International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF registry

Jesse F. Veenis [a], Hans-Peter Brunner-La Rocca [b], Gerard C.M. Linssen [c], Frank J.J. Smeele [d], Noëmi T.A.E. Wouters [e], Paul H.M. Westendorp [f], Philip C. Rademaker [g], Martin E.W. Hemels [h], Michiel Rienstra [i], Arno W. Hoes [j], Jasper J. Brugts [a,*], for theCHECK-HF investigators

[a] Erasmus MC, University Medical Center Rotterdam, Thorax Center, Department of Cardiology, Rotterdam, the Netherlands
[b] Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands
[c] Department of Cardiology, Hospital Group Twente, Almelo and Hengelo, the Netherlands
[d] Department of Cardiology, Slingeland Ziekenhuis, Doetinchem, the Netherlands
[e] Department of Cardiology, Amphia Ziekenhuis, Breda, the Netherlands
[f] Department of Cardiology, Rivas Beatrixziekenhuis, Gronichem, the Netherlands
[g] Department of Cardiology, ZorgZaam Ziekenhuis, Terneuzen, the Netherlands
[h] Department of Cardiology, Rijnstate Ziekenhuis, Arnhem, the Netherlands
[i] Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[j] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and Utrecht University, the Netherlands

ARTICLE INFO

Article history:
Received 10 January 2020
Received in revised form 18 February 2020
Accepted 2 March 2020
Available online xxxx

Keywords:
Heart failure
HFrEF
Atrial fibrillation
Guideline adherence
Treatment

ABSTRACT

Background: Atrial fibrillation (AF) is common in chronic heart failure (HF) patients and influences the choice and effects of drug and device therapy. In this large real-world HF registry, we studied whether the presence of AF affects the prescription of guideline-recommended HF therapy.
Methods: We analyzed 8253 patients with chronic HF with reduced ejection fraction (HFrEF) from 34 Dutch outpatient clinics included in the period between 2013 and 2016 treated according to the 2012 ESC guidelines.
Results: 2109 (25.6%) of these patients were in AF (mean age 76.8 ± 9.2 years, 65.0% were men) and 6.144 (74.4%) had no AF (mean age 70.7 ± 12.2 years, 63.6% were men). Patients with AF more often received beta-blockers (81.7% vs. 79.7%, $p = 0.04$), MRAs (57.1% vs. 51.7%, $p < 0.01$), diuretics (89.7% vs. 80.6%, $p < 0.01$) and digoxin (40.1% vs. 9.3%, $p < 0.01$) compared to patients without AF, whereas they less often receive renin-angiotensin-system (RAS)-inhibitors (76.1% vs. 83.1%, $p < 0.01$). The number of patients who received beta-blockers, RAS-inhibitor and MRA at ≥50% of the recommended target dose was comparable between those with and without AF (16.6% vs. 15.2%, $p = 0.07$).
Conclusion: In this large cohort of chronic HFrEF patients, the prevalence of AF was high and we observed significant differences in prescription of both guideline-recommended HF between patients with and without AF.
© 2020 Elsevier B.V. All rights reserved.

1. Introduction

Atrial fibrillation (AF) is a common comorbidity in chronic heart failure (HF) patients, with a prevalence that has been reported from 10% up to 50–60%, depending on age and severity of HF [1–3]. Pathophysiological changes in HF can lead to AF and vice versa [2,4]. HF induces elevated filling pressures in the atria, leading to interstitial fibrosis of the left atrium, eventually leading to AF. Furthermore, calcium handling is altered in HF patients, and due to alterations in the electric properties of the atrial tissue in HF patients, AF can be induced. Otherwise, AF affects the left ventricular function due to loss of atrial contraction, irregular ventricular heart rhythm, and often rapid ventricular response, leading to and sustaining HF.

Multiple studies have shown that incident AF in chronic HF patients is associated with an increased risk of all-cause mortality, cardiovascular mortality, stroke and transient ischemic attack [1,5]. Moreover, concomitant AF may influence the choice of HF therapy, as the effects of therapies may differ in HF patients with AF [6]. There are European Society of Cardiology (ESC) guidelines for both HF and AF, providing clear recommendations for the treatment of both conditions [7,8]. Information on the ESC HF guideline adherence in patients with and without AF is relatively scarce.

Therefore, the aim of this study was to (1) investigate the adherence to the HF ESC guidelines in HF patients with reduced ejection fraction

* Corresponding author at: Department of Cardiology, Erasmus University Medical Centre, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: j.brugts@erasmusmc.nl (J.J. Brugts).

https://doi.org/10.1016/j.ijcard.2020.03.001
0167-5273/© 2020 Elsevier B.V. All rights reserved.

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001

(HFrEF) depending on the existence of underlying AF as well as to (2) provide insight in the prescription of antiarrhythmic drugs and anticoagulation therapy in HFrEF patients with AF in a practice-based registry.

2. Methods

The design and methods of the CHECK-HF (Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry have been reported in detail earlier [9]. Briefly, the CHECK-HF registry consists of 10,910 patients with chronic HF from a total of 34 participating Dutch centers, participating in the inclusion of this cross-sectional observational cohort. Between 2013 and 2016, all centers included patients diagnosed with HF-based on symptoms, signs, ECG, biomarkers and echocardiography according to the 2012 ESC Guideline on HF [10], who were seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present. No NT-proBNP threshold levels were used as inclusion criteria in this registry. The study was conducted according to the Declaration of Helsinki. Ethical approval was provided for anonymously analyzing existing patient data by the Ethical Committee of the Maastricht University Medical Center, the Netherlands.

