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Original research

Brady- and tachyarrhythmias detected by continuous rhythm monitoring in paroxysmal atrial fibrillation

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ABSTRACT

Objective Atrial fibrillation (AF) is associated with adverse events including conduction disturbances, ventricular arrhythmias and sudden death. The aim of this study was to examine brady- and tachyarrhythmias using continuous rhythm monitoring in patients with paroxysmal self-terminating AF (PAF).

Methods In this multicentre observational substudy to the Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodelling and Vascular destabilisation in the progression of AF (RACE V), we included 392 patients with PAF and at least 2 years of continuous rhythm monitoring. All patients received an implantable loop recorder, and all detected episodes of tachycardia ≥182 beats per minute (BPM), bradycardia ≤30 BPM or pauses ≥5 s were adjudicated by three physicians.

Results Over 1272 patient-years of continuous rhythm monitoring, we adjudicated 1940 episodes in 175 patients (45%): 106 (27%) patients experienced rapid AF or atrial flutter (AFL), pauses ≥5 s or bradycardias ≤30 BPM occurred in 47 (12%) patients and in 22 (6%) patients, we observed both episode types. No sustained ventricular tachycardias occurred. In the multivariable analysis, age >70 years (HR 2.3, 95% CI 1.4 to 3.9), longer PR interval (HR 1.9, 1.1–3.1), CHA_2DS_2-VASc score ≥2 (HR 2.2, 1.1–4.5) and treatment with verapamil or diltiazem (HR 0.4, 0.2–1.0) were significantly associated with bradyarrhythmia episodes. Age >70 years was associated with lower rates of tachyarrhythmias.

Conclusions In a cohort exclusive to patients with PAF, almost half experienced severe bradyarrhythmias or AF/AFL with rapid ventricular rates. Our data highlight a higher than anticipated bradyarrhythmia risk in PAF.

Trial registration number NCT02726698.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial fibrillation (AF) has been associated with adverse events and constitutes a significant, global healthcare challenge. Paucity exists on the occurrence of bradyarrhythmia and ventricular tachyarrhythmias.

WHAT THIS STUDY ADDS

⇒ This study used continuous rhythm monitoring to describe the occurrence of brady- and tachyarrhythmia episodes in patients with documented self-terminating paroxysmal AF. Severe brady- and tachyarrhythmias were common in paroxysmal AF; AF or atrial flutter with high ventricular rates (>182 beats per minute) was observed in 27% of patients, and bradycardias (≤30 beats per minute) or pauses (≥5 seconds) occurred in 18% of patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results from this study highlight a higher than anticipated prevalence of bradyarrhythmias in patients with self-terminating paroxysmal AF. In selected patient subgroups, intensified monitoring may be appropriate to instigate timely intervention and prevent disease progression.

INTRODUCTION

Atrial fibrillation (AF) is a progressive disease and a source of substantial morbidity and mortality worldwide. It is promoted by ageing and a wide range of risk factors and comorbidities, and it may in time self-sustain via progressive atrial cardiomyopathy.[1] While AF is known to occur in association with sick sinus syndrome,[2] we know less about the extent and clinical significance of bradyarrhythmias in paroxysmal self-terminating AF (PAF). Pharmacological rate and rhythm control are central components of AF management regardless of persistence pattern[3 4] but may predispose to bradyarrhythmias, especially when used in older patients.[5 6] Conversely, treatment restraint may increase tachyarrhythmia risk. Our knowledge about episodic brady- and tachyarrhythmias in different stages of AF is incomplete. Symptomology and clinical findings often fail to correlate, and even symptomatic episodes are difficult to recognise with intermittent monitoring.[7 8] The emergence of implantable cardiac monitors has provided new opportunities to capture and characterise patterns of arrhythmia even in PAF.[9–11] Early identification of patients at risk of severe arrhythmias including symptomatic bradycardia and prolonged ventricular pauses may enable timely intervention and tailored management to prevent

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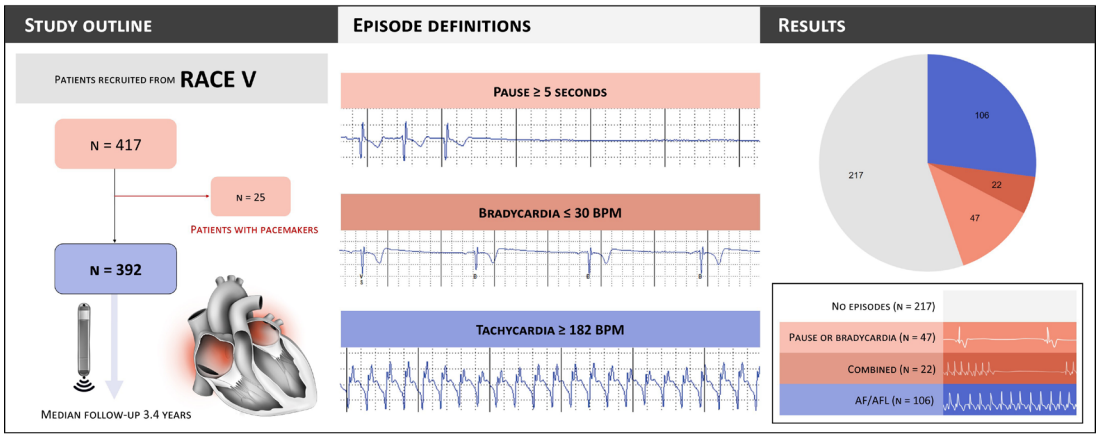

