Symptom management strategies

Rhythm vs rate control in patients with atrial fibrillation in the Balkan region: Data from the BALKAN-AF survey

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Published in:
International Journal of Clinical Practice

DOI (link to publication from Publisher):
10.1111/ijcp.14080

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

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Article type : Original Paper

Manuscript type: Clinical Investigation

Symptom management strategies: rhythm versus rate control in patients with atrial fibrillation in the Balkan region: Data from the BALKAN-AF Survey

Short title: BALKAN-AF survey: rhythm vs. rate control

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/IJCP.14080

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Acknowledgements

We thank all BALKAN-AF investigators for their hard work.

Abstract

Background Symptom-focused management is one of the cornerstones of optimal atrial fibrillation (AF) therapy.

Objectives To evaluate the use of rhythm control and rate control strategy. Second, to identify predictors of the use of amiodarone in patients with rhythm control and of the use of rhythm control strategy in patients with paroxysmal AF in the Balkans.

Methods Prospective enrolment of consecutive patients from 7 Balkan countries to the BALKAN-AF survey was performed.

Results Of 2,712 enrolled patients, 2,522 (93.0%) with complete data were included: 1,622 (64.3%) patients were assigned to rate control strategy and 900 (35.7%) to rhythm control. Patients with rhythm control were younger, more often hospitalized for AF and with less comorbidities (all $p < 0.05$) than those with rate control. Symptom score [European Heart Rhythm Association (EHRA)] was not an independent predictor of a rhythm control strategy [odds ratio (OR) 0.99, 95% confidence interval (CI) 0.90-1.10, $p = 0.945$]. The most commonly chosen antiarrhythmic agents were amiodarone (49.7%), followed by propafenone (24.3%).

Conclusion More than one third of patients in BALKAN-AF survey received a rhythm control strategy, and these patients tended to be younger with less comorbidities than those managed with rate control. EHRA symptom score is not significantly associated with rhythm control strategy. The most commonly used antiarrhythmic agents were amiodarone, followed by propafenone.

Keywords: amiodarone, atrial fibrillation, oral anticoagulants, rate control, rhythm control

What is already known about the topic?

Better symptom management with the use of rate or rhythm control is one of the components of the Atrial fibrillation Better Care pathway for holistic management of atrial fibrillation. Both rate and rhythm strategy tend to be non-inferior in case of mortality, stroke and hospitalization.

What does this article add?

In the largest prospective AF dataset from the Balkans, more than one third of patients received a rhythm control strategy, and these patients tended to be younger with less comorbidities than those managed with rate control. EHRA symptom score is not significantly associated with rhythm control. The most commonly used antiarrhythmic agents were amiodarone, followed by propafenone.

Introduction

The Atrial fibrillation Better Care (ABC) pathway for holistic management of atrial fibrillation (AF) is based on simple approach (A, Avoid stroke, B, Better symptom management, C, Cardiovascular and comorbidity risk reduction) [1]. One of the components of this pathway for integrated care management is better symptom management with the use of rate or rhythm control. Such a management strategy based on symptoms enables to hierarchize the initial management strategy, with the decision being patient-centred [1].

Rate control is the strategy that tend to be usually adequate to improve symptoms related with AF [2]. The evidence for the optimal type and intensity of rate control strategy are scarce [3-5]. The aim of a rhythm control strategy is to reduce AF-related symptoms by maintaining sinus rhythm

and reducing the recurrence of AF. The use of antiarrhythmic agents allows the maintenance of sinus rhythm, which is approximately two times greater compared with placebo [6-8]. When antiarrhythmic drugs are ineffective, catheter ablation or combination therapy may be chosen [9-11].

Both rate and rhythm strategy tend to be non-inferior in case of mortality, stroke and hospitalization [3, 7, 12-16]. Some studies showed contradictory results with lower mortality in patients on rhythm control strategy when compared to rate control [17-19].

The BALKAN-AF was a registry conducted in seven countries (Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Montenegro, Romania and Serbia) in the Balkan region, to find out contemporary management of AF patients in the region encompassing approximately 50 million inhabitants. Moreover, data regarding this region in large, international AF registries are scarce [20].

The aim of this study was to (i) evaluate the use of rhythm control and rate control strategy and (ii) identify predictors of the use of amiodarone in patients with rhythm control and of the use of rhythm control strategy in patients with paroxysmal AF in seven Balkan countries.

Materials and Methods

Details on the BALKAN-AF survey have been formerly described [20]. In brief, data regarding consecutive subjects with electrocardiographically documented 'non-valvular' AF were collected prospectively. Cardiologist or an internal medicine specialist, where cardiologist was not available evaluated and examined patients. University, non-university hospitals and outpatient health centres (a total of 49 centres), localized around the Balkans, were sites in registry.

