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CLINICAL RESEARCH
Atrial fibrillation

Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation

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Aim The impact of rate and rhythm control strategies on outcomes in patients with atrial fibrillation (AF) remains controversial. Our aims were: to report use of rate and rhythm control strategies in European patients from the EURObservational Research Program AF General Pilot Registry. Secondly, to evaluate outcomes according to assigned strategies.

Methods and results Use of pure rate and rhythm control agents was described according to European regions. 1-year follow-up data were reported. Among rate control strategies, beta-blockers were the most commonly used drug. Proportions of patients assigned to rhythm control varied greatly between countries, and amiodarone was the most used rhythm control drug. Of the original 3119 patients, 1036 (33.2%) were assigned to rate control only and 355 (11.4%) to rhythm control only. Patients assigned to a rate control strategy were older ($P < 0.0001$) and more likely female ($P = 0.0266$). Patients assigned to a rate control strategy had higher rates for any thrombo-embolic event ($P = 0.0245$), cardiovascular death ($P = 0.0437$), and all-cause death ($P < 0.0001$). Kaplan–Meier analysis showed that rate control strategy was associated with a higher risk for all-cause death ($P < 0.001$). On Cox regression analysis, rate control strategy was independently associated with all-cause death ($P = 0.0256$). A propensity matched analysis only found a trend for the association between rate control and all-cause death ($P = 0.0664$).

Conclusion In a European AF patients' cohort, a pure rate control strategy was associated with a higher risk for adverse events at 1-year follow-up, and partially adjusted analysis suggested that rate control independently increased the risk for all-cause death. A fully adjusted propensity score matched analysis found that this association was no longer statistically significant, suggesting an important role of comorbidities in determining the higher risk for all-cause death.

Keywords Atrial fibrillation • Rate control • Rhythm control • Major adverse events • All-cause death • Registry

Introduction

Apart from stroke prevention, another important aspect of atrial fibrillation (AF) management involves symptom control with the physician having to decide whether to employ a rate control, rhythm control or a combination strategy with regard to each individual AF patient. For the majority of patients, current European Society of Cardiology (ESC) Guidelines suggest that rate control should be the initial preferred management strategy, with rhythm control strategy suggested in AF patients who remain symptomatic despite adequate ventricular rate control.[1] Moreover, rate control therapy would be essential in the clinical management of AF patients, even in those who

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What's new?

- The impact of rate and rhythm control strategies in atrial fibrillation (AF) patients on outcomes in real world cohorts is less certain.
- AF patients managed with a rate control strategy reported more adverse outcomes than those managed with a rhythm control strategy.
- A rate control strategy was associated with a higher risk for all-cause death, even if this association was found to be non statistically significant after full adjustments with propensity score matched analysis.
- Adequately powered randomized control trials may still be needed, as well as large prospective 'real world' cohorts, to fully assess the impact of rate and rhythm control strategies on adverse outcomes in AF patients.

ultimately require a rhythm control strategy.[2] Nonetheless, physicians still frequently consider the two strategies as mutually exclusive alternatives, despite rate control being part of rhythm control.

Whilst both rate and rhythm control strategies do improve symptoms, there is no conclusive evidence to demonstrate an improved survival with either strategy.[2–5] Various studies addressing the basic issue of whether converting AF back to sinus rhythm confers mortality benefits have been on-going for over 10 years. Multiple randomized controlled trials (RCTs) comparing rate and rhythm control therapies in patients with AF have not demonstrated any evidence of superiority in terms of death or systemic embolism with either strategy.[3–7] Other studies have suggested contradictory results with lower mortality shown with rhythm control compared with rate control.[8–10] One issue with the large trials comparing rhythm vs. rate control strategies has been the low rate of sinus rhythm restoration and maintenance. In the RACE study, for example, less than 40% of patients were in sinus rhythm at the end of the study.[5]

It has been suggested that an early rhythm control strategy with either a combination of pharmacological and ablation therapies may help in halting AF progression and improve patient outcomes. For example, the early treatment of atrial fibrillation for stroke prevention trial (EAST) is one such study evaluating outcomes of patients with new onset AF managed with either rhythm control therapy or rate control therapy.[11]

The EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot Registry was a registry sponsored by the ESC and conducted in nine European countries to ascertain contemporary management of AF patients amongst European cardiologists. In this analysis, we report on the use of pure rate control management *strategy* vs. pure rhythm control management *strategy* in this 'real life' registry. Secondly, we assessed adverse outcomes with rate or rhythm control strategies over a 1-year follow-up.