Figure 1 Central illustration. Study overview and main findings. AF, atrial fibrillation; AFL, atrial flutter; BPM, beats per minute; RACE V, Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodelling, and Vascular destabilization in the progression of AF.

disease progression and adverse events caused by inadequate or inappropriate rate control.

Using continuous rhythm monitoring, the aim of this study was to examine the prevalence and characteristics of severe brady- and tachyarrhythmia episodes in patients with self-terminating PAF.

METHODS

Patient population

For this predefined subanalysis of the Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of AF study (RACE V, NCT02726698), we recruited patients with a minimum possibility of 2 years of follow-up. The RACE V study is a Dutch prospective, multicentre observational study aimed to investigate predictors of AF progression in patients with PAF. A detailed description of RACE V was previously published.[11 12] Inclusion criteria for the RACE V study were the following: >18 years of age, documented self-terminating PAF with a duration <10 years, CHA_2DS_2-VASc score ≤5 with no other indication for oral anticoagulation and willingness to undergo implantation of an implantable loop recorder (ILR). Exclusion criteria were triggered AF, congenital heart disease, prior or planned pulmonary vein isolation (PVI), current usage or expected initiation of amiodarone treatment, pregnancy or life expectancy <2.5 years. For this substudy, we included patients with a minimum of 2 years of continuous rhythm monitoring. Patients with pacemakers at baseline were excluded (figure 1).

Baseline assessments included a clinical examination, echocardiography and blood biochemistry, and follow-up visits were scheduled at 12 and 30 months. Choice in treatment strategy was at the discretion of the physician and in accordance with the European Society of Cardiology AF guidelines.[3]

The RACE V study was conducted in concordance with the Declaration of Helsinki, and all patients gave written, informed consent. The study protocol was approved by Medische Ethische Toetsings Commissie van de Universiteit Medisch Centrum Groningen (METc UMCG) (METc no: METc 2016/16) and all participating centres.

ILR implantation and transmission

All patients received a LINQ Reveal ILR (Medtronic, Minnesota, USA) injected subcutaneously in the fourth intercostal space. The ILR was connected to a CareLink remote monitoring system (Medtronic). To prevent data loss, patients were instructed to perform daily automated and weekly manual transmissions. The ILR was set to automated detection of AF ≥2 min (regardless of rate), tachycardias ≥182 beats per minute (BPM), pauses ≥4.5 s and bradycardias ≤50 BPM.

Episode definitions and adjudication

An episode was defined as either of the following: tachycardia ≥182 BPM (cycle length ≤330 ms) of ≥24 beats, bradycardia ≤30 BPM (cycle length ≥2000 ms) of ≥12 beats and pauses ≥5 seconds (figure 1). AF episodes with rates <182 BPM were not assessed in this study. All ILR-detected episodes were manually adjudicated (MHJPF, MVDL, IVG) and reclassified if needed. Only validated episodes were included. Non-AF supraventricular tachyarrhythmia episodes were classified as atrial flutter (AFL), and in case both AF and AFL were present in a single recording, the episode was categorised as AF.

Variable definitions

Information about clinical outcomes resulting in death, disability or incapacity; requiring unexpected or prolonged hospitalisation; and any life-threatening condition were collected for all patients throughout follow-up. Other events that might jeopardise the patient or prompt an intervention were also registered. Clinical outcomes assessed for this study were the following: all-cause mortality, unplanned heart failure hospitalisations, syncope or arrhythmia-related complaints, any interventional cardiac procedure, cardiac surgery and electrical or chemical cardioversion. Episodes detected between 21:00 and 06:00 were considered nighttime occurrences. Pharmacological rate control therapy was defined as treatment with either of the following: beta-blockers; verapamil, diltiazem or digoxin; and pharmacological rhythm control was defined as treatment with either class I or class III antiarrhythmic drugs (AADs). For this analysis, we defined AF progression as a transition from self-terminating AF to persistent or permanent AF (non-self-terminating AF).

Statistical analyses

Baseline characteristics were presented for all patients and in groups according to episode type(s). Categorical variables were expressed as frequencies with percentages, and continuous variables as means with SDs or medians with IQRs, as appropriate.

