New-generation atrial antitachycardia pacing (Reactive ATP) is associated with reduced risk of persistent or permanent atrial fibrillation in patients with bradycardia: Results from the MINERVA randomized multicenter international trial

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BACKGROUND Atrial fibrillation (AF) is a frequent comorbidity in patients with pacemaker and is a recognized cause of mortality, morbidity, and quality-of-life impairment. The international MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure trial established that atrial preventive pacing and atrial antitachycardia pacing (DDDRP) in combination with managed ventricular pacing (MVP) reduce permanent AF occurrence in comparison with standard dual-chamber pacing (DDDR).

OBJECTIVE We aimed to determine the role of new-generation atrial antitachycardia pacing (Reactive ATP) in preventing AF disease progression.

METHODS Patients with dual-chamber pacemaker and with previous atrial tachyarrhythmias were randomly assigned to DDDR (n = 385 (33%)), MVP (n = 398 (34%)), or DDDRP+MVP (n = 383 (33%)) group. The incidence of permanent AF, as defined by the study investigator, or persistent AF, defined as ≥7 consecutive days with AF, was estimated using the Kaplan-Meier method, while its association with patients' characteristics was evaluated via multivariable Cox regression.

RESULTS At 2 years, the incidence of permanent or persistent AF was 26% (95% confidence interval [CI] 22%–31%) in the DDDR group, 25% (95% CI 21%–30%) in the MVP group, and 15% (95% CI 12%–20%) in the DDDRP+MVP group ($P < .001$ vs DDDR; $P = .002$ vs MVP). Generalized estimating equation–adjusted Reactive ATP efficacy was 44.4% (95% CI 41.3%–47.6%). Multivariate modeling identified high Reactive ATP efficacy (>44.4%) as a significant predictor of reduced permanent or persistent AF risk (hazard ratio 0.32; 95% CI 0.13–0.781; $P = .012$) and episodes' characteristics, such as long atrial arrhythmia cycle length, regularity, and the number of rhythm transitions, as predictors of high ATP efficacy.

CONCLUSION In patients with bradycardia, DDDRP+MVP delays AF disease progression, with Reactive ATP efficacy being an independent predictor of permanent or persistent AF reduction.

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KEYWORDS Atrial fibrillation; Pacemaker; Antitachycardia pacing; Reactive ATP

ABBREVIATIONS **AF** = atrial fibrillation; **ATP** = antitachycardia pacing; **AV** = atrioventricular; **CI** = confidence interval; **DDDR** = dual-chamber pacing; **DDDRP** = atrial preventive pacing and atrial antitachycardia pacing; **HR** = hazard rati; **IQR** = interquartile rang; **MINERVA** = MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failur; **MVP** = managed ventricular pacin

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Introduction

Atrial fibrillation (AF), which is recognized as a cause of mortality, morbidity, and quality-of-life impairment, is the most common sustained cardiac arrhythmia encountered in clinical practice, and its incidence is increasing rapidly worldwide.[1] Atrial tachyarrhythmias, which comprise AF, atrial flutters, and atrial tachycardias, are frequent comorbidities in patients with indications for implantable cardiac devices.[1–6] Reentrant atrial tachyarrhythmias are susceptible to termination by means of atrial antitachycardia pacing (ATP).[7–10] Accordingly, some dual-chamber pacemakers and defibrillators incorporate suites of atrial ATP therapies that are automatically applied on detection of atrial tachyarrhythmias. The efficacy of atrial ATP in terminating atrial tachyarrhythmias has been measured in a range between 30% and 60%.[5–10] Although high ATP efficacy has been associated with a reduction in atrial tachyarrhythmias burden over time,[9] the clinical impact of atrial ATP has not been reliably demonstrated in randomized clinical trials.[5,6,8] The MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure (MINERVA) randomized trial[11] was designed to investigate the effect of a combination of atrial preventive pacing and atrial ATP (DDDRP), and managed ventricular pacing (MVP), a pacing mode designed to give priority to intrinsic ventricular activation, thereby minimizing the adverse effects of unnecessary right ventricular pacing.[12–14] The main results of the trial[15] show that this combination of algorithms was associated with a statistically and clinically significant 61% lower risk of progression to permanent AF on 2-year follow-up in patients with bradycardia and paroxysmal or persistent atrial tachyarrhythmias when compared with standard dual-chamber pacing (DDDR). The prespecified secondary analysis of the MINERVA study, which is reported here, aimed to determine the relationship between AF progression and efficacy of Reactive ATP. The latter is a new-generation atrial ATP that attempts termination of atrial tachyarrhythmias at onset and after any change in rate or regularity when the episode may be most amenable to termination by pacing.

