Archives of Cardiovascular Disease (2019) 112, 153—161

Available online at ScienceDirect www.sciencedirect.com

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CLINICAL RESEARCH

Occurrence of significant long PR intervals in patients implanted for sinus node dysfunction and monitored with SafeR™: The PRECISE study

Allongement de l'intervalle PR chez des patients implantés pour dysfonction sinusale et programmés en mode SafeR™ : résultats de l'étude PRECISE

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Received 18 May 2018; received in revised form 3 August 2018; accepted 17 September 2018
Available online 26 December 2018

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; AVB, atrioventricular block; AVB1, first-degree atrioventricular block; CI, confidence interval; OR, odds ratio; SND, sinus node dysfunction.

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https://doi.org/10.1016/j.acvd.2018.09.005

KEYWORDS
First-degree atrioventricular block;
Atrial fibrillation;
Dual-chamber pacemaker;
SafeR;
Long PR interval

Summary
Background. — Long PR intervals may increase cardiovascular complications, including atrial fibrillation. In pacemakers, the SafeR™ mode monitors PR intervals, switching from AAI to DDD when criteria for atrioventricular block are met.
Aims. — The PRECISE study evaluated the incidence and predictors of long PR intervals and their association with incident atrial fibrillation after 1 year in patients implanted for sinus node dysfunction and free from significant conduction disorders at baseline.
Methods. — This French, prospective, multicentre, observational trial enrolled patients implanted with a REPLY™ dual-chamber pacemaker. Pacemaker memory recorded long PR intervals (defined as first-degree atrioventricular block mode switches occurring after six consecutive PR/AR intervals ≥ 350/450 ms) and atrial fibrillation incidence (fallback mode switch > 1 minute/day). Predictors were identified from baseline variables (age, sex, AR and PR intervals, atrial rhythm disorder and medication) using logistic regression.
Results. — Of 291 patients with sinus node dysfunction enrolled, 214 were free from significant conduction disorders at baseline (mean age 79 ± 8 years; 44% men; PR/AR intervals < 350/450 ms). After 1 year, long PR intervals had occurred in 116 patients (54%) and atrial fibrillation in 63 patients (30%). Amiodarone was the only independent predictor of long PR interval occurrence (odds ratio 2.50, 95% confidence interval 1.20—5.21; $P = 0.014$). There was a strong trend towards an association between long PR interval and atrial fibrillation incidence (odds ratio 1.86, 95% confidence interval 0.97—3.61; $P = 0.051$).
Conclusions. — Half of the patients with pure sinus node dysfunction developed long PR intervals in the year following pacemaker implantation. Amiodarone was the only independent predictor of long PR intervals. There was a strong trend towards an association between long PR intervals and incident atrial fibrillation.

MOTS CLÉS
Bloc atrio-ventriculaire du premier degré ;
Fibrillation auriculaire ;
Stimulateur cardiaque double chambre ;
SafeR ;
Intervalle PR long

Résumé
Contexte. — L'allongement de l'intervalle PR peut entraîner des complications cardiovasculaires, y compris la fibrillation auriculaire. Dans certains modèles de stimulateur cardiaque, le mode SafeR permet de mesurer les intervalles PR au cours du temps.
Objectifs. — L'étude PRECISE a pour objectif de déterminer l'incidence des PR longs chez des patients implantés pour dysfonction sinusale sans troubles de conduction.
Méthodes. — Les patients, implantés d'un stimulateur cardiaque double chambre REPLY™, sont inclus et suivis pendant un an dans l'étude PRECISE, une étude française prospective, multicentrique et observationnelle. Un PR long est diagnostiqué dès que 6 intervalles consécutifs PR/AR ≥ 350/450 ms sont enregistrés. Un épisode de fibrillation auriculaire est défini par un repli > 1 minute par jour. La valeur prédictive de l'allongement du PR des caractéristiques à l'inclusion (âge, sexe, intervalles AR et PR, maladie de rythme auriculaire, médicaments) est analysée par la méthode de régression logistique.
Résultats. — Parmi 291 patients inclus, 214 patients (âge 79 ± 8 ans ; mâle 44 %) ne présentaient pas de troubles de conduction à l'inclusion (PR/AR < 350/450 ms). À 1 an, 116 patients (54 %) ont présenté des épisodes de long PR, et 63 patients (30 %) ont présenté au moins un épisode de fibrillation auriculaire. La prise d'amiodarone est le seul facteur prédictif indépendant de l'allongement du PR (OR 2,50, IC 95 % 1,20—5,21 ; $p = 0,014$). Une tendance vers une association entre PR long et fibrillation auriculaire est observée (OR 1,86, IC 95 % 0,97—3,61 ; $p = 0,051$).
Conclusions. — Dans l'année qui suit l'implantation d'un stimulateur cardiaque pour dysfonction sinusale, la moitié des patients présente au moins un épisode de PR long. La prise d'amiodarone est le seul facteur prédictif indépendant de l'allongement du PR. Une potentielle association entre l'allongement du PR et la fibrillation auriculaire peut être observée.