Table 1 Baseline characteristics for all patients and according to the alert type

	All patients	Patients without episodes	Patients with tachyarrhythmias	Patients with bradyarrhythmia episodes	Patients with b brady- and tachyarrhythmia episodes
Total	392 (100)	217 (100)	106 (100)	47 (100)	22 (100)
Age (years), median (IQR)	64 (57–70)	66 (58–70)	62 (54–67)	68 (60–74)	66 (61–73)
Women, n (%)	169 (43)	95 (44)	43 (41)	21 (45)	10 (46)
BMI* (kg/m^2), median (IQR)	27 (24–30)	27 (24–31)	26 (23–30)	27 (25–30)	27 (25–32)
EHRA class, n (%)					
I	33 (8)	16 (7)	10 (9)	5 (11)	2 (9)
IIa	124 (32)	71 (33)	28 (26)	17 (36)	8 (36)
IIb	165 (42)	89 (41)	53 (50)	18 (38)	5 (23)
III	68 (17)	40 (18)	14 (13)	7 (15)	7 (32)
IV	2 (1)	1 (0)	1 (1)	0	0
No of comorbidities‡, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	3 (2–4)	3 (2–4)
CHA_2DS_2-VASc score					
<2	100 (26)	64 (29)	27 (25)	6 (13)	3 (13)
≥2	292 (74)	153 (71)	79 (75)	41 (87)	19 (86)
ECG characteristics					
SR at baseline, n (%)	386 (98)	213 (98)	106 (100)	45 (96)	22 (100)
PR interval* (ms), mean±SD	167±27	166±26	162±27	176±29	182±29
Comorbidity					
Hypertension, n (%)	313 (80)	177 (82)	76 (72)	42 (89)	18 (82)
Coronary artery disease, n (%)	41 (10)	23 (11)	5 (5)	10 (21)	3 (14)
Diabetes mellitus*, n (%)	27 (7)	11 (5)	5 (5)	6 (13)	5 (23)
COPD, n (%)	22 (6)	15 (7)	3 (3)	2 (4)	2 (9)
Renal failure, n (%)	26 (7)	12 (6)	6 (6)	6 (13)	2 (9)
eGFR (mL/min/173 m^2), mean±SD	79±15	79±14	83±15	76±16	75±15
Thyroid dysfunction, n (%)	30 (8)	19 (9)	7 (7)	2 (4)	2 (9)
Peripheral vascular disease, n (%)	3 (1)	1 (0)	1 (1)	0	1 (5)
AF management					
Rate control†, n (%)	266 (68)	155 (71)	65 (61)	34 (72)	10 (45)
Medication*					
Beta-blockers, n (%)	193 (49)	111 (51)	44 (42)	30 (64)	14 (64)
Verapamil or diltiazem, n (%)	72 (18)	44 (20)	21 (20)	4 (9)	3 (14)
Digoxin, n (%)	5 (1)	1 (0)	2 (2)	1 (2)	1 (5)
Class I AADs, n (%)	92 (24)	51 (24)	30 (29)	9 (19)	2 (9)
Class III AADs, n (%)	16 (4)	5 (2)	2 (2)	5 (11)	4 (18)
Anticoagulants, n (%)	268 (69)	150 (69)	56 (53)	42 (89)	20 (91)
Statins, n (%)	130 (33)	68 (31)	31 (30)	22 (47)	9 (41)
Diuretics, n (%)	59 (15)	34 (16)	10 (10)	11 (23)	4 (18)
ACEi or ARB, n (%)	142 (36)	76 (35)	35 (33)	22 (47)	9 (41)
Aldosterone receptor antagonist, n (%)	3 (1)	1 (0)	1 (1)	1 (1)	0

*Data were incomplete for BMI (n=3 missing), PR interval (n=5 missing), diabetes mellitus (n=1 missing) and medication (n=1 missing for all drugs).
†Defined as treatment with either of the following: beta-blockers, non-dihydropyridine calcium channel blockers or digoxin.
‡The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI >25 kg/m^2, moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR <60).
AAD, antiarrhythmic drug; ACEi, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; SR, sinus rhythm.

Group comparisons were accomplished using the Student's t-test provided they were normally distributed. Patients were followed until ILR disconnection, death or end of the present substudy (1 March 2022), whichever came first. A Cox proportional hazard regression model was applied to assess the association between several predefined covariates and time to the first occurring episode of brady- or tachyarrhythmia (assessed separately). The assumption of proportionality was tested using Schoenfeld residuals. Seven a priori selected candidate covariates were assessed: age, sex, PR interval, CHA_2DS_2-VASc score, beta-blockers, verapamil or diltiazem treatment and AAD treatment. For the regression analyses, PR interval was dichotomised at the median. All analyses were conducted for complete cases only as missing information in relevant covariates was only observed in five patients. A two-sided p-value of ≤0.05 was considered statistically significant. All statistical analyses were completed using Stata 17.0 (StataCorp, Minnesota, USA).