Methods

Details on the EORP-AF study design, baseline and 1-year prospective results have been previously reported.[12,13] In brief, EORP-AF was a prospective registry of consecutive AF patients managed by cardiologists, in nine countries (Belgium, Denmark, Netherlands, Norway, Poland, Romania, Greece, Italy, and Portugal). All patients entered the study after signing a written informed consent. The study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

The study enrolled both in- and outpatients accessing cardiology services (either hospital or office-based centres) with AF as a primary or secondary diagnosis. The qualifying AF event was recorded by a 12-lead ECG, 24 h ECG Holter, or other electrocardiographic documentation and should have been occurred within the 12 months before enrolment. Follow-up data were recorded 1 year after enrolment date according to procedures previously described.[13] From February 2012 to March 2013, a total of 3119 AF patients were enrolled.

We described the use of rate and rhythm control strategies among EORP-AF patients according to four European regions, arbitrarily defined as follows: (i) Eastern Europe: Poland and Romania; (ii) Southern Europe: Greece, Italy, and Portugal; (iii) Western Europe: Belgium and Netherlands; (iv) Northern Europe: Denmark and Norway. Rate and rhythm control strategies were defined according to ESC guidelines.[1,14] To evaluate the impact of rate and rhythm control strategies on adverse outcomes and mortality, we only considered AF patients reported by their enrolling cardiologist as being treated with rate control only and rhythm control only (and not both strategies). During the baseline assessment, all investigators had to define the clinical management strategy, according to the primary and/or prevalent approach. We recognize that rate control would be used even in those AF patients that ultimately require rhythm control, those assigned to the 'rate control only' group were considered as being primarily and prevalently assigned to a rate control *strategy*, while those considered for the 'rhythm control only' group were primarily and prevalently assigned to a rhythm control *strategy*.

Thrombo-embolic risk was defined according to the CHA_2DS_2-VASc score.[15] 'Low risk' patients were defined as a CHA_2DS_2-VASc 0 in males or 1 in females; 'moderate risk' was defined as male patients with a CHA_2DS_2-VASc score 1; and 'high risk' was defined as CHA_2DS_2-VASc score ≥ 2. Bleeding risk was assessed according to the HAS-BLED score.[16]

During the pre-specified 1-year follow-up, the occurrence of major adverse events was recorded. Based on the study protocol, events recorded were as follows: cardiovascular (CV) death; all-cause death; and any thrombo-embolic event (TE) [defined as the occurrence of any thrombosis-related complication, i.e. stroke, transient ischemic attack (TIA), acute coronary syndrome, coronary intervention, cardiac arrest, peripheral or pulmonary embolism]. Follow-up data were collected according to any centre procedures, both from follow-up visits and/or consultation of medical notes.

Statistical analysis

Continuous variables were reported as mean ± SD or as median and inter-quartile range.

Between-group comparisons were made by using a non-parametric test (Kruskal–Wallis test).

Categorical variables were reported as percentages. Between-group comparisons were made by using a χ^2 test or a Fisher's exact test if any expected cell count was less than five. For categorical variables with more than two possible values, exact *P*-values have been estimated according to the Monte Carlo method.

Evaluation of factors significantly associated with all-cause death used a Cox proportional hazards analysis. All demographic variables underwent a univariate analysis. All variables with a *P*-value <0.10 for the association to all-cause death at the univariate analysis, were inserted in the stepwise

Table 1 Use of rate and rhythm control treatments across regions

	Eastern Europe (n = 1306)	Southern Europe (n = 1044)	Western Europe (n = 325)	Northern Europe (n = 444)
Rate control				
Beta-blockers	995/1303 (76.4%)	633/1039 (60.9%)	196/325 (60.3%)	335/442 (75.8%)
Calcium channel blockers	59/1303 (4.5%)	101/1040 (9.7%)	11/325 (3.4%)	19/443 (4.3%)
Digoxin	349/1304 (26.8%)	137/1040 (13.2%)	53/325 (16.3%)	74/443 (16.7%)
Rhythm control				
Dronedarone	–	4/1041 (0.4%)	–	5/443 (1.1%)
Flecainide	16/1303 (1.2%)	71/1041 (6.8%)	39/325 (12.0%)	27/443 (6.1%)
Propafenone	121/1304 (9.3%)	40/1041 (3.8%)	3/325 (0.9%)	–
Sotalol	36/1304 (2.8%)	36/1041 (3.5%)	58/325 (17.8%)	4/444 (0.9%)
Amiodarone	355/1303 (27.2%)	190/1041 (18.3%)	52/325 (16.0%)	66/444 (14.9%)
Direct current cardioversion	172/1277 (13.5%)	230/1037 (22.2%)	116/325 (35.7%)	185/441 (42.0%)
Left atrial catheter ablation	54/1298 (4.2%)	69/1043 (6.6%)	23/325 (7.1%)	85/443 (19.2%)
Surgical AF ablation	5/1303 (0.4%)	2/365 (0.5%)	–	4/443 (0.9%)

AF, atrial fibrillation.

multivariate model. Additional stepwise models were then performed inserting in any model a specific class of anti-atherosclerotic drugs. A Hosmer and Lemeshow Goodness-of-Fit Test was used to verify that the models were optimal. A two-sided P-value <0.05 was considered statistically significant.