This 14-week, multicenter, observational snapshot registry was designed and performed by the Serbian Atrial Fibrillation Association (SAFA). The BALKAN-AF survey was performed from December 2014 to February 2015. This survey was presented to the National Cardiology Societies/ relevant Working Groups in particular Balkan countries. In the Balkan region the registry was approved by the National and/ or local Institutional Review Board. An informed consent form was gathered from all the patients before enrollment to the survey. The study protocol is in agreement with the ethical guidelines of the 1975 Declaration of Helsinki.

Patients younger than 18 years, with prosthetic mechanical heart valves, with moderate or severe mitral stenosis or any significant heart valve disease with indications to surgical treatment were excluded from the study.

SAFA designed classic electronic case report forms which were sent to collect data. Following information was obtained: patients' clinical characteristics and characteristics of AF, health care location, patients' physical findings and management at visit. Cardiovascular risk factors, diseases and risk scores were defined according to particular European Society of Cardiology guidelines, other guidelines, scientific statements and textbooks showed previously in Supplementary Information [21]. Diagnostic assessment and treatment associated with AF was collected at enrolling visit and previous 12 months. Stroke risk was evaluated based on CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/ transient ischaemic attack (TIA), vascular disease, age 65-74 years, sex category (female)] score [22]. Bleeding risk was evaluated according to HAS-BLED [hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio (INR), elderly (>65 years), drugs or alcohol concomitantly] score [23].

Systematic monitoring of centres and follow-up visits were not performed. National coordinators and all investigators were responsible for consecutiveness of enrolled patients, correctness and completeness of data.

In this study, patients were assigned to rhythm or rate control as declared by the responsible physician/ investigator. "Inadequately controlled heart rate (HR)" (HR <50 or >110 beats per minute) was one of the reasons for receiving rhythm control strategy.
This 'real life' registry contains data on the use of rate control management and rhythm control management, which are not 'pure'.

Statistical analysis

Continuous variables were reported as mean and standard deviation and categorical variables as absolute frequencies and percentages. Between-group comparisons were performed with Student's t-test or Mann-Whitney test. The descriptive analysis involved baseline characteristics of patients with rate and rhythm control strategy. The comparative analyses among patients with rhythm control were made using univariate and multivariate logistic regression analyses. Statistically significant variables in univariate logistic regression model were put into multivariate logistic

regression model to identify multivariable predictors of the use of rhythm control in patients with paroxysmal AF and of amiodarone use in the rhythm control group. Results are presented as odds ratio (OR) with 95% confidence interval (CI). A two-sided *p* value of less than 0.05 was considered as statistically significant. All analyses were calculated using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 2,712 enrolled patients, 2,522 (93.0%) had available data on rhythm or rate control strategy. 1,622 (64.3%) patients were assigned to rate control and 900 (35.7%) to rhythm control (Table 1).

Demographic and AF-related characteristics

Patients assigned to rhythm control were younger, less likely to be female than patients with rate control, and, as expected, were not classified as having permanent AF, (all $p<0.05$). The rhythm control group was more likely to have paroxysmal AF, persistent AF and shorter duration of AF history than patients with rate control, (all $p<0.001$). There were no significant differences in mean European Heart Rhythm Association (EHRA) symptom score, ($p=0.979$). Patients with rhythm control were more likely to have symptoms attributable to AF (as judged by responsible physician/investigator) including palpitations, whilst patients in rate control were more likely to have shortness of breath, (all $p < 0.001$), Table 1. Other variables are shown in Table 1.

Rate vs. rhythm control, in relation to EHRA score

Rhythm control was more often chosen in patients with higher EHRA symptom score (EHRA II-III) than in those with low EHRA symptom score. More than half of the highly symptomatic patients (EHRA III-IV) was not medicated with rhythm control therapy (Figure 1).

On univariate analysis, EHRA symptom score was not an independent predictor of rhythm control strategy (OR 0.99, 95% CI 0.90-1.10, $p = 0.945$). Moreover, EHRA symptom score was an independent predictor of rate control strategy on univariate analysis (OR 1.14, 95% CI 1.03-1.25, $p = 0.011$) but not on multivariate analysis.

Inadequately controlled HR, (HR <50 or >110 beats per minute) was present in 21.3% of patients in rate control and 32.6% of patients in rhythm control strategy (supplementary Table 1).