RESULTS

Patients

We identified a total of 417 patients from the RACE V study; 25 patients with pacemakers at baseline were excluded. Our final study population comprised 392 patients with implanted ILRs (figure 1). Baseline characteristics and echocardiographic parameters are presented in tables 1–2. Patients had a median age of 64 (IQR 57–70) years, 43% (n=169) were women, 74% (n=292) had a CHA_2DS_2-VASc score ≥2 (median 2, IQR 1–3, referencing

Table 2 Echocardiographic parameters at baseline expressed in means±SDs

	All patients	Patients without episodes	Patients with tachyarrhythmia episodes	Patients with bradyarrhythmia episodes	Patients with brady- and tachyarrhythmia episodes	P value bradyarrhythmia versus no episodes	P value bradyarrhythmia versus tachyarrhythmia
Total	276 (100)	153 (100)	82 (100)	27 (100)	14 (100)		
LVEF (%), mean±SD	51±8	51±9	50±7	52±7	50±8	0.855	0.326
LVEDV (mL/m^2), mean±SD	129±34	125±32	135±38	128±35	139±38	0.259	0.659
LVESV (mL/m^2), mean±SD	64±21	61±20	68±23	62±21	70±23	0.387	0.448
LAVI (mL/m^2), mean±SD	31±10	30±10	32±10	34±12	35±10	0.023*	0.217
RAVI (mL/m^2), mean±SD	26±9	25±9	26±9	27±10	28±9	0.149	0.545
Left atrial strain (%), mean±SD							
Reservoir	38±12	39±12	39±13	32±8	39±13	0.018*	0.064
Contraction	18±7	18±7	17±6	15±8	17±8	0.036*	0.166
Conduit	21±9	21±8	21±10	17±6	22±10	0.138	0.144
Right atrial strain (%), mean±SD							
Reservoir	39±12	39±13	40±10	37±10	40±10	0.640	0.412
Contraction	18±7	18±7	18±6	17±6	20±4	0.840	0.600
Conduit	21±8	21±9	22±8	19±7	15±6	0.419	0.151

Complete data were available for 276 (70%) patients.
*Indicates statistical significance.
LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RAVI, right atrial volume index.;

the inclusion criteria, the maximum possible score was 5) and 68% (n=266) of patients were in pharmacological rate control therapy (figure 2). Mean left ventricular ejection fraction (LVEF) was 51±8% at baseline.

Median follow-up was 3.4 years (IQR 3.0–3.7) or 1272 patient-years (PYs) of continuous rhythm monitoring, and we adjudicated a total of 1940 bradyarrhythmia or tachyarrhythmia episodes in 175 patients (45%). Twenty-six patients (7%) had ≥20 episodes and accounted for more than 60% of the total number of episodes. Many displayed both brady- and tachyarrhythmia episodes (online supplemental figure S1). Patients with bradyarrhythmiass were generally older, had more comorbidities and were more often in rate control therapy compared with patients with tachyarrhythmias (table 1). Compared with patients without episodes, we observed a significantly larger left atrial (LA) volume index and lower LA reservoir and contractile function in patients with bradyarrhythmias (table 2). Four

