Rate and Rhythm Control Treatment in the Elderly and Very Elderly Patients With Atrial Fibrillation: An Observational Cohort Study of 1497 Patients

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Abstract: Stroke prevention and rate or rhythm control are crucial in the management of atrial fibrillation (AF). There is recent evidence for benefit of early rhythm control, yet rate control is the first choice in elderly patients. However, the efficacy and safety of rate and rhythm control in the elderly population remains largely unexplored. Therefore, we analyzed electronic health record data and investigated prescribing patterns and mortality of both strategies in elderly patients with AF. Data from patients with AF who were aged ≥75 years, used a pharmacological rate or rhythm control strategy, and visited Cardiology Centers of the Netherlands between 2007 and 2018 were extracted. Of the 1497 patients (54% female), 316 (21%) were prescribed rhythm control and 1181

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(79%) rate control. Patients aged >85 years (OR: 2.28; 95% CI: 1.51-3.44, $P < 0.001$) and those with permanent AF (OR: 2.71; 95% CI: 1.67-4.41, $P < 0.001$) were more likely to receive rate control, whereas those with paroxysmal AF were less likely to receive rate control (OR: 0.42; 95% CI: 0.32-0.56, $P < 0.001$). After correction for relevant confounders, the mortality risk for patients using rhythm control and patients using rate control was similar (HR: 0.89; 95% CI: 0.70-1.12, $P = 0.31$). A more liberal approach towards prescribing a rhythm control strategy to the elderly patients with AF may be warranted and seems safe. Our data underscore the need for prospective studies to provide definite answers on efficacy and safety of rhythm control in elderly patients with AF. (Curr Probl Cardiol 2022;47:100996.)

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated prevalence of 1%-4% in Western countries and it mainly affects patients aged 65 years and older.[1,2] The prevalence of AF is expected to increase by approximately 2.5-fold within the forthcoming decades, in part due to ageing of the global population.[1-6] Patients with AF are at increased risk of (all-cause) mortality, thromboembolic events, and the development of heart failure.[6] Treatment of AF is challenging, particularly in elderly patients with multiple comorbidities, and includes 2 important pillars: stroke prevention and arrhythmia treatment with a rate or rhythm control strategy.[6,7]

Rate control therapy is aimed at slowing down the ventricular response rate, and is considered the preferred therapy in elderly patients and in patients with no or minor symptoms of AF.[8] Rhythm control therapy, on the other hand, is aimed at restoring sinus rhythm and is recommended to improve symptoms and quality of life in patients with symptomatic AF.[6,9] Several randomized clinical trials have compared rate vs rhythm control strategies and reported no significant differences in mortality and morbidity.[9-12] Of note, these studies were undertaken in an era during which indications for anticoagulant therapy were less stringent than today. However, the evidence base for the decision between rate and rhythm control in elderly patients with AF is small, as these patients were excluded from most studies. Current observational evidence indicates no significant differences in morbidity and mortality between both

strategies in the elderly.[13] On the other hand, a recent randomized trial in the general AF population shows that early rhythm control compared to rate control resulted in a lower rate of the combined endpoint of death, stroke, and serious adverse events, with lower rates of stroke and cardiovascular death in particular.[14] Nevertheless, there have been suggestions that elderly patients experience more complications of antiarrhythmic therapy, especially those with multiple comorbidities and/or a decreased renal function.[15-17] In addition, treating physicians seem to prefer rate control over rhythm control in elderly patients also because guidelines recommend using rhythm control only in symptomatic "younger" (not further specified) patients.[6,8] However, the efficacy and safety of both strategies in patients aged ≥75 years remains insufficiently explored, and in the light of the rapidly growing population of elderly patients with AF, more insight in daily practice patterns and safety of both treatment strategies is urgently needed.[1-5,9,10,13,16,18,19] Ideally, a randomized trial would be performed to study the safety of both strategies in this population, but in the absence of such trials, observational studies are a first step in exploring the association between rhythm control and mortality risk in the elderly. Therefore, we analyzed electronic health record (EHR) data from outpatient cardiology clinics to investigate the following questions: (1) what is the proportion of rate and rhythm control in elderly patients with AF?; (2) Is there an association between a rhythm control strategy and higher mortality risks in the elderly patients with AF?; (3) Are there clinical characteristics that predispose for 1 strategy above the other? We hypothesize that clinicians mainly base their decision for a rate or rhythm control strategy on the age and the extent of a patients' comorbidities. Furthermore, we hypothesize that, because of the potential adverse drug effects (including lethal side effects) of antiarrhythmic drugs (AAD), older patients and those with more comorbidities are more likely to be prescribed a rate control strategy.[19,20]

Methods

Study Population

Data were extracted from the EHR of the Cardiology Centers of the Netherlands (CCN). CCN comprises thirteen cardiology outpatient clinics located across the Netherlands, which all perform the same standardized cardiac screening protocol. The database has been described earlier,[21] but to shortly summarize it consists of 109,515 unique patients who visited the CCN between 2007 and February 2018 for screening or treatment of cardiovascular disease. Patients undergo a standardized screening protocol, including an intake by a nurse to collect information

on medical history, medication use, lifestyle and co-morbidities. In addition, a blood sample is taken, and a trans-thoracic echocardiography (TTE) and an electrocardiography (ECG) at rest and during exercise are performed. For current analyses, patients aged 75 years or older with an ECG confirmed AF diagnosis who were prescribed a pharmacological rate or rhythm control strategy were selected. Baseline characteristics were obtained from the visit to the CCN within 31 days of the AF diagnosis date, or from the first appointment when the diagnosis date was unknown. Patients who did not show up at the visit around the AF diagnosis date or did not use rate nor rhythm control medication were excluded (Fig 1).