Predictors of rhythm control in EHRA III-IV

Univariate analysis is showed in the Supplementary Information. On multivariate analysis, capital city, AF being main reason for the hospitalization, palpitations, symptoms attributable to AF, and mean HR were independent predictors of increased use of rhythm control. HF was an independent predictor of decreased use of rhythm control strategy (supplementary Table 2).

Physical findings and comorbidity

Patients with rhythm control have more often higher mean HR (96.2±31.8 vs. 91.0±26.2) and inadequately controlled HR (HR <50 or >110 beats per minute), than those with rate control (32.6% vs. 21.3% respectively, both $p < 0.05$). The rhythm control group was less likely to be affected by comorbidities than those in rate control with the exception of hypertension ($p=0.051$), peripheral artery disease (PAD) ($p=0.055$) and obesity ($p=0.318$), Table 2.

Stroke and bleeding risk factors

Patients selected to rhythm control strategy had lower mean CHA_2DS_2-VASc score (2.7±1.7 vs. 3.8±1.8) and mean HAS-BLED score (1.6±1.1 vs. 2.2±1.2) than those with rate control, (both $p<0.001$). The rhythm control group includes significantly lower proportion of patients with CHA_2DS_2-VASc score ≥2 and with HAS-BLED score ≥3 (both $p < 0.001$) than those with rate control. They have also significantly higher proportion of 'low risk' patients with CHA_2DS_2-VASc score of 0 in males or of 1 in females ($p <0.001$) than patients with rate control (Table 2).

AF management settings and diagnostic assessment

In patients assigned to rhythm control, AF was more often main reason for the hospitalization ($p <0.001$). The rhythm control group has significantly higher proportion of patients managed in academic healthcare facility and treated by cardiologists than patients with rate control (both $p < 0.001$). Patients with rate control had significantly higher proportion of subjects having outpatient visit ($p <0.001$) than those with rhythm control. Patients assigned to rhythm control had more often blood tests and other diagnostic assessment than patients with rate control (all $p <0.001$), Table 3.

Stroke prevention strategies

Subjects with rhythm control strategy had significantly higher proportion of patients with non-vitamin K antagonist oral anticoagulants (NOAC) and single antiplatelet therapy alone (both $p < 0.05$) than those with rate control. Patients with rate control have significantly higher proportion of patients with overall OAC, OAC alone and VKA (all $p < 0.001$) than those with rhythm control, Table 3.

Arrhythmia-directed management strategies

Beta-blockers were the most often used among rate control drugs (82.3%), followed by digoxin (36.6%). Amiodarone was the most commonly used anti-arrhythmic agent (49.7%), followed by propafenone (24.3%), Table 3. The rate of amiodarone use in first-diagnosed AF was 55.0% and among reduced ejection fraction (HFrEF) patients 59.9%.

Electrical cardioversion (ECV) was the most commonly used among non-pharmacological therapies of rhythm control (10.8%), followed by AF catheter ablation (6.7%). Surgical ablation was not widely chosen (0.1%). Propafenone was used in approximately 10% of patients with structural heart disease, Figure 2.

Patients with rhythm control were managed less often with loop diuretics and polypharmacy (defined as the use of five or more drugs [24]), (both $p < 0.001$), Table 3.

Predictors of rhythm control strategy in patients with paroxysmal AF

Univariate analysis is showed in the online supplement. On multivariate analysis, non-emergency centre, management by cardiologist, symptoms attributable to AF, palpitations, mean HR, hypertension and AF as the main reason for the hospitalization were independent predictors of increased use of rhythm control strategy in patients with paroxysmal AF, whereas heart failure (HF) and mean CHA_2DS_2-VASc score value were independent predictors of decreased likelihood of rhythm control use in patients with paroxysmal AF, Table 4.

Predictors of amiodarone use in patients with rhythm control strategy

Univariate analysis is presented in the Supplementary Information. On multivariate analysis, treatment by cardiologist, chest pain, dilated cardiomyopathy (DCM), and mean CHA_2DS_2-VASc score value were associated with increased likelihood of amiodarone use. Paroxysmal AF and outpatient visit were negatively associated with the use of amiodarone, Table 5.

Discussion

In the largest prospective AF dataset from the Balkans, rate control is more frequently chosen strategy for symptom management (64.3%) than rhythm control (35.7%). Our principal findings were as follows: *i)* patients assigned to rhythm control strategy were younger, with less concomitant diseases and lower stroke and bleeding risk, but more likely to have symptoms attributable to AF, inadequately controlled HR and paroxysmal AF than patients with rate control*, ii)* EHRA symptom score is not significantly associated with rhythm control strategy, *iii)* among rhythm control drugs, amiodarone was the most often used one, whereas beta-blockers were most commonly used agents for rate control strategy, *i*v) the use of rhythm control strategy in patients with paroxysmal AF has been significantly associated with the presence of AF-related symptoms*, and v)* non-pharmacological therapies were less often used compared with ECV.

