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VICTORIA Study Grp; Ponikowski, Piotr; Alemayehu, Wendimagegn; Oto, Ali; Bahit, M. Cecilia; Noori, Ebrahim; Patel, Mahesh J.; Butler, Javed; Ezekowitz, Justin A.; Hernandez, Adrian F.

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2285

ESC European Society of Cardiology

European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2285

RESEARCH ARTICLE

Vericiguat in patients with atrial fibrillation and heart failure with reduced ejection fraction: insights from the VICTORIA trial

Piotr Ponikowski[1], Wendimagegn Alemayehu[2], Ali Oto[3], M. Cecilia Bahit[4], Ebrahim Noori[5], Mahesh J. Patel[6], Javed Butler[7], Justin A. Ezekowitz[2], Adrian F. Hernandez[8], Carolyn S.P. Lam[9], Christopher M. O'Connor[10], Burkert Pieske[11], Lothar Roessig[12], Adriaan A. Voors[13], Cynthia Westerhout[2], and Paul W. Armstrong[2]*, for the VICTORIA Study Group

[1]Department of Heart Disease, Medical University, Wroclaw, Poland; [2]Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada; [3]Department of Cardiology, Memorial Hospital, Ankara, Turkey; [4]INECO Neurociencias Oroño, Rosario, Argentina; [5]County Hospital Fejér, Szent György Hospital, Székesfehérvár, Hungary; [6]Merck and Co Inc, Kenilworth, NJ, USA; [7]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [8]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [9]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [10]Inova Heart and Vascular Institute, Falls Church, VA, USA; [11]Charité University Medicine, German Heart Center, Berlin, Germany; [12]Bayer AG, Wuppertal, Germany; and [13]University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

Received 9 June 2021; revised 24 June 2021; accepted 25 June 2021

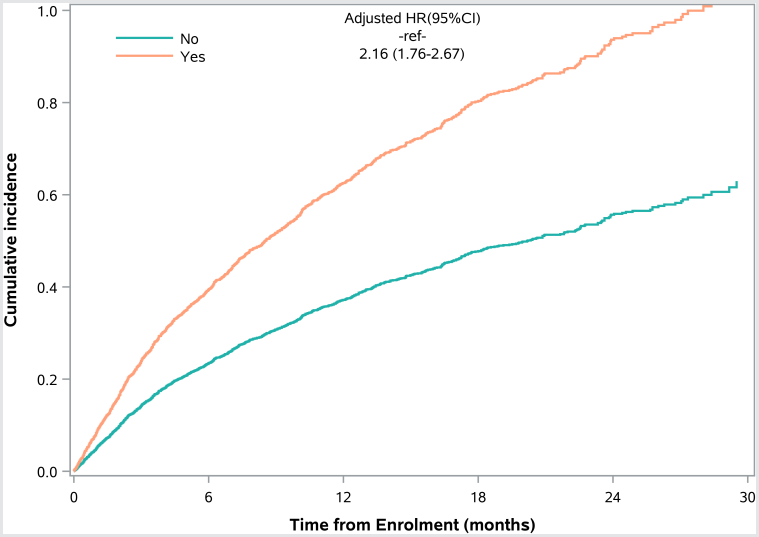
Aims We evaluated the relation between baseline and new-onset atrial fibrillation (AF) and outcomes, and assessed whether vericiguat modified the likelihood of new-onset AF in patients with worsening heart failure (HF) with reduced ejection fraction in VICTORIA.

Methods and results Of 5050 patients randomized, 5010 with recorded AF status at baseline were analysed. Patients were classified into three groups: no known AF (n = 2661, 53%), history of AF alone (n = 992, 20%), and AF on randomization electrocardiogram (n = 1357, 27%). Compared with those with no AF, those with history of AF alone had a higher risk of cardiovascular death [adjusted hazard ratio (HR) 1.21, 95% confidence interval (CI) 1.01–1.47] without excess myocardial infarction or stroke; neither type of AF was associated with a higher risk of the primary composite outcome (time to cardiovascular death or first HF hospitalization), HF hospitalizations, or all cause-death. The beneficial effect of vericiguat on the primary composite outcome and its components was evident irrespective of AF status at baseline. Over a median follow-up of 10.8 months, new-onset AF occurred in 6.1% of those with no AF and 18.3% with history of AF alone ($P < 0.0001$). These events were not influenced by vericiguat treatment (adjusted HR 0.93, 95% CI 0.75–1.16; P = 0.51), but were associated with an increase in the hazard of both primary and secondary outcomes.

Conclusions Atrial fibrillation was present in nearly half of this high-risk population with worsening HF. A history of AF alone at baseline portends an increased risk of cardiovascular death. Neither type of AF affected the beneficial effect of vericiguat. Development of AF post-randomization was associated with an increase in both cardiovascular death and HF hospitalization which was not influenced by vericiguat.

*Corresponding author. Katz Group Centre for Pharmacy and Health Research, University of Alberta, 4-120, Edmonton, Alberta T6G 2E1, Canada. Tel: +1 780 492-0591, Email: paul.armstrong@ualberta.ca

Graphical Abstract



Cumulative incidence rate of the primary outcome in patients who developed atrial fibrillation (AF) post-randomization vs. those who did not. This analysis is based on the time-dependent AF status of patients. The hazard ratios (HRs) are as reported in *Table 3*. Patient's event count starts from the time of the new onset of AF. For the duration up to developing AF, the same patient is considered in the risk set no AF group with no event yet. CI, confidence interval.

Keywords Heart failure • Atrial fibrillation • Vericiguat

Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia complicating the natural course of heart failure with reduced ejection fraction (HFrEF), reaching a prevalence of 50% in patients with advanced disease.[1–4] It remains unclear whether AF itself is an independent prognosticator of poor outcome or rather a reflection of the underlying heart failure (HF) severity.[1,2,4–7] This uncertainty, coupled with associated conflicting reports of its significance, may represent inclusion of heterogeneous HF populations receiving different therapies as well as the presence of known and unknown confounders. Recent studies indicate that type of AF may be an important factor with recognition that new-onset AF may be particularly unfavourable.[8,9] In this context, reports that therapies recommended for HF (angiotensin-converting enzyme inhibitors, beta-blockers, or mineralocorticoid receptor antagonists) may reduce the incidence of AF in patients with HFrEF[10,11] seem to support broader use of these drugs. Recent analyses of large randomized clinical trials suggest that the effects of some guideline-recommended treatments may differ according to whether AF is present.[11,12]

The VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) assessed the efficacy and safety of vericiguat in patients with chronic HFrEF and recent decompensation.[13,14] In this very high-risk population, vericiguat significantly reduced the incidence of the composite endpoint of time to cardiovascular death or first HF hospitalization. The prevalence of AF was high in the VICTORIA trial, with 45% of patients reporting a history of AF,[14] but the relation between AF and outcomes as well as the treatment benefit of vericiguat in this population are unknown. We therefore aimed to determine the relation between the clinical outcomes and presence of AF at baseline and the occurrence of new-onset AF post-randomization. We also evaluated whether the treatment effects of vericiguat were related to the presence of AF and the subsequent risk of new-onset AF post-randomization.