Rate and Rhythm Control Therapy

Patients using sotalol, flecainide, phenytoin, disopyramide, amiodarone, or an AAD not further specified were assigned to the rhythm control group. Patients using a beta-blocker, non-dihydropyridine calcium antagonists, digoxin, and none of the before mentioned rhythm control medicaments were assigned to the rate control group. Patients using medication from both groups were presumed to follow a rhythm control strategy. One-off prescriptions were excluded, as were prescriptions initiated more than 90 days before or after the AF diagnosis. Medication prescriptions were identified with pattern matching based on a combination of generic compound names and brand names.

Definitions

Comorbidities were obtained from the EHR defined by an explicit description, or inferred from medication use, diagnostics tests (ECG or TTE) or described (cardiac) interventions (ie, coronary interventions or ablation procedures). See Supplementary Table 1 for an elaborate description of the definitions. Recorded cerebrovascular events were not specified into ischemic or hemorrhagic stroke. Therefore, when calculating the CHA_2DS_2-VASc scores we assumed that all cerebrovascular events were ischemic of nature, based on the higher incidence.[22,23] Ejection fraction (EF) based on TTE results was scored in qualitative categories according to the American College of Cardiology (normal function: EF $\geq$ 50%, mild dysfunction: EF 40%-49%, moderate dysfunction: EF 30%-39%, severe dysfunction: EF $<$ 30%).[24] Due to possible traceability of anonymized patients, the national mortality registry did not provide the exact numbers

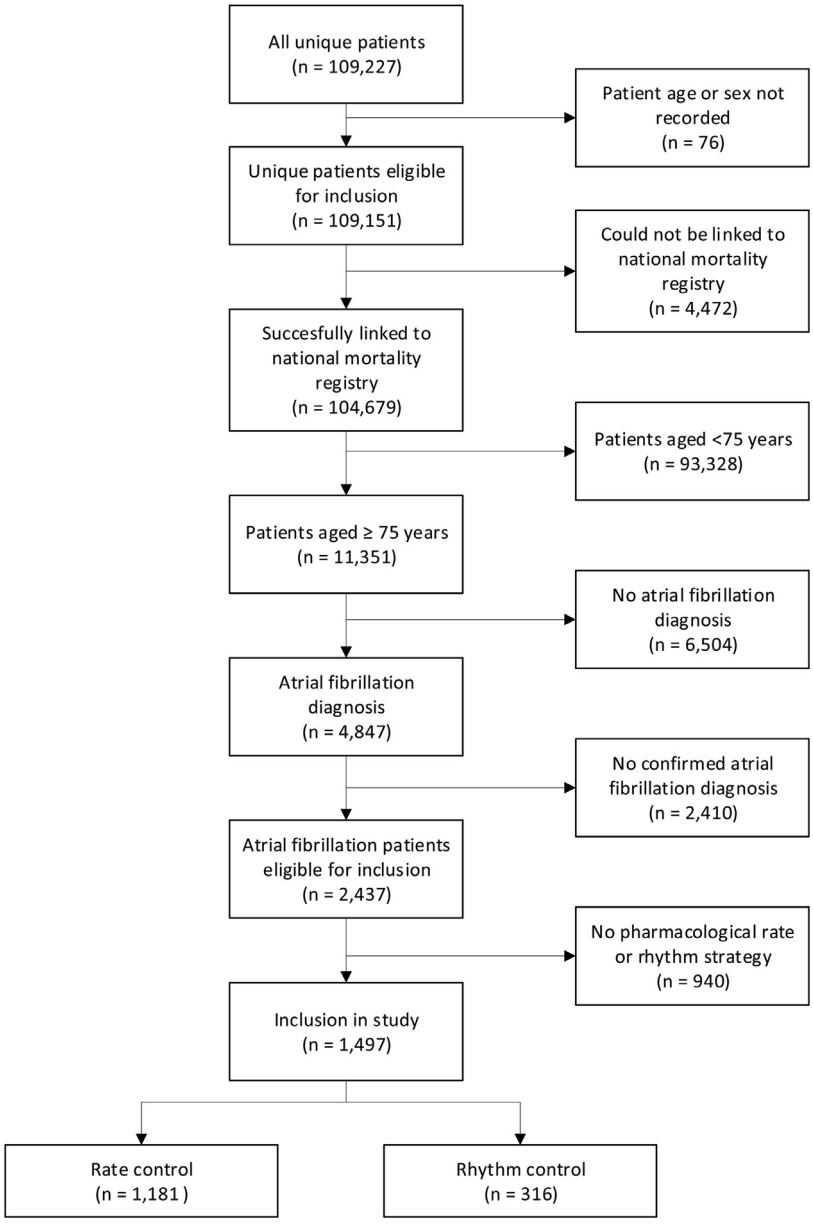

FIG 1. Patient selection flow chart.

of patients with a certain comorbidity if fewer than 10 patients in the cohort suffered from it (eg, congenital heart disease; Table 1).

