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ORIGINAL RESEARCH ARTICLE

Choice and Outcomes of Rate Control versus Rhythm Control in Elderly Patients with Atrial Fibrillation: A Report from the REPOSI Study

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Abstract

Background Among rate-control or rhythm-control strategies, there is conflicting evidence as to which is the best management approach for non-valvular atrial fibrillation (AF) in elderly patients.

Design We performed an ancillary analysis from the 'Registro Politerapie SIMI' study, enrolling elderly inpatients from internal medicine and geriatric wards.

Methods We considered patients enrolled from 2008 to 2014 with an AF diagnosis at admission, treated with a rate-control-only or rhythm-control-only strategy.

Results Among 1114 patients, 241 (21.6%) were managed with observation only and 122 (11%) were managed with both the rate- and rhythm-control approaches. Of the remaining 751 patients, 626 (83.4%) were managed with a rate-control-only strategy and 125 (16.6%) were managed with a rhythm-control-only strategy. Rate-control-managed patients were older ($p = 0.002$), had a higher Short Blessed Test (SBT; $p = 0.022$) and a lower Barthel Index ($p = 0.047$). Polypharmacy ($p = 0.001$), heart failure ($p = 0.005$) and diabetes ($p = 0.016$) were more prevalent among these patients. Median CHA_2DS_2-VASc score was higher among rate-control-managed patients ($p = 0.001$). SBT [odds ratio (OR) 0.97, 95% confidence interval (CI) 0.94–1.00, $p = 0.037$], diabetes (OR 0.48, 95% CI 0.26–0.87, $p = 0.016$) and polypharmacy (OR 0.58, 95% CI 0.34–0.99, $p = 0.045$) were negatively associated with a rhythm-control strategy. At follow-up, no difference was

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found between rate- and rhythm-control strategies for cardiovascular (CV) and all-cause deaths (6.1 vs. 5.6%, $p = 0.89$; and 15.9 vs. 14.1%, $p = 0.70$, respectively).
Conclusion A rate-control strategy is the most widely used among elderly AF patients with multiple comorbidities and polypharmacy. No differences were evident in CV death and all-cause death at follow-up.

Key Points

Rate control is the preferred therapeutic choice in elderly atrial fibrillation (AF) patients with multiple comorbidities and polypharmacy.

No difference is evident between the rate- and rhythm-control strategies in cardiovascular death and all-cause death in elderly AF patients.

1 Introduction

Atrial fibrillation (AF) is a major public health burden and is the most common cardiac arrhythmia worldwide, with a major impact on morbidity and mortality [1–3]. The main goals of therapy in AF are the prevention of cardioembolic events with anticoagulation and the management of symptoms with a rhythm- or rate-control strategy [3–5].

Randomized clinical trials have compared the effectiveness of rhythm- and rate-control strategies. Rate control was non-inferior to rhythm control for several primary outcomes related to symptom management, as well as cardiac adverse events and overall mortality [6–9]. Rhythm control was also associated with a higher risk of rehospitalization [8, 9]. Furthermore, data from a large observational study showed no superiority for rhythm-control compared with a rate-control strategy in regard to outcomes such as stroke, heart failure or mortality, but rhythm control was associated with more cardiovascular (CV) hospitalizations [10]. On the other hand, observational studies on hospitalized AF patients suggest that rhythm-control strategies may have a marginal benefit on mortality compared with rate control during long-term follow-up [11]. In randomized trials, the mean age of patients was generally lower than 70 years, while in observational studies, the mean age of patients was approximately 75 years. Thus, limited data on the outcomes regarding rate- or rhythm-control strategies are available for elderly patients.

With these gaps of knowledge in elderly patients, we chose to compare clinical outcomes related to rate-control versus rhythm-control strategies for the management of AF in elderly patients admitted to internal medicine and geriatric wards in the frame of the prospective Registro Politerapie SIMI (REPOSI) registry.

2 Methods

This study represents an ancillary analysis from the REPOSI study [12], a multicentre collaborative observational registry jointly held by the Italian Society of Internal Medicine (SIMI), the Ca' Granda Maggiore Policlinico Hospital Foundation, and the Mario Negri Institute of Pharmacological Research, and based on a network of internal medicine and geriatric wards in Italy and Spain. Full details on study design and specific aims have been reported [12].