Background

First-degree atrioventricular block (AVB1) is a disease of the cardiac electrical conduction system, in which the PR interval lasts for > 200 ms. Prolongation of the PR interval beyond 200 ms is generally asymptomatic and benign [1,2], although patients with prolonged PR intervals are more likely to become symptomatic with mild or moderate exercise [3]. Moreover, some studies have suggested that long PR intervals may increase the risk of cardiovascular complications, including atrial fibrillation (AF) [4,5].

Patients with AF are at increased risk of death, particularly cardiovascular death [6]. AF is the cause of 20—30% of strokes, and represents a substantial burden in secondary healthcare, with an annual hospitalization rate of 10—40%. This condition also affects patients' everyday lives because of its association with depressed mood and impaired quality of life [6]. The monitoring and management of long PR intervals and AF are therefore important clinical needs.

The SafeR™ algorithm (MicroPort CRM, Clamart, France) continuously monitors atrioventricular (AV) conduction and diagnoses AV blocks (AVBs) when they occur [7,8]. The SafeR algorithm has been validated for all types of AVB, and its safety profile has been assessed in both sinus node dysfunction (SND) and AVB populations [8,9]. More recently, a subanalysis revealed that 25% of patients with SND had a long PR interval at baseline, responsible for a high proportion of AVB1 switches, and that patients with long PR intervals were 1.68 times more likely to develop persistent AF (hazard ratio 1.68, 95% confidence interval [CI] 1.06—2.65; $P = 0.027$) [10]. This result is in accordance with previously published data reporting an association between long PR intervals and AF [11,12].

The PRECISE (Evolution of PR interval lengthening in patients implanted with a dual-chamber pacemaker with an algorithm for spontaneous AV conduction preservation) observational study, conducted in patients with SND, focused specifically on long PR intervals, as assessed by AVB1 switches, with the aim of further investigating:

- the incidence and predictors of long PR intervals; and;
- the association between long PR intervals and AF (ClinicalTrials.gov Identifier: NCT02586480).

Methods

Study design and follow-up

The PRECISE study was a multicentre, observational, prospective, cohort study. Enrolment took place between April 2012 and September 2013, and the clinical investigation ended in January 2015. Patients aged ≥ 18 years were enrolled at 48 centres throughout France if they were eligible for pacemaker implantation (de novo, upgrade or replacement), according to contemporary guidelines [13,14], and had received a SafeR-equipped dual-chamber pacemaker <3 months before enrolment. Patients were excluded if they had permanent AF or permanent high-degree AVB.

SafeR mode was activated at the time of implantation. Follow-up visits were scheduled 6 months (±3 months) and 12 months (±3 months) after implantation. The study was declared to all national competent authorities. Patients gave their informed consent, and the study conduct complied with ISO 14155 and the principles of the Declaration of Helsinki.

SafeR pacing mode

The SafeR algorithm (MicroPort CRM, Clamart, France) preserves AV conduction by pacing in AAI mode by default, and switching to DDD mode when AVB occurs. When in transitional DDD mode, the pacemaker switches back to AAI mode as soon as it identifies the return of intrinsic conduction [7].

Mode switch occurs in the presence of all types of AVB (AVB1 and second- and third-degree AVB). More specifically, in the presence of AVB1, the algorithm does not allow more than six consecutive PR or AR intervals longer than a programmable value (nominally 350 and 450 ms, respectively). If a seventh long PR interval is detected, the algorithm switches to DDD pacing mode (Fig. 1). SafeR allows the management of long PR intervals according to patients' individual needs through the programming of the following parameters: minimum and maximum long PR interval, mode switch at rest and during exercise or only during exercise.