Methods

Study design, patient population, and follow-up

The details of the MINERVA study design have already been provided.[11,15] In brief, the MINERVA trial was a multicenter, randomized, single-blind, controlled trial involving 63 cardiology centers in 15 countries, as listed in the Online Supplemental Appendix. The study was approved by the ethics committees of all participating centers and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent. Inclusion criteria were standard indications for permanent DDDR and a history of AF, atrial flutter, or atrial tachycardia (at least 1 documented episode in the last 12 months). The main exclusion criteria were history of permanent AF, third-degree atrioventricular (AV) block, or history of AV node ablation or AF ablation. After implantation of bipolar leads in the right atrium and ventricle and of a dual-chamber pacemaker (EnRhythm, Medtronic Inc, Minneapolis, MN), eligible patients were randomly assigned in a 1:1:1 manner to (1) standard DDDR (control DDDR group), (2) atrial preventive pacing, atrial ATP, and MVP (DDDRP+MVP group), and (3) DDDR with MVP (MVP group) (Figure 1). Patients underwent follow-up examination in their respective therapy groups 3 and 6 months after implantation and thereafter every 6 months until the last enrolled patient had reached 2 years of observation.

Reactive ATP

The EnRhythm pacemaker can respond to a sustained atrial tachyarrhythmia by delivering atrial ATP therapy, which can be programmed as a Ramp, a series of pacing stimuli delivered at decreasing intervals, or as a Burst+, a series of pulses followed by 2 premature stimuli.

The new-generation atrial ATP, Reactive ATP, monitors the atrial rhythm within an atrial tachyarrhythmia detection zone, which is subdivided into subzones; specifically selecting an atrial tachyarrhythmia interval of 400 ms, the atrial tachyarrhythmia zone, comprised between 100 and 400 ms, is divided into six 50 ms subzones for regular rhythms and into three 100 ms subzones for irregular rhythms. Each subzone is supplied with a separate set of atrial ATP therapies that were 10 Ramp sequences, 10 Burst+ sequences, and 10 Ramp sequences in the MINERVA trial. If the rhythm shifts into a different subzone because of a change in cycle length or regularity, the device delivers therapies from those available in the new subzone.

Analysis objectives, end points, and design

The main objective of this prespecified secondary analysis of the MINERVA study was to evaluate the relationship between Reactive ATP efficacy and AF progression.

The main end point of the analysis reported was time to first permanent or persistent AF. The definition of permanent AF was based on clinical assessment by the center investigator (long AF duration coupled with decision not to cardiovert the patient) and required AF to be documented during 2 consecutive follow-up visits, which, as per study design, were separated by at least 3 months. This end point was adjudicated by an independent event adjudication