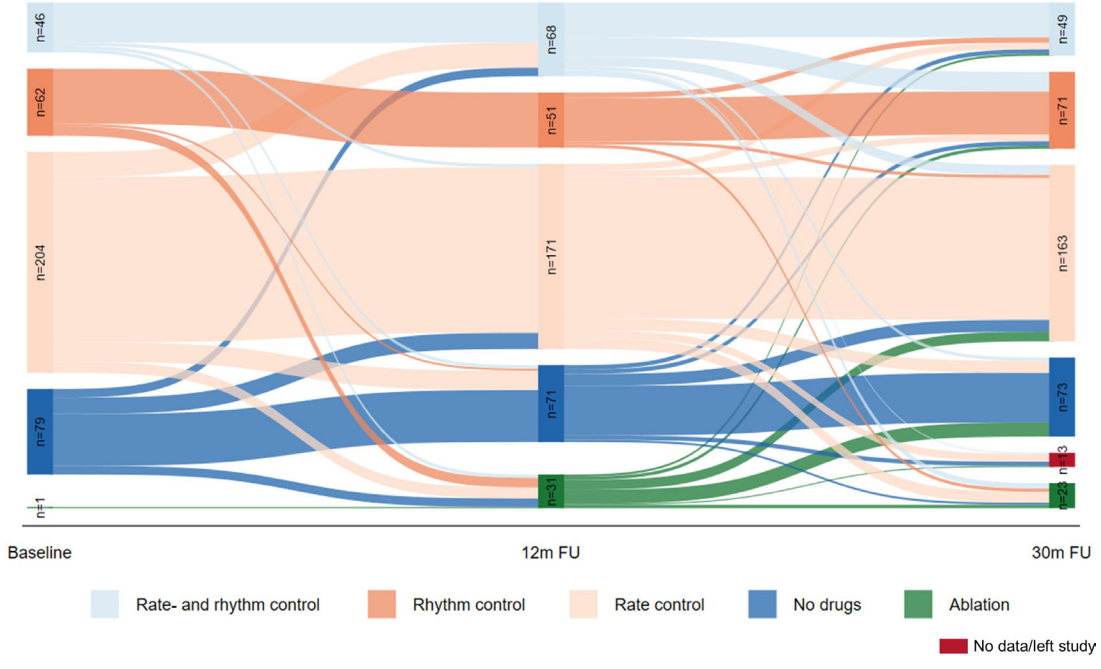

Figure 2 Sankey diagram showing changes in rate and rhythm control drug use over follow-up for all patients included in this study (n=392). Patients who underwent an atrial fibrillation (AF) ablation were listed as such regardless of underlying pharmacological AF therapy. 12m FU=12-month follow-up visit; 30m FU=30-month follow-up visit.

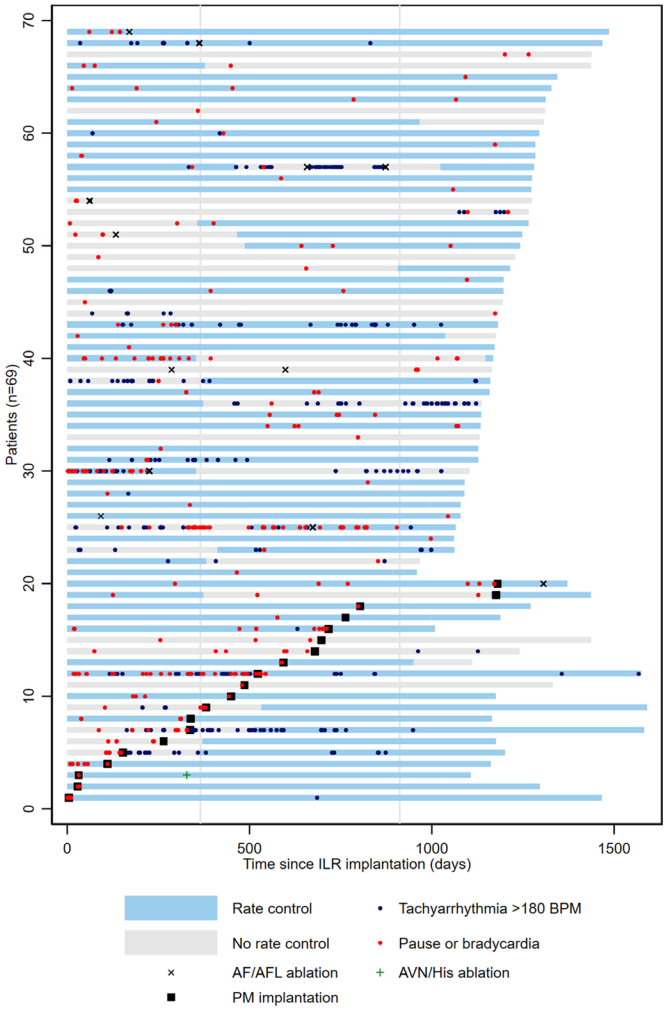

Figure 3 Pacemaker implantations and rate control strategy at baseline, 1-year and 2.5-year follow-up visits in patients with pauses ≥5 s or bradycardias ≤30 BPM (n=69). In 22 patients, both bradyarrhythmia and tachyarrhythmia episodes were detected. Dots indicate days with episode registrations. AF, atrial fibrillation; AFL, atrial flutter; AVN, atrioventricular node; BPM, beats per minute; ILR, implantable loop recorder; PM, pacemaker.

Table 3 Episode characteristics (n=1940 episodes in 175 patients)

	AF/AFL ≥180 BPM	Bradycardia ≤30 BMP or AVB	Pauses ≥5 s
Total (%)	1512 (100)	110 (100)	318 (100)
Duration (minutes), median (IQR)	1.5 (0.7–3.4)	0.5 (0.4–0.8)	
Maximum rate (BPM)	214		
Median rate (BPM)	207		
Underlying rhythm			
Sinus rhythm		110 (100)	96 (30)
AF/AFL		0	222 (70)
Daytime (06:00–21:00)	1385 (92)	52 (47)	144 (45)
Night-time (21:00–06:00)	127 (8)	58 (53)	174 (55)
After progression to persistent or permanent AF	118 (8)	0	16 (5)

AF, atrial fibrillation; AFL, atrial flutter; AVB, atrioventricular block; BPM, beats per minute.

patients died (1%) during follow-up; three had neither bradyarrhythmia nor tachyarrhythmia episodes prior to death.