TABLE 1. Baseline characteristics

Baseline characteristics	Rhythm control (n = 316)	Rate control (n = 1181)	*P*-value	Not recorded in EHR*
Sex (female)	159 (50)	649 (55)	0.16	
Median age	79 ± 4	81 ± 5	<0.001	
Age 75-80 y	223 (71)	581 (49)	<0.001	
Age 80-85 y	62 (20)	337 (29)	<0.001	
Age 85-90 y	27 (9)	216 (18)	<0.001	
Age >90 y	4 (1)	47 (4)	<0.001	
BMI‡	26.3 ± 3.9	26.5 ± 4.6	0.56	
Alchol use	134 (42)	534 (45)	0.64	497 (33)
Smoking	170 (54)	672 (57)	0.04	214 (14)
Calculated CHA2DS2-VASc score†	3.8 ± 1.2	4.1 ±1.3	0.001	
Type of atrial fibrillation				
Paroxysmal	144 (46)	241 (20)	<0,001	
Persistent	13 (4)	110 (9.3	0.004	
Permanent	21 (7)	257 (22)	<0.001	
Not specified	138 (44)	576 (49)	0.12	
Medical history				
Hypertension	210 (67)	834 (71)	0.36	42 (3)
Diabetes mellitus	37 (12)	214 (18)	0.002	96 (6)
Vascular disease	19 (6)	76 (6)	0.89	
Dyslipidemia	147 (47)	523 (44)	0.27	53 (4)
Cerebrovascular disease	44 (14)	186 (16)	0.48	
Heart failure	47 (15)	260 (22)	0.007	
Coronary heart disease	67 (21)	246 (21)	0.95	
Valvular heart disease	110 (35)	541 (46)	0.001	
Congenital heart disease	<10	<10	0.2	
Heart valve intervention	<10	16 (1.4)	1	
Symptoms				
Chest pain	17 (5)	46 (4)	0.31	
Dyspnea	13 (4)	132 (11)	<0.001	
Palpitations	32 (10)	107 (9)	0.64	
Fatigue	<10	20 (2)	1.0	
Number of reported Symptoms			<0.001	32 (2)
0 symptoms	159 (50)	534 (45)		
1 symptom	126 (40)	590 (50)		
≥2 symptoms	17 (5)	39 (3)		
Lab results				
eGFR (ml/min)	53.5 ± 16.8	49.8 ± 17.7	0.02	644 (43)
Cardiovascular Medication				
Amiodarone	63 (20)	0 (0)	<0.001	
Flecainide	85 (27)	0 (0)	<0.001	
Sotalol	135 (43)	0 (0)	<0.001	
Other AAD	33 (10)	0 (0)	<0.001	
Beta blocker	<10	879 (74)	<0.001	
Non-dihydropyridines	<10	122 (10)	<0.001	

(*continued*)

TABLE 1. (*continued*)

Baseline characteristics	Rhythm control (n = 316)	Rate control (n = 1181)	*P*-value	Not recorded in EHR*
Digoxin	<10	337 (29)	<0.001	
Anti-platelet medication	63 (20)	191 (16)	0.13	
Oral-anticoagulant use	249 (79)	1000 (85)	0.02	
Vitamin K antagonist	189 (59)	782 (66)	0.02	
Direct oral anticoagulant	64 (20)	223 (19)	0.64	
Antihypertensive medication	166 (53)	579 (58)	0.13	
Loop diuretics	89 (29)	433 (37)	0.006	
Mineralcorticoid	34 (11)	157 (13)	0.27	
Dihydropyridines	79 (25)	209 (18)	0.004	
Nitrates	44 (14)	168 (14)	0.96	
Anti-diabetic medication	30 (10)	178 (15)	0.01	
Cholesterol lowering medication	123 (39)	476 (40)	0.70	
Alpha blocker	25 (8)	111 (9)	0.48	
Polypharmacy (use of ≥5 medicaments)	8 (3)	60 (5)	0.08	

Data are expressed in n (%) or Mean ± SD
BMI, body mass index; eGFR, estimated glomerular filtration rate.
*Number of patients with missing data
†CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes Mellitus, previous Stroke (2 points), Vascular disease, Age 65-75, female Sex
‡The body mass index is the weight in kilograms divided by the square of the height in meters.

Primary Outcomes

The primary outcome was all-cause mortality. Passive follow-up for all-cause mortality was available for 95.9% of the study population via linkage to the national mortality registry (Statistics Netherlands) of the Netherlands. This registry continuously collects all official cause of death reports submitted by medical doctors and coroners in the Netherlands and is updated quarterly. For the current analyses, all-cause mortality was available until February 12th 2020. Follow-up time for patients who were still alive was censored at February 12th 2020.

Statistical Analyses

Continuous variables are presented as mean (± standard deviation) or median [interquartile range] depending on their distribution. Comparisons between groups were made using the unpaired sample t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables.

Categorical variables are expressed as frequencies with percentages and were compared using the Pearson Chi-squared test. The association

between clinical parameters and the choice for rhythm or rate control therapy was assessed using univariable logistic regression models. A stepwise backward selection multivariable regression analysis was performed with a cut-off *P*-value of 0.10.