A dedicated database was used to register all available records of the included patients, including baseline characteristics, laboratory markers, device implantation rates, as well as prescription and dosages of medication. Furthermore, information on contraindications and drug intolerance were collected. For HF medical therapy, sotalol was analyzed separately from other beta-blockers. Target doses of guideline recommended HF therapy are presented in Supplementary Table 1.

Patients were classified based on left ventricular ejection fraction (LVEF) or visual assessment of the left ventricle (LV) function into HFrEF (LVEF <50% (n = 8360 (76.6%)) and HF with preserved ejection fraction (HFpEF) (LVEF≥50% (n = 2267 (20.8%) according to 2012 ESC HF guidelines [10]. In 283 (2.6%) patients data on LV function was insufficient to classify patients, these patients, and all HFpEF patients, were excluded from this analysis. Based on a 12-lead ECG, performed during the most recent out-patient clinic visit, HFrEF patients were divided into those with documented AF (or a documented history of AF), sinus rhythm or other cardiac rhythms, in 107 (1.3%) patients data on cardiac rhythm was missing, and these patients were excluded from this analysis. Thus, a total of 8253 HFrEF patients with AF or without AF (including sinus, pacemaker, and ectopic rhythm) was included.

2.1. Statistical analysis

Continuous data are expressed as mean value ± standard deviation (SD) or median and interquartile range, depending on the distribution of the data, and compared by the unpaired *t*-test or Mann-Whitney *U* test when appropriate. Categorical data are expressed as counts and percentages, and compared by the Pearson Chi-square test. In order to investigate whether the observed differences according to AF were independent of potential confounders, such as age and sex, univariable and multivariable logistic regression were used. The results of these regression analyses are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided p-value of 0.05 was considered statistically significant.

In model 1, we adjusted for heart rate (per 10 beats/min). In model 2, we further adjusted for age, sex, New York Heart Association (NYHA) classification, and LVEF. In model 3, we further included all comorbidities which were significantly related to the outcome variable at statistical level p-value <0.05 using the enter method in a binary logistic regression model.

For some of these potential confounders, data were missing and were imputed using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used. Otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of 5 imputations were performed, and the pooled data were analyzed. The imputed data was only used for the multivariable analysis. For all reported data of the multivariable analysis, we compared crude and imputed p-values as well as the ORs and CIs in order to analyze whether imputation changed the results, and if no significant changes occurred, we only presented the imputed values in the main analyses.

A sensitivity analysis was conducted for patients with documented AF (n = 2109) and documented sinus rhythm (n = 4901).

For a sub-analysis according to the newer 2016 ESC HF guidelines, patients with an assessed LVEF <50% were categorized into HF with mid-range ejection fraction (HFmrEF) (LVEF 40–49% (n = 1559 (18.9%)) and HFrEF (LVEF<40% (n = 5625 (68.2%), only in those patients with a exactly specified LVEF or into patients with only a semi-quantitative analysis of the LV function (n = 1069 (13.0%)). For a sub-analysis according to type of AF, patients diagnosed with AF were categorized into those with paroxysmal, persistent, permanent AF or AF of unknown type. All analyses were performed with SPSS Statistical Package version 25.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics

Of all HFrEF patients, 2109 (25.6%) patients had AF on the entry-ECG at the most recent out-patient clinic visit or had a documented history of AF, 4901 (59.4%) had sinus rhythm, 1141 (13.8%) had pacemaker rhythm and 102 (1.2) had an ectopic rhythm (in total 6144 (74.4%) had no AF). The prevalence of AF increased in higher NYHA-classifications (NYHA I 18.0%, NYHA II 24.8%, NYHA III 31.2% and NYHA IV 30.8%, p < 0.01). Patients with AF were significantly older compared to patients without AF (76.8 ± 9.2 vs. 70.7 ± 12.2 years resp., p < 0.01), were more often in NYHA III/IV (33.4% vs. 25.2% resp., p < 0.01), and had more comorbidities compared to patients without AF as shown in Table 1.

3.2. Pharmacological therapy

Patients with AF significantly more often received beta-blockers (81.7% vs. 79.7%, p = 0.04), mineralocorticoid receptor antagonists (MRAs) (57.1% vs. 51.7%, p < 0.01), diuretics (89.7% vs. 80.6%, p < 0.01), digoxin (40.1% vs. 9.3%, p < 0.01), oral anticoagulation (OACs) (82.4% vs. 41.7%, p < 0.01) and non-vitamin K antagonist oral anticoagulant (NOACs) (7.3% vs. 3.6%, p < 0.01), and less often RAS-inhibitors (76.1% vs. 83.1%, p < 0.01), amiodarone (12.9% vs. 15.2%, p = 0.04), and sotalol (2.7% vs. 5.6%, p < 0.01) compared to patients without AF, as shown in Fig. 1A. 89.7% of the patients with AF receive (N)OAC therapy as compared to 45.4% of those without AF (p < 0.01). Reasons for prescription of anticoagulation in patients without AF were artificial valves, severe LV dysfunction or LV thrombus. As shown in Fig. 1C, there were no significant differences in the number of patients who received triple HF therapy, consisting of beta-blocker, RAS-inhibitor, and MRA. Additionally, patients with sinus rhythm had more often an implantable cardioverter defibrillator (29.0% vs. 15.4%, p < 0.01) or a cardiac resynchronization therapy device (9.9% vs. 7.3, p < 0.01) compared to patients with AF.