Briefly, REPOSI was conducted for 3 non-consecutive years (2008, 2010, 2012) and then annually from 2014 onwards. In each of these years, consecutive patients admitted to the participating wards and aged >65 years were enrolled over a period of 4 weeks on a quarterly basis (i.e. February, June, September and December). The study protocol was first approved by the Ethics Committee of the Ca' Granda Maggiore Policlinico Hospital Foundation and then ratified for each enrolling site by the local committees. The study was conducted according to Good Clinical Practice recommendations and the Declaration of Helsinki. Concomitant diagnoses at admission were coded according to the International Classification of Diseases, 9th Revision (ICD-9) system. Medication use at admission was assessed according to the Anatomic Therapeutic Chemical (ATC) classification system.

For the purposes of this analysis, we included all patients admitted from 2008 to 2014 with a diagnosis of AF and treated with a rate- or rhythm-control management strategy. AF was classified according to ICD-9 code 427.31. A rate-control strategy was defined for patients treated with β-blockers (ATC C07*), calcium-channel blockers (ATC C08C*) or digoxin (ATC C01AA05), while rhythm control was defined for patients treated with class IC anti-arrhythmic drugs (ATC C01BC*) or class III anti-arrhythmic drugs (ATC C01BD*). Adequate heart rate control was classified according to the prevailing European Society of Cardiology (ESC) guidelines, i.e. heart rate <110 beats per min (bpm) at admission [13].

Interactions of comorbidities were evaluated by means of the Cumulative Illness Rating Scale (CIRS) severity index and comorbidity index [14, 15]. Polypharmacy was defined by the contemporary use of five or more drugs [12]. Cognitive status was evaluated using the Short Blessed

Test (SBT) [16], the presence of depression was investigated using a Geriatric Depression Scale (GDS) [17], and patient functional status was assessed using the Barthel index [18].

Follow-up data were collected at 3 and/or 12 months after discharge through a patient telephone interview, or, if the patient was no longer alive, from the next of kin. According to the causes of death reported in the electronic case report form, a CV death was classified as such when it was related to any cardiac or vascular reason. Both all-cause and CV deaths were considered study outcomes.

2.1 Statistical Analysis

Variables with normal distribution were expressed as means and standard deviations (SDs), and tested for differences using the Student's *t* test. Non-normal variables were expressed as medians and interquartile ranges (IQRs), and differences were tested using the Mann–Whitney *U* test or Kruskall–Wallis analysis of variance (ANOVA) test accordingly. Categorical variables, expressed as counts and percentages, were analysed using the Chi-square test.

A logistic regression analysis was performed to establish clinical factors associated with rhythm-control management. All variables with a p value <0.10 in the comparison between the two groups at baseline were included in a univariate analysis, and the univariate predictors with a statistical significance of $<10\%$ were included in a multivariate logistic model. A linear regression analysis, adjusted for age, sex and CIRS, was performed to analyse the relationship between rhythm control and heart rate at admission.

A survival analysis was performed according to the rate- and rhythm-control strategies. A log-rank test was only performed for the 'all-cause' death outcome owing to a low number of events for CV death. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

3 Results

Of 1114 patients with AF at admission, 241 (21.6%) were managed with observation only (neither rate- nor rhythm-control drugs were prescribed), and 122 (11%) were managed with both rate- and rhythm-control drugs. Of the remaining 751 patients included in this analysis, 626 (83.4%) were managed with rate-control drugs only, and 125 (16.6%) were managed with rhythm-control drugs only.

Baseline characteristics at hospital admission for these 751 patients, according to rate- or rhythm-control strategies, are summarized in Table 1. Comparison of demographic and clinical characteristics between the two groups indicated that rate-control-managed patients were older (*U* test 32.112, $p = 0.002$) and had a higher SBT (*U* test 17.440, $p = 0.022$) and lower Barthel Index (*U* test 25.558, $p = 0.047$). Polypharmacy (Chi-square test 10.846, $p = 0.001$), heart failure (Chi-square test 7.858, $p = 0.005$) and diabetes (Chi-square test 5.775, $p = 0.016$) were more prevalent among these patients. Furthermore, median CHA_2DS_2-VASc score was higher among rate-control-managed patients (*U* test 34.031, $p = 0.001$), but the proportion of those at high risk (score ≥ 2) was not different between the two groups (Chi-square test 2.448, $p = 0.12$). Patients managed with rate-control drugs were more likely prescribed oral anticoagulant (OAC) monotherapy than those managed with rhythm-control drugs, who, conversely, were more untreated and were prescribed antiplatelet monotherapy (Chi square test 7.906, $p = 0.048$).

3.1 Logistic Regression Analysis for Rhythm Control

After univariate analysis, a multivariate logistic analysis found that the SBT [odds ratio (OR) 0.97, 95% confidence interval (CI) 0.94–1.00, $p = 0.037$], diabetes (OR 0.48, 95% CI 0.26–0.87, $p = 0.016$) and polypharmacy (OR 0.58, 95% CI 0.34–0.99, $p = 0.045$) were inversely associated with the use of a rhythm-control strategy.