The relationship between rate- or rhythm control and all-cause mortality was evaluated using Cox regression, using rhythm control as the reference category. The regression model was adjusted for possible confounders using forward selection stepwise regression (see supplementary table 2). We also performed an interaction analyses to study if the mortality risk differs for patients in the rhythm control group with and without permanent AF or polypharmacy. Missing data were imputed with multiple imputation using the mice package before running the survival analysis.[25] A 2-sided *P*-value of <0.05 was considered significant. Data analysis was performed with R version 3.5.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Statement

The Cardiology Center of the Netherlands data were made available under implied consent and transferred to the University Medical Center Utrecht under the Dutch Personal Data Protection Act. This study used data collected during the regular care process and did not subject participants to additional procedures or impose behavioural patterns on them. The Medical Research Ethics Committee of the University Medical Center Utrecht declared that the Medical Research Involving Human Subjects Act does not apply to this study (proposal number 17/359).

Results

Study Population

In total, 1497 patients met the inclusion criteria (Fig 1). Of these, 316 (21%) patients were prescribed a rhythm control strategy and 1181 (79%) patients were given a rate control strategy. Seventy-six percent of the patients started the therapy immediately after their appointment at CCN, 8.5% already used it before the appointment and 14.5% started it in the period after the appointment. Patients prescribed rhythm control therapy were younger (79 $\pm$ 4 years vs 81 $\pm$ 5 years, $P< 0.001$) and more frequently had paroxysmal AF (46% vs 20%, $P< 0.001$). Heart failure (15% vs 22%, $P= 0.007$), valvular heart disease (35% vs 46%, $P= 0.001$) and diabetes mellitus (12% vs 18%, $P= 0.002$) were less common in the

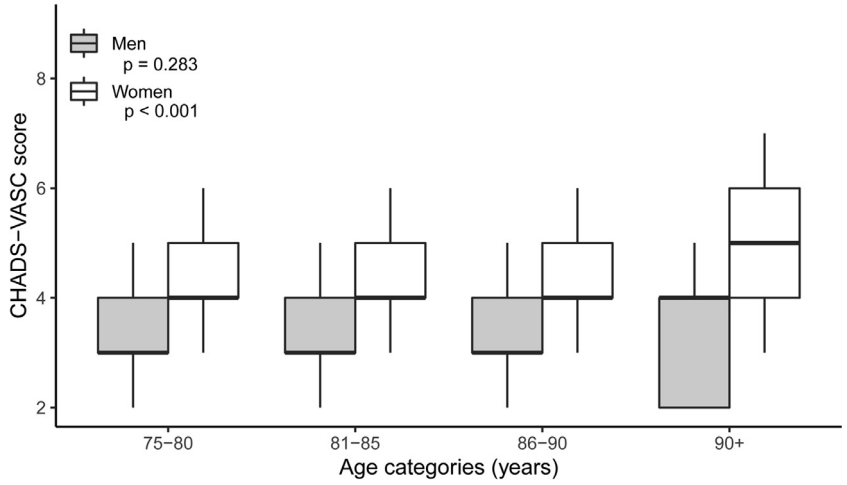

FIG 2. Median CHA_2DS_2-VASc score in each age category. The median (bold line) score per age category is displayed in a box-plot.CHA2DS2-VASc: Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes Mellitus, previous Stroke (2 points), Vascular disease, Age 65-75, female Sex.

rhythm control group, yet we found no difference in the median CHA_2DS_2-VASc score in both groups (Table 1). The median CHA_2DS_2-VASc score did not differ in the different age categories other than due to the extra point for female sex in the score (Fig 2). The number of patients reporting AF related symptoms was remarkably low, with less frequent documentation of dyspnea in the rhythm control group (4% vs 11%, $P<$ 0.001). The proportion of patients with rhythm control significantly decreased with increasing age ($P<$ 0.001; Fig 3). We found no significant differences in the distribution of a rate and rhythm control strategy when comparing the group of patients who visited CCN between 2007-2012 and 2013-2018 (resp. 22% and 19% on rhythm control).

On the ECG, mean heart rate was significantly higher in the rate control group (84 ± 25 bpm vs 71 ± 21 bpm, $P<$ 0.001), probably caused by the larger proportion of patients in that group with AF during the test (64% vs 24%, $P<$ 0.001; Table 2). There were no significant differences in conduction time between the groups, however the uncorrected QT interval was longer in the rhythm control group (in which 43% of patients used sotalol and 20% amiodarone) than in the rate control group ($P<$ 0.001, Table 2). The majority of patients in both groups had a normal left ventricular function on echocardiography. However, the prevalence of a reduced left ventricular function and valvular diseases was larger in the rate control group compared to the rhythm control group (Table 3).

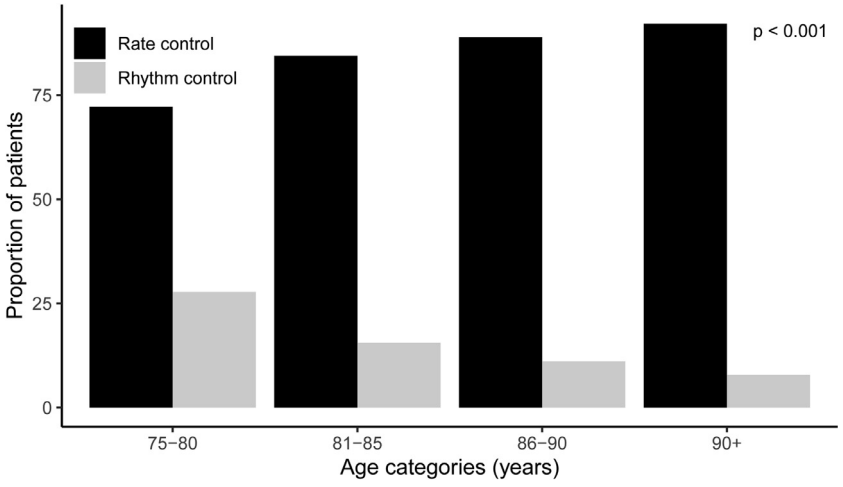

FIG 3. Distribution of the use of a rate and rhythm control strategy per age category.