Bradyarrhythmia episodes

A total of 69 patients (18%) experienced one or more bradyarrhythmia episodes during follow-up (figure 3); 22 occurred in patients with concomitant tachyarrhythmias. Of the 428 bradyarrhythmia episodes in 69 patients, 318 (74%) were pauses ≥5 s, and 47% of bradyarrhythmias occurred during night (n=41 patients, 10% of total population) (table 3 and online supplemental table S6). Exclusively nocturnal episodes were observed in 13 (19%) patients with bradyarrhythmia (online supplemental figure 4A). 70% of pauses occurred during AF/AFL or at the termination of AF/AFL. Bradycardias were generally short-lasting with a median duration of 0.5 min (IQR 0.4–0.8 min).

In the multivariable analysis, age >70 years (HR 2.4, 95% CI 1.4 to 3.9), PR interval >165 ms (HR 1.9, 95% CI 1.1 to 3.1) and CHA_2DS_2-VASc score ≥2 (HR 2.2, 95% CI 1.1 to 4.5) were significantly associated with higher rates of bradyarrhythmia episodes, whereas verapamil or diltiazem treatment was associated with lower bradyarrhythmia rates (HR 0.4, 95% CI 0.2 to 1.0) (figure 4a and online supplemental figure 6).

Tachyarrhythmia episodes

Tachyarrhythmia episodes occurred in 128 (33%) patients; 106 had tachyarrhythmia episodes only and in these patients, we observed a median of 4 (IQR 1–11) episodes per person (online supplemental table S2). The vast majority were caused by AF with rapid ventricular response (median rate was 207 BPM, IQR 194–222), and 95% occurred during daytime (online supplemental figure 4B). No episodes of sustained ventricular tachycardia (VT) were observed; all broad complex tachycardias had characteristics of AFL or AF with aberrancy (online supplemental figure S3). Fewer patients with tachyarrhythmias were in pharmacological rate control therapy (n=65, 61%) at baseline; however, only age ≥70 years was associated with a significantly lower tachyarrhythmia risk (HR 0.4, 95% CI 0.2 to 0.7) in the multivariable analysis (figure 4b). Tachyarrhythmia episodes were mostly short-lasting, and many occurred in rapid successions of up to 25 individually registered episodes (online supplemental figure 4A,B and online supplemental figure 7).

Patients with alternating bradyarrhythmia and tachyarrhythmia

Patients who experienced a combination of brady- and tachyarrhythmias (n=22) were characterised by higher episode burdens (figure 3 and online supplemental figure S1). We validated a median of 14 (IQR 10–40) episodes per patient. Except for differences in rate or rhythm control strategy at baseline, patient characteristics for this group mirrored those seen in patients with bradyarrhythmia; they were generally older and had more comorbidities than patients with tachyarrhythmias.

Adverse outcomes and AF progression

Despite high episode burdens in a large proportion of patients, syncope and heart failure hospitalisations were rare: four were hospitalised due to heart failure and three due to syncope. None were directly related to an ILR-detected episode (table 4). The most common causes for hospitalisation were AF-related symptoms and planned cardioversion. Progression to persistent or permanent AF was observed in 54 (14%) of patients, and more patients with brady- or tachyarrhythmia episodes experienced progression (36 of 175, 21%, vs 18 of 217, 9%). Episode

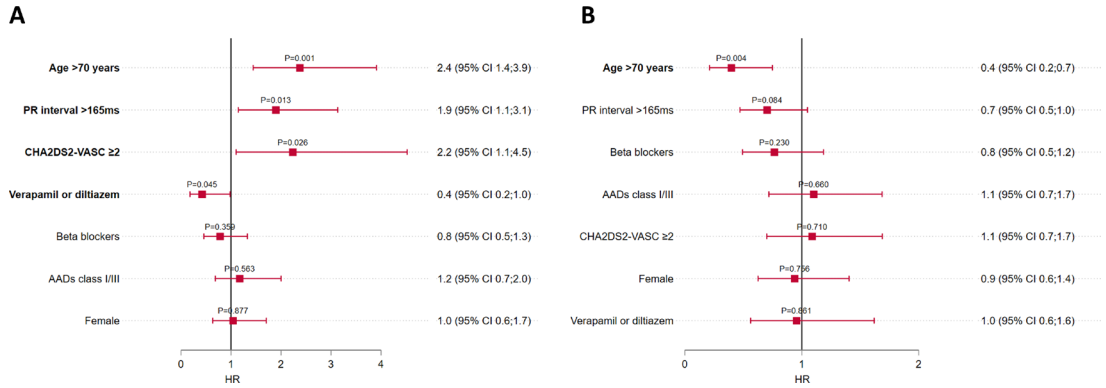

Figure 4 Results from the multivariable analyses in patients with bradyarrhythmia and tachyarrhythmia episodes. Bold text indicates statistical significance. (A) Risk factors for bradyarrhythmia episodes and (B) risk factors for tachyarrhythmia episodes. AADs, antiarrhythmic drugs; BB, beta-blocker; IRR, incidence rate ratio.

occurrence in relation to timing of progression is shown in online supplemental figure S5.