The Balkan region has generally been under-represented in prior registries or trials. In the EURObservational Research Programme Atrial Fibrillation Pilot Registry (EORP-AF Pilot) [25], rate control was also more often used than rhythm control. The general trend with younger patients with less comorbidities who were chosen for rhythm control strategy is present also in EORP-AF Pilot Registry, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry and Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORDAF) [25-27]. In our analysis, women received more commonly rate control what was consistent with other dataset [28]. Patients with more prevalent concomitant diseases might have been assigned to rate control strategy because of contraindications to anti-arrhythmic drugs for rhythm control. Younger patients with less comorbidities appear to be more active and may complain of higher burden of symptoms during daily activities.

A history of AF duration of less than 1-year was present in only 18% of patients in the rhythm control strategy group and this possibly influenced the choice of strategies and treatments.
Patients with more prevalent symptoms attributable to AF managed with rhythm control strategy were also seen in other registries [25, 26, 29, 30]. In our study and in Prevention of thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF), more than half of the highly symptomatic patients (EHRA III-IV) was not medicated with rhythm control therapy [31].

In the Balkan region HF was an independent predictor of decreased use of rhythm control strategy. This was also seen in other registry [27]. Of note, catheter ablation based rhythm control compared with amiodarone therapy significantly reduces AF recurrences and re-hospitalizations and improves quality of life in AF patients with HF [2, 32].

Adequate heart rate control

In this study, patients qualified to rhythm control were more likely to have HR inadequately controlled (<50 or > 110 bpm) than patients with rate control. Importantly, the majority of patients with suboptimally controlled HR in both groups remained highly symptomatic (EHRA II-IV). According to guidelines, lenient rate control is indicated as an initial approach, unless symptoms require stricter rate control [2]. Importantly, an attempt should be made to improve physician' skills to successfully deliver symptom-focused management.

Rhythm control agents

Amiodarone was the most often used anti-arrhythmic agent (49.7%) for rhythm control in the Balkan region, followed by propafenone (24.3%). In the EORP-AF Pilot Registry [25], the PREFER in AF registry [31], the Central Registry of the German Competence NETwork on Atrial Fibrillation (AFNET) [33] and in the EuroHeart survey [30] amiodarone was also most often used antiarrhythmic agent for rhythm control. However, in the BALKAN-AF survey the proportion of patients medicated with amiodarone was the highest when compared to the above mentioned studies where the proportion of patients on amiodarone varies from 13.8% to 35.0%. Similarly to our study, class Ic agents are the second from the most frequently used anti-arrhythmic drugs in other registries [25, 30, 31, 33]. However, the proportion of Ic agents is lower in the above mentioned registries than in our study [25, 30, 31, 33].

The use of specific antiarrhythmic agents reflects their availability in the participating countries. Vernakalant, for example, is not available in any of the participating countries, whereas flecainid has been available only in some of the participating countries at the time of BALKAN-AF survey.

Rate control agents

In this study, beta-blockers followed by digoxin were also the most often used agents for rate control. This is also consistent with other datasets [17, 34]. Rate control drugs were used in about

15% of patients with paroxysmal AF. However, treatment of patients with paroxysmal AF with digoxin may be associated with longer attacks [35].

Symptom-focused management

In our study, symptoms attributable to AF, palpitations and mean HR were independent predictors of increased use of rhythm control strategy in patients with paroxysmal AF. Management of paroxysmal AF has appeared to be more symptom directed what is similar to other European registry [36, 37]. This symptom-oriented approach follows an integrated management of AF according to ABC pathway [1, 38]. Unfortunately, a high proportion of symptomatic patients still did not receive rhythm control management. One possibility may be that some patients had history of unsuccessful rhythm control therapy. Possibly some patients have contraindications for particular antiarrhythmic agents or are reluctant to rhythm control strategy. Non-pharmacological therapies like AF catheter ablation and surgical AF ablation were also less commonly used for rhythm control strategy than ECV. This is also reflected in other registries [30, 33, 36].

Many countries in the Balkan region are still in development. Therefore, implementation of guideline-adherent recommendations for AF management from the European Society of Cardiology guidelines into daily clinical practice in the Balkan region may be suboptimal and modified by factors different from those in other parts of Europe, and the management of AF in the Balkans may differ accordingly. Hence the value of this registry, which reports on an European region that did not have much prior published data.