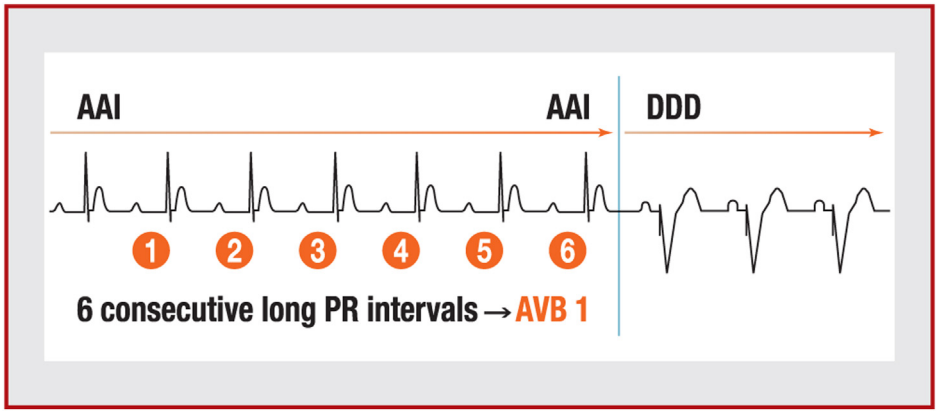

Figure 1. SafeR mode and the criterion for first-degree atrioventricular block (AVB1). AAI: atrium [paced] atrium [sensed] inhibited [response to sensing]; DDD, dual [paced] dual [sensed] dual [response to sensing].
Mode Safe R et critères de BAV du premier degré.

Data

At each visit, the following data were collected: serious adverse events, symptoms, clinical condition and device data extracted from the pacemaker's memory. The data were reported to an electronic data system managed by the contract research organization Evamed (Hérouville-Saint-Clair, France).

Device data included fallback mode switch statistics, SafeR statistics and pacemaker-generated atrial and ventricular electrograms of AVB switches. These electrogram strips were verified and adjudicated by physicians for each patient, to ensure the appropriateness of the switch, based on the review of two independent A and V channels, which ensured robust adjudication thanks to good data quality. If an inappropriate switch was detected, all readings for this patient were excluded from subsequent analyses to safeguard the reliability of results.

Objectives and endpoints

The aim of the PRECISE study was to evaluate the incidence of long PR intervals at 1 year in patients implanted for SND without any conduction disorders at baseline, and the association between long PR intervals and AF incidence.

The primary endpoint of long PR intervals was defined as adjudicated AVB1 switches, ascertained from SafeR statistics. The secondary endpoint of AF incidence was defined as fallback mode switch lasting > 1 minute in 24 hours, ascertained from fallback mode switch statistics.

Statistical methods

The incidence of long PR intervals was analysed overall and according to day/night (8 am to 10 pm/10 pm to 8 am) distribution. Logistic regression was performed to estimate the odds ratio (OR) of experiencing the event for patients with SND with 200 ms < baseline PR interval < 350 ms compared with patients with SND with baseline PR interval < 200 ms. Predictors of long PR intervals were identified using univariate and multivariable logistic regression models using baseline variables, including age, sex, AR and PR intervals, atrial rhythm disorder and medications. In addition, a time-to-first event analysis was performed with the help of a Kaplan-Meier plot for the onset of long PR intervals. The incidence of AF was analysed overall. A logistic regression was performed to estimate the OR of experiencing an AF event for patients with long PR intervals compared with patients without long PR intervals. Predictors of AF were identified using logistic regression models with the baseline variables described above. Data are summarized as number (percentage), mean ± standard deviation or median [interquartile range]. All statistical analyses were performed with the SAS® statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population and follow-up

Two hundred and ninety-one patients with SND were enrolled in the study. In four patients, SafeR was disabled before the end of follow-up at 1 year; in 72 patients, baseline PR interval was not measured; and in one patient, the baseline PR interval was >350 ms. Therefore subsequent analyses could only be performed in 214 patients with a confirmed baseline PR/AR interval < 350/450 ms. This group contained 143 patients with a baseline PR interval < 200 ms, and 71 patients with a baseline PR interval ranging from 200 ms to 350 ms (Figs. 2 and 3).