3.2 Heart Rate Control

Median heart rate at admission was significantly higher in patients managed with a rate-control strategy than in those managed with rhythm control [median (IQR) 80 (72–96) vs. 76 (66–88) bpm, respectively; *U* test 30.558, $p<0.001$], but no significant differences were found in the prevalence of adequate heart rate control between the two groups (90.7% vs. 91.2%, respectively; Chi-square test 0.036, $p = 0.85$). A rhythm-control strategy was negatively associated with a lower heart rate at admission, even after adjustment for age, sex and Cumulative Index Rating Scale (standardized $\beta = -0.128$, $t = -3.141$, $p = 0.002$).

3.3 Follow-Up Analysis

Follow-up data were available for 418 of 751 (55.7%) patients. Rates of CV death and all-cause deaths were not different between the rate- and rhythm-control groups (6.1 vs. 5.6%; Chi-square test 0.018, $p = 0.89$, and 15.9 vs. 14.1%; Chi-square test 0.140, $p = 0.70$, respectively). Kaplan–Meier analysis showed no significant differences

Table 1 Baseline characteristics of patients according to the management strategy for atrial fibrillation

	Rate control [$n = 626$]	Rhythm control [$n = 125$]	U/Chi-square test	*P*-Value
Age, years (median [IQR])	82 [76–86]	80 [74–84]	32.112[a]	0.002
Female	320 (51.1)	64 (51.2)	0.000[b]	0.99
SBT (median [IQR]) *547*	10 [4–17]	7 [2–14]	17.440[a]	0.022
GDS (median [IQR]) *519*	1 [0–2]	1 [0–3]	18.926[a]	0.91
Barthel Index (median [IQR]) *584*	87 [53–100]	91 [69–100]	25.558[a]	0.047
CIRS (median [IQR]) *590*				
Severity Index	1.69 [1.53–1.94]	1.69 [1.46–1.98]	22.575[a]	0.46
Comorbidity Index	3 [2–5]	3 [2–5]	22.351[a]	0.37
Polypharmacy *546*	508 (81.2)	85 (68.0)	10.846[b]	0.001
Hypertension	497 (79.4)	92 (73.6)	2.067[b]	0.15
Hypercholesterolemia	48 (7.7)	9 (7.2)	0.033[b]	0.86
Heart failure	193 (30.8)	23 (18.4)	7.858[b]	0.005
Coronary artery disease	167 (26.7)	25 (20.0)	2.441[b]	0.12
Myocardial infarction	20 (3.2)	2 (1.6)	0.932[b]	0.33
Peripheral arterial disease	23 (3.7)	3 (2.4)	0.506[b]	0.48
Stroke/TIA	78 (12.5)	16 (12.8)	0.011[b]	0.92
Diabetes mellitus	192 (30.7)	25 (20.0)	5.775[b]	0.016
Chronic kidney disease	160 (25.6)	26 (20.8)	1.267[b]	0.26
COPD	172 (27.5)	27 (21.6)	1.847[b]	0.17
Cancer	72 (11.5)	21 (16.8)	2.696[b]	0.101
CHA_2DS_2-VASc (median [IQR])	4 [3–5]	3 [3–5]	34.031[a]	0.001
Thromboembolic risk				
Moderate risk	8 (1.3)	4 (3.2)	2.448[b]	0.12
High risk	618 (98.7)	121 (96.8)		
Antithrombotic therapy				
None	133 (21.2)	33 (26.4)	7.906[b]	0.048
Only antiplatelet	189 (30.2)	47 (37.6)		
Only OAC	282 (45.0)	44 (35.2)		
Antiplatelet plus OAC	22 (3.5)	1 (0.8)		

Data are expressed as *n* (%) unless otherwise specified

[a]Mann–Whitney *U* test

[b]Chi-square test

CIRS Cumulative Index Rating Scale, *COPD* chronic obstructive pulmonary disease, *GDS* Geriatric Depression Scale, *IQR* interquartile range, *OAC* oral anticoagulant, *SBT* Short Blessed Test, *TIA* transient ischemic attack

between the two treatment groups (log-rank 0.002, $p = 0.96$) for the occurrence of all-cause death.

3.4 Sensitivity Analysis

In order to deepen this analysis, we performed a sensitivity analysis comparing baseline characteristics of the rate-control- and rhythm-control-only groups with those managed with observation only and those managed with a composite rate- and rhythm-control strategy (Electronic supplementary Table S1).