Methods

Population

The design, baseline characteristics, and results of the VICTORIA trial (NCT02861534) have been previously reported.[13,14] In brief, the trial included 5050 patients with worsening chronic HF [New York Heart Association (NYHA) functional classes II to IV], a left ventricular ejection fraction <45%, elevated natriuretic peptide levels, and recent HF decompensation. Patients were randomly assigned in a 1:1 ratio to receive vericiguat or placebo. Patients in sinus rhythm had to have B-type natriuretic peptide (BNP) ≥300 pg/mL or

N-terminal pro-hormone BNP (NT-proBNP) ≥1000 pg/mL; patients with AF had to have BNP ≥500 pg/mL or NT-proBNP ≥1600 pg/mL. Guideline-based therapies for patients with HFrEF were encouraged before randomization, including the use of sacubitril/valsartan. The trial protocol was approved by regulatory agencies in participating countries, as well as the ethics committees and institutional review boards at participating sites. All patients provided written informed consent.

Definition of atrial fibrillation status

Information on AF at randomization was based on medical history available from the case report forms and investigator evaluation of an electrocardiogram (ECG) performed at randomization (atrial flutter was combined to define AF status). Patients were subsequently classified into three groups: no known AF, history of AF alone (without AF on ECG at randomization), and AF present on randomization ECG. Among patients without AF at the randomization visit (i.e. without known AF or with only history of AF), we also assessed those with new-onset AF that developed after randomization during study follow-up. AF on ECG or from the clinical report (as an endpoint or adverse event report) during the study was defined as post-randomization onset.

In all patients with known AF status, we calculated the CHA_2DS_2-VASc score (congestive HF, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, and sex) using individual patient characteristics at randomization.[15]

Study outcomes

The primary outcome of the VICTORIA trial was the composite endpoint of time to cardiovascular death or first HF hospitalization.[13] In addition, we also evaluated the individual components of the composite outcome and the secondary composite outcome of death from any cause or first HF hospitalization, and all-cause death. For the purposes of this analysis, hospitalization for stroke and myocardial infarction were also outcomes of interest. All clinical outcomes observed up to the primary analysis cutoff date (18 June 2019) were included.

Statistical analysis

Baseline characteristics are presented as means and standard deviations and medians and 25th, 75th percentiles for continuous variables, and as counts and percentages for categorical variables. Incidence rates for the outcomes of interest are presented per 100 person-years according to AF status or treatment arm. Relative hazard ratios (HRs) with 95% confidence intervals (CIs) of outcomes according to type of AF were calculated using the Cox proportional hazards model, using no AF as reference. Similarly, the Cox proportional hazards regression model was used to estimate the relative effect of vericiguat treatment (HR, 95% CI) in each of the AF status groups. The interaction of the randomized study treatment (vericiguat or placebo) with AF status was included in the models, and *P*-values for the interactions were reported. Furthermore, the models are adjusted for the covariates in the VICTORIA prediction models (online supplementary *Table S1*) and stratification variables (race/region) were considered in all analyses.

In patients with no AF at enrolment or those with history of AF alone, a Cox regression model was used to examine the association between vericiguat treatment and new-onset AF during post-randomization follow-up. HRs and 95% CIs were estimated in both unadjusted and adjusted Cox regression models. A separate analysis assessing the association of post-randomization AF as a time-varying covariate with the occurrence and time course of the primary and secondary outcomes was performed. These analyses were adjusted for history of AF in addition to the adjustment covariates described above. Furthermore, treatment interaction was tested to assess whether the association between post-randomization AF and clinical outcomes was different between the arms, and arm specific HRs (95% CIs) were estimated. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). A 2-sided test result with a *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Of 5050 patients randomized in the VICTORIA trial, 5010 with recorded AF status from medical history and/or ECG at randomization were included in this analysis. At baseline, there were 2661 (53%) patients without AF in their medical history or on their randomization ECG, and 2349 (47%) who had either a history of AF alone ($n = 992$, 20%) or AF on randomization ECG ($n = 1357$, 27%; seven of whom had no history of AF).

The baseline characteristics of patients by AF status at their randomization visit are presented in *Table 1*. Patients with either type of AF were older, more often male, were more frequently in NYHA class III–IV at randomization, had poorer renal function and more prevalent history of stroke, chronic obstructive pulmonary disease, and anaemia, and less prevalent type II diabetes mellitus, and higher MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk scores than those without AF. Those with history AF alone had the lowest use of triple medical therapy but highest use of implantable cardioverter defibrillators and biventricular pacemakers. Antithrombotic therapy and treatment with amiodarone were used more frequently in patients with AF. Both patients with a history of AF and those with AF at randomization had higher NT-proBNP levels that those without AF ($P < 0.001$). The average CHA_2DS_2-VASc score was lower in patients without AF (mean 4.1; $P < 0.001$) than in patients with history of AF alone and those with AF on randomization ECG (mean 4.4).

Association between atrial fibrillation status at randomization and study outcomes

Incidence rates and HRs for the risk of each outcome of interest according to AF status at randomization are presented in *Figure 1* and online supplementary *Table S2*. In unadjusted analyses, rates of the primary composite endpoint (cardiovascular death or HF hospitalization), HF hospitalization, and all-cause mortality were higher in patients with history of AF alone compared with those without a history of AF. In those with AF on randomization ECG, rates of HF hospitalization and all-cause death were also higher, whereas rates of hospitalization for stroke and myocardial infarction were nominally lower compared with patients without a history of AF.

Table 1 Baseline characteristics of patients by atrial fibrillation status at randomization