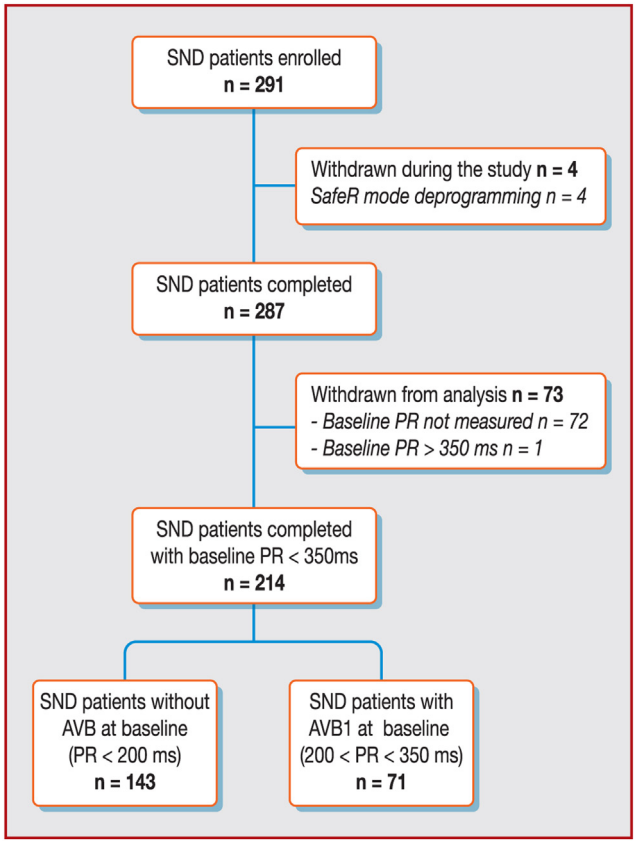

Figure 2. Patient flowchart. AVB: atrioventricular block; AVB1: first-degree atrioventricular block; SND: sinus node dysfunction. *Organigramme patient.*

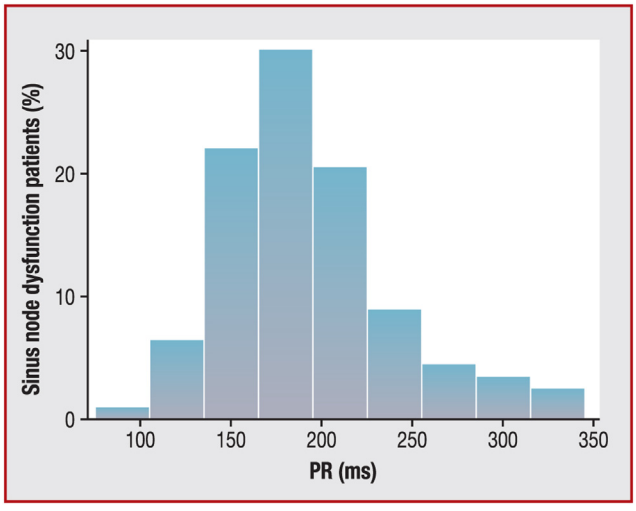

Figure 3. PR interval distribution in patients with sinus node dysfunction with PR interval < 350 ms at baseline.
Distribution des intervalles PR à l'état basal.

Table 1 Baseline characteristics of patients with sinus node dysfunction with baseline PR interval < 350 ms ($n = 214$).
Caractéristiques des patients avec dysfonction sinusale et PR < 350 ms.

Clinical characteristics	
Men	95 (44.4)
Age at enrolment (years)	78.9 ± 8.4
Atrial rhythm disorder[a]	113 (55.4)
Flutter	8 (3.9)
Fibrillation	99 (48.5)
Other	6 (2.9)
Medication[b]	
Sotalol	14 (6.9)
Digoxin	3 (1.5)
Non-dihydropyridine CCB[c]	3 (1.5)
Flecainide	13 (6.4)
Beta-blocker	65 (32.2)
Amiodarone	43 (21.3)
Other	81 (40.1)
None	44 (21.8)
Electrical characteristics[d]	
Mean PR (ms)	192 ± 49
Median PR (ms)	188 [160; 220]
Mean AR (ms)	244 ± 56
Median AR (ms)	240 [200; 266]
Intervention	
First implant	193 (90.2)
Replacement	20 (9.3)
Upgrade	1 (0.5)
Pacemaker model	
REPLY DR™	213 (99.5)
REPLY D™	1 (0.5)

Data are expressed as number (%), mean ± standard deviation or median [interquartile range]. CCB: calcium channel blocker.
[a] Values missing for 10 patients.
[b] Values missing for 12 patients.
[c] Diltiazem or verapamil.
[d] P: sensed atrium; A: paced atrium; R: sensed ventricle.

Patients were elderly (mean age 78.9 ± 8.4 years) and nearly half (48.5%) had a history of AF (Table 1). The most common medications were beta-blockers (32.2%) and amiodarone (21.3%). The mean PR interval was 192 ± 49 ms; the mean AR interval was 244 ± 56 ms. All patients were implanted with a REPLY™ dual-chamber pacemaker (MicroPort CRM, Clamart, France). For most ($n = 193$, 90.2%), this was their first implant. The mean duration of follow-up was 370 ± 78 days.