Medication

Beta-blockers were prescribed most often in the rate control group (74%), whereas sotalol was the most common AAD in the rhythm control group (43%). In the rhythm control group, 21 patients had permanent AF and of these patients 7 used sotalol, 2 flecainide and 3 an unknown AAD. Eighty-three percent of patients used oral anticoagulants to prevent AF-associated stroke, of which 65% used vitamin K antagonists and 19% direct oral anticoagulants (Table 1).

TABLE 2. ECG variables

ECG variables	Rhythm control (n = 316)	Rate control (n = 1181)	*P*-value	Not recorded in EHR*
Heart rate (bpm)	71 ± 21	84 ± 25	<0.001	
Heart rhythm			<0.001	88 (6)
Sinus rhythm	193 (61)	305 (26)		
Atrial fibrillation	76 (24)	756 (64)		
Atrial flutter	<10	28 (2)		
Paced rhythm	<10	10 (1)		
Other rhythm	11 (4)	18 (2)		
PR-interval (msec)	189 ± 38	183 ± 38	0.05	
QRS-duration (msec)	110 ± 28	106 ± 27	0.04	
QT-time (msec)	423 ± 50	387 ± 48	<0.001	
QTc-time (msec)	453 ± 38	448 ± 39	0.07	
Signs of LVH	16 (5)	68 (6)	0.84	530 (35)

Data are expressed in n (%) or Mean ± SD.
BPM, Beats Per Minute; LVH, Left Ventricular Hypertrophy; msec, millisecond; QTc, corrected QT interval; EHR, Electronic Health Record.
*Number of patients with missing data.

TABLE 3. Trans-thoracic echocardiogram variables

TTE variables	Rhythm control (n = 316)	Rate control (n = 1181)	*P*-value	Not recorded in EHR*
Heart rate in sinusrhythm (bpm)	64 ± 13	67 ± 20	0.182	
Heart rhythm			<0.001	
Sinus rhythm	171 (54)	305 (26)		
Atrial fibrillation	65 (21)	656 (56)		
Other or unknown	80 (25)	220 (19)		
Left ventricular ejection fraction			<0.001	347 (23)
≥50%	198 (63)	588 (50)		
40%-50%	20 (6)	206 (17)		
30%-40%	15 (5)	87 (7)		
<30%	6 (2)	30 (3)		
Valvular disease				
Aortic valve stenosis	14 (4)	102 (9)	0.03	1262 (84)
Aortic valve regurgitation	<10	<10	0.31	
Mitral valve regurgitation	24 (8)	147 (12)	0.02	
Tricuspid valve regurgitation	58 (18)	334 (28)	<0.001	
Pulmonary valve regurgitation	0	<10	1.0	
Valvular disease not further specified	23 (7)	83 (7)	0.98	
Left ventricular hypertrophy (category)				
No	171 (54)	581 (49)	0.001	
Mild	38 (12)	213 (18)		
Moderate or severe	9 (3)	55 (5)		
Other or unknown	98 (31)	332 (28)		
Left atrial diameter	41 ± 8	44 ± 8	<0.001	

Data are expressed in n (%) or Mean ± SD.
BPM, Beats Per Minute; EHR, Electronic Health Record.
*Number of patients with missing data.

Factors Associated With Rate or Rhythm Control

In univariable analysis, age >85 years (OR: 2.63, CI: 1.77-3.91, $P < 0.001$), persistent AF (OR: 2.39, CI: 1.33-4.32, $P = 0.004$), permanent AF (OR: 3.71, CI: 2.25-6.10, $P < 0.001$), diabetes mellitus (OR: 1.62, CI: 1.12-2.36, $P = 0.011$), valvular heart disease (OR: 1.58, CI: 1.22-2.05, $P = 0.001$), heart failure (OR 1.62, CI: 1.15-2.27, $P = 0.006$) and symptoms of dyspnea (OR: 2.93; CI: 1.64-5.26, $P < 0.001$) were associated with a preference for rate control. Conversely, paroxysmal AF (OR: 0.31, CI: 0.24-0.40, $P < 0.001$) was associated with a preference for rhythm control (Fig 4). Multivariable regression analyses revealed that age >85 years (OR: 2.28, CI: 1.51-3.44, $P < 0.001$), permanent AF (OR: 2.71, CI: 1.67-4.41, $P < 0.001$) and dyspnea (OR: 2.14, CI: 1.17-3.92, $P = 0.013$) were associated with choosing rate control and paroxysmal AF (OR: 0.42, CI: 0.32-0.56, $P < 0.001$) with rhythm control (Fig 5). Despite the higher absolute number of comorbidities in the rate control

group at baseline (Table 1), no significant associations were found we found for specific comorbidities.