	No AF ($n = 2661$)	History of AF alone ($n = 992$)	AF on ECG at enrolment ($n = 1357$)[a]	Total ($n = 5010$)[b]
Age, years				
n	2661	992	1357	5010
Mean (SD)	64.5 (12.8)	70.4 (10.5)	70.7 (10.5)	67.3 (12.2)
Median (25th, 75th)	66.0 (56.0, 74.0)	71.0 (64.0, 78.0)	72.0 (64.0, 78.0)	69.0 (60.0, 76.0)
Sex				
Male	1930/2661 (72.5)	801/992 (80.7)	1078/1357 (79.4)	3809/5010 (76.0)
Female	731/2661 (27.5)	191/992 (19.3)	279/1357 (20.6)	1201/5010 (24.0)
Geographic region				
Eastern Europe	900/2661 (33.8)	304/992 (30.6)	482/1357 (35.5)	1686/5010 (33.7)
Western Europe	328/2661 (12.3)	240/992 (24.2)	308/1357 (22.7)	876/5010 (17.5)
Asia Pacific	677/2661 (25.4)	183/992 (18.4)	319/1357 (23.5)	1179/5010 (23.5)
Latin and South America	477/2661 (17.9)	96/992 (9.7)	147/1357 (10.8)	720/5010 (14.4)
North America	279/2661 (10.5)	169/992 (17.0)	101/1357 (7.4)	549/5010 (11.0)
Index event				
HF hospitalization within 3 months	1758/2661 (66.1)	658/992 (66.3)	937/1357 (69.0)	3353/5010 (66.9)
HF hospitalization 3–6 months	441/2661 (16.6)	183/992 (18.4)	236/1357 (17.4)	860/5010 (17.2)
IV diuretic for HF (without hospitalization) within 3 months	462/2661 (17.4)	151/992 (15.2)	184/1357 (13.6)	797/5010 (15.9)
BMI, kg/m^2				
n	2647	980	1345	4972
Mean (SD)	27.6 (6.1)	27.6 (5.8)	28.1 (5.7)	27.8 (5.9)
Median (25th, 75th)	26.7 (23.5, 30.7)	26.7 (23.7, 30.5)	27.4 (24.1, 31.4)	26.9 (23.7, 30.9)
Medical history				
EF recorded at screening, %				
n	2656	987	1355	4998
Mean (SD)	28.3 (8.2)	28.9 (8.5)	30.2 (8.2)	29.0 (8.3)
Median (25th, 75th)	28.0 (22.0, 35.0)	30.0 (22.0, 35.0)	30.0 (25.0, 37.0)	30.0 (23.0, 35.0)
EF < 40%	2337/2656 (88.0)	835/987 (84.6)	1110/1355 (81.9)	4282/4998 (85.7)
NYHA class at baseline				
I/II	1655/2660 (62.2)	570/992 (57.5)	729/1356 (53.8)	2954/5008 (59.0)
III/IV	1005/2660 (37.8)	422/992 (42.5)	627/1356 (46.2)	2054/5008 (41.0)
SBP, mmHg				
n	2661	992	1357	5010
Mean (SD)	121.8 (16.1)	121.7 (16.0)	120.2 (14.7)	121.4 (15.7)
Median (25th, 75th)	119.0 (109.0, 132.0)	119.0 (109.0, 131.0)	118.0 (108.0, 129.0)	119.0 (109.0, 131.0)
DBP, mmHg				
n	2661	992	1357	5010
Mean (SD)	73.1 (11.2)	70.6 (10.3)	73.7 (11.1)	72.8 (11.0)
Median (25th, 75th)	73.0 (65.0, 80.0)	70.0 (63.0, 78.0)	73.0 (66.0, 81.0)	72.0 (65.0, 80.0)

Table 1 (Continued)

	No AF (n = 2661)	History of AF alone (n = 992)	AF on ECG at enrolment (n = 1357)[a]	Total (n = 5010)[b]
Heart rate, bpm				
n	2660	992	1357	5009
Mean (SD)	72.9 (12.4)	69.8 (12.0)	76.0 (14.2)	73.1 (13.0)
Median (25th, 75th)	72.0 (64.0, 81.0)	69.0 (61.0, 77.0)	75.0 (67.0, 84.0)	72.0 (64.0, 81.0)
Diabetes mellitus	1309/2661 (49.2)	447/992 (45.1)	599/1357 (44.1)	2355/5010 (47.0)
Hypertension	2066/2661 (77.6)	791/992 (79.7)	1109/1357 (81.7)	3966/5010 (79.2)
Stroke	265/2661 (10.0)	123/992 (12.4)	187/1357 (13.8)	575/5010 (11.5)
COPD	408/2661 (15.3)	214/992 (21.6)	240/1357 (17.7)	862/5010 (17.2)
PAD	310/2661 (11.6)	162/992 (16.3)	151/1357 (11.1)	623/5010 (12.4)
Anaemia	483/2661 (18.2)	279/992 (28.1)	301/1357 (22.2)	1063/5010 (21.2)
CAD per site	1533/2661 (57.6)	617/992 (62.2)	770/1357 (56.7)	2920/5010 (58.3)
Time from primary diagnosis of HFrEF to randomization, years				
n	2661	991	1357	5009
Mean (SD)	4.1 (5.0)	5.8 (6.0)	5.2 (5.6)	4.7 (5.4)
Median (25th, 75th)	2.2 (0.7, 5.8)	4.0 (1.3, 8.4)	3.4 (1.0, 7.5)	2.9 (0.8, 6.8)
Standard of care therapy				
ACE-I or ARB	2014/2661 (75.7)	674/992 (67.9)	991/1356 (73.1)	3679/5009 (73.4)
Beta-blocker	2470/2661 (92.8)	930/992 (93.8)	1262/1356 (93.1)	4662/5009 (93.1)
MRA	1951/2661 (73.3)	640/992 (64.5)	930/1356 (68.6)	3521/5009 (70.3)
ARNI (sacubitril/valsartan)	388/2661 (14.6)	163/992 (16.4)	176/1356 (13.0)	727/5009 (14.5)
Triple therapy	1687/2661 (63.4)	530/992 (53.4)	771/1357 (56.8)	2988/5010 (59.6)
ICD	618/2661 (23.2)	462/992 (46.6)	312/1356 (23.0)	1392/5009 (27.8)
Biventricular pacemaker	291/2661 (10.9)	296/992 (29.8)	150/1356 (11.1)	737/5009 (14.7)
Concomitant medications				
Ticagrelor	58/2661 (2.2)	8/992 (0.8)	7/1357 (0.5)	73/5010 (1.5)
ASA	1693/2661 (63.6)	326/992 (32.9)	337/1357 (24.8)	2356/5010 (47.0)
Clopidogrel	620/2661 (23.3)	138/992 (13.9)	123/1357 (9.1)	881/5010 (17.6)
Warfarin	189/2661 (7.1)	257/992 (25.9)	421/1357 (31.0)	867/5010 (17.3)
Dabigatran	13/2661 (0.5)	57/992 (5.7)	122/1357 (9.0)	192/5010 (3.8)
Rivaroxaban	52/2661 (2.0)	141/992 (14.2)	241/1357 (17.8)	434/5010 (8.7)
Apixaban	53/2661 (2.0)	196/992 (19.8)	239/1357 (17.6)	488/5010 (9.7)
Amiodarone	238/2661 (8.9)	372/992 (37.5)	194/1357 (14.3)	804/5010 (16.0)
Laboratory results				
Haemoglobin, g/dL				
n	2553	946	1303	4802
Mean (SD)	13.4 (1.9)	13.2 (1.9)	13.5 (1.9)	13.4 (1.9)
Median (25th, 75th)	13.5 (12.1, 14.8)	13.1 (11.9, 14.5)	13.5 (12.2, 14.8)	13.4 (12.1, 14.7)

Table 1 (Continued)