Study outcome

Incidence of long PR intervals

Over half ($n = 116$, 54.2%) of the 214 patients experienced one or more long PR intervals during the study. A greater percentage of patients with SND with 200 ms < baseline PR interval < 350 ms experienced a long PR interval during the study than patients with SND with baseline PR interval < 200 ms: 62.0% (44/71) vs. 50.4% (72/143).

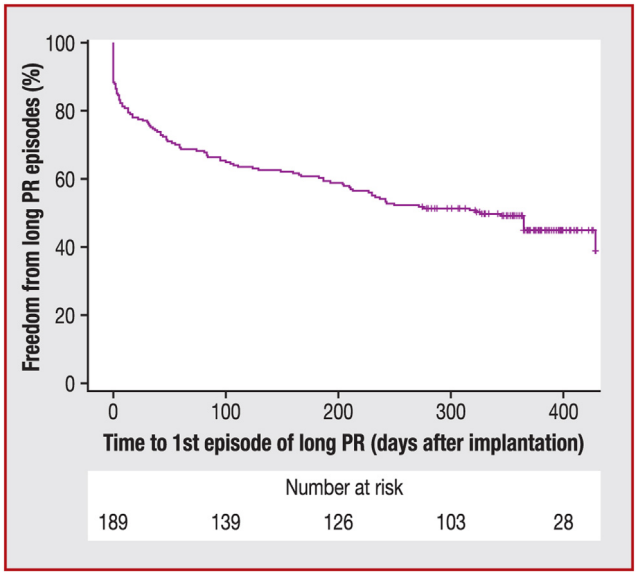

Figure 4. Kaplan-Meier curve showing time-to-first occurrence of long PR interval ($n = 214$).
Courbe de kaplan-Meier montrant le délai de survenue du premier intervalle PR long.

Nearly a quarter (23.4%) of the 214 patients experienced a first long PR interval within 30 days of implantation (Fig. 4). As time progressed, 31.3%, 33.6% and 39.3% of these 214 patients experienced a first long PR interval within 60, 90 and 180 days, respectively. The majority (92/116, 79.3%) of patients experienced long PR intervals during both the day and the night, some (20/116, 17.2%) during the day only and a few (4/116, 3.5%) during the night only.

Predictors of long PR interval

Preliminary (univariate) analysis indicated that long PR intervals during the study were potentially associated with a history of atrial rhythm disorder, prolonged baseline PR and the use of flecainide or amiodarone (Table 2). Confirmation by multivariable analysis showed that only the use of amiodarone was an independent predictor of long PR intervals (OR 2.50, 95% CI 1.20—5.21; $P = 0.014$).

Incidence and predictors of AF: association with long PR intervals

Almost a third of patients ($n = 63$, 29.6%) had at least one episode of AF during the study. History of atrial rhythm disorders, medication, amiodarone, long PR interval (AVB1 switch) and age were shown by univariate analysis to be potentially associated with the incidence of AF (Table 3). Further analysis (multivariable) confirmed that only a history of atrial rhythm disorders at baseline was associated with AF incidence (OR 1.78, 95% CI 1.02—3.10; $P = 0.044$). Almost twice as many patients with long PR interval occurrence experienced incident AF than patients without long PR interval occurrence (19.3% vs. 10.3%; OR 1.86, 95% CI 0.97—3.61; $P = 0.051$).

Table 2 Univariate analysis of the incidence of long PR intervals in patients with sinus node dysfunction and baseline PR interval < 350 ms.
Analyses univariées de l'incidence des intervalles PR.