A propensity score matched (PSM) analysis was also computed. The propensity score was estimated according to all variables considered at baseline (see Supplementary material online, *Table S1*), and propensity-based matching was used to create samples of patients treated by the therapy under study and not treated who were similar in terms of propensity score, i.e. in terms of probability of receiving the therapy. Unmatched observations were discarded, thus leading to possibly non-representative samples of the original database; however, because the patients analysed were matched on many confounders simultaneously, such analyses are likely to provide a more valid estimate of the treatment effect. A 1:1 matching optimal algorithm without replacement was used, where all treated patients were matched to the closest control within a range of 0.20 standard deviations of the logit of the estimated propensity score. The success of the propensity score matching was assessed by checking standardized differences between the groups before and after matching, i.e. the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable, expressed as a percentage. Balancing was considered as successful, if the standardized differences were less than 10% for variables used for propensity score development. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 3119 patients were enrolled, with the majority of patients recruited from Eastern (n = 1306; 41.9%) and Southern Europe (n = 1044; 33.5%), while only 444 (14.2%) and 325 (10.4%) patients were enrolled, respectively, in Northern and Western Europe. In terms of baseline characteristics, the percentage of patients with paroxysmal AF was higher in Northern Europe (46.7%) compared with the other three regions (23.6%, 22.2%, and 25.6%, respectively, in Eastern, Southern, and Western Europe).

Across the four regions, beta-blockers were the most commonly used rate control agents, followed by digoxin (*Table 1*). The proportion of patients with inadequate rate control (defined as a heart rate <50 beats per minute (bpm) or > 110 bpm) ranged between 20% and 30% of patients across the four regions (*Table 2*). In particular, patients with inadequate rate control are more likely to be non- (or slightly) symptomatic (EHRA I or EHRA II) in three out of four regions (*Table 2*). Conversely, patients from Eastern Europe with inadequate rate control are more symptomatic (61.6% EHRA III or IV).

There was a wide range amongst the nine European countries in the percentage of AF patients being treated with rhythm control agents. Only 25.9% of patients were prescribed with antiarrhythmic drugs in Norway, but the percentage progressively increased in Italy (33.1%), Poland (43.4%), Netherlands (46.5%), and Romania (50.6%). More than half of patients were treated with antiarrhythmic drugs in Portugal (54.3%), Belgium (63.2%), and Greece (66.7%), while in Denmark, up to three quarter of patients were treated with an antiarrhythmic drug. Amiodarone was generally the most widely prescribed anti-arrhythmic agent across the regions studied with the exception of Western Europe where sotalol was the most popular anti-arrhythmic agent followed by amiodarone (*Table 1*). Flecainide was the second most commonly prescribed antiarrhythmic in Southern and Northern Europe (*Figure 1*); the majority of patients prescribed flecainide across the regions had minimal or no structural heart disease with the exception of Western Europe where the majority of patients on flecainide had hypertensive heart disease (i.e. cardiomyopathy and hypertrophy) (19.4% vs. 1.3% in Eastern Europe and 6.5% in Southern Europe). Generally, propafenone was not widely prescribed across the regions except in Eastern Europe, where it was the most common agent prescribed after amiodarone. Dronedarone was used in only a very small proportion of patients.

Direct current cardioversion was the most common non-pharmacological strategy used for rhythm control across the four

Table 2 Proportion of patients with inadequate rate control according to symptomatic status across the four regions

	Eastern Europe (n =1281)	Southern Europe (n =1001)	Western Europe (n = 323)	Northern Europe (n = 437)
Patients with inadequate HR[a]	380/1281 (29.7%)	218/1001 (21.8%)	64/323 (19.8%)	125/437 (28.6%)
EHRA I/II	146/380 (38.4%)	145/218 (66.5%)	44/64 (68.7%)	97/125 (77.6%)
EHRA III/IV	234/380 (61.6%)	73/218 (33.5%)	20/64 (31.3%)	28/125 (22.4%)

[a]HR <50 or >110 bpm.
Bpm, beats per minute; EHRA, European Heart Rhythm Association; HR, heart rate.