Mortality

The mean follow-up period in the rate control group was 4.1 ± 2.3 years and 4.5 ± 2.3 years in the rhythm control group. At the end of follow up, the primary endpoint occurred in 475 (40.2%) patients in the rate control group and in 91 (28.8%) patients in the rhythm control group. This corresponds to a significant lower unadjusted mortality risk for patients in the rhythm control group compared to patients in the rate control group (HR: 0.64; 95% CI: 0.51-0.80, $P < 0.001$). After correction for significant confounders (age >85 years, female sex, paroxysmal AF, diabetes mellitus, valvular heart disease, heart failure and polypharmacy), the mortality risk was similar in both groups (HR: 0.89; 95% CI:0.70-1.12, $P = 0.314$). Interaction analyses showed significant interactions for polypharmacy ($P_{interaction} = 0.003$) and permanent AF ($P_{interaction} = 0.002$). This indicates that the mortality risk in the rhythm control group for patients with permanent AF (HR: 1.84: 95% CI: 0.97-3.51) or polypharmacy was higher (HR 1.72; 95% CI: 0.62-4.78 than for patients without these conditions (resp. HR: 0.82; 95% CI: 0.63-1.05, and HR: 0.85; 95% CI 0.67-1.08).

Discussion

In this EHR study, we compared the clinical characteristics and mortality risks of patients with AF aged ≥75 years using a pharmacological rate or rhythm control strategy. The cohort consisted of relatively cardiac healthy elderly patients with on average a normal left ventricular function, normal ECG and few reported symptoms. We found that rate control was the most frequently prescribed strategy, and the proportion of patients on this strategy was positively correlated with age. We found a trend toward the prescription of a rate control strategy to the patients with multiple comorbidities and an older age at baseline, as also described by previous studies.[19,26,27] However, no significant associations were found for other comorbidities than age in the multivariable regression analyses. A possible explanation for this trend is that AADs have a potential proarrhythmic effect and may cause severe side effects that occur more often in patients with multiple comorbidities.[15-17] Subsequently, AAD use has been associated with more frequent follow-up appointments and more hospitalizations.[16,17] It has also been suggested that younger patients

	OR	95% CI		P-value
Age>85 years	2.63	1.77	3.91	0.000
Female sex	1.20	0.94	1.54	0.142
BMI	1.01	0.98	1.04	0.600
Persistent AF	2.39	1.33	4.32	0.004
Paroxysmal AF	0.31	0.24	0.40	0.000
AF type not specified	1.23	0.96	1.58	0.107
Permanent AF	3.91	2.46	6.21	0.000
Hypertension	1.25	0.96	1.64	0.100
Diabetes mellitus	1.64	1.13	2.38	0.009
Valvular heart disease	1.58	1.22	2.05	0.001
Heart failure	1.62	1.15	2.27	0.006
Coronary heart disease	0.98	0.72	1.33	0.885
Vascular disease	1.08	0.64	1.81	0.784
Palpitations symptoms	0.88	0.58	1.34	0.562
Dyspnea symptoms	2.93	1.64	5.26	0.000
Polypharmacy*	2.06	0.97	4.36	0.058
EF 30–40%^	1.59	0.46	5.50	0.433
EF 40–50%^	2.65	0.83	8.51	0.094
EF >50%^	0.75	0.26	2.16	0.566

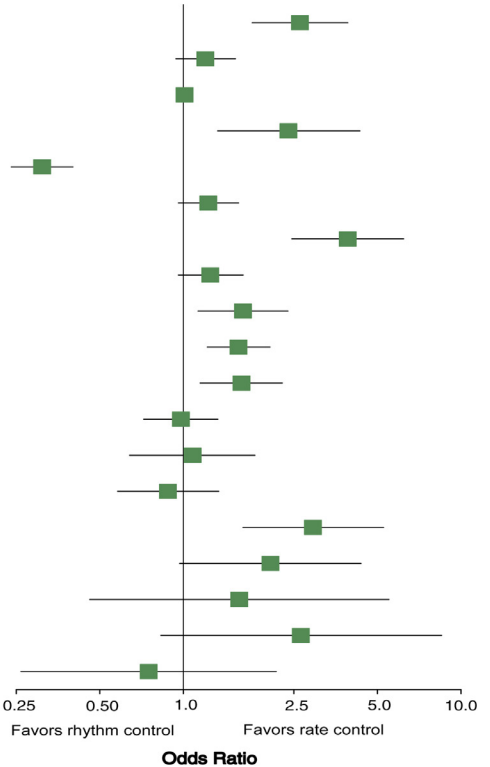

FIG 4. Forest plot univariable cox regression analyses. *: Polypharmacy is defined as the use of >5 medications ^: The odds ratios of the EF categories are compared with the reference category EF <30%. AF: atrial fibrillation; BMI, body mass index; CI, confidence interval; OR, odds ratio.