	No AF (n = 2661)	History of AF alone (n = 992)	AF on ECG at enrolment (n = 1357)[a]	Total (n = 5010)[b]
Sodium (mEq/L)				
n	2642	972	1334	4948
Mean (SD)	139.8 (3.3)	139.9 (3.3)	140.0 (3.6)	139.9 (3.4)
Median (25th, 75th)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)
eGFR at randomization, mL/min/1.73 m^2				
n	2639	968	1328	4935
Mean (SD)	65.7 (28.8)	54.9 (23.2)	57.7 (24.8)	61.4 (27.1)
Median (25th, 75th)	62.4 (44.3, 83.4)	51.9 (37.4, 68.9)	53.9 (39.0, 73.3)	58.3 (41.2, 77.0)
eGFR categories at randomization, mL/min/1.73 m^2				
≤30	226/2661 (8.5)	122/992 (12.3)	155/1357 (11.4)	503/5010 (10.0)
>30 to ≤60	992/2661 (37.3)	489/992 (49.3)	631/1357 (46.5)	2112/5010 (42.2)
>60	1421/2661 (53.4)	357/992 (36.0)	542/1357 (39.9)	2320/5010 (46.3)
Missing	22/2661 (0.8)	24/992 (2.4)	29/1357 (2.1)	75/5010 (1.5)
Core lab NT-proBNP at randomization, pg/mL				
n	2565	924	1291	4780
Mean (SD)	4495.5 (6062.4)	4603.8 (7978.4)	5238.1 (7087.1)	4717.0 (6758.2)
Median (25th, 75th)	2506.0 (1331.0, 5015.0)	2714.5 (1551.5, 5269.0)	3454.0 (2143.0, 5898.0)	2811.5 (1556.0, 5308.5)
Study treatment				
Vericiguat	1377/2661 (51.7)	482/992 (48.6)	649/1357 (47.8)	2508/5010 (50.1)
Placebo	1284/2661 (48.3)	510/992 (51.4)	708/1357 (52.2)	2502/5010 (49.9)
CHA_2DS_2-VASc score				
n	2661	992	1357	5010
Mean (SD)	4.1 (1.6)	4.4 (1.5)	4.4 (1.6)	4.2 (1.6)
Median (25th, 75th)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
MAGGIC risk score				
n	2623	958	1320	4901
Mean (SD)	22.7 (6.3)	25.5 (6.6)	24.8 (6.5)	23.8 (6.5)
Median (25th, 75th)	23.0 (18.0, 27.0)	26.0 (21.0, 30.0)	25.0 (20.0, 29.0)	24.0 (19.0, 28.0)

Data presented as *n*/N (%), unless otherwise indicated.

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, and sex; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IV, intravenous; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation.

[a]Of 1357 patients, 1350 had both AF on their medical history and ECG at enrolment; the remaining 7 patients had only AF on ECG at enrolment (no medical history).

[b]40 patients did not have ECGs at enrolment.

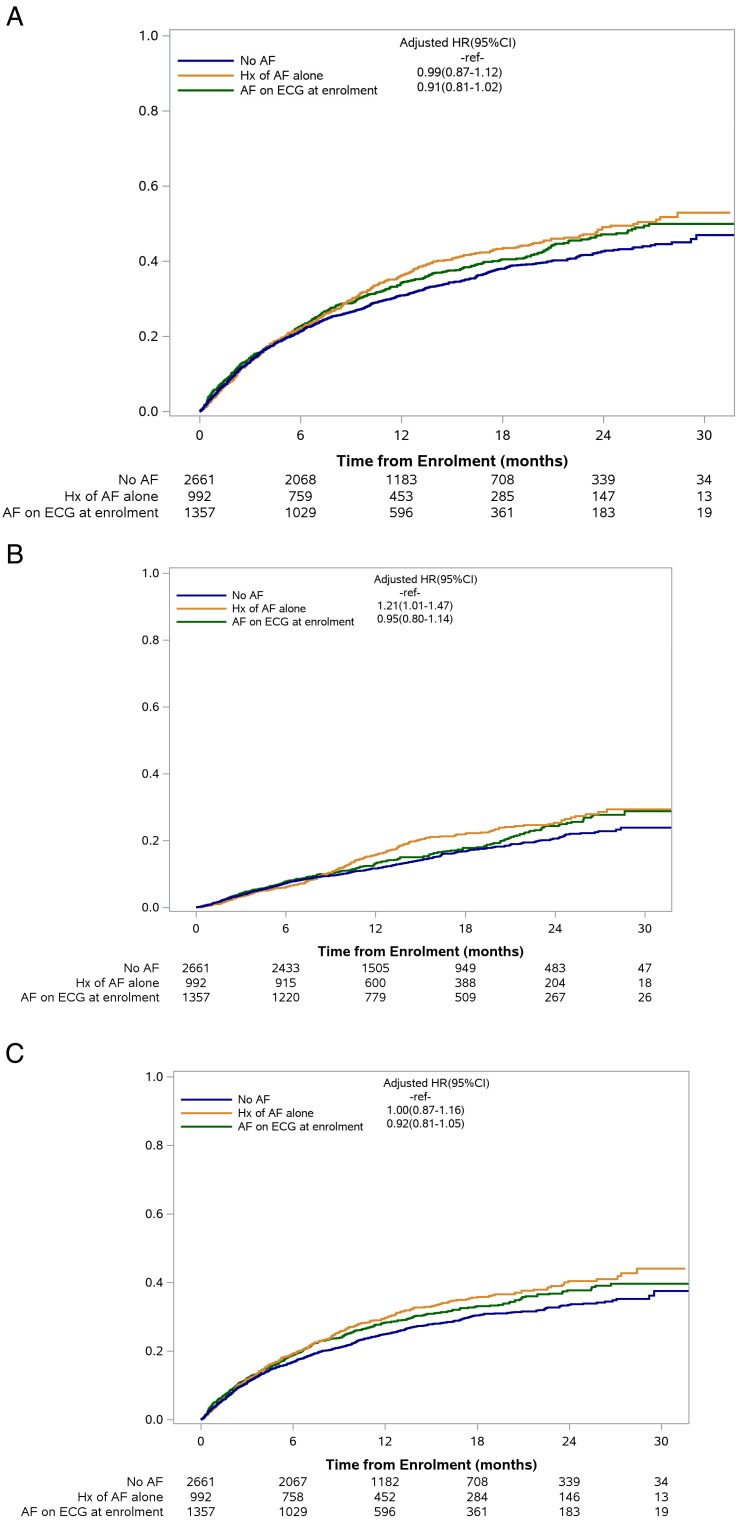


Figure 1 Kaplan–Meier curve of (*A*) primary composite outcome of time to cardiovascular death or first heart failure hospitalization or cardiovascular death, and the component outcomes (*B*) cardiovascular death, and (*C*) heart failure hospitalization. AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; Hx, history.

Adjustment for the covariates in the VICTORIA prediction models revealed that compared with the no AF group, only those with history of AF alone had a higher risk of cardiovascular death (adjusted HR 1.21, 95% CI 1.01–1.47), whereas neither type of AF was associated with a higher risk of the primary composite outcome, HF hospitalization, or all cause-death in this analysis.