The prescribed dosages of beta-blocker, RAS-inhibitors, and MRA are presented in Fig. 1B. Patients with AF significantly more often received beta-blocker at target dose as compared to patients without AF, and there were no significant differences in the prescribed dosages of RAS-inhibitors and MRAs. As shown in Fig. 1D, there was no significant difference in the number of patients who received triple HF therapy at ≥50% at the target dose.

A sensitivity analysis excluding patients with pacemaker rhythm and ectopic rhythm produced qualitatively similar results with the exception of beta-blockers, which difference was no longer significant (Supplementary Fig. 1).

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001

Table 1
Patient characteristics of HFrEF patients according to AF.

	Overall population (n = 8253)	Patients with AF (n = 2109)	Patients without AF (n = 6144)	p-Value
Age (years) (n = 8244)	72.3 ± 11.8	76.8 ± 9.2	70.7 ± 12.2	<0.01
Male gender (n = 8216)	5258 (64.0)	1366 (65.0)	3892 (63.6)	0.25
BMI, kg/m2 (n = 7599)	27.2 ± 5.2	27.1 ± 5.1	27.2 ± 5.2	0.48
NYHA (n = 8160)				
I	1291 (15.8)	232 (11.1)	1059 (17.4)	
II	4644 (56.9)	1154 (55.5)	3490 (57.4)	
III	2079 (25.5)	648 (31.2)	1431 (23.5)	
IV	146 (1.8)	45 (2.2)	101 (1.7)	<0.01
LVEF, % (n = 6097)	32.7 ± 10.6	35.3 ± 10.9	31.8 ± 10.3	<0.01
Cause of HF (n = 7998)				
Ischemic cause of HF	4122 (51.5)	850 (41.6)	3272 (54.9)	
Non-ischemic cause of HF	3876 (48.5)	1192 (58.4)	2684 (45.1)	<0.01
Systolic BP, mmHg (n = 8159)	125.7 ± 20.7	124.4 ± 20.2	126.1 ± 20.8	<0.01
Diastolic BP, mmHg (n = 8164)	71.2 ± 11.4	71.6 ± 12.0	71.0 ± 11.1	0.04
Heart rate, bpm (n = 8199)	72.0 ± 13.9	77.0 ± 16.7	70.3 ± 12.3	<0.01
LBBB (n = 8253)	1411 (17.1)	324 (15.4)	1087 (17.7)	0.01
QRS ≥130 ms (n = 6899)	2757 (40.0)	549 (32.4)	2208 (42.4)	<0.01
eGFR (n = 5813)	59.7 ± 24.6	57.6 ± 24.2	60.4 ± 24.7	<0.01
eGFR (n = 5813)				
<30	655 (11.3)	180 (12.1)	475 (11.0)	
30–59	2410 (41.5)	671 (45.2)	1739 (40.2)	
≥60	2748 (47.3)	632 (42.6)	2116 (48.9)	<0.01
Comorbidity (n = 7399)				
Hypertension	2949 (39.9)	843 (44.3)	2106 (38.3)	<0.01
Diabetes mellitus	2148 (29.0)	589 (31.0)	1559 (28.4)	0.03
COPD	1372 (18.5)	358 (18.8)	1014 (18.4)	0.72
OSAS	491 (6.6)	120 (6.3)	371 (6.7)	0.51
Thyroid disease	551 (7.4)	160 (8.4)	391 (7.1)	0.06
Renal insufficiency[a]	3901 (56.3)	1156 (63.3)	2745 (53.8)	<0.01
No relevant comorbidity	840 (13.6)	158 (9.6)	682 (15.0)	<0.01
Previous interventions (n = 6529)				
PCI	1658 (25.4)	310 (18.6)	1348 (27.7)	<0.01
CABG	1450 (22.2)	363 (21.8)	1087 (22.4)	0.63
Valve intervention	523 (8.0)	173 (10.4)	350 (7.2)	<0.01
Cardiac rhythm				
Sinus rhythm	4901 (59.4)	–	4901 (79.8)	
Ectopic rhythm	102 (1.2)	–	102 (1.7)	
Pacemaker rhythm	1141 (13.8)	–	1141 (18.6)	
Paroxysmal AF	305 (3.7)	305 (14.5)	–	–
Persisted AF	370 (4.5)	370 (17.5)	–	
Permanent AF	1116 (13.5)	1116 (52.9)	–	
AF of unknown type	318 (3.9)	318 (15.1)	–	

AF, Atrial Fibrillation; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, Left-Bundle Branch Block; eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Graft.

[a] Defined as eGFR <60 mL/min or a history of renal failure.

As shown in Table 2, after adjusting for heart rate, patients with AF had still higher odds of receiving beta-blockers, MRAs, diuretics, digoxin, OACs and NOACs, and lower odds of receiving RAS-inhibitors and sotalol. After additional adjustment for other potential confounders, patients with AF had higher odds of receiving beta-blockers, MRAs, diuretics, digoxin, OACs and NOACs and lower odds of receiving sotalol compared to patients without AF. Multiple imputation did not change the results.