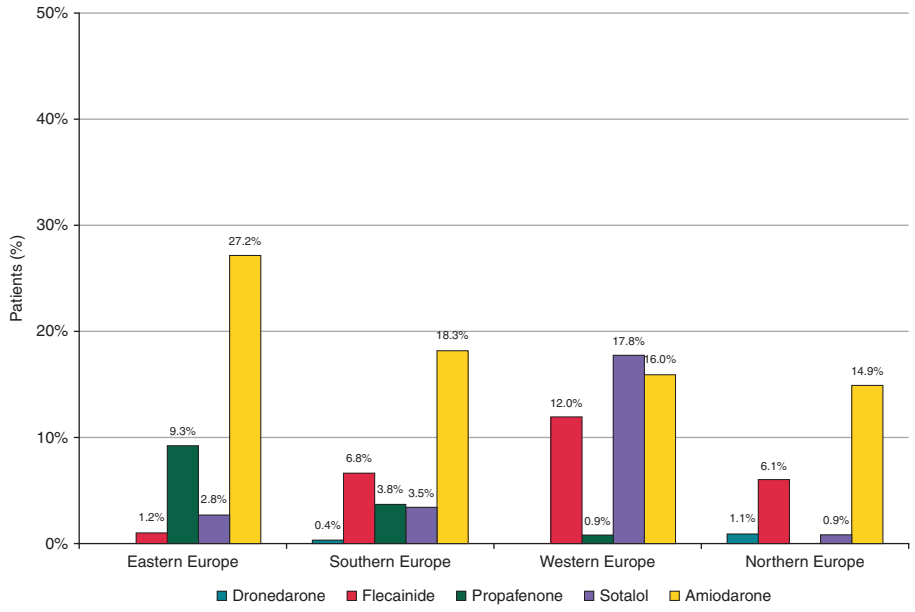

Figure 1 Distribution of anti-arrhythmic treatments according to European regions.

regions followed by left atrial catheter ablation (*Table 1*). Regions with the higher proportion of direct current cardioversion also had a proportionally higher rate of left atrial catheter ablation use. Surgical ablation was not widely used, with only Northern Europe reporting a rate of 0.9% (*Figure 2*).

Of the original cohort, 1036 (33.2%) patients were assigned to a *pure* rate control management *strategy* whilst 355 (11.4%) were assigned to a *pure* rhythm control management *strategy* (*Table 3*). For this analysis comparing rate vs. rhythm control *strategies*, all patients that were managed with a mixed strategy (i.e. both rate and rhythm control), or only managed with clinical observation at the baseline were excluded. Patients assigned to rhythm control only were younger ($P < 0.0001$) and less commonly female ($P = 0.0266$). Patients assigned to rhythm control only strategy had a significantly lower proportion of patients with other comorbidities, including coronary artery disease ($P = 0.0004$), chronic heart failure ($P < 0.0001$), valvular heart disease ($P < 0.0001$), chronic obstructive pulmonary disease ($P = 0.0048$), chronic kidney disease, and peripheral vascular disease (both $P < 0.0001$), when compared with the rate control group.

The rate control group had a significantly higher proportion of patients with established cardiovascular risk factors including diabetes ($P = 0.0175$), hypertension ($P = 0.0060$), previous ischaemic thrombo-embolic complications ($P = 0.0014$), and haemorrhagic events ($P = 0.0335$). Moreover, patients assigned to rate control were more likely reported to report no physical activity ($P < 0.0001$). Thus, AF patients assigned to rate control had a higher CHA_2DS_2-VASc score ($P < 0.0001$), as well as a higher proportion of patients at high thrombo-embolic risk (CHA_2DS_2-VASc ≥ 2) ($P < 0.0001$). Baseline bleeding risk was higher in the rate control patients ($P = 0.0003$). Patients managed with rate control strategy were more likely asymptomatic compared with those assigned to rhythm control arm (<0.0001). Patients in the rate control strategy were more likely diagnosed with not paroxysmal AF ($P < 0.0001$).

Follow-up analysis

Patients assigned to the rate control only strategy had a higher rate of stroke/TIA compared with those assigned to rhythm control only, of borderline significance ($P = 0.0537$). For any TE, the proportion in the rate control group was two-fold that in rhythm control group

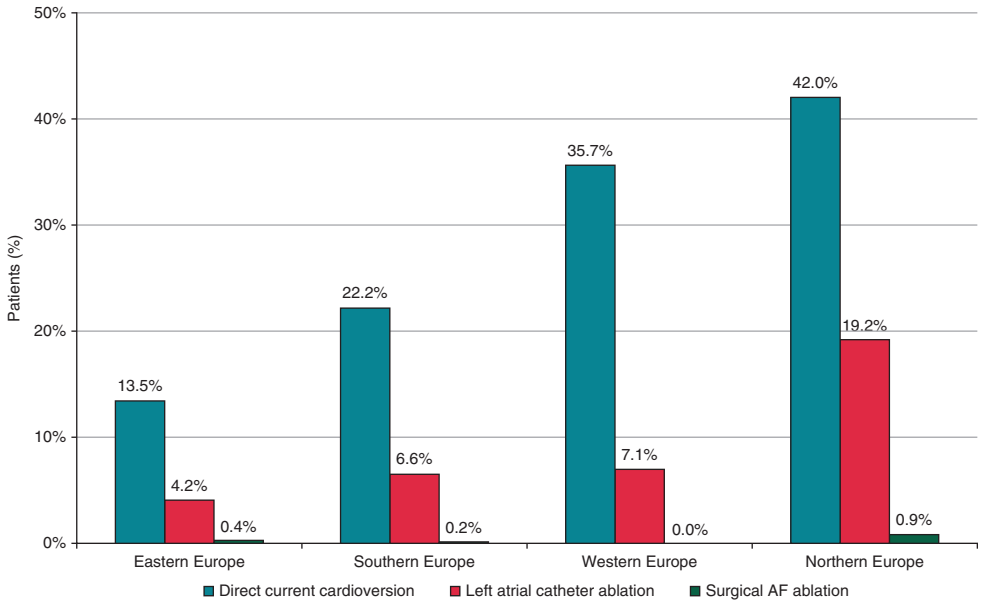

Figure 2 Distribution of non-pharmacological anti-arrhythmic strategies across the European regions.