Variable	*n* (%)	Incidence of long PR intervals		Comparison	OR (95% CI)	*P*
		Yes[a] (*n* = 116)	No[a] (*n* = 98)			
Age	214			>75 versus <75 years	1.06 (0.59—1.91)	0.85
<75 years	62 (29.0)	33 (53.2)	29 (46.8)			
>75 years	152 (71.0)	83 (54.6)	69 (45.4)			
Sex	214			Male versus female	1.31 (0.76—2.25)	0.33
Female	119 (55.6)	61 (51.3)	58 (48.7)			
Male	95 (44.4)	55 (57.9)	40 (42.1)			
Atrial rhythm disorder[b]	204			Yes versus No	1.78 (1.02—3.10)	0.044
No	91 (44.6)	41 (45.1)	50 (55.0)			
Yes	113 (55.4)	67 (59.3)	46 (40.7)			
PR interval						
Patients	199	105 (52.8)	94 (47.2)		1.01 (1.00—1.01)	0.094
Duration (ms)		198 ± 50	186 ± 46			
AR interval						
Patients	102	57 (55.9)	45 (44.1)		1.00 (1.00—1.01)	0.60
Duration (ms)		247 ± 61	241 ± 50			
Medication	202			Yes versus No	1.74 (0.89—3.42)	0.11
No	44 (21.8)	19 (43.2)	25 (56.8)			
Yes	158 (78.2)	90 (57.0)	68 (43.0)			
Sotalol	214			Yes versus No	1.40 (0.45—4.39)	0.56
No	200 (93.5)	107 (53.5)	93 (46.5)			
Yes	14 (6.5)	9 (64.3)	5 (35.7)			
Digoxin	214			Yes versus No	1.52 (0.14—17.15)	0.73
No	211 (98.6)	114 (54.0)	97 (46.0)			
Yes	3 (1.4)	2 (66.7)	1 (33.3)			
Non-dihydropyridine CCB[c]	214			Yes versus No	NA	NA
No	211 (98.6)	116 (55.0)	95 (45.0)			
Yes	3 (1.4)	0 (0.00)	3 (100.00)			
Flecainide	214			Yes versus No	0.31 (0.09—1.04)	0.057
No	201 (93.9)	112 (55.7)	89 (44.3)			
Yes	13 (6.1)	4 (30.8)	9 (69.2)			
Beta-blocker	214			Yes versus No	1.24 (0.65—2.35)	0.52
No	149 (69.6)	77 (51.7)	72 (48.3)			
Yes	65 (30.4)	39 (60.0)	26 (40.0)			
Amiodarone	214			Yes versus No	2.12 (1.00—4.46)	0.049
No	171 (79.9)	86 (50.3)	85 (49.7)			
Yes	43 (20.1)	30 (69.8)	13 (30.2)			

CCB: calcium channel blocker; CI: confidence interval; NA: not applicable; OR: odds ratio.
[a] Data are expressed as number (%) or mean ± standard deviation.
[b] At baseline.
[c] Diltiazem or verapamil.

Safety

There were no deaths in the SND population. Ten patients (4.7%) developed 12 adverse events, of which nine were serious adverse events: ventricular tachycardia (*n* = 2), stroke (*n* = 2), coronary artery procedure (*n* = 1), pocket infection (*n* = 1), acute coronary syndrome (*n* = 1), weakness (*n* = 1) and renal failure (*n* = 1). There were no events that were related to the study device. There was one report of diaphragmatic stimulation related to unipolar stimulation, which was overcome by switching to bipolar stimulation.

Discussion

Over half of patients with SND with a baseline PR interval < 350 ms in the PRECISE study experienced one or more long PR intervals in the year after pacemaker

Table 3 Univariate analysis of the incidence of atrial fibrillation in patients with sinus node dysfunction and baseline PR < 350 ms.
Analyses multivariées de l'incidence de atriale fibrillation.