3.3. Medical therapy in patients with HFmrEF according to 2016 ESC guidelines

Medical therapy did not differ between patients with HF with mid-range ejection fraction (HFmrEF) and HFrEF in this registry according to the latest HF guidelines. Baseline parameters are shown in Supplementary Table 2. A sub-analysis of only HFmrEF patients showed a similar medical therapy pattern between patients with and without AF as in HFrEF patients (Supplementary Fig. 2).

3.4. Baseline characteristics and medical therapy according AF type

Several significant differences in baseline characteristic were observed between the different AF type cohorts, as shown in Supplementary Table 3. Additionally, patients diagnosed with paroxysmal AF and HF received less often HF medical therapy compared to the other AF types, while sotalol and amiodarone were more often prescribed (Supplementary Table 3).

4. Discussion

In this large practice-based outpatient registry, one-quarter of the HFrEF patients had documented AF. Patients with AF were significantly older and had more symptomatic HF. The differences in the prescription rates of antiarrhythmic drugs, anticoagulation and guideline-recommended HF therapy according to AF, could not be fully explained by heart rate, age or other patient characteristics. These results provide more insight into the clinical profile of HF patients with AF and the guideline adherence in these patients.

4.1. Pharmacological therapy

The efficacy of beta-blockers in chronic HF patients in sinus rhythm has clearly been demonstrated [8], and is reflected in high prescription rates in recent large HF registries [11–13], as well as in this registry. However, the efficacy of beta-blockers in HF patients with AF remains unclear. Several explanations for a different efficacy of beta-blockers