($P = 0.0245$). Cardiovascular death occurrence rate was higher in the rate control group ($P = 0.0437$). Similarly, all-cause death occurred more frequently in patients assigned to rate control only strategy than in those in rhythm control one ($P < 0.0001$) (*Table 4*).

Kaplan–Meier analysis shows that a rate control strategy was associated with a higher risk for all-cause death ($P < 0.001$) (*Figure 3*). When assessing survival in different geographical regions according to management strategy, only patients from Southern Europe assigned to rate control had a higher risk for all-cause death (see Supplementary material online, *Figure S1*) when compared with rate control patients from other regions ($P = 0.0118$). No regional difference (see Supplementary material online, *Figure S2*) was found in terms of mortality for rhythm control patients ($P = 0.4273$).

On multivariable Cox regression analysis, a rate control strategy was independently associated with a higher risk for all-cause death (hazard ratio: 2.83, 95% confidence interval: 1.14–7.05, $P = 0.0256$) (*Table 5*).

Propensity score matched analysis

In order to account for comorbidities in determining the higher risk for all-cause death, a PSM analysis was also performed (see Supplementary material online). After the PSM, a total of 199 patients were eligible for analysis, both for the rate control only and rhythm control only strategies (see Supplementary material online, *Table S1*). Patients assigned to rate control had more prevalent coronary artery disease, myocardial infarction and previous revascularization procedures, whilst patients assigned to rhythm control had more prevalent stable angina. Rate control patients were more frequently smokers and less likely to undertake physical activity. There was high thrombo-embolic risk profile in the rate control group.

Outcome rates (see Supplementary material online, *Table S2*) at follow-up were not different between the two groups after propensity score matching. Cox regression analysis (see Supplementary ma terial online, *Table S3*) after PSM found that age ($P = 0.0467$), chronic kidney disease ($P = 0.0010$), and diabetes mellitus ($P = 0.0055$) were independently associated with all-cause death. A rate control strategy had a non-significant trend for higher mortality, with wide confidence intervals [hazard ratio (HR): 3.45, 95% confidence interval (CI): 0.92–12.97, $P = 0.0664$].

Discussion

This analysis of the EORP-AF pilot general registry provides us with a 'snapshot' of the prevailing use of rhythm and rate control therapies throughout the four major regions in Europe, showing how frequently physicians decide for either a pure rate control strategy or rhythm control strategy. First, patients managed with rate control only tend to be older and with more comorbidities. Secondly, among rhythm control agents, amiodarone was the most popular drug throughout the four European areas. Thirdly, non-pharmacological methods of rhythm control were less frequently used compared with direct current cardioversion. Last, a rate control strategy was associated with a higher risk for any TE, CV death, and all-cause death at 1-year follow-up. Even if rate control was associated with an increased risk for all-cause death on Cox regression analysis, PSM analysis did not verify those results, showing a non-significant trend for higher risk of all-cause death, partially suggesting that an interaction with a worst clinical status could be considered.

Amiodarone was the most popular anti-arrhythmic pharmacological agent prescribed for rhythm control amongst the majority of

Table 3 Baseline characteristics of patients assigned to rate control and rhythm control only