Variable	*n* (%)	Incidence of atrial fibrillation		Comparison	OR (95% CI)	*P*
		Yes[a] (*n* = 64)	No[a] (*n* = 150)			
Age	214			>75 versus <75 years	1.90 (0.95—3.83)	0.071
<75 years	62 (29.0)	13 (21.0)	49 (79.0)			
>75 years	152 (71.0)	51 (33.6)	101 (66.5)			
Sex	214			Male versus Female	0.96 (0.53—1.74)	0.90
Female	119 (55.6)	36 (30.3)	83 (69.8)			
Male	95 (44.4)	28 (29.5)	67 (70.5)			
Atrial rhythm disorder[b]	204			Yes versus No	5.77 (2.78—11.99)	<0.001
No	91 (44.6)	11 (12.1)	80 (87.9)			
Yes	113 (55.4)	50 (44.3)	63 (55.8)			
PR interval						
Patients	199	60 (30.2)	139 (69.9)		1.00 (0.99—1.00)	0.32
Duration (ms)		187 ± 48	195 ± 49			
AR interval						
Patients	102	30 (29.4)	72 (70.6)		1.00 (0.99—1.01)	0.68
Duration (ms)		248 ± 55	243 ± 57			
Long PR interval (AVB1 switch)	214			Yes versus No	1.72 (0.92—3.24)	0.091
No	98 (45.8)	23 (23.5)	75 (76.5)			
Yes	116 (54.2)	41 (35.3)	75 (64.7)			
Ventricular pacing	214			>30% versus 30%	1.29 (0.52—3.20)	0.59
<30%	191 (89.3)	56 (29.3)	135 (70.7)			
>30%	23 (10.8)	8 (34.8)	15 (65.2)			
Medication	202			Yes versus No	4.40 (1.64—11.79)	0.003
No	44 (21.8)	5 (11.4)	39 (88.6)			
Yes	158 (78.2)	57 (36.1)	101 (63.9)			
Sotalol	214			Yes versus No	1.37 (0.45—4.16)	0.58
No	200 (93.5)	58 (29.0)	142 (71.0)			
Yes	14 (6.5)	6 (42.9)	8 (57.1)			
Digoxin	214			Yes versus No	3.64 (0.32—41.01)	0.30
No	211 (98.6)	62 (29.4)	149 (70.6)			
Yes	3 (1.4)	2 (66.7)	1 (33.3)			
Non-dihydropyridine CCB[c]	214			Yes versus No	0.88 (0.08—9.97)	0.92
No	211 (98.6)	63 (29.9)	148 (70.1)			
Yes	3 (1.4)	1 (33.3)	2 (66.7)			
Flecainide	214			Yes versus No	0.51 (0.13—1.92)	0.32
No	201 (93.9)	61 (30.4)	140 (69.7)			
Yes	13 (6.1)	3 (23.1)	10 (76.9)			
Beta-blocker	214			Yes versus No	1.49 (0.77—2.88)	0.23
No	149 (69.6)	37 (24.8)	112 (75.2)			
Yes	65 (30.4)	27 (41.5)	38 (58.5)			
Amiodarone	214			Yes versus No	1.83 (0.90—3.75)	0.097
No	171 (79.9)	44 (25.7)	127 (74.3)			
Yes	43 (20.1)	20 (46.5)	23 (53.5)			

AF: atrial fibrillation; AVB1: first-degree atrioventricular block; CCB: calcium channel blocker; CI: confidence interval; OR: odds ratio.
[a] Data are expressed as number (%) or mean ± standard deviation.
[b] At baseline.
[c] Diltiazem or verapamil.

implantation, with most episodes being potentially clinically relevant (i.e. not occurring solely at night). Most long PR intervals, the incidence of which was non-linear, occurred in the first 3 months. The use of amiodarone was an independent predictor of long PR intervals. Patients with long PR intervals were more likely to have incident AF than those without long PR intervals. Our findings add to the limited evidence about the development of long PR intervals in

contemporary patients with SND, and their association with AF.

Because the SafeR algorithm enabled the continuous recording of PR conduction delays, the percentage of patients with SND with long PR intervals (54.2%) was higher than previously reported in studies using electrocardiogram monitoring [15], but in line with previously reported findings in SafeR-monitored patients with SND from the 3-year ANSWER (EvaluAtioN of the SafeR mode in patients With a dual-chambER pacemaker indication) study [10,16]. Nevertheless, this result remains unexpectedly high. In MOde Selection Trial (MOST) [15], investigators reported the incidence of long PR intervals >200 ms in 2010 pacemaker-implanted patients with SND and normal PR interval at baseline. Fewer patients with SND (24.6%) developed long PR intervals after 33 months — nearly three times the follow-up duration in the PRECISE study. The shorter duration of the PRECISE study and the relatively higher long PR interval threshold (>350 ms for electrogram versus >200 ms for electrocardiogram) should in theory have led to a lower incidence rate of long PR intervals in our study. However, as already mentioned, PR in the PRECISE study was measured continuously rather than intermittently, which explains the high incidence of long PR intervals observed.