Association between the atrial fibrillation status at randomization and efficacy of vericiguat

The beneficial effect of vericiguat on the primary composite outcome and its components was evident regardless of AF status at baseline (all adjusted *P* for interaction ≥0.1) (*Table 2*, *Figure 2*). Additionally, AF status at randomization did not affect treatment effect of vericiguat on the composite of HF hospitalization or all-cause death and all-cause death alone (*Table 2*).

New-onset atrial fibrillation post-randomization

Over a median follow-up of 10.8 months, among 3653 patients without a history of AF or AF on ECG at randomization, new-onset AF post-randomization occurred in 345 (9.4%) patients; 163 (6.1%) of these had no prior AF and 182 (18.3%) had history of AF alone ($P < 0.0001$). The incidence of new-onset AF did not differ between patients receiving vericiguat and placebo (event rate: 7.5 vs. 8.7/100 person-years; adjusted HR 0.93, 95% CI 0.75–1.16; $P = 0.51$). The Kaplan–Meier curves comparing the cumulative event rates between the vericiguat and placebo arms are presented in *Figure 3*.

In *Table 3* the association between post-randomization AF and primary and secondary outcomes is shown according to treatment groups. Whereas there was a consistent increase in the hazard of both primary and secondary outcomes, this excess was not modified by vericiguat therapy. The cumulative incidence rate of the primary outcome in patients who developed AF post-randomization was significantly higher than in those who did not develop AF (adjusted HR 2.16, 95% CI 1.76–2.67) (*Figure 4*).

Discussion

There are several novel findings in this analysis. Nearly half of this high-risk population of patients with HFrEF and recent HF decompensation had AF. Only patients with history of AF (but no AF on enrolment ECG) had worse outcomes as compared with those without AF. New-onset AF developing post-randomization was relatively common (in 1 out of 10 patients) during a rather short follow-up of less than 1 year, was distributed evenly by treatment groups, and was associated with an excess risk of both the primary and secondary outcomes. The beneficial effect of vericiguat was unaffected by any type of AF at baseline.

Patients included in the VICTORIA trial were at very high risk of mortality and morbidity despite optimized management of their HF, as evidenced by an annualized rate of 37.8% of the primary composite outcome of cardiovascular death or HF hospitalization.[14] Although vericiguat achieved a meaningful absolute rate reduction of 4.2 events per 100 person-years at risk, further improvement in the outcomes in this population is both desirable and challenging. Targeting coexisting cardiovascular and non-cardiovascular comorbidities provides an attractive therapeutic option. Among comorbidities affecting these patients, AF is of particular importance, not only due to high prevalence, but also due to potential detrimental consequences of AF on the natural course of HF.

Whereas history of AF alone portended an increased risk of cardiovascular death, neither type of AF was associated with a higher risk of the primary composite outcome, HF hospitalization, or all cause-death. The conflicting results of prior studies[1,4–10,16,17] as to whether AF may appear as an independent predictor of adverse outcomes or rather indicate severity of the underlying disease may therefore reflect lack of different models of adjustments for other prognosticators in heterogeneous HF populations. Prior older studies also had less than optimal use of disease-modifying therapies. The most recent analysis comprising contemporary HFrEF populations from the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbidity-mortality in Patients With Chronic Heart Failure) trials reported a lower prevalence of AF (36% had a history of AF at randomization, both paroxysmal or persistent/permanent).[9] However, both studies required a run-in period to ensure tolerability, and the populations included had less advanced disease with a lower risk of cardiovascular outcomes and substantially longer median follow-up times of 27 and 36.6 months, respectively (as opposed to 10.8 months in our study). In those studies, after adjustment for other prognostic variables (including natriuretic peptide levels), only paroxysmal AF was associated with a higher risk of HF hospitalization but not with cardiovascular death or all-cause death.[9] Although the reasons for differences between those studies and the current work are uncertain, one may surmise that some episodes of paroxysmal AF may lead to haemodynamic decompensation and subsequent hospital admission.[9] In our study as with others,[9,10] AF present on enrolment ECG did not affect outcomes whereas intermittent AF was independently related to an increased risk of cardiovascular mortality (but not HF hospitalization). The underlying explanation for these findings is unclear. Moreover, if cardiovascular mortality was related to progressive HF worsening, a prior increase in HF hospitalization would have been expected. Further investigation of the association of history of AF alone and sudden death in this high-risk population seems warranted. Interestingly, in the recent EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) study,[18] an early rhythm control strategy was associated with a lower risk of cardiovascular outcomes than usual care among patients with recently diagnosed AF (of whom more than 50% were in sinus rhythm at baseline) and additional cardiovascular risk factors. These findings suggest that AF detected early appears to contribute to increased risk of cardiovascular death and stroke, but the pathophysiological mechanism(s) underlying such a relationship remains unknown.[19]

Table 2 **Treatment effect of vericiguat on primary and secondary outcomes according to atrial fibrillation status at randomization; unadjusted and adjusted treatment effects (vericiguat vs. placebo) in hazard ratio (95% confidence interval) and event rates per 100 person-years (by arm)**