The limited use of AF ablation may be associated with limited access to this management option in the Balkan region. At the time of BALKAN-AF survey, AF catheter ablation was not available at all in Bosnia & Herzegovina and Albania, and was limited to very few hospitals in other countries.

Non-emergency centre, management by cardiologist, symptoms attributable to AF, palpitations, mean HR and AF as the main reason for hospitalization were independent predictors of increased use of rhythm control in patients with paroxysmal AF, whereas HF and mean CHA_2DS_2-VASc score were negatively associated with rhythm control use in subjects with paroxysmal AF. In the Balkan region, cardiologists chose rhythm control therapy more often than other specialists. In other study, cardiologists were also more likely to choose rhythm control therapy than other

specialists [17]. Those with rhythm control strategy were also more often hospitalized because of AF, than patients with rate control. A similar pattern has been found in other study [39].

In the Balkans, HF was linked with decreased use of rhythm control strategy in patients with paroxysmal AF. According to guidelines, a rhythm control strategy should be used in patients who develop HF with reduced ejection fraction, as a result of tachycardiomyopathy, to make left ventricle function better after restoration of sinus rhythm [2, 40, 41].

In our study, treatment by cardiologist, chest pain, DCM and mean CHA_2DS_2-VASc score were associated with increased use of amiodarone, whereas paroxysmal AF and outpatients visits were independent predictors of decreased use of amiodarone. In one study [42], greater amiodarone use was also associated with physician specialty because electrophysiologists and cardiologists chose amiodarone more frequently than other specialists. DCM was associated with increased use of amiodarone probably due to its safety in patients with HF and indication for prevention of recurrent symptomatic AF in patients with HF [2, 7]. Paroxysmal AF if accompanied by repetitive symptoms and HF should ideally be managed with amiodarone, although the CASTLE-AF trial suggested that catheter ablation was associated with lower rates of death from any cause and hospital readmissions for HF along with reducing the burden of AF and improving the left ventricular ejection fraction when compared to medical therapy in AF patients with HF [43].

Propafenone is well tolerated, safe and effective in patients with recurrent AF [44]. On the other hand, propafenone is not indicated in patients with HF or significant ischaemic heart disease [2]. Unfortunately, in the Balkans about 10% of patients with HF assigned to rhythm control received propafenone despite contraindications. Moreover, about 10% of individuals with ischaemic heart disease qualified to rhythm control strategy were prescribed propafenone.

In the Balkan region, better symptom management including patient-centered, symptom directed decisions should be highlighted. Unfortunately, more than half of the patients with EHRA III-IV symptom scores were not medicated with rhythm control strategy. Non-pharmacological therapies might be more commonly used for rhythm control than they were in the BALKAN-AF survey. Unfortunately, a low use of AF ablation reflected the limited amount of electrophysiology units in the Balkan region. Amiodarone seem to be overused in the Balkan region. Moreover, significant proportion of patients is prescribed propafenone despite structural heart disease. Thus, the choice of optimal agent for rhythm control therapy should be emphasised.

The use of single antiplatelet or DAPT alone was commonly seen in BALKAN-AF patients. This has been observed in most of the 'real-world' AF registries conducted in the same time period [45]. In a previous study from the BALKAN-AF cohort [21], patients with chronic coronary syndromes were more likely to be prescribed aspirin or DAPT or OAC plus antiplatelet agent instead of OAC monotherapy. Also, prior myocardial infarction was an independent predictor of OAC non-use in the Balkan region.

Limitations

There are various limitations of our study that should be noticed. One is no follow-up data to evaluate outcomes. Possible selection bias is evident because of different healthcare settings in the participating countries. Moreover, information about patient/prescriber treatment preferences is lacking. Also, data from the registry are limited to the Balkan population, but this is the largest AF dataset from this region. Moreover, physicians knew that their recommendations on diagnostic assessment and management would be recorded. Registries are likely to attract selected highly motivated patients and their treatment at enrolment may reflect higher compliance. However, due to enrolment of consecutive patients, the probability for a physician to enrol mainly patients with increased compliance is limited. Access to the AF catheter ablation and surgical AF ablation might have been limited in the Balkan region what reflected the small proportion of patients managed with those methods. Data on tachycardiomyopathy are not available. Finally, tests for difference in proportions between rate and rhythm control group were not performed.

Conclusions

More than one third of patients in BALKAN-AF received a rhythm control strategy, and these patients tended to be younger with less comorbidities than those managed with rate control. EHRA symptom score is not significantly associated with rhythm control. The most commonly used antiarrhythmic agents were amiodarone, followed by propafenone.