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001

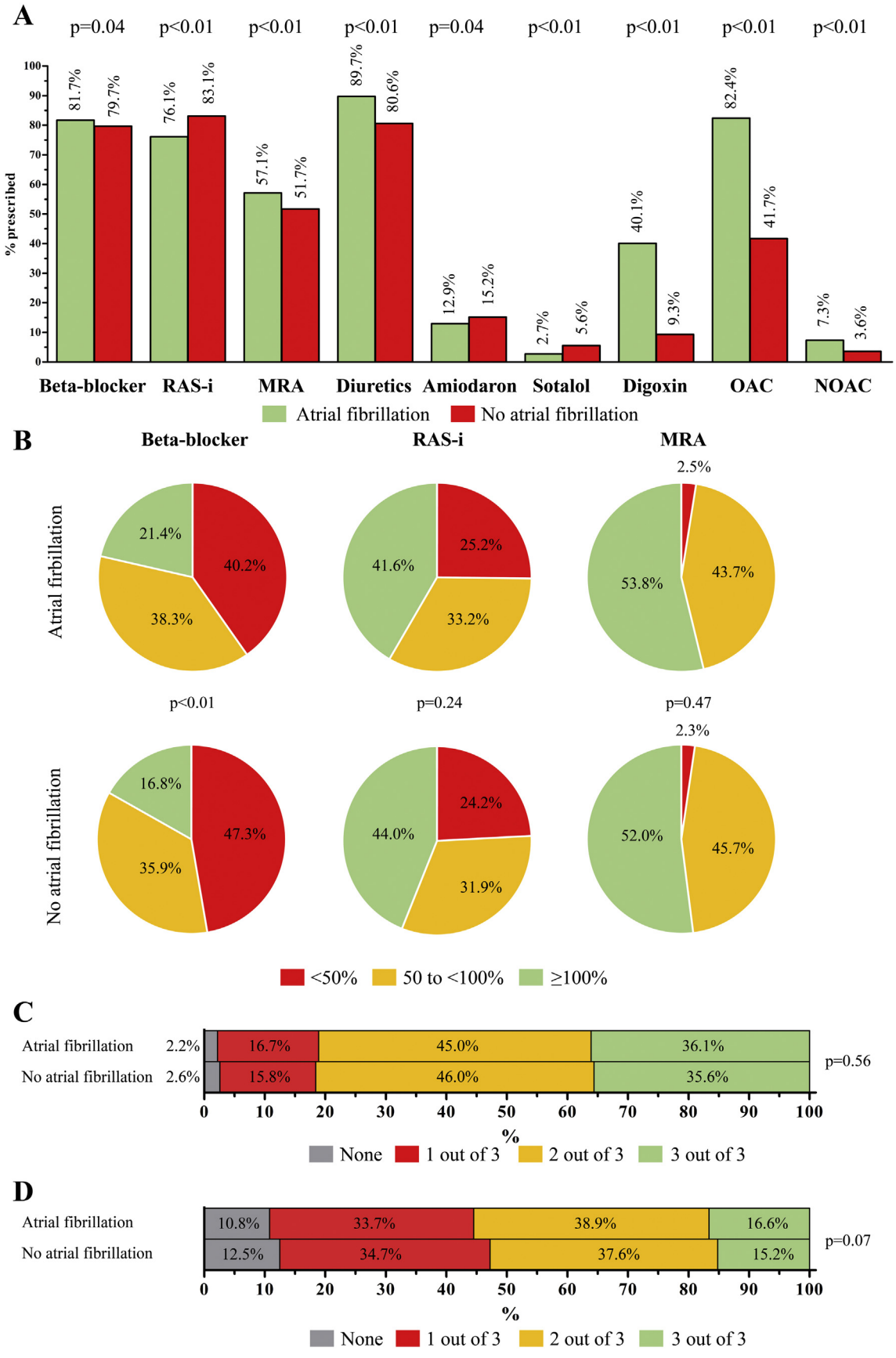

Fig. 1. A Prescription rates of HF therapy, antiarrhythmic drugs and anticoagulation therapy, **B** prescribed dosages of HF therapy expressed as percentage of recommended target dose, **C** combination of beta-blocker, RAS-inhibitor and MRA, **D** and combination of beta-blocker, RAS-inhibitor and MRA at least ≥50% of target dose prescribed, between patients with and without atrial fibrillation.

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001

Table 2
Multivariable analysis: the likelihood of receiving HF therapy in patients with AF compared with patients without AF.

	Univariable		Multivariable					
	OR	p-value	Model 1		Model 2		Model 3	
			OR	p-Value	OR	p-Value	OR	p-Value
Beta-blocker	1.14 [1.01–1.30]	0.04	1.18 [1.04–1.35]	0.01	1.34 [1.17–1.53]	<0.01	1.34 [1.17–1.54]	<0.01
RAS-inhibitor	0.65 [0.57–0.73]	<0.01	0.72 [0.64–0.82]	<0.01	0.93 [0.82–1.06]	0.28	0.92 [0.80–1.05]	0.19
MRA	1.25 [1.13–1.38]	<0.01	1.28 [1.16–1.42]	<0.01	1.40 [1.26–1.56]	<0.01	1.41 [1.26–1.57]	<0.01
Diuretics	2.09 [1.79–2.44]	<0.01	2.00 [1.71–2.34]	<0.01	1.61 [1.36–1.89]	<0.01	1.63 [1.38–1.92]	<0.01
Amiodarone	0.82 [0.68–0.99]	0.04	0.93 [0.77–1.13]	0.47	0.93 [0.76–1.13]	0.45	0.93 [0.76–1.14]	0.48
Sotalol	0.47 [0.36–0.63]	<0.01	0.53 [0.39–0.70]	<0.01	0.54 [0.40–0.73]	<0.01	0.54 [0.40–0.72]	<0.01
Digoxin	6.53 [5.77–7.38]	<0.01	6.17 [5.44–7.00]	<0.01	6.13 [5.37–6.99]	<0.01	6.16 [5.40–7.03]	<0.01
OAC	6.53 [5.75–7.41]	<0.01	6.60 [5.80–7.51]	<0.01	6.12 [5.36–6.98]	<0.01	6.22 [5.45–7.11]	<0.01
NOAC	2.10 [1.69–2.62]	<0.01	2.09 [1.66–2.62]	<0.01	2.28 [1.80–2.89]	<0.01	2.26 [1.80–2.87]	<0.01

Model 1 included heart rate (per 10 beats/min).
Model 2 included heart rate (per 10 beats/min), age, gender, NYHA classification, left ventricular ejection fraction.
Model 3 included heart rate (per 10 beats/min), age, gender, NYHA classification, left ventricular ejection fraction, hypertension, diabetes mellitus, COPD, OSAS, thyroid disease, renal insufficiency (defined as eGFR <60 mL/min or a history of renal insufficiency), and atrial fibrillation.
AF, Atrial Fibrillation; RAS, Renin-Angiotensin System; MRA, Mineralocorticoid Receptor Antagonists.

in HF patients with AF have been proposed. Studies investigating the relationship between heart rate and mortality outcomes in HF patients reported inconsistent results. Sub-analysis from randomized controlled trials did not show an association between mortality and heart rate [14], while observational cohorts did, although these cohorts are at risk for selection bias [15]. A recent meta-analysis demonstrated that a higher heart rate was not associated with a higher mortality rate in HF patients having AF [16]. Furthermore, differences in structural or cellular function in patients with AF could lead to a difference in the efficacy of beta-blockers in these patients [17]. A higher heart rate could compensate for the loss of the atrial kick in AF patients, and thus reducing the effect of beta-blockers [18]. Moreover, irregularity might be less with a higher heart rate.

In a meta-analysis based on individual patient data of basically all major randomized controlled trials, Rienstra et al. demonstrated that the beta-blockers did not reduce the risk of mortality in HF patients with AF, in contrast to HF patients with sinus rhythm [19]. However, this analysis was published after 2016 and could, therefore, not influence the prescription pattern in CHECK-HF. Additional registries are required to see if this individual patient data based meta-analysis influenced the prescription pattern of beta-blockers in HFrEF patients with AF. Multiple other meta-analyses have investigated this relationship with mixed results [6,20]. Several important factors might contribute to the observed differences. Importantly, studies demonstrating a reduction in all-cause mortality in HF patients with AF using beta-blockers were all cohort studies [6]. The risk of inclusion and prescription bias limited the results of these studies. Furthermore, patients included in the randomized controlled trials were on average more symptomatic patients compared with patients included in the cohort studies. It could be that these less symptomatic patients could tolerate beta-blockers better, and in a higher dose, and therefore benefit more from beta-blockers, although this clearly is not the case in patients with sinus rhythm. In a non-randomized cohort study, a dose-dependent effect of beta-blockers in HF patients with AF has been demonstrated, with the largest reduction of events in patients up titrated to the recommended dosage [21].