	Rate control *n* = 1036	Rhythm control *n* = 355	*P*
Demographics			
Age, *years* median (IQR)	73.0 (65.0–79.0)	66.0 (59.0–73.0)	<0.0001
Age ≥75 years, *n* (%)	464/1036 (44.8%)	74/355 (20.8%)	<0.0001
Female gender, *n* (%)	419/1036 (40.4%)	120/355 (33.8%)	0.0266
Concomitant disease, *n* (%)			
Lone AF	15/1036 (1.4%)	36/355 (10.1%)	<0.0001
Coronary artery disease	379/903 (42.0%)	88/290 (30.3%)	0.0004
Myocardial infarction	199/379 (52.5%)	45/88 (51.1%)	0.8167
PTCA/CABG	204/379 (53.8%)	42/88 (47.7%)	0.3020
Stable angina	121/379 (31.9%)	37/88 (42.0%)	0.0707
Chronic heart failure	554/1013 (54.7%)	77/317 (24.3%)	<0.0001
NYHA III/IV	264/554 (47.7%)	26/77 (33.8%)	0.0220
Valvular heart disease	705/1008 (69.9%)	162/318 (50.9%)	<0.0001
Dilated cardiomyopathy	136/1008 (13.5%)	22/317 (6.9%)	0.0017
Hypertrophic cardiomyopathy	31/1009 (3.1%)	14/317 (4.4%)	0.2490
Restrictive cardiomyopathy	6/1010 (0.6%)	–	0.3455[a]
Hypertensive cardiomyopathy	191/1008 (18.9%)	51/317 (16.1%)	0.2503
Other cardiac disease	106/998 (10.6%)	19/315 (6.0%)	0.0155
Chronic obstructive pulmonary disease	146/1025 (14.2%)	30/355 (8.5%)	0.0048
Hyperthyroidism	32/1004 (3.2%)	11/352 (3.1%)	0.9543
Hypothyroidism	86/1006 (8.5%)	22/352 (6.3%)	0.1701
Chronic kidney disease	179/1035 (17.3%)	28/354 (7.9%)	<0.0001
Peripheral vascular disease	153/1016 (15.1%)	22/342 (6.4%)	<0.0001
Cardiovascular risk factors, n (%)			
Diabetes	236/1028 (23.0%)	60/354 (16.9%)	0.0175
Hypertension	739/1033 (71.5%)	225/353 (63.7%)	0.0060
Current smoker	110/1001 (11.0%)	38/340 (11.2%)	0.9241
Hypercholesterolaemia	480/1006 (47.7%)	154/350 (44.0%)	0.2304
Alcohol ≥2–3 units/day	95/964 (9.9%)	36/324 (11.1%)	0.5175
Physical activity			<0.0001
None	469/970 (48.4%)	107/320 (33.4%)	
Occasional	309/970 (31.9%)	103/320 (32.2%)	
Regular	161/970 (16.6%)	85/320 (26.6%)	
Intense	31/970 (3.2%)	25/320 (7.8%)	
Comorbidities, *n* (%)			
Ischaemic thrombo-embolic complications	164/1033 (15.9%)	32/355 (9.0%)	0.0014
Previous stroke	68/1034 (6.6%)	17/355 (4.8%)	0.2253
Previous transient ischaemic attack	64/1029 (6.2%)	9/355 (2.5%)	0.0074
Haemorrhagic events	99/1032 (9.6%)	21/355 (5.9%)	0.0335
Haemorrhagic stroke	1/99 (1.0%)	1/21 (4.8%)	0.3206[a]
Major bleeding	26/99 (26.3%)	4/21 (19.0%)	0.4880
Malignancy	53/1018 (5.2%)	25/349 (7.2%)	0.1738
Symptoms, *n* (%)			
EHRA I	577/1036 (55.7%)	146/355 (41.1%)	<0.0001
EHRA II-IV	459/1036 (44.3%)	209/355 (58.9%)	
Type of AF, *n* (%)			<0.0001
Paroxysmal AF	113/1008 (11.2%)	147/351 (41.9%)	
Not paroxysmal AF	895/1008 (88.8%)	204/351 (58.1%)	
CHA_2DS_2-VASc median (IQR)	4 (2–5)	2 (1–4)	<0.0001
Thrombo-embolic Risk, *n* (%)			<0.0001
Low risk	41/1036 (4.0%)	59/355 (16.6%)	

continued

Table 3 *Continued*

	Rate control $n = 1036$	Rhythm control $n = 355$	*P*
Moderate risk	77/1036 (7.4%)	66/355 (18.6%)	
High risk	918/1036 (88.6%)	230/355 (64.8%)	
HAS-BLED median (IQR)	1 (1–2)	1 (0–2)	<0.0001
0–2	857/1036 (82.7%)	322/355 (90.7%)	0.0003
≥3	179/1036 (17.3%)	33/355 (9.3%)	

Kruskal–Wallis test is used for quantitative data. χ^2 or Fisher's exact test [a] is used for binary variables.
AF, atrial fibrillation; CABG, coronary artery by-pass graft; EHRA, European Heart Rhythm Association; IQR, inter-quartile range; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty.

Table 4 Outcome rates at 1-year follow-up according to baseline strategy

N (%)	Rate control $n = 1036$	Rhythm control $n = 355$	*P*
Stroke/TIA	16/916 (1.7%)	1/338 (0.3%)	0.0537
Any TE	49/916 (5.3%)	8/338 (2.4%)	0.0245
Cardiovascular death	39/992 (3.9%)	6/355 (1.7%)	0.0437
All-cause death	102/1036 (9.8%)	9/355 (2.5%)	<0.0001

TE, thrombo-embolic event; TIA, transient ischemic attack.

the European regions surveyed. This finding appears to be consistent and unchanged with the Euro Heart Survey which demonstrated that amiodarone was the most used agent for rhythm control across the majority of atrial fibrillation sub-types.[17] The ESC guidelines generally recommend amiodarone as first line rhythm control in with NYHA III/IV and 'unstable NYHA II'. From our registry data we observe a positive trend between the prevalence of heart failure and the use of amiodarone. Regions with higher prevalence of heart failure had a higher proportion of amiodarone use, which is in line with current guidelines.[1] Flecainide on the other hand, is not recommended for use in patients with chronic heart failure and coronary artery disease. This recommendation has generally been adhered to with the majority of patients prescribed flecainide across the regions having minimal or no structural heart disease with the exception of Western Europe where the majority of patients on flecainide had hypertensive heart disease.