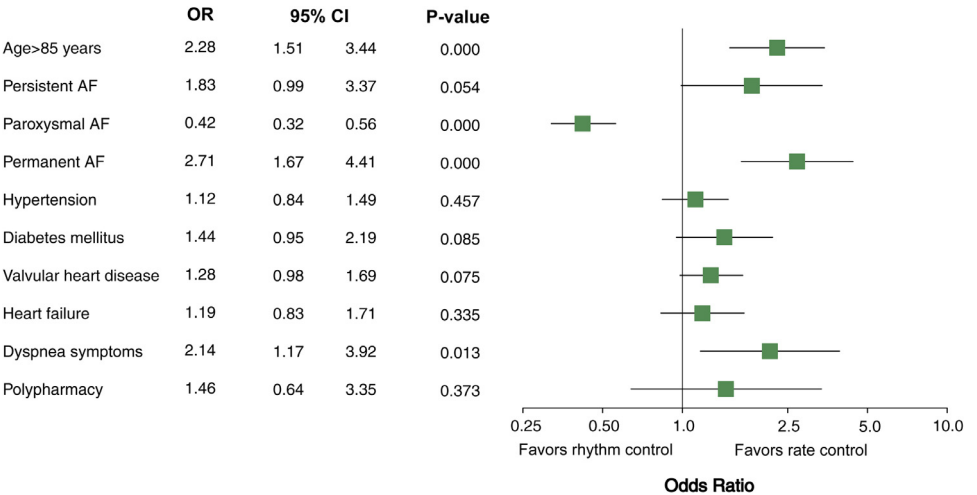

FIG 5. Forest plot multivariable cox regression analyses. *: Polypharmacy is defined as the use of >5 medications. CI, confidence interval; OR, odds ratio.

more often suffer from symptomatic AF and are therefore more motivated to undergo pharmacological or invasive therapy, despite possible side effects.[19] In the rhythm control group, 85 patients used flecainide but only a small number of patients used an atrioventricular nodal-blocking drug, despite the class IIA recommendation in the European guidelines.[6] No additional information was available about the reason for not prescribing an atrioventricular nodal-blocking drug, so it is not known whether a these were contraindicated in these patients due to for example a preexistent bradycardia or if it was caused by poor guideline compliance.

Despite the recommendation of the European guidelines to prescribe rhythm control to improve AF-related symptoms, we found that patients with dyspnea complaints in our cohort were over a twofold more likely to receive rate control instead of rhythm control.[6,28] Of note, the number of patients explicitly reporting symptoms was remarkably low, with only 10% of the patients with rhythm control reporting palpitations and 11% of the patients with rate control reporting dyspnea. This may, in part, be explained by underreported symptoms by physician, patient or both, or that very symptomatic patients were underrepresented in this secondary care outpatient cohort. An alternative explanation is that elderly patients, especially those with paroxysmal AF, are more often asymptomatic than younger patients.[29,30] However, we cannot interpret how the burden of AF symptoms in the rate and rhythm control group was exactly assessed, and to which extent symptomatic patients were labeled as asymptomatic.

After correction for multiple significant confounders, no significant difference was found in the mortality risk for the elderly patients with AF on a pharmacological rhythm control strategy vs a rate control strategy (HR: 0.9, $P = 0.368$). Of note, due to the observational nature of the data we cannot assume our findings are causal. The observed similar mortality risk is in accordance with the results of previous observational cohort studies.[13,16,19] This suggests that a more liberal approach in prescribing rhythm control to the healthier elderly patient with symptomatic AF may be safe, also because the adjusted mortality risk seemed to be slightly lower in the rhythm control group, although this was not statistically significant. However, benefits and risks of such therapies still need to be evaluated on an individual basis. Additionally, catheter ablation as rhythm control strategy also has been proven to be both effective and safe in elderly patients with AF, although this evidence comes from relatively small cohorts.[14,31-34] Catheter ablation was not included in this study due to a lack of data about this treatment, so we speculate that

future studies including catheter ablation as a therapy in the rhythm control group might even show better results for the elderly patients with AF.

A definite conclusion regarding optimal therapy in elderly AF patients must be derived from a prospective (non-inferiority) trial in this population. More research about the safety and clinical outcomes of both strategies in elderly AF patients is necessary, in particular since they represent a rapidly growing population of patients and too little is known about treatment of the arrhythmia in these patients.[1-5,13,16,19] Moreover, evidence that early rhythm control is beneficial in AF patients who are treated with contemporary anticoagulant medication and that side effects of antiarrhythmic medication are rare is emerging.[14] Our finding that permanent AF was associated with a higher risk of mortality in the rhythm control group underscores the notion that antiarrhythmic medication should be reserved for those in whom restoration of sinus rhythm is desired.[35] In our study, it is not known whether these patients had another indication for the use of these medicaments.

The strengths of our study are that we were able to study a relatively large cohort of an often underrepresented and yet growing group of elderly patients with AF. This enabled us to study the mortality risk and clinical characteristics of these patients in a representative "real world" cohort and to show a detailed description of current management of AF in this group. The main limitation of our study is that data collection was driven by medical need and thus not performed systematically.[36] Consequently, some patient files were incomplete and certain parameters relevant for patients with AF (eg, data about respiratory diseases, thyroid diseases) were lacking or only available for a small number of patients. We were unable to perform a propensity score matching analyses to adjust for selection bias because there were only 316 patients in the rhythm control group so this approach would have led to loss of statistical power. Passive follow-up for approximately 4000 patients was not available because linkage to the national statistics databased failed, potentially because patients changed address, or the patient's information was registered incorrectly.