Funding

BALKAN-AF was not sponsored or funded.

Conflicts of interest

Dr Kozieł, dr Mihajlovic, dr Pavlović, dr Paparisto, professor Music, dr Dan, professor Kusljugic, professor Trendafilova , professor G.A. Dan – the authors declare they have no conflict of interest.

Professor Nedeljkovic has been a speaker for Bayer Serbia.

Professor Lip has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo (no fees).

Professor Potpara has been a consultant for Bayer/Jansen and BMS/Pfizer (no fees).

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Table 1. Demographic and atrial fibrillation-related characteristics

Variable	**Rate control n = 1622 (64.3%)**	**Rhythm control n = 900 (35.7%)**	**p value**
Mean age (years)	71.0 ±10.0	65.6 ± 11.2	<0.001
Age ≥ 75 years	669 (41.2)	201 (22.3)	<0.001
Female sex	749 (46.2)	402 (44.7)	0.022
Alcohol abuse	71 (4.4)	35 (3.9)	0.349
Paroxysmal AF	239 (14.7)	616 (68.4)	<0.001
Persistent AF	210 (12.9)	211 (23.4)	<0.001
Permanent AF	1005 (62.0)	0 (0.0)	<0.001
AF history of less than 1 year	216 (13.3)	163 (18.1)	<0.001
AF history of more than 5 years	384 (23.7)	130 (14.4)	<0.001
Asymptomatic AF currently*	350 (21.6)	437 (48.6)	0.001
Symptoms attributable to AF	1310 (80.8)	689 (76.6)	0.001
Symptoms			
Palpitations	659 (40.6)	551 (61.2)	<0.001
Chest pain	389 (24.0)	215 (23.4)	0.996
Shortness of breath	885 (54.6)	348 (38.7)	<0.001
Syncope	72 (4.4)	35 (3.9)	0.796
Dizziness	288 (17.8)	125 (13.9)	0.015
Fatigue	740 (45.6)	296 (32.9)	<0.001
Fear, anxiety	170 (10.5)	92 (10.2)	0.302
EHRA symptom score (mean)	2.2 ± 0.8	2.2 ± 0.8	0.979
EHRA I	311 (19.2)	210 (23.3)	0.001
EHRA II	784 (48.3)	390 (43.3)	0.098
EHRA III	442 (27.3)	248 (27.6)	0.432
EHRA IV	85 (5.2)	51 (5.7)	0.409

*As judged by responsible physician/ investigator

AF, atrial fibrillation, EHRA, European Heart Rhythm Association.

Table 2. Physical findings, comorbidities, stroke and bleeding risk factors and baseline stroke and bleeding risk profile

Variable	Rate control n = 1622 (64.3%)	Rhythm control n = 900 (35.7%)	p value
Heart rate	91.0 ± 26.2	96.2 ± 31.8	0.001
Heart rate <50 or >110 bpm	346 (21.3)	293 (32.6)	<0.001
SBP (mean, mmHg)	135.0 ± 22.3	135.2 ± 20.5	0.541
DBP (mean, mmHg)	80.9 ± 12.3	82.4 ± 11.6	0.198
Lone AF	15 (0.9)	37 (4.1)	<0.001
HF	914 (56.4)	198 (22.0)	<0.001
Symptomatic HF	872 (53.8)	191 (21.2)	<0.001
HFrEF	420 (25.9)	81 (9.0)	<0.001
DCM	185 (11.4)	30 (3.3)	<0.001
Hypertension	1307 (80.6)	719 (79.9)	0.051
CAD	538 (33.2)	225 (25.0)	<0.001
Prior MI	255 (15.7)	82 (9.1)	<0.001
History of PCI/stenting	121 (7.5)	79 (8.8)	0.025
Mitral valve regurgitation	645 (39.8)	178 (19.8)	<0.001
Aortic valve disease	219 (13.5)	66 (7.3)	<0.001
PAD	85 (5.2)	28 (3.1)	0.055
Thyroid disease	141 (8.7)	121 (13.4)	<0.001
Diabetes mellitus	449 (27.7)	183 (20.3)	<0.001