RAS-inhibitors are a cornerstone in chronic HF treatment [8], and could be used to prevent the occurrence of new paroxysmal AF episodes in HF patients [22,23]. As shown in our registry, the prescription rate of RAS-inhibitors in both HF patients with and without AF was high, and the observed difference between the groups was explained by significant confounders.

Two studies have compared the efficacy of MRAs in chronic HF patients with and without AF, demonstrating similar effects in the prevention of cardiovascular deaths and HF-related hospitalizations [24,25]. Moreover, MRAs reduced the risk of any future AF event in HF patients, although this was only investigated in a post-hoc analysis [25]. We found that patients with AF more often receive MRAs, even after adjustment for several significant confounders. However, prescription rates were relatively low in both groups. Recent registries, investigating the guideline adherence of MRA in chronic HF patients without AF, showed similar prescription rates between 40 and 60% [13,26]. HF patients with AF might be considered to be sicker and were more often symptomatic, indicated by the higher prevalence of AF in more symptomatic HF patients.

4.2. Antiarrhythmic drugs

In chronic HF patients, rhythm control for AF has not been shown to be superior over rate control [27], and adequate rate control prevented unfavorable ventricular remodeling in HF patients [28]. Moreover, in the ESC AF guidelines, it is recommended (Class IA indication) that rate control should be the initial approach in elderly patients with minor AF-related symptoms [7]. Additionally, the ESC HF guidelines recommend reserving rhythm control for HF patients with a reversible cause of AF, or those who do not tolerate AF [8]. This could explain the relatively low prescription rates of amiodarone and sotalol in our registry. Sotalol is considered to be contraindicated in HFrEF, explaining the low prescription rate. However, a substantial portion of HF patients without AF did receive amiodarone and sotalol. These drugs might be prescribed due to ventricular tachycardia and premature ventricular complexes in patients without AF. Unfortunately, we cannot determine the prescription indication of these medications from our data.

In low dosages, digoxin exerts mainly neurohormonal effects, which could be beneficial primarily for reducing hospitalizations in chronic HF patients without AF [29]. The effect of digoxin in HF patients without AF has been investigated in only one randomized controlled trial [30], and showed a neutral effect on mortality, but a beneficial effect on hospitalizations. Since then, post-hoc analyses from observational cohorts demonstrated higher mortality in HF patients without AF treated with digoxin. However, these results are at great risk for prescription bias, with sicker HF patients receiving more often digoxin. Additionally, the use of digoxin in patients with AF without HF is controversial as well, as a meta-analysis demonstrated an association between digoxin use in AF patients and an increased risk of all-cause and cardiovascular mortality [31]. However, these results are based on post-hoc analyses from observational cohorts which are at great risk for prescription bias, with sicker patients more likely to receive digoxin. Therefore, it remains unclear whether it is safe to use digoxin in patients with both AF and HF. The upcoming DECISION trial (NCT03783429), a multicenter randomized controlled trial, will provide more insight into the effect of digoxin in HF patients with AF.

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001

4.3. Anticoagulation therapy

The importance of adequate anticoagulation therapy, in order to prevent stroke, systemic embolism but also excess of bleedings in HF patients with AF, is well known [32]. However, the PINNACLE-AF registry and the EuroHeart survey demonstrated that only approximately 60–70% of HFrEF patients received anticoagulation therapy [33,34]. In contrast, the prescription rates in CHECK-HF were higher, which might be explained by the close monitoring of the Dutch thrombosis service, reducing the risk of potential bleedings. Recently, two meta-analyses showed the efficacy and safety of NOACs in chronic HF patients with AF [35,36]. The prescription rates of NOACs in our registry were very low, reflecting the period of 2013 up to 2016, in which NOACs were just introduced in Dutch clinical practice. We expect that the prescription rates also in HF patients have risen significantly since then. In contrast, the prescription rates of oral anticoagulation therapy were very high in patients with AF.

5. Limitations and strengths

This practice-based registry has some limitations that should be noted. Due to the cross-sectional design of the registry, no follow-up data on patient outcomes is available. Also, some data was missing in our study, which could have caused some bias, although multiple imputation did not influence the results. Furthermore, patients were divided based on a 12-lead ECG, performed during the most recent out-patient clinic visit, or a documented history of AF. The history of AF might have been incomplete, and paroxysmal AF patients could have been missed. Additionally, no details on the indication for OAC/NOAC or anti-arrhythmic therapy, such as a history of ventricular arrhythmias, was available. Furthermore, in the newer guidelines [8], HF categories based on LVEF have been changes, our analysis was limited by a small number of patients where LV function was semi-quantitatively analyzed with echocardiography, and some newer treatment strategies, such as the uptake sacubitril/valsartan (substitution for ACE-i/ARB) or NOACs were only in small numbers used in this time period. Still, NOACs improbably influences the already high us of anticoagulation in AF and the use of RAS-inhibitors was high in both patients with and without AF. Therefore, it is unlikely that the conclusions from CHECK-HF are influenced by the focus on the period between 2012 and 2016. The major strengths of this study are the large sample size and the reflection of true clinical practice of the nationwide outpatient HF management, with detailed information on HF medication prescription rate and prescribed dosages.