Dual-chamber pacemakers were implanted—at the discretion of the treating cardiologist—in 22 patients; 20 (87%) after ILR-detected bradyarrhythmia episodes; 1 as part of a pace-and-ablate strategy, 1 due to complete atrioventricular block (AVB) and the remainder due to sick sinus syndrome. Pacemaker implantations were as prevalent in patients with combined episodes as in patients with bradyarrhythmia episodes only (6 of 22 patients, 27%, and 14 of 47 patients, 30%, respectively).

DISCUSSION

In this predefined RACE V subanalysis, the aim was to investigate the prevalence of brady- and tachyarrhythmias in patients with self-terminating PAF. We found that (1) almost 45% of patients experienced brady- and/or tachyarrhythmia episodes, (2) pauses ≥5 s or short-lasting bradycardias ≤30 BPM were observed in almost 18%, (3) significant risk factors for bradyarrhythmia episodes were older age, longer PR interval and CHA_2DS_2-VASc score ≥2, whereas a lower risk was observed with verapamil or diltiazem treatment at baseline, (4) AF with rapid ventricular rates was the most common arrhythmia (106 of 175 patients, 61%), (5) progression to persistent or permanent AF was most frequently observed in patients with bradyarrhythmia and tachyarrhythmia episodes, and finally, no sustained VTs were observed in this population.

A surprising finding of this study was the high proportion of patients with severe bradyarrhythmias; nearly one-fifth experienced at least one episode. Roughly 50% of pauses occurred in sinus rhythm or at the termination of AF/AFL, and the remainder comprised AVBs or ventricular pauses during AF/AFL. This observed propensity for bradyarrhythmia episodes in PAF could be driven by more severe atrial remodelling with resultant sinus node disease and/or AV conduction impairment. In the multivariable analysis, higher age, longer PR interval and a CHA_2DS_2-VASc score ≥2 were independent risk factors for bradyarrhythmia episodes, whereas non-dihydropyridine calcium channel blockers (ND-CCBs), verapamil and diltiazem, were associated with reduced risk.[13–16] Atrial remodelling is known to advance with age, AF and an array of AF-associated conditions,[1] and the pathophysiological mechanisms involved in AF and sinus node disease largely overlap. In patients with bradyarrhythmia, we observed LA enlargement and reduced strain on echocardiography. LA structural and functional remodelling

Table 4 Follow-up data: no alerts versus alerts

	Patients without episodes	Patients with tachyarrhythmia episodes	Patients with bradyarrhythmia episodes	Patients with brady- and tachyarrhythmia episodes
Total	217 (100)	106 (100)	47 (100)	22 (100)
ILR follow-up time (years)	3.4 (3.0–3.7)	3.5 (3.2–3.7)	3.2 (2.2–3.5)	3.1 (2.0–3.3)
Alerts per patient	0	4 (1–11)	2 (1–5)	16 (10–40)
Progression to permanent or persistent AF	18 (9)	17 (16)	11 (23)	8 (36)
Pacemaker implantation	2 (1)*	0	14 (30)	6 (27)
Hospitalisation for HF	1 (0)	0	3 (6)	0
Hospitalisation for syncope	1 (0)	1 (1)	2 (4)	0
AF/AFL-related hospitalisation	41 (19)	41 (39)	14 (30)	9 (41)
Chemical or electrical cardioversion	24 (11)	17 (16)	3 (6)	3 (14)
PVI	10 (5)	20 (19)	4 (9)	4 (18)
AVN ablation	1 (0)	2 (2)	0	0
AFL ablation, AF-related surgery or combined AF/AFL procedures†	2 (1)	4 (4)	2 (4)	1 (5)
All-cause death	3 (3)	1 (1)	0	0

*One patient received a pacemaker on a pace-and-ablate strategy and the other due to symptomatic pauses <5 s.
†Includes combined AF or AFL ablation, maze procedures and left atrial appendage clipping.
AF, atrial fibrillation; AFL, atrial flutter; AVN, atrioventricular node; HF, heart failure; ILR, implantable loop recorder; PVI, pulmonary vein isolation.

has previously been associated with incident AF, and higher AF recurrence rates after PVI, and AF frequently coexists with sick sinus syndrome.[1 17 18] It is possible that bradyarrhythmia episodes in AF are markers of more advanced atrial remodelling regardless of AF persistence pattern, and this could set the stage for both AF and bradyarrhythmiacardias. However, more research is needed to clarify the nature of this association. Of interest, in our, although limited data, progression to persistent or permanent AF was two to four times more common in patients with brady- and tachyarrhythmia episodes compared with patients without episodes.