	No AF (*n* = 2661)	History of AF alone (*n* = 992)	AF on ECG at enrolment (*n* = 1357)	Any AF from history and/or on ECG (*n* = 2349)	Interaction *P*-value[a]
Primary outcome					
Patients with events, *n* (%)	921 (34.6)	408 (41.1)	519 (38.2)	927 (39.5)	
Event rate/100 person-years (vericiguat vs. placebo)	31.2 vs. 36.2	36.6 vs. 40.6	36.7 vs. 37.8	36.6 vs. 39.0	
Unadjusted HR (95% CI)	0.86 (0.76–0.98) (*P* = 0.02)	0.92 (0.75–1.11) (*P* = 0.38)	0.97 (0.82–1.16) (*P* = 0.77)	0.95 (0.83–1.08) (*P* = 0.42)	0.53
Adjusted[b] HR (95% CI)	0.85 (0.74–0.96) (*P* = 0.01)	0.93 (0.76–1.13) (*P* = 0.47)	0.96 (0.81–1.15) (*P* = 0.66)	0.95 (0.83–1.08) (*P* = 0.42)	0.48
Adjusted HR (95% CI)	0.84 (0.74–0.96) (*P* = 0.01)	0.90 (0.74–1.11) (*P* = 0.33)	0.97 (0.81–1.16) (*P* = 0.77)	0.94 (0.83–1.08) (*P* = 0.40)	0.45
Cardiovascular death					
Patients with events, *n* (%)	404 (15.2)	200 (20.2)	238 (17.5)	438 (18.6)	
Event rate/100 person-years (vericiguat vs. placebo)	11.2 vs. 13.2	13.8 vs. 17.0	15.3 vs. 12.6	14.6 vs. 14.5	
Unadjusted HR (95% CI)	0.85 (0.70–1.03) (*P* = 0.10)	0.82 (0.62–1.09) (*P* = 0.17)	1.19 (0.93–1.54) (*P* = 0.17)	1.01 (0.84–1.22) (*P* = 0.91)	0.07
Adjusted[b] HR (95% CI)	0.84 (0.69–1.03) (*P* = 0.09)	0.82 (0.61–1.09) (*P* = 0.18)	1.17 (0.90–1.53) (*P* = 0.23)	1.00 (0.82–1.21) (*P* = 0.99)	0.10
Adjusted HR (95%CI)	0.86 (0.70–1.06) (*P* = 0.16)	0.83 (0.62–1.11) (*P* = 0.21)	1.14 (0.88–1.49) (*P* = 0.32)	0.99 (0.82–1.21) (*P* = 0.96)	0.18
HF hospitalization					
Patients with events, *n* (%)	698 (26.2)	322 (32.5)	403 (29.7)	725 (30.9)	
Event rate/100 person-years (vericiguat vs. placebo)	23.3 vs. 27.6	30.3 vs. 30.8	27.9 vs. 29.9	28.9 vs. 30.3	
Unadjusted HR (95% CI)	0.85 (0.73–0.99) (*P* = 0.03)	1.00 (0.80–1.24) (*P* = 0.97)	0.94 (0.77–1.14) (*P* = 0.54)	0.97 (0.83–1.12) (*P* = 0.64)	0.47
Adjusted[b] HR (95% CI)	0.84 (0.73–0.98) (*P* = 0.03)	1.02 (0.81–1.27) (*P* = 0.89)	0.93 (0.76–1.13) (*P* = 0.45)	0.97 (0.83–1.12) (*P* = 0.64)	0.39
Adjusted HR (95%CI)	0.83 (0.71–0.97) (*P* = 0.02)	0.98 (0.78–1.23) (*P* = 0.83)	0.93 (0.76–1.14) (*P* = 0.51)	0.95 (0.82–1.11) (*P* = 0.54)	0.44
HF hospitalization/all-cause mortality					
Patients with events, *n* (%)	973 (36.6)	431 (43.4)	564 (41.6)	995 (42.4)	
Event rate/100 person-years (vericiguat vs. placebo)	32.8 vs. 38.2	38.9 vs. 42.6	39.9 vs. 41.0	39.5 vs. 41.7	
Unadjusted HR (95% CI)	0.86 (0.76–0.98) (*P* = 0.02)	0.93 (0.77–1.12) (*P* = 0.43)	0.98 (0.83–1.15) (*P* = 0.79)	0.95 (0.84–1.08) (*P* = 0.47)	0.50
Adjusted[b] HR (95% CI)	0.84 (0.74–0.95) (*P* = 0.01)	0.93 (0.77–1.13) (*P* = 0.48)	0.96 (0.81–1.14) (*P* = 0.67)	0.95 (0.84–1.08) (*P* = 0.43)	0.38
Adjusted HR (95% CI)	0.84 (0.73–0.95) (*P* = 0.01)	0.90 (0.74–1.10) (*P* = 0.30)	0.99 (0.83–1.17) (*P* = 0.86)	0.95 (0.83–1.08) (*P* = 0.42)	0.33
All-cause mortality					
Patients with events, *n* (%)	487 (18.3)	240 (24.2)	306 (22.5)	546 (23.2)	
Event rate/100 person-years (vericiguat vs. placebo)	13.8 vs. 15.7	16.9 vs. 20.1	19.4 vs. 16.4	18.3 vs. 18.0	
Unadjusted HR (95% CI)	0.88 (0.74–1.05) (*P* = 0.15)	0.85 (0.66–1.10) (*P* = 0.23)	1.17 (0.94–1.47) (*P* = 0.17)	1.02 (0.86–1.21) (*P* = 0.81)	0.09
Adjusted[b] HR (95% CI)	0.85 (0.71–1.03) (*P* = 0.10)	0.86 (0.66–1.12) (*P* = 0.26)	1.10 (0.88–1.39) (*P* = 0.40)	0.99 (0.83–1.18) (*P* = 0.93)	0.19
Adjusted HR (95% CI)	0.87 (0.72–1.06) (*P* = 0.16)	0.87 (0.66–1.14) (*P* = 0.30)	1.10 (0.87–1.39) (*P* = 0.42)	1.00 (0.83–1.19) (*P* = 0.97)	0.27

AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HF, heart failure; HR, hazard ratio.
[a]Test of significance of the difference in the treatment effect of vericiguat across the first three AF groups.
[b]Adjusted for VICTORIA prognostic model without N-terminal pro-hormone B-type natriuretic peptide.