Anaemia	273 (16.8)	74 (8.2)	<0.001
CKD	273 (16.8)	95 (10.6)	<0.001
COPD	250 (15.4)	63 (7.0)	<0.001
Sleep apnea	37 (2.3)	16 (17.8)	<0.001
Dementia	60 (3.7)	16 (1.8)	<0.001
Malignancy	84 (5.2)	29 (3.2)	<0.001
Liver disease	68 (4.2)	18 (2.0)	<0.001
Prior stroke	210 (12.9)	54 (6.0)	<0.001
Prior TIA	60 (3.7)	21 (2.3)	0.002
Prior SE	19 (1.1)	1 (0.1)	0.006
Prior bleeding	96 (5.9)	21 (2.3)	0.002
Obesity	413 (25.5)	223 (24.8)	0.318
Multimorbidity *	1484 (91.5)	706 (78.4)	<0.001
CHA_2DS_2-VASc (mean)	3.8 ± 1.8	2.7 ± 1.7	<0.001
CHA_2DS_2-VASc = 0	23 (1.4)	58 (6.4)	<0.001
CHA_2DS_2-VASc 0 (males) or 1 (females)	34 (2.1)	81 (9.0)	<0.001
CHA_2DS_2-VASc = 1	102 (6.3)	160 (17.8)	<0.001
CHA_2DS_2-VASc ≥2	1497 (92.3)	682 (75.8)	<0.001
HAS-BLED (mean)	2.2 ± 1.2	1.6 ± 1.1	<0.001
HAS-BLED ≥3	594 (36.6)	179 (19.9)	<0.001

*Multimorbidity, the presence of two or more long-term conditions [45].

bpm, beats per minute, AF, atrial fibrillation, DBP, diastolic blood pressure, SBP, systolic blood pressure, HF, heart failure, rEF, reduced ejection fraction, DCM, dilated cardiomyopathy, CAD, coronary artery disease, MI, myocardial infarction, PCI, percutaneous coronary intervention, PAD, peripheral artery disease, CKD, chronic kidney disease, COPD, chronic obstructive pulmonary disease, TIA, transient ischaemic attack, SE, systemic embolism, CHA_2DS_2-VASc, congestive heart failure, hypertension, age $\geq$75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category (female), HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (>65 years), drugs or alcohol concomitantly.

Table 3. Atrial fibrillation management

Variable	**Rate control** **N = 1622 (64.3%)**	**Rhythm control** **N = 900 (35.7%)**	**p-value**
AF management settings			
AF was the main reason for the hospitalization	636 (39.2)	667 (74.1)	<0.001
Outpatient visit	146 (9.0)	62 (6.9)	0.007
Academic healthcare facility	1268 (78.2)	730 (81.1)	0.040
AF managed by a cardiologist	1236 (76.2)	762 (84.7)	<0.001
Diagnostic assessment			
Routine biochemistry	1257 (77.5)	771 (85.7)	<0.001
Thyroid hormones measurement	467 (28.8)	449 (49.9)	<0.001
Transthoracic echocardiography	1244 (76.7)	778 (86.4)	<0.001
Holter monitoring (rhythm)	350 (21.6)	328 (36.4)	<0.001
Stroke prevention (in patients with with CHA_2DS-VA_2Sc score [more than 0 (male) or 1 (female)]	**N = 1588**	**N = 819**	
No antithrombotic	118 (7.4)	67 (8.2)	0.060

therapy			
Overall OAC	1241 (78.1)	587 (71.7)	<0.001
OAC alone	1045 (65.8)	493 (60.2)	<0.001
VKA	1064 (67.0)	444 (54.2)	<0.001
NOAC	177 (11.1)	143 (17.5)	<0.001
Single antiplatelet therapy alone	175 (11.0)	124 (15.1)	0.001
DAPT alone	54 (3.4)	41 (5.0)	0.073
Dual antithrombotic therapy	149 (9.4)	65 (7.9)	0.791
Triple antithrombotic therapy	47 (3.0)	29 (3.5)	0.897
Stroke prevention(in patients with CHA_2DS-VA_2Sc score ≥2)	**N = 1497**	**N = 682**	
No antithrombotic therapy	111 (7.4)	51 (7.5)	0.899
Overall OAC	1172 (78.3)	483 (70.8)	<0.001
OAC alone	982 (65.6)	396 (58.1)	<0.001
VKA	1008 (67.3)	370 (54.3)	<0.001
NOAC	164 (11.0)	113 (16.6)	<0.001
Single antiplatelet therapy alone	161 (10.8)	111 (16.3)	<0.001
DAPT alone	53 (3.5)	37 (5.4)	0.083
Dual antithrombotic	144 (9.6)	60 (8.8)	0.052