We observed a significant association between treatment with ND-CCBs and lower rates of bradyarrhythmia episodes. ND-CCBs reduce myocardial contractility and AV conduction by restricting calcium influx into myocytes, and verapamil was previously associated with less AF progression in PAF.[19] In the RATAF study, diltiazem was more effective in reducing ventricular rate and arrhythmia-related symptoms,[20] and in experimental settings, verapamil has been shown to reduce atrial remodelling.[21] Furthermore, ND-CCBs have a negative dromotropic effect on the AV node, but in contrast to beta-blockers, only have a very limited effect on the sinus node. Therefore, higher dosages of ND-CCBs are tolerated, with appropriate rate control, during paroxysms of AF without sinus bradycardia outside the AF episodes. It is also worth recognising that ND-CCBs are contraindicated in patients with reduced LVEF,[3] and despite multivariable adjustment, patients in ND-CCB treatment could differ on parameters not accounted for in our analysis. Finally, rate control in patients with tachycardia–bradycardia episodes is particularly challenging, and if patients were already symptomatic at baseline, it might have influenced prescription patterns.

In our study, a high proportion of bradyarrhythmia episodes occurred during night. Sleep-disordered breathing is common in patients with AF and associated with high cardiovascular morbidity.[22] Although several risk factors for AF and sleep-disordered breathing coincide, our knowledge about the influence of silent, lone or nocturnal bradyarrhythmias in patients with PAF on long-term prognosis—including the risk of permanent conduction system disorders—is incomplete. Continuous rhythm monitoring in different patient populations is key to provide insights into the epidemiology of cardiac arrhythmias: to establish treatment thresholds for subclinical arrhythmias and to describe the natural history of arrhythmic diseases.

While AF has been linked to an increased risk of sudden cardiac death—predominantly in patients with heart failure[23 24], no cases of sustained or non-sustained VT were observed in this study despite the inclusion of >1200 PYs of continuous rhythm monitoring. This is reassuring and suggests that VT risk is minimal in our population of patients with self-terminating PAF. Fast-conducted AF was the most common arrhythmia, and these patients were distinct from patients with bradyarrhythmia by being younger, having less comorbidities and fewer were in pharmacological rate or rhythm control at baseline. Even so, only age was independently associated with higher tachycardia risk. Lack of statistical significance for beta-blocker therapy could result from low power in this analysis, but younger, less comorbid patients are also more prone to higher heart rates, which may explain our results. Arrhythmia-related hospitalisations were common in this patient group, and almost one-fourth eventually underwent an AF-related ablation procedure.

In AF, symptomatology is often unreliable and a poor marker of prognosis and arrhythmia burden,[7] and a significant heterogeneity in AF outcomes persists regardless of AF classification and initial presenting pattern. In recent years, the focus has gradually shifted towards a multicomponent approach to AF, involving both clinical and structural parameters, and including underlying morbidities and symptoms.[3 25] A finer characterisation of AF may help determine when to initiate or withhold treatment and may be used to identify suitable candidates for early intervention. Preferably this is done in collaboration with the patient as is currently more common practice compared with when we started this trial.

Study limitations

Several limitations must be addressed. First, results from this study rely on an adequate detection algorithm by the ILR; only tachycardias, bradycardias or pauses were assessed, and text-only episodes were dismissed. Hence, we likely underestimate the true period prevalence of brady- and tachyarrhythmias in this population. In addition, ILRs only provide a one-lead ECG recording, and some degree of misclassification may have persisted despite episode-level adjudication. For this study, episode adjudication was not performed by an independent committee. However, to reduce bias, we used a predefined set of criteria, and episode assessments were blinded to all baseline characteristics. Second, only very rapid tachycardias were assessed for this study (≥182 BPM), which may be preferential to younger patients. Tachycardia–bradycardia episodes below this threshold may not have been acknowledged as such. Third, treatment strategy, including the decision to implant a pacemaker or ablate was at the discretion of the treating physicians. Information about symptomology at the time of episode detection was only available in case of serious adverse outcomes, predominantly those with the requirement for clinical intervention. Likewise, changes in medication that may have been instituted and/or abandoned between follow-up visits were not available to us, and outcome definitions for heart failure and syncope were not adjudicated end points in RACE V. Fourth, AF recurrence and increase in AF burden (beyond progression to persistent or permanent AF) were not specifically assessed in this study although these significantly influence choice in treatment strategy as well as long-term outcomes. Fifth, no naive-AF control group was available for comparative assessment of arrhythmic burden. Finally, follow-up was restricted to time with an ILR. Longer term follow-up is warranted to clarify the long-term clinical outcomes associated with severe brady- and tachyarrhythmias in early AF.

CONCLUSION

In a population of patients with PAF and over >1200 PYs of continuous rhythm monitoring, bradyarrhythmias were observed in nearly one in five patients, and AF or AFL with rapid ventricular rates were observed in 45% of patients. No sustained VTs occurred. Our data highlight the multiplicity of AF including a higher than anticipated frequency of bradyarrhythmias.

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