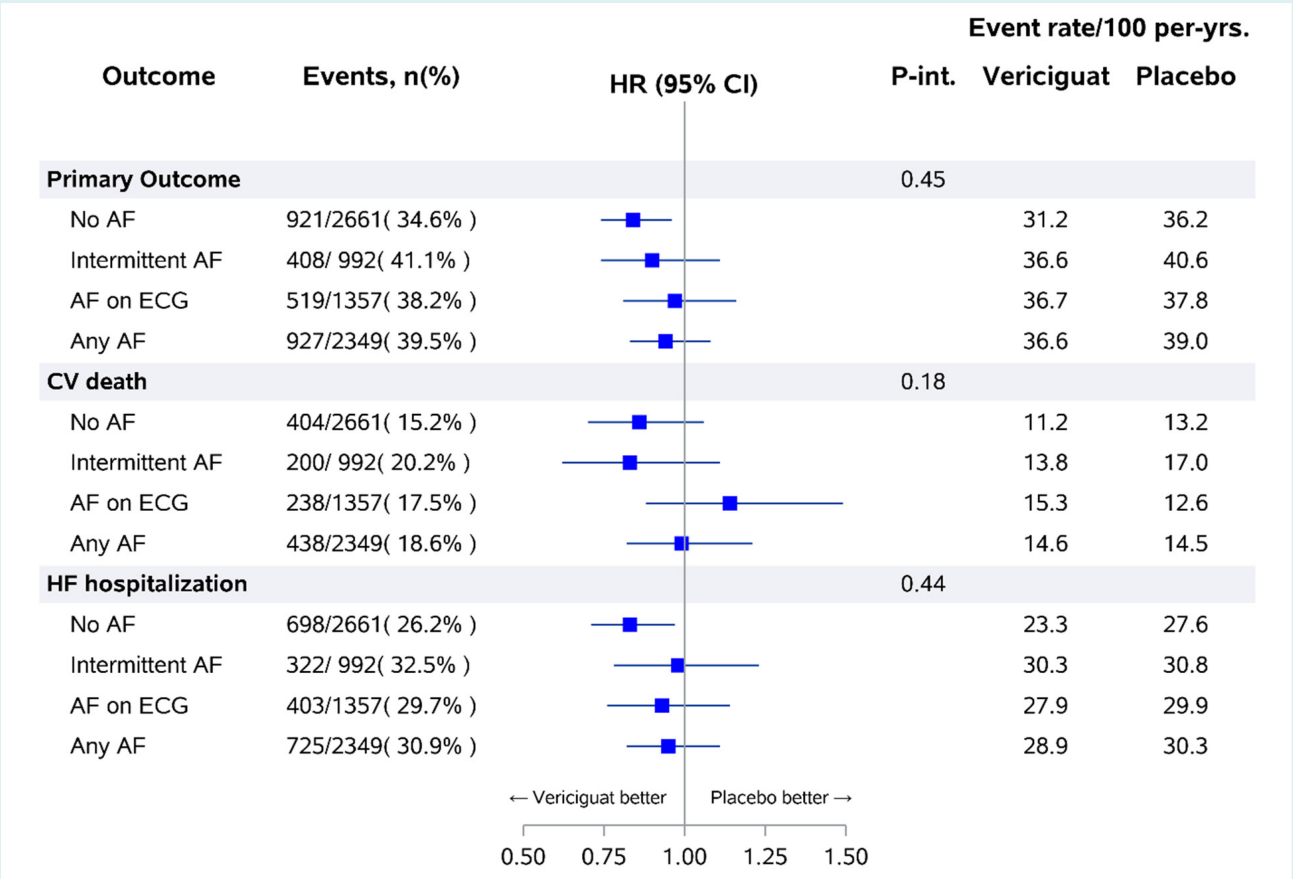


Figure 2 Effect of vericiguat on the primary composite outcome and its components. AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; HF, heart failure; HR, hazard ratio.

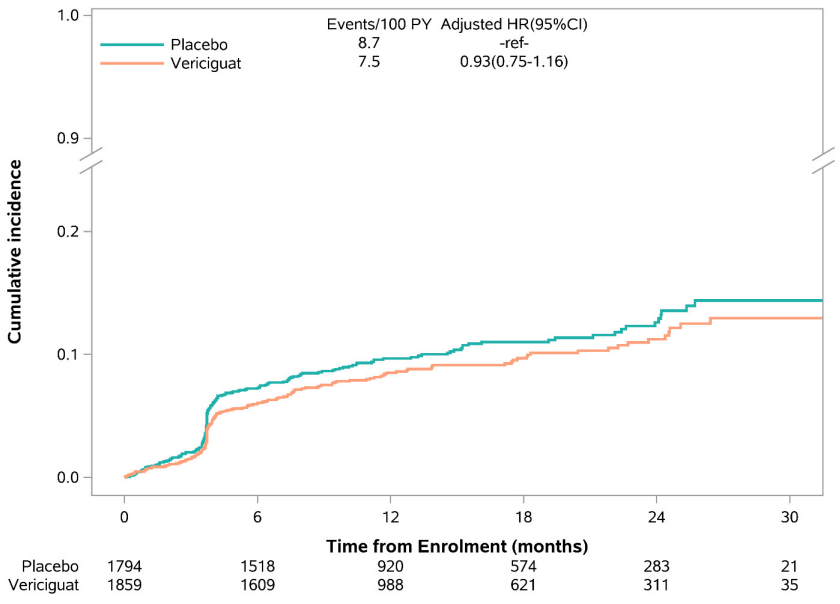


Figure 3 Kaplan–Meier curve of time to atrial fibrillation in post-randomization follow-up, according to randomization arm. CI, confidence interval; HR, hazard ratio.

Table 3 Associations of post-randomization onset of atrial fibrillation with primary and secondary outcomes, in all patients and stratified by treatment arm

	All patients (*n* = 3653)	Placebo (*n* = 1794)	Vericiguat (*n* = 1859)	Interaction *P*-value[a]
Primary outcome				
Patients with events, *n* (%)	1329 (36.4)	686 (38.2)	643 (34.6)	
Unadjusted HR (95% CI)	2.22 (1.82–2.71)	2.03 (1.56–2.66)	2.43 (1.83–3.22)	0.37
Adjusted[a] HR (95% CI)	2.16 (1.76–2.67)	2.11 (1.58–2.81)	2.23 (1.66–2.98)	0.79
Cardiovascular death				
Patients with events, *n* (%)	604 (16.5)	321 (17.9)	283 (15.2)	
Unadjusted HR (95% CI)	1.91 (1.47–2.47)	2.03 (1.45–2.84)	1.74 (1.17–2.58)	0.55
Adjusted[b] HR (95% CI)	1.71 (1.29–2.27)	1.83 (1.25–2.68)	1.59 (1.06–2.40)	0.62
HF hospitalization				
Patients with events, *n* (%)	1020 (27.9)	522 (29.1)	498 (26.8)	
Unadjusted HR (95% CI)	2.45 (1.96–3.05)	2.27 (1.69–3.07)	2.63 (1.92–3.61)	0.50
Adjusted[b] HR (95% CI)	2.39 (1.90–3.02)	2.40 (1.75–3.30)	2.39 (1.73–3.31)	0.99
HF hospitalization/all-cause mortality				
Patients with events, *n* (%)	1404 (38.4)	723 (40.3)	681 (36.6)	
Unadjusted HR (95% CI)	2.14 (1.76–2.60)	1.96 (1.51–2.55)	2.33 (1.77–3.08)	0.37
Adjusted[b] HR (95% CI)	2.09 (1.70–2.57)	2.00 (1.51–2.65)	2.19 (1.64–2.92)	0.65
All-cause mortality				
Patients with events, *n* (%)	727 (19.9)	380 (21.2)	347 (18.7)	
Unadjusted HR (95% CI)	1.74 (1.37–2.22)	1.78 (1.29–2.45)	1.68 (1.18–2.41)	0.82
Adjusted[b] HR (95% CI)	1.57 (1.20–2.04)	1.62 (1.12–2.33)	1.52 (1.05–2.21)	0.82

CI, confidence interval; HF, heart failure; HR, hazard ratio.
Stratification variable (race/region) will be considered in all analyses.
[a]Test of significance of the difference in the association of post-randomization atrial fibrillation with outcome, according to treatment arm.
[b]Adjusted for VICTORIA prognostic model with N-terminal pro-hormone B-type natriuretic peptide + medical history of atrial fibrillation.

We adjusted for natriuretic peptide levels in assessing the prognostic importance of AF and used different natriuretic peptide inclusion thresholds for those with and without AF on enrolment. Although patients with history of AF alone had baseline NT-proBNP levels lower than those with AF on enrolment ECG (median 2714 vs. 3454 pg/mL), they had higher rates of cardiovascular events. The finding that a given concentration of NT-proBNP in patients with HFrEF was associated with a similar risk of cardiovascular death or hospitalization for HF in patients with and without AF lends further support to our finding of the detrimental impact of history of AF alone.[18]

In this study, the rates of hospitalization for myocardial infarction and stroke were nominally higher in patients without AF. Recent data from the COMMANDER-HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial showed a reduction of thromboembolic events with low-dose rivaroxaban in patients with HF and sinus rhythm.[19] Given there was also less use of anticoagulation therapy in those without AF in our study, these findings warrant further investigation.