There were significant differences at baseline between the patients treated with rate and rhythm control therapy with a general trend for older patients with multiple comorbidities and risk factors to be managed with a rate control therapy. This difference in baseline characteristics is consistent with similar findings from previous studies evaluating differences between rhythm and rate control.[3,5] Gender differences in rate and rhythm control use could possibly be related to differences in symptomatic status. In a previous EORP-AF subgroup analysis about gender differences, female patients were found to be more likely asymptomatic than male ones.[18]

At present, current practice in deciding whether a patient is assigned to rate or rhythm control therapy is largely based on symptoms. It is plausible that the patients who are older with more comorbidities, such as heart failure and coronary artery disease, may be less active in their daily life and therefore may report lower burden of symptoms due to inactivity rather than good control AF symptoms on exercise. Our data supports this, with a higher proportion of rate control patients in EHRA I category (i.e. no/minimal symptoms) compared with the rhythm control group where the majority of patients were in EHRA II–IV category. Many antiarrhythmic drugs are also contraindicated in AF patients with multiple comorbidities, and given the lower burden of AF symptoms, they are more likely to be managed with rate control therapy with beta blockers, digoxin, and calcium channel blockers.

The causes of the differences in cardiovascular death, all-cause death and any TE between the two groups are likely to be multifactorial in nature. It is difficult to precisely establish the relative contributions of the successful rhythm control and established risk factors for cardiac mortality to explain the differences in outcome data. In terms of established cardiac risk factors, the rate control group had a higher proportion of patients with increased risk of cardiovascular death. Conversely, the rhythm control group had a higher proportion of patients in the paroxysmal atrial fibrillation group, which has been shown in multiple studies to convey a better prognosis compared with non-paroxysmal AF groups.[19,20]

Multiple RCTs comparing rate and rhythm control therapies in patients with AF did not demonstrate any evidence of superiority in terms of death or systemic embolism in either arm.[3–7] Other studies have suggested a lower mortality demonstrated in rhythm control arms.[8–10] For example, a large observational study from North America demonstrated a lower mortality in patients with new onset AF who were managed with a long-term rhythm control strategy.[8] Other non-randomized studies with their associated confounding factors have demonstrated fewer strokes[21] and also fewer deaths[8] in patients managed with rhythm control compared with rate control therapy.

One contemporary observational registry from North America (ORBIT-AF) comparing rate and rhythm control therapy outcomes found baseline differences between the two groups, which were similar to our findings.[22] Patients in the rate control group were more likely to be older with more baseline comorbidities and cardiovascular risk factors compared with the rhythm control group. Their follow-up period was longer than EORP-AF, with a mean follow-up of around 2 years, and an unadjusted analysis revealed that the

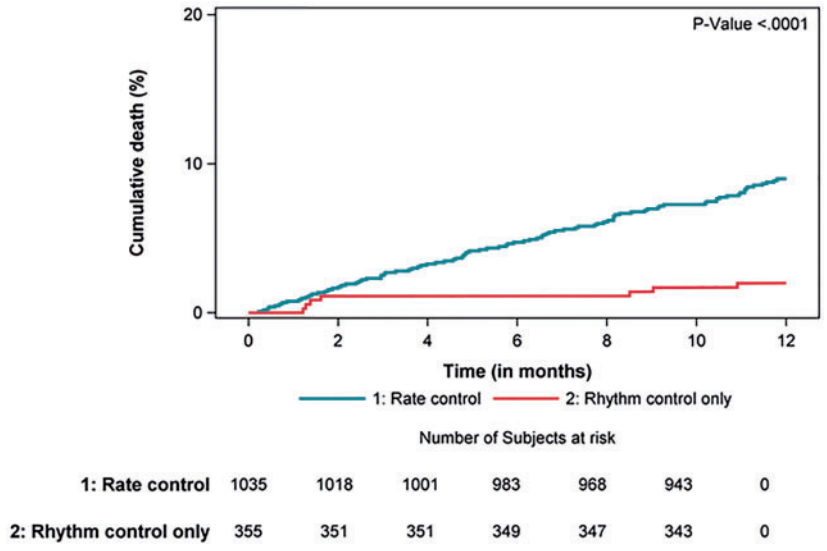

Figure 3 Kaplan–Meier curves for all-cause death according to baseline strategy.