therapy			
Triple antithrombotic therapy	46 (3.1)	27 (4.0)	0.063
Symptom management			
Non-pharmacological AF therapies			
AF catheter ablation	5 (0.3)	60 (6.7)	<0.001
Surgical AF ablation	0 (0)	1 (0.1)	0.153
ECV	17 (1.0)	97 (10.8)	<0.001
AV node ablation with PM implantation	6 (0.4)	4 (0.4)	0.632
Pharmacological AF therapies			
Digoxin	594 (36.6)	53 (5.9)	<0.001
Verapamil	82 (5.1)	29 (3.2)	0.004
Diltiazem	15 (0.9)	2 (0.2)	0.116
Beta blockers	1335 (82.3)	588 (65.3)	<0.001
Propafenone	20 (1.2)	219 (24.3)	<0.001
Flecainide	4 (0.2)	4 (0.4)	0.012
Sotalol	3 (0.2)	18 (0.2)	0.979
Amiodarone	229 (14.1)	447 (49.7)	<0.001
Dronedarone	2 (0.1)	2 (0.2)	0.074
Other therapy			
ACEi	766 (47.2)	450 (50.0)	0.515
AT1 receptor blockers	325 (20.0)	171 (19.0)	0.353

Loop diuretics	878 (54.1)	200 (22.2)	<0.001
Statins	656 (40.4)	389 (43.2)	0.097
Polypharmacy	978 (60.3)	482 (53.6)	<0.001

*Polypharmacy, the use of five or more drugs [24],

ACEi, angiotensin converting enzyme inhibitors, AF, atrial fibrillation, OAC, oral anticoagulants, VKA, vitamin K antagonists, NOAC, non-vitamin K oral antagonists, DAPT, dual antiplatelet therapy, ECV, electrical cardioversion, AV, atrioventricular, PM, pacemaker.

Table 4. Independent predictors of use of rhythm control strategy in patients with paroxysmal AF

Variable	Multivariate analysis		
	OR	**95% CI**	**p-value**
Non-emergency centre	2.51	1.65-3.82	<0.001
Management by cardiologist	2.56	1.70-3.84	<0.001
Palpitations	1.77	1.20-2.61	0.004
Symptoms attributable to AF*	1.65	1.15-2.37	0.006
Mean heart rate	1.09	1.07-1.16	<0.001
Hypertension	2.03	1.41-2.92	<0.001
AF was the main reason for hospitalization	2.99	2.27-3.94	<0.001
Mean CHA_2DS_2-VASc score	0.80	0.73-0.87	<0.001
Heart failure	0.67	0.47-0.94	0.022

*As judged by the responsible physician/investigator.

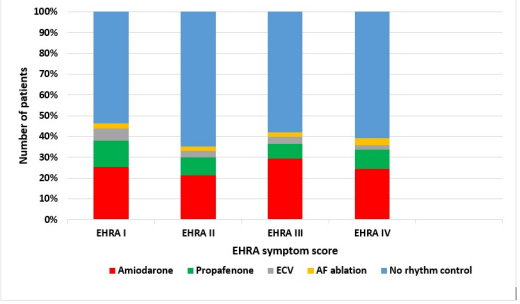
AF, atrial fibrillation, CI, confidence interval, OR, odds ratio, CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category (female).

Table 5. Independent predictors of use of amiodarone in patients with rhythm control strategy

Variable	**Multivariate analysis**		
	OR	**95% CI**	**p-value**
Management by cardiologist	1.98	1.43-2.91	0.001
Chest pain	1.62	1.17-2.23	0.003
DCM	2.56	1.12-5.83	0.025
Mean CHA_2DS_2-VASc score	1.13	1.05-1.22	0.001
Paroxysmal AF	0.63	0.47-0.85	0.002
Outpatient visit	0.36	0.20-0.64	0.001

AF, atrial fibrillation, CI, confidence interval, OR, odds ratio, CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category (female), DCM, dilated cardiomyopathy.

Figure 1. The use of management strategies in patients according to EHRA symptom score



AF, atrial fibrillation, EHRA, European Heart Rhythm Association, ECV, electrical cardioversion

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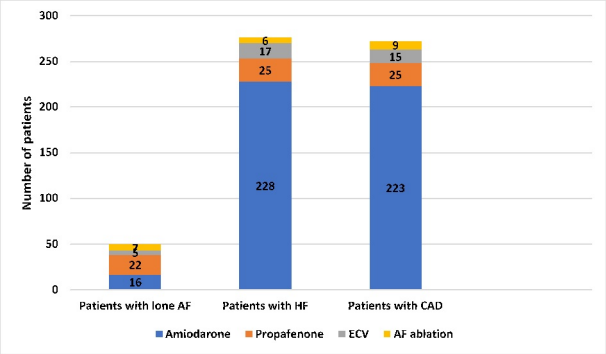
Figure 2. The use of management strategies by type of heart disease



AF, atrial fibrillation, ECV, electrical cardioversion, CAD, coronary artery disease, HF, heart failure

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