The prevalence of AF developing post-randomization, with an overall incidence of around 8 events per 100 person-years, coupled with a twofold increase in the risk of all cardiovascular events (including cardiovascular death), indicates an important unmet need in this patient subset. Swedberg *et al.*[20] found that in patients with HFrEF who received long-term treatment with beta-blockers in the COMET (Carvedilol or Metoprolol European Trial) trial, only new-onset AF was an independent predictor of subsequent all-cause mortality, regardless of treatment allocation (metoprolol or carvedilol). In the combined analysis of the more recent trials in patients with HFrEF – PARADIGM-HF and ATMOSPHERE – new-onset AF was also associated with a twofold increase in the risk of adverse outcomes: primary endpoint (cardiovascular death or HF hospitalization), HF hospitalization, stroke and all-cause mortality.[9] Reduction of recurrent AF by novel therapies, such as catheter ablation, might reduce their subsequent risk.

Some limitations of our study should be noted. Although the information on AF status in all patients was collected prospectively, all the analyses were post-hoc. Given the eligibility criteria of the VICTORIA trial, our results may not be applicable to all high-risk patients with HF and recent decompensation, particularly those with a left ventricular ejection fraction >45%. Although collection of the information on the development of AF post-randomization was pre-specified, it was based on physician reports and structured follow-up evaluations which may have underestimated the prevalence of these events. Finally, the number of patients hospitalized for stroke or myocardial infarction was relatively small.

In this high-risk HF population, AF was present in nearly half of all patients. A history of AF alone portended an increased

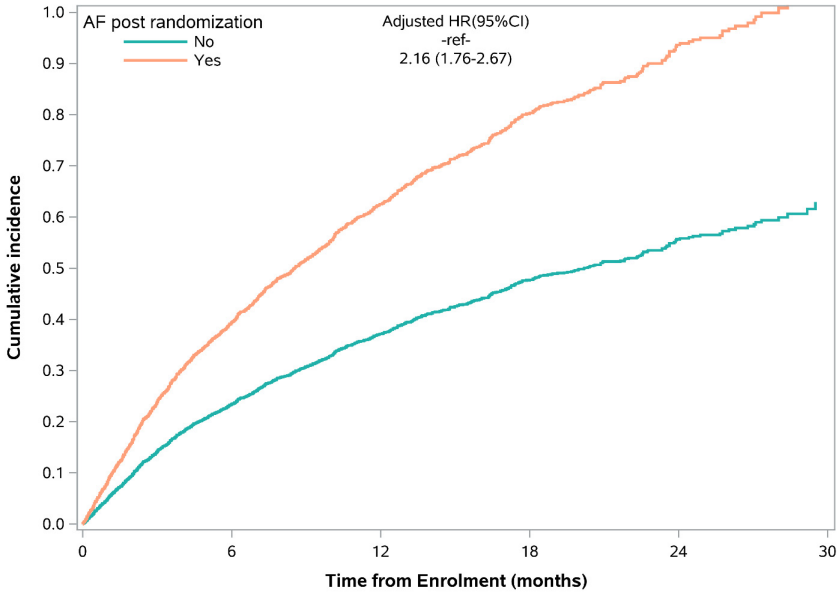


Figure 4 Cumulative incidence rate of the primary outcome in patients who developed atrial fibrillation (AF) post-randomization vs. those who did not. This analysis is based on the time-dependent AF status of patients. The hazard ratios (HRs) are as reported in *Table 3*. Patient's event count starts from the time of the new onset of AF. For the duration up to developing AF, the same patient is considered in the risk set no AF group with no event yet. CI, confidence interval.

risk of cardiovascular death and new-onset AF that developed during follow-up was also associated with a greater risk of worse outcome, but their occurrence was not influenced by vericiguat. Neither type of AF affected the beneficial effect of vericiguat.

Supplementary Information

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

Acknowledgements

The authors would like to thank Lisa Soulard of the Canadian VIGOUR Centre and Elizabeth E.S. Cook of the Duke Clinical Research Institute for their assistance in the preparation of this manuscript.

Funding

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and Bayer AG.

Conflict of interest: P.P. has received research grants from Vifor Pharma Ltd, and Servier; has received consulting fees from MSD, Novartis, Vifor Pharma Ltd, Servier, Bristol-Myers Squibb, Boehringer Ingelheim, Respicardia, AstraZeneca, Cibiem, RenalGuardSolution, and Berlin Chemie. A.O. has received speaker honoraria from Daiichi Sankyo, Menarini, Bayer, and Pfizer/BMS, as well as research funding from BMS/Pfizer (ERISTA), Merck, and Bayer. M.C.B. has received educational grants from Boehringer Ingelheim and honoraria from Merck & Co. M.J.P. is an employee of Merck. J.B. has received consulting fees from Bayer, Merck, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceutical, Janssen, Luitpold, Medtronic, Novartis, Vifor, and Novo Nordisk. J.A.E. has received research grants from Bayer, Merck, Servier, Amgen, Sanofi, Novartis, Cytokinetics, American Regent, and Applied Therapeutics; has received consulting fees from Bayer, Merck, Servier, Amgen, Sanofi, Novartis, Cytokinetics, American Regent, and Applied Therapeutics. A.F.H. has received research grants from Merck, AstraZeneca, Novartis, and Verily; and has received consulting fees from Merck, Bayer, Amgen, AstraZeneca, and Novartis. C.S.P.L. has received research grants from Bayer, National Medical Research Council of Singapore, Boston Scientific, Roche Diagnostic, Medtronic, Vifor Pharma, and AstraZeneca; has received consulting fees from Merck, Bayer, Boston Scientific, Roche Diagnostic, Vifor Pharma, AstraZeneca, Novartis, Amgen, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth Bio Therapeutics, Novo Nordisk, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd, and Corpus; has a patents pending for PCT/SG2016/050217 and 16/216,929; and is the Cofounder and non-executive director of eKo.ai. C.M.O'C. has received research funding from Merck; and has received consulting fees from Bayer, Dey LP, and Bristol-Myers Squibb Foundation. B.P. has received research grants from MSD, Bayer, and Servier; has received consulting fees from MSD, Bayer, Servier, Bristol-Myers Squibb, MedScape, Daiichi-Sankyo, and Novartis; and has received non-financial support from MSD, Bayer, and Novartis. L.R. is an employee of Bayer. A.A.V. has received research grants from Boehringer Ingelheim

and Roche Diagnostics; and has received consulting fees from Merck, Bayer, Amgen, AstraZeneca, Boehringer Ingelheim, Cytokinetics, Myokardia, Novartis, Servier, and Roche Diagnostics. P.W.A. has received research grants from Merck, Bayer, Sanofi-Aventis Recherche & Développement, Boehringer Ingelheim, and CSL Limited; and has received consulting fees from Merck, Bayer, AstraZeneca, and Novartis. All other authors have nothing to disclose.

Data availability statement

The data will be made available as outlined in the VICTORIA data sharing charter that is on the CVC website: https://thecvc.ca/publications/data-sharing/victoria/.

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