Table 5 Cox regression analysis for all-cause death

	HR	95% CI	P
Age (per year)	1.04	1.02–1.07	0.0012
Rate control (vs. rhythm control)	2.83	1.14–7.05	0.0256
Previous TIA	2.14	1.15–3.99	0.0159
Chronic heart failure	2.76	1.65–4.61	0.0001
Chronic kidney disease	2.01	1.31–3.09	0.0015
Diabetes	2.02	1.33–3.08	0.0010
Physical activity			
None (ref.)	–	–	–
Occasional	0.40	0.23–0.67	0.0005
Regular	0.29	0.11–0.72	0.0080
Intense	0.65	0.16–2.70	0.5540

CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

rhythm control group had a significantly lower all cause death, cardiovascular death and also lower first stroke, embolism, and TIAs. Similar to our analysis, these differences were non-significant between the two strategies in a fully adjusted analysis.

Large observational studies have shown that patients undergoing AF ablation may have a significant lower risk for all-cause death[23] and stroke.[23,24] Friberg and colleagues reported data from Swedish registries in 361 913 AF patients (mean follow-up: 4.4 years), and found that AF patients that underwent catheter ablation had a consistent lower risk for stroke [hazard ratio (HR): 0.69] and all-cause death (HR: 0.50). This risk reduction was more pronounced in patients at high thrombo-embolic risk and those without any AF relapse within 6 months.[23] In the Intermountain AF Study, 4212 patients undergoing AF ablation had a consistent lower thrombo-embolic risk compared with age and sex matched AF controls without ablation.[24]

Inconsistency between RCTs and observational studies of rate vs. rhythm control could be related to the strict control of comorbidities warranted by RCTs, resulting in an overall reduction of adverse events, beyond any specific efficacy of rate or rhythm control. In observational studies, controlling for all the possible bias would be more difficult, and consequently, the beneficial effect with rhythm control strategy could be related to residual confounders. Indeed, results coming from our PSM analysis showed that the higher risk found associated with the rate control strategy is less evident when comparing to fully matched controls. Notwithstanding the very low numbers in the PSM groups, there remains a trend with the rate control only strategy for a higher risk of all-cause death.

These differences and discrepancies in current evidence further highlight the need for trials specifically addressing the basic issue of whether rhythm or rate control strategy delivers superior outcomes. Several on-going studies, such as EAST[11] and the Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) [ClinicalTrials.gov Identifier: NCT00911508] (testing the hypothesis that catheter ablation procedure would be superior compared with standard drug therapy in reducing major outcomes) are attempting to address this important issue.

Limitations

This study is an observational registry and this poses inherent limitations by virtue of the study design, and a modest follow-up duration. The patient recruitment has been consecutive which tends to overcome the limitations of an observational design to a certain extent. The countries involved in this registry were from Europe only and the results may not be generalized to developing countries for instance, where there are differences in management of AF as outlined

by previous studies.[25] There was a proportion of patients lost to follow-up (15%) which does limit the analysis to some extent but this figure is much less than the lost to follow-up rate noted in the original EuroHeart survey. Full details on the non-cardiovascular deaths were also unavailable.

As this is a 'real-world' observational study, residual confounding remains a possibility given the difficulties in accounting for all the potential confounders in such studies that could possibly generate bias in data analysis and interpretation, affecting the reliability of our results. Given the risks associated with rhythm control therapy, pharmacological and non-pharmacological, the physician must carefully assess the patient's medical history before choosing an appropriate treatment. This choice based on medical history also likely gives rise to the possibility of confounding by indication. We noted that only a relatively small proportion of patients underwent ablation (surgical and left atrial catheter) and it is therefore difficult to accurately assess the impact of these therapies in this registry. Given the small numbers after propensity score matching, the analysis could be considered as exploratory and hypothesis generating, rather than being definitive. Such real world data would also be no substitute for a controlled clinical trial.

Lastly, a more contemporary approach would like to regard rate control as a pivotal management approach, independent of whether a rhythm control *strategy* approach is decided.[2] Even if our methodology to this ancillary analysis would be considered reductionist, we believe that our approach is more reflective of real world clinical practice, where there is always one prevalent clinical *strategy* being used.

Conclusion

In this 1-year follow-up analysis of the EORP-AF pilot general registry, we provide data on the contemporary use of the various rate and rhythm control therapies in four European regions. We found that in daily clinical practice, physicians often choose a *pure* rate control *strategy* or a *pure* rhythm control *strategy*, although these approaches are no longer considered as being mutually exclusive. We found some geographical variation in choice of rate vs. rhythm control as the preferential strategy, and that a pure rate control strategy was associated with a higher risk for adverse events at 1-year follow-up, and partially adjusted analysis suggested that rate control independently increased the risk for all-cause death. However, a fully adjusted PSM analysis found that this association was no longer statistically significant, suggesting an important role of comorbidities in determining the higher risk for all-cause death.

Supplementary material

Supplementary material is available at *Europace* online.

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