Patients with long PR intervals were more likely to have new episodes of AF than those without long PR intervals. Similar results were obtained in MOST, where a trend towards an association between long PR intervals and AF incidence (30.5% for AVB1 vs. 23.4% for normal AV conduction; hazard ratio 1.22, 95% CI 0.97—1.53; $P = 0.089$) was also observed [15]. Similarly, in the DANPACE (Danish multicentre randomized trial on single-lead atrial pacing versus dual-chamber pacing in sick sinus syndrome) study, a longer baseline PQ interval was associated with an increased risk of AF in 650 pacemaker-implanted patients with sick sinus syndrome [5]. The mean PQ interval at baseline was 179 ± 30 ms, the mean follow-up was 3.7 years and mode switch was used to detect the time spent in AF. The incidence of AF was higher among patients with a higher baseline PQ interval (>180 versus $\leq$180 ms; $P < 0.001$) [5]. Finally, a trend towards an association between long PR interval (>230 ms) and persistent atrial tachycardia/AF (hazard ratio 2.11, 95% CI 0.87—5.10; $P = 0.097$) was also seen after 2 years in Prefer for Elective Replacement Managed Ventricular Pacing (PreFER MVP) [12], which enrolled 630 previously-implanted patients (92% pacemakers, with SND [62%] or AVB [23%]) with an intrinsic PR interval of 210 ms [interquartile range, 170—230 ms] at baseline. All these results are in accordance with previous evidence indicating that a prolonged PR interval is an independent risk factor for AF [17,18], associated with a general tripling of risk for advanced conduction system disease and a specific doubling of risk for AF [4,19,20].

The clinical association of SND and AF is probably the result of electrophysiological and anatomical remodelling [21]. Remodelling is a gradual process [22]. At a cellular level, cell numbers in the sinoatrial node diminish naturally over time. Disease accelerates the shrinking of the sinoatrial node and the substitution of nodal tissue with fibrolipid tissue [23]. In the sinoatrial node, remodelling leads to sinoatrial node arrest and re-entry, while in the atrium, remodelling leads to re-entry and production of its triggering mechanisms. There is still uncertainty about the relationship between sinoatrial dysfunction and atrial myocardium dysfunction, especially with regard to which causes which [22]. For example, even short-term exposure to AF is enough to cause dysfunction and remodelling in the sinoatrial node [21]. It has been suggested that SND and AF might be different phenotypes of a related pathophysiological mechanism (e.g. fibrosis) [24].

Today, the management of AF is improving thanks to a multifaceted approach focusing on intense risk factor management as well as anticoagulation and control of heart rate and rhythm [25]. Other steps that could advance the management of AF include using new imaging techniques to better demarcate atrial fibrosis [26,27] and appropriate algorithms to minimize ventricular pacing [16,28], as some algorithms may not suit all types of patient (e.g. managed ventricular pacing in patients with long PR intervals) [12].

Our data support the current practice of implanting SND patients with a dual-chamber pacemaker. Given the high incidence of long PR intervals in patients with pure SND reported in our study, and the potential negative impact of long PR intervals on the development of AF, we believe that the choice of a dual-chamber pacemaker with an algorithm for long PR interval management might be useful for these patients.

Study limitations

Care should be taken in generalizing these results, as the population size was relatively small and the follow-up duration was short. Furthermore, a lack of monitoring meant that a quarter of enrolled patients could not be included in the analysis because PR interval values were not measured at baseline. The incidence of long PR intervals may have been overestimated because of selection bias; doctors may have inadvertently selected patients at greater risk of AVB1, knowing that these patients were likely to benefit from having a SafeR-enabled dual-chamber pacemaker. Fallback mode switch has high sensitivity and specificity for detection of AF, but over- and undersensing of AF can occur. Although simultaneous readings of cardiac electrical activity obtained using electrograms and electrocardiograms should be similar, there were no data from surface electrocardiograms to confirm that this was the case. Information about the exact position of the lead in the right atrium may have had an effect on the results, but was not recorded. The choice of 350 ms as the long PR interval cut-off was dictated by hardware rather than clinically, but it was judged lengthy enough to be clinically relevant. Typical limitations associated with observational studies, e.g. lack of placebo group and confounding, were present.

Conclusions

Among patients with SND, the implantation of a SafeR-enabled dual-chamber pacemaker allowed the safe and effective detection of long PR intervals and incident AF in 54.2% and 29.6% of patients during the year following implant. The significant predictors of long PR intervals and incident AF were amiodarone treatment and history of atrial rhythm disorder, respectively.

Funding

The PRECISE study was sponsored by MicroPort CRM (Clamart, France).

Acknowledgements

We would like to thank the trial participants and investigators who made the study possible; Bérangère Leroy for her support in study management; John Plant, BPharm, and Anne Rousseau-Plasse, PhD, for editorial assistance; and Françoise Tondu for statistical support.

Disclosure of interest

All authors. Fees from the company MicroPort CRM.

N. L.: consulting fees from the companies Medtronic, Boston Scientific, Saint-Jude Medical and MicroPort CRM.

S. M.: employee of the company MicroPort CRM.

The other authors have not supplied their declaration of competing interest.

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