Conclusion

Elderlypatients with AF more often receive a rate than a rhythm control strategy. When prescribed, rhythm control is preferentially given to the relatively younger patients with paroxysmal AF. However, a rhythm control strategy was not associated with a higher mortality risk. This suggests that a more liberal approach to prescribing a rhythm control strategy to

symptomatic healthier elderly patients with AF is safe, and, given the emerging evidence of prognostic benefit, may be warranted more often. However, a randomized (non-inferiority) trial is needed to validate our findings.

Author Contributions

TK, conceived the research question, performed part of the raw data cleaning and data analyses, and wrote the manuscript. SB conceived the research question, cleaned the raw date, performed data analyses and critically reviewed the manuscript. JN conceived the research question and critically reviewed the manuscript. IT and GS collected the raw data and reviewed the manuscript. HR conceived the research question, obtained funding, supported data analyses and critically reviewed the manuscript. JG conceived the research question, obtained funding, supported data analyses and critically reviewed the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100996.

REFERENCES

1. Zulkifly H, Lip G, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract* 2018;72:e13070. https://doi.org/10.1111/ijcp.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5.
3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;155:469–73.
4. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;386:154–62.
5. He W, Goodkin D, Kowal P. An aging world: 2015. US Census Bureau 2016:P95/. 16-1.

6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;42:373–498.
7. Ayan M, Pothineni NV, Siraj A, Mehta JL. Cardiac drug therapy-considerations in the elderly. *J Geriatr Cardiol* 2016;13:992–7.
8. Poposka L. What is the best strategy to follow in very old patients with atrial fibrillation: rate or rhythm control? *E-Journal Cardiol Pract* 2019;17.
9. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33.
10. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834–40.
11. Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, et al. Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Arch Intern Med* 2012;172:997–1004.
12. Caldeira D, David C, Sampaio C. Rate versus rhythm control in atrial fibrillation and clinical outcomes: updated systematic review and meta-analysis of randomized controlled trials. *Arch Cardiovasc Dis* 2012;105:226–38.
13. Depoorter L, Sels L, Deschodt M, Van Grootven B, Van der Linden L, Tournoy J. Clinical outcomes of rate vs rhythm control for atrial fibrillation in older people: a systematic review and meta-analysis. *Drugs Aging* 2019;37:19–26.
14. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305–16.
15. Dalgaard F, Pallisgaard JL, Nume AK, et al. Rate or rhythm control in older atrial fibrillation patients: risk of fall-related injuries and syncope. *J Am Geriatr Soc* 2019;67:2023–30.
16. Shariff N, Desai RV, Patel K, et al. Rate-control versus rhythm-control strategies and outcomes in septuagenarians with atrial fibrillation. *Am J Med* 2013;126:887–93.
17. Kumana CR, Cheung BM, Cheung GT, Ovedal T, Pederson B, Lauder IJ. Rhythm vs. rate control of atrial fibrillation meta-analysed by number needed to treat. *Br J Clin Pharmacol* 2005;60:347–54.
18. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. *JAMA Intern Med* 2014;174:1868–70.
19. Paciullo F, Proietti M, Bianconi V, et al. Choice and outcomes of rate control versus rhythm control in elderly patients with atrial fibrillation: a report from the REPOSI study. *Drugs Aging* 2018;35:365–73.
20. Maan A, Zhang Z, Qin Z, et al. Impact of treatment crossovers on clinical outcomes in the rate and rhythm control strategies for atrial fibrillation: insights from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. Pacing and clinical electrophysiology. *PACE* 2017;40:770–8.
21. Bots SH, Siegersma KR, Onland-Moret NC, et al. Routine clinical care data from thirteen cardiac outpatient clinics: design of the Cardiology Centers of the Netherlands (CCN) database. *BMC Cardiovasc Disord* 2021;21:287.

22. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017;135:e146–603.
23. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–72.
24. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39. e14.
25. Buuren Sv G-OK. Mice: multivariate imputation by chained equations in R. *Journal Stat Softw* 2011;45:1–68.
26. Camm AJ, Breithardt G, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). *J Am Coll Cardiol* 2011;58:493–501.
27. Miura K, Ikemura N, Kimura T, et al. Treatment strategies and subsequent changes in the patient-reported quality-of-life among elderly patients with atrial fibrillation. *Am Heart J* 2020;222:83–92.
28. Rienstra M, Lubitz SA, Mahida S, et al. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation* 2012;125:2933–43.
29. Esato M, Chun YH, An Y, et al. Clinical impact of asymptomatic presentation status in patients with paroxysmal and sustained atrial fibrillation: the Fushimi AF Registry. *Chest* 2017;152:1266–75.
30. Dagres N, Nieuwlaat R, Vardas PE, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol* 2007;49:572–7.
31. Bunch TJ, Weiss JP, Crandall BG, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in octogenarians. *Pacing Clin Electrophysiol* 2010;33:146–52.
32. Nademanee K, Amnueypol M, Lee F, et al. Benefits and risks of catheter ablation in elderly patients with atrial fibrillation. *Heart rhythm* 2015;12:44–51.
33. Zado E, Callans DJ, Riley M, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol* 2008;19:621–6.
34. Corrado A, Patel D, Riedlbauchova L, et al. Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. *J Cardiovasc Electrophysiol* 2008;19:807–11.
35. Nattel S. Dronedarone in atrial fibrillation—Jekyll and Hyde? *N Engl J Med* 2011;365:2321–2.
36. Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *J Am Med Inform Assoc* 2013;20:144–51.