6. Conclusion

In this national registry, consisting of 8253 chronic HFrEF patients, significant differences exist in prescription rates of guideline-recommended HF therapy between patients with and without AF. These results show the need for a better understanding of the efficacy and adherence of guideline-recommended HF therapy in patients with AF.

Compliance with ethical standards

Funding: Servier, the Netherlands, funded the inclusion of data and software programme. The steering committee (HBRLR, GL, AH, JB) received no funding for this project. This analysis was initiated by the authors and was designed, conducted, interpreted, and reported independently of the sponsor. The current study had no other funding source or any with a participating role in outcome assessment, or writing of the manuscript. All authors had joint responsibility for the decision to submit for publication.

CRediT authorship contribution statement

Jesse F. Veenis: Formal analysis, Methodology, Visualization, Writing - original draft. **Hans-Peter Brunner-La Rocca:** Conceptualization, Data curation, Supervision, Writing - review & editing. **Gerard C.M. Linssen:** Conceptualization, Investigation, Writing - review & editing. **Frank J.J. Smeele:** Investigation, Writing - review & editing. **Noëmi T.A.E. Wouters:** Investigation, Writing - review & editing. **Paul H.M. Westendorp:** Investigation, Writing - review & editing. **Philip C. Rademaker:** Investigation, Writing - review & editing. **Martin E.W. Hemels:** Investigation, Writing - review & editing. **Michiel Rienstra:** Conceptualization, Investigation, Writing - review & editing. **Arno W. Hoes:** Conceptualization, Methodology, Project administration, Writing - review & editing. **Jasper J. Brugts:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - review & editing.

Declaration of competing interest

All authors report no conflict of interest.

Acknowledgments

We greatly acknowledge the participation of HF nurses and cardiologists of all sites for including patients and entering patient data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.03.001.

References

[1] U. Sartipy, U. Dahlstrom, M. Fu, L.H. Lund, Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction, JACC Heart Fail. 5 (2017) 565–574.
[2] W.H. Maisel, L.W. Stevenson, Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy, Am. J. Cardiol. 91 (2003) 2D–8D.
[3] G.C. Linssen, M. Rienstra, T. Jaarsma, A.A. Voors, I.C. van Gelder, H.L. Hillege, et al., Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction, Eur. J. Heart Fail. 13 (2011) 1111–1120.
[4] S. Prabhu, A. Voskoboinik, D.M. Kaye, P.M. Kistler, Atrial fibrillation and heart failure - cause or effect? Heart Lung Circ. 26 (2017) 967–974.
[5] T.S. Cherian, P. Shrader, G.C. Fonarow, L.A. Allen, J.P. Piccini, E.D. Peterson, et al., Effect of atrial fibrillation on mortality, stroke risk, and quality-of-life scores in patients with heart failure (from the outcomes registry for better informed treatment of atrial fibrillation [ORBIT-AF]), Am. J. Cardiol. 119 (2017) 1763–1769.
[6] G. Ma, Q. Fang, F. Wang, The effect of beta-blockers on mortality in patients with heart failure and atrial fibrillation: a meta-analysis of observational cohort and randomized controlled studies, Cardiol. J. 26 (2019) 744–752.
[7] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962.
[8] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 18 (2016) 891–975.
[9] J.J. Brugts, G.C.M. Linssen, A.W. Hoes, H.P. Brunner-La Rocca, investigators C-H, Real-world heart failure management in 10,910 patients with chronic heart failure in the Netherlands: design and rationale of the Chronic Heart failure ESC guideline-based Cardiology practice Quality project (CHECK-HF) registry, Neth. Hear. J. 26 (2018) 272–279.
[10] J.J. McMurray, S. Adamopoulos, S.D. Anker, A. Auricchio, M. Bohm, K. Dickstein, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 33 (2012) 1787–1847.
[11] H.P. Brunner-La Rocca, G.C. Linssen, F.J. Smeele, A.A. van Drimmelen, H.J. Schaafsma, P.H. Westendorp, et al., Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF registry, JACC Heart Fail. 7 (2019) 13–21.
[12] D.E. Forman, C.P. Cannon, A.F. Hernandez, L. Liang, C. Yancy, G.C. Fonarow, et al., Influence of age on the management of heart failure: findings from Get With the Guidelines-Heart Failure (GWTG-HF), Am. Heart J. 157 (2009) 1010–1017.
[13] A.P. Maggioni, S.D. Anker, U. Dahlstrom, G. Filippatos, P. Ponikowski, F. Zannad, et al., Are hospitalized or ambulatory patients with heart failure treated in accordance