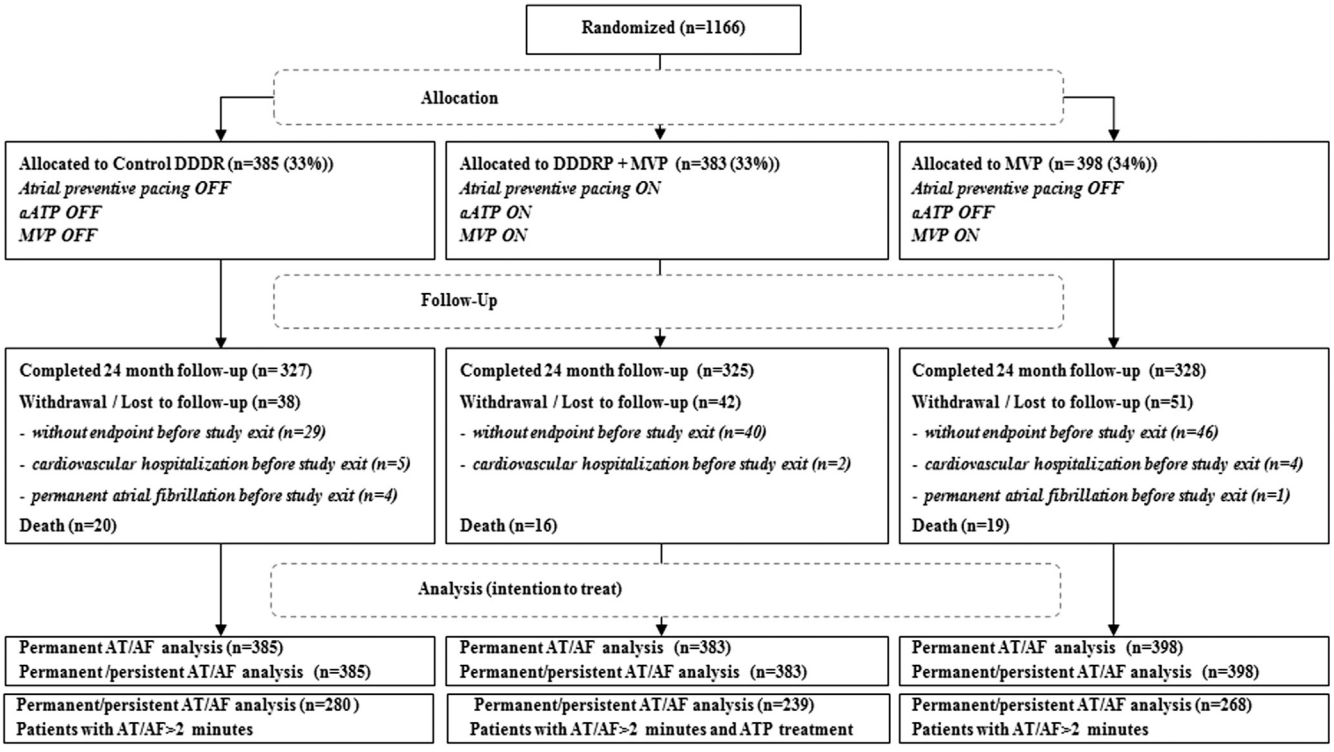

Figure 1 Study flowchart. AF = atrial fibrillation; AT = atrial tachyarrhythmia; ATP = antitachycardia pacing; DDDR = dual-chamber pacing; DDDRP = atrial preventive pacing and atrial antitachycardia pacing; MVP = managed ventricular pacing.

committee according to guidelines.[1] Persistent AF was defined as at least 7 consecutive days with 22 hours of device-recorded AF per day or at least 1 day with an episode of AF lasting at least 22 hours that was interrupted with an electrical or chemical cardioversion.

Secondary end points were ATP efficacy, atrial tachyarrhythmia cycle length, defined as the median of 12 atrial cycle lengths, atrial pacing percentage, ventricular pacing percentage, atrial tachyarrhythmia regularity (an episode was defined as regular if, on ordering the last 12 atrial intervals as a function of cycle length and ignoring the smallest and the largest ones, the difference between the 2nd and the 11th intervals on the list was $<25\%$ of the median atrial cycle length), and number of rate and regularity transitions that occurred during an atrial tachyarrhythmia episode (a transition being a jump from one to another of the described atrial tachyarrhythmia detection subzones).

Time to first permanent or persistent AF was first evaluated in the 3 randomized cohorts by considering as time zero the day of randomization. In order to evaluate the association between permanent or persistent AF occurrence and ATP efficacy, a second analysis considered a run-in period of 6 months after randomization. Each patient with tachyarrhythmia episodes in the first 6 months was characterized by baseline values for ATP efficacy and other device-detected variables, such as tachyarrhythmia cycle length, atrial pacing, and ventricular pacing, as estimated in this run-in period. The development of permanent or persistent AF was then evaluated after the run-in period. In this way, the patients' baseline characteristics, both clinical and device-derived ones, possible predictors, and permanent or persistent AF occurrence, the outcome, were derived from independent time intervals. DDDRP+MVP patients were then divided into 2 cohorts—high or low ATP efficacy—according to the fact that their ATP efficacy was greater or lower than the median ATP efficacy estimated in the overall DDDRP+MVP patient population. The selection of DDDRP+MVP patients on the basis of their ATP efficacy induced automatically the selection of patients with atrial tachyarrhythmia episodes longer than 2 minutes, since the time required for episode detection is about 1 minute and because ATP delivery was programmed after 1 minute of sustained arrhythmia. Consequently, the risk of permanent or persistent AF was evaluated in 4 patients' subgroups: 239 DDDRP+MVP patients with treated episodes (121 in the low ATP efficacy group and 118 in the high ATP efficacy group), and 268 patients in the MVP group and 280 patients in the control DDDR group, who had atrial tachyarrhythmias longer than 2 minutes.

Statistical analysis

The analysis set included all the patients randomized, according to the intention-to-treat principle, and data throughout the 2-year follow-up period.

Continuous data were described as means and SDs or as median and interquartile range (IQR), as appropriate; categorical data were expressed as counts and percentages.

Homogeneity of baseline characteristics was assessed by using the *t* test or Wilcoxon test for continuous variables, as appropriate, and the χ^2 test for categorical variables.

