

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

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## 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.

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**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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#### 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). 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<sub>2</sub>DS<sub>2</sub>-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. 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 and to have permanent AF than patients with rate control, (all  $p < 0.05$ ). The rhythm control group was more likely to have paroxysmal AF and shorter duration of AF history than patients with rate control, (both  $p < 0.001$ ). 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 heart rhythm (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 ( $96.2 \pm 31.8$  vs.  $91.0 \pm 26.2$ ) 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<sub>2</sub>DS<sub>2</sub>-VASc score ( $2.7 \pm 1.7$  vs.  $3.8 \pm 1.8$ ) and mean HAS-BLED score ( $1.6 \pm 1.1$  vs.  $2.2 \pm 1.2$ ) than those with rate control, (both  $p < 0.001$ ). The rhythm control group includes significantly lower proportion of patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  and with HAS-BLED score  $\geq 3$  (both  $p < 0.001$ ) than those with rate control. They have also significantly higher proportion of 'low risk' patients with CHA<sub>2</sub>DS<sub>2</sub>-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 no antithrombotic therapy, non-vitamin K antagonist oral anticoagulants (NOAC), dual antiplatelet therapy (DAPT) alone (all  $p < 0.05$ ) 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.

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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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.

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].

### *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].

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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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 [2]. Unfortunately, in the Balkans about 10% of patients with HF assigned to rhythm control received propafenone despite contraindications.

### *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.

### **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.

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### **Conflicts of interest**

Dr Koziel, 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).

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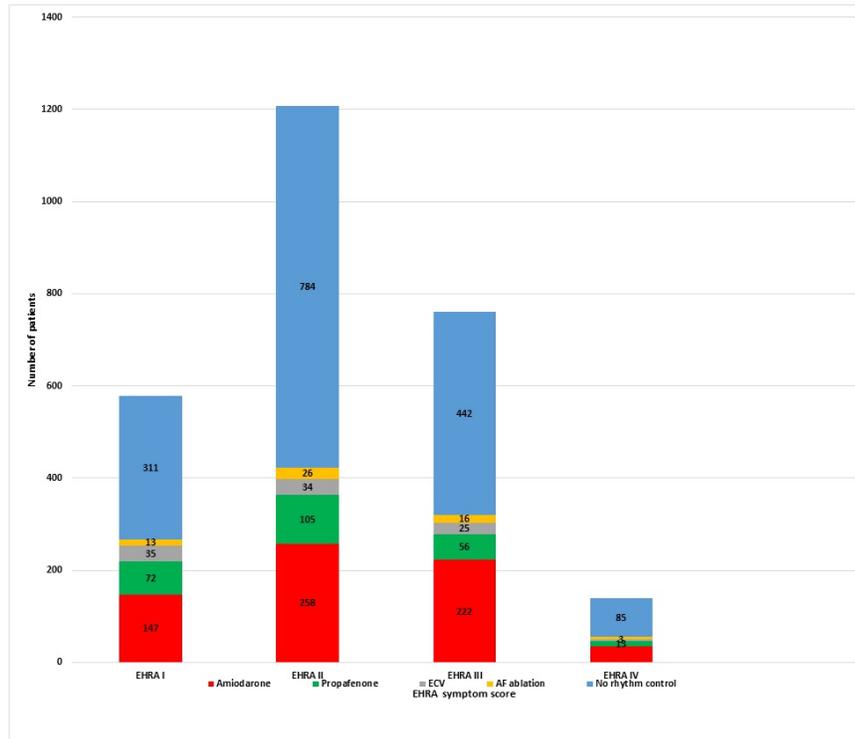
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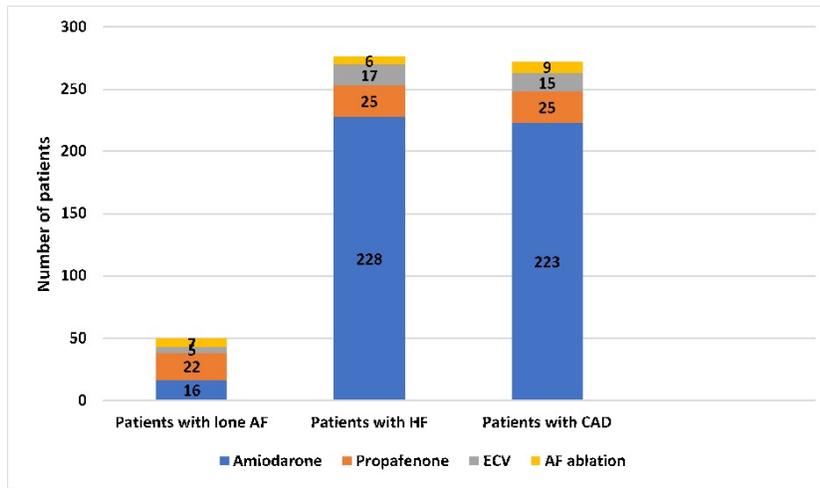
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Figure 1. The use of management strategies in patients according to EHRA symptom score



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

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