ARTICLE IN PRESS

with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry, Eur. J. Heart Fail. 15 (2013) 1173–1184.
[14] B.A. Mulder, K. Damman, D.J. Van Veldhuisen, I.C. Van Gelder, M. Rienstra, Heart rate and outcome in heart failure with reduced ejection fraction: differences between atrial fibrillation and sinus rhythm-a CIBIS II analysis, Clin. Cardiol. 40 (2017) 740–745.
[15] S.J. Li, U. Sartipy, L.H. Lund, U. Dahlstrom, M. Adiels, M. Petzold, et al., Prognostic significance of resting heart rate and use of beta-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: findings from the Swedish Heart Failure Registry, Circ. Heart Fail. 8 (2015) 871–879.
[16] J. Simpson, D. Castagno, R.N. Doughty, K.K. Poppe, N. Earle, I. Squire, et al., Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis, Eur. J. Heart Fail. 17 (2015) 1182–1191.
[17] V. Rudolph, R.P. Andrie, T.K. Rudolph, K. Friedrichs, A. Klinke, B. Hirsch-Hoffmann, et al., Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation, Nat. Med. 16 (2010) 470–474.
[18] J.M. Rawles, What is meant by a "controlled" ventricular rate in atrial fibrillation? Br. Heart J. 63 (1990) 157–161.
[19] M. Rienstra, K. Damman, B.A. Mulder, I.C. Van Gelder, J.J. McMurray, D.J. Van Veldhuisen, Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis, JACC Heart Fail. 1 (2013) 21–28.
[20] D. Kotecha, M.D. Flather, D.G. Altman, J. Holmes, G. Rosano, J. Wikstrand, et al., Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure, J. Am. Coll. Cardiol. 69 (2017) 2885–2896.
[21] J. Campodonico, M. Piepoli, F. Clemenza, A. Bonomi, S. Paolillo, E. Salvioni, et al., Dose-dependent efficacy of beta-blocker in patients with chronic heart failure and atrial fibrillation, Int. J. Cardiol. 273 (2018) 141–146.
[22] M.P. Schneider, T.A. Hua, M. Bohm, K. Wachtell, S.E. Kjeldsen, R.E. Schmieder, Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis, J. Am. Coll. Cardiol. 55 (2010) 2299–2307.
[23] T. Yamauchi, Y. Sakata, M. Miura, S. Tadaki, R. Ushigome, K. Sato, et al., Prognostic impact of new-onset atrial fibrillation in patients with chronic heart failure - a report from the CHART-2 study, Circ. J. 80 (2016) 157–167.
[24] M. Cikes, B. Claggett, A.M. Shah, A.S. Desai, E.F. Lewis, S.J. Shah, et al., Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial, JACC Heart Fail. 6 (2018) 689–697.
[25] K. Swedberg, F. Zannad, J.J. McMurray, H. Krum, D.J. van Veldhuisen, H. Shi, et al., Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study, J. Am. Coll. Cardiol. 59 (2012) 1598–1603.
[26] W. von Scheidt, C. Zugck, M. Pauschinger, R. Hambrecht, O. Bruder, A. Hartmann, et al., Characteristics, management modalities and outcome in chronic systolic heart failure patients treated in tertiary care centers: results from the EVIdence based TreAtment in Heart Failure (EVITA-HF) registry, Clin. Res. Cardiol. 103 (2014) 1006–1014.
[27] J. Cadrin-Tourigny, D.G. Wyse, D. Roy, L. Blondeau, S. Levesque, M. Talajic, et al., Efficacy of amiodarone in patients with atrial fibrillation with and without left ventricular dysfunction: a pooled analysis of AFFIRM and AF-CHF trials, J. Cardiovasc. Electrophysiol. 25 (2014) 1306–1313.
[28] V.E. Hagens, D.J. Van Veldhuisen, O. Kamp, M. Rienstra, H.A. Bosker, N.J. Veeger, et al., Effect of rate and rhythm control on left ventricular function and cardiac dimensions in patients with persistent atrial fibrillation: results from the RAte Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study, Heart Rhythm. 2 (2005) 19–24.
[29] A. Ahmed, M.W. Rich, T.E. Love, D.M. Lloyd-Jones, I.B. Aban, W.S. Colucci, et al., Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial, Eur. Heart J. 27 (2006) 178–186.
[30] Investigation G. Digitalis, The effect of digoxin on mortality and morbidity in patients with heart failure, N. Engl. J. Med. 336 (1997) 525–533.
[31] W. Qureshi, W.T. O'Neal, E.Z. Soliman, M.H. Al-Mallah, Systematic review and meta-analysis of mortality and digoxin use in atrial fibrillation, Cardiol. J. 23 (2016) 333–343.
[32] M. Agarwal, S. Apostolakis, D.A. Lane, G.Y. Lip, The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review, Clin. Ther. 36 (2014) 1135–1144.
[33] R. Nieuwlaat, L.W. Eurlings, J.G. Cleland, S.M. Cobbe, P.E. Vardas, A. Capucci, et al., Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation, J. Am. Coll. Cardiol. 53 (2009) 1690–1698.
[34] J.P. Contreras, K.N. Hong, J. Castillo, L.N. Marzec, J.C. Hsu, C.P. Cannon, et al., Anticoagulation in patients with atrial fibrillation and heart failure: insights from the NCDR PINNACLE-AF registry, Clin. Cardiol. 42 (2019) 339–345.
[35] G. Savarese, R.P. Giugliano, G.M. Rosano, J. McMurray, G. Magnani, G. Filippatos, et al., Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis, JACC Heart Fail. 4 (2016) 870–880.
[36] Q. Xiong, Y.C. Lau, K. Senoo, D.A. Lane, K. Hong, G.Y. Lip, Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials, Eur. J. Heart Fail. 17 (2015) 1192–1200.

Please cite this article as: J.F. Veenis, H.-P. Brunner-La Rocca, G.C.M. Linssen, et al., Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: The CHECK-HF r..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.03.001