doi: 10.20452/pamw.16227, indexed in Pubmed: 35253416.
36. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
37. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, et al. Causes of death in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol. 2016; 68(23): 2508–2521, doi: 10.1016/j.jacc.2016.09.944, indexed in Pubmed: 27931607.
38. Chung S, Kim TH, Uhm JS, et al. Stroke and Systemic Embolism and Other Adverse Outcomes of Heart Failure With Preserved and Reduced Ejection Fraction in Patients With Atrial Fibrillation (from the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation [CODE-AF]). Am J Cardiol. 2020; 125(1): 68–75, doi: 10.1016/j.amjcard.2019.09.035, indexed in Pubmed: 31699363.
39. Liu J, Nishida M, Inui H, et al. Rivaroxaban suppresses the progression of ischemic cardiomyopathy in a murine model of diet-induced myocardial infarction. J Atheroscler Thromb. 2019; 26(10): 915–930, doi: 10.5551/jat.48405, indexed in Pubmed: 30867376.
40. Bode MF, Auriemma AC, Grover SP, et al. The factor Xa inhibitor rivaroxaban reduces cardiac dysfunction in a mouse model of myocardial infarction. Thromb Res. 2018; 167: 128–134, doi: 10.1016/j.thromres.2018.05.015, indexed in Pubmed: 29843086.
41. Loffredo L, Perri L, Violi F. Myocardial infarction and atrial fibrillation: different impact of anti-IIa vs anti-Xa new oral anticoagulants: a meta-analysis of the interventional trials. Int J Cardiol. 2015; 178: 8–9, doi: 10.1016/j.ijcard.2014.10.124, indexed in Pubmed: 25464208.
42. Chatterjee S, Sharma A, Uchino K, et al. Rivaroxaban and risk of myocardial infarction: insights from a meta-analysis and trial sequential analysis of randomized clinical trials. Coron Artery Dis. 2013; 24(8): 628–635, doi: 10.1097/MCA.0000000000000031, indexed in Pubmed: 24145765.
43. Akao M, Yasuda S, Kaikita K, et al. Rivaroxaban monotherapy versus combination therapy according to patient risk of stroke and bleeding in atrial fibrillation and stable coronary disease: AFIRE trial subanalysis. Am Heart J. 2021; 236: 59–68, doi: 10.1016/j.ahj.2021.02.021, indexed in Pubmed: 33657403.
44. Senoo K, Lip GYH, Lane DA, et al. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. Stroke. 2015; 46(9): 2523–2528, doi: 10.1161/STROKEAHA.115.009487, indexed in Pubmed: 26205373.
45. Tan C, Dinh D, Brennan A, et al. Characteristics and clinical outcomes in patients with heart failure with preserved ejection fraction compared to heart failure with reduced ejection fraction: insights from the VCOR heart failure snapshot. Heart Lung Circ. 2022; 31(5): 623–628, doi: 10.1016/j.hlc.2021.09.019, indexed in Pubmed: 34742643.