Patients managed with observation only were found to be the oldest, while those managed with a composite strategy were the youngest (Kruskal–Wallis test 24.899, $p < 0.001$). Patients assigned to the observation-only strategy were cognitively impaired as much as those assigned to rate-control only, while patients treated with the combined strategy were those less likely to be cognitively impaired according to the SBT (Kruskal–Wallis test 35.065, $p < 0.001$). Even though there was a non-significant difference, patients assigned to the observation strategy were as much functionally impaired as those assigned to rate control, as evaluated by the Barthel Index, while those treated with both strategies were the most competent (Kruskal–Wallis test 7.493, $p = 0.058$). Patients assigned to the observation-only strategy were less burdened with

polypharmacy, while those assigned to both strategies were more burdened with polypharmacy (Chi-square test 79.349, $p < 0.001$). Patients treated with a combined strategy were also more affected with hypertension and coronary artery disease.

4 Discussion

In this cohort of elderly AF patients, a rate-control strategy was the most widely used, especially among patients with multiple comorbidities and related polypharmacy. Conversely, patients on a rhythm-control strategy were healthier, with less comorbidities, less polypharmacy and a less compromised cognitive status. No difference was found in terms of major adverse outcomes between the two management strategies.

After several randomized trials found no difference between the rate-control and rhythm-control strategies for prognosis [7, 8, 19], a significant reduction in the use of rhythm-control management was evident, with rate control being the more widely used strategy [10, 11, 20, 21]. Our data not only confirm previous evidence but also show, in a large contemporary 'real-world' cohort, that rate control remains the preferred management in elderly patients, with 83% of our cases being managed with rate-control drugs.

The main indication for rhythm control is the management of symptoms [22], with no specific guidance in relation to the degree of frailty or advanced age. In the present study, the choice of rate control seems associated with functional status, with these patients being more frail, with more comorbidities, more medications, and a worse cognitive status. This choice is likely to be explained by the fact that the rate control may be perceived as being more conservative and less likely to burden these patients with side effects, more frequent follow-ups or hospitalizations [23, 24]. In addition, rate control has been associated with an improvement of health-related quality of life in elderly patients [25, 26]. Importantly, differential management strategies did not significantly affect outcomes during the short-term follow-up observation in our cohort, suggesting a more prominent role of comorbidities.

Our data in elderly patients with AF should be integrated in the context of more general data available from the literature. The role of either rate- or rhythm-control management in predicting long-term outcomes in AF is still largely debated. While randomized trials found no differences in outcomes [7, 8], some observational studies suggest a better prognosis for rhythm control [27, 28], while others report that the difference between rate and rhythm control is no longer significant after full adjustment for comorbidities [10]. In elderly patients, scarce data are available, with rhythm control being reported as associated with both better [29] and worse outcomes [30].

The further comparison between the rate-control-only and rhythm-control-only groups and those assigned to observation only, as well as those treated with both strategies, confirmed and extended the main results. Indeed, we found that patients treated with an observation-only approach were the oldest and were slightly more cognitively and functionally compromised than those assigned to rate-control only. Conversely, those patients treated with both strategies were younger and significantly more 'fit' than the others and were keen to receive a more aggressive approach, which is probably justified by the fact that these patients are significantly more burdened with CV comorbidities. The fact that observation-only patients are less burdened with polypharmacy could be related to their severely impaired clinical status, which did not allow several drugs to be prescribed.

The arguably 'more conservative' approach of the observation-only and rate-control-only strategies in very old and complex patients could be a reasonable choice given the possibly easier management approach, favoring symptom control and improvement in quality of life. Nonetheless, given the small sample size and the nature of the study, this study is intended to simply be hypotheses-generating and larger studies would be needed to further verify our data and assumptions.

The main limitation of this study is its observational nature, with the likelihood of residual confounders that could not be accounted for. This subgroup analysis was not prespecified, therefore we had limited power to identify differences between the groups. Moreover, we were not able to consider other possible rhythm-control management procedures (i.e. direct cardioversion, ablation procedure). Indeed, data regarding the choice of rate control or rhythm control were indirectly based on drug prescription data collected at baseline. In addition, no specific data were available about type of AF and AF-related symptoms. Last, the limited follow-up data after hospital release could reduce the generalizability of our conclusions. Despite these limitations, we believe that these data provide a representative 'real-world' snapshot of rate- and rhythm-control management strategies in elderly patients with AF.

5 Conclusions

We found that in elderly AF patients, a rate-control strategy is the most widely used, especially among those with multiple concomitant illnesses and polypharmacy. No significant differences were evident in CV death and all-cause death at follow-up between the rate- or rhythm-control strategies. A rate-control strategy could be

considered as the best choice for elderly AF patients; however, further data are needed to confirm our hypotheses.

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Compliance with ethical standards

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