In order to adjust for multiple episodes per patient, the ATP efficacy was adjusted by means of the generalized estimating equation (GEE) method. Logistic regression was used to evaluate the association between ATP efficacy and patients' or episodes' characteristics, and the odds ratios together with their 95% confidence intervals (CIs) were reported.

To analyze the time to first permanent or persistent AF, the Kaplan-Meier method was used and cumulative hazard curves were compared by means of the log-rank test. The risk of permanent or persistent AF was evaluated using the Cox proportional hazards regression model, and hazard ratios (HRs) with 95% CIs were computed to compare risk profiles. All variables that were significant at the .10 level were further analyzed in a multivariable backward elimination model. The proportional hazard assumptions were tested by using Schoenfeld residuals. All tests were 2-sided, and a P value of $<.05$ was considered to indicate statistical significance. SAS 9.3 (SAS Institute Inc, Cary, NC) was used for statistical analyses.

Results

A total of 1166 patients were randomized and followed up, as shown in Figure 1. The baseline characteristics of the 1166 patients have already been described.[15] At baseline, 982 patients (86%) had a history of AF, 228 (20%) had a history of atrial flutter, and 197 (17%) had a history of atrial tachycardia. As described previously,[15] the median ventricular pacing percentage was 2% (25th–75th percentile 0%–11%) in the DDDRP+MVP group, 1% (25th–75th percentile 0%–9%) in the MVP group, and 53% (25th–75th percentile 15%–84%) in control DDDR group ($P < .001$ vs MVP and vs DDDRP+MVP).

AF occurrence and cycle length

Within 2 years of follow-up, 804 patients suffered AF longer than 5 minutes, specifically 269 (69.9%) in the control DDDR arm, 273 (68.6%) in the MVP arm ($P = .689$ vs control DDDR), and 262 (68.4%) in the DDDRP+MVP arm ($P = .571$ vs control DDDR; $P = .856$ vs MVP). The median AF burden was 17 min/d in control DDDR patients, 9 min/d in MVP patients, and 4 min/d in DDDRP+MVP patients ($P = .002$ vs control DDDR; $P = .032$ vs MVP). The median atrial cycle length at onset, as measured for the 89,411 atrial tachyarrhythmia episodes saved in device diagnostics with complete data, was 246 ms (IQR 214–278 ms), which corresponds to a median rate of 244 beats/min (IQR 216–280 beats/min).

Permanent or persistent AF

At 2 years, permanent or persistent AF occurred in 222 of 1166 patients (19.0%), specifically in 91 (actuarial incidence 26.2%; 95% CI 21.8%–31.2%) patients in the control DDDR arm, 83 (actuarial incidence 25.0%; 95% CI 20.6%–30.1%) patients in the MVP arm, and 48 (actuarial incidence 15.1%; 95% CI 11.6%–19.6%) patients in the DDDRP+MVP arm (HR 0.52; 95% CI 0.36–0.73; $P < .001$ vs control DDDR; HR 0.57; 95% CI 0.40–0.81; $P = .002$ vs MVP).

Reactive ATP efficacy and its association with permanent or persistent AF

In the DDDRP+MVP arm, 25,639 atrial tachyarrhythmia episodes longer than 2 minutes were treated by ATP in 239 patients, and the generalized estimating equation–adjusted Reactive ATP efficacy was 44.4% (95% CI 41.3%–47.6%). These patients were compared with 280 control DDDR and 268 MVP patients who suffered atrial tachyarrhythmia episodes longer than 2 minutes. Table 1 lists baseline characteristics of these patient subgroups and of DDDRP+MVP patients divided in 2 subgroups: low ATP efficacy patients ($\leq$44.4%) and high ATP efficacy patients ($>$44.4%). In these patient subgroups, the actuarial incidence of permanent or persistent AF at 2 years (Figure 2) was 33.6% (95% CI 28.2%–39.7%) in the control DDDR group, 30.6% (95% CI 25.1%–36.9%) in the MVP group, 27.9% (95% CI 20.5%–37.4%) in the DDDRP+MVP–low ATP efficacy group (log-rank test, $P = .0475$ vs control DDDR; $P = .3121$ vs MVP), and 13.5% (95% CI 8.2%–21.8%) in the DDDRP+MVP–high ATP efficacy group (log-rank test, $P < .001$ vs control DDDR, $P = .0197$ vs MVP, and $P = .0315$ vs DDDRP+MVP–low ATP efficacy).

Table 2 shows the univariate and multivariate association between permanent or persistent AF and patients' characteristics in the DDDRP+MVP arm. In particular, permanent or persistent AF risk was significantly reduced in patients with high Reactive ATP efficacy ($>$44.4%) (HR 0.32; 95% CI 0.13–0.78; $P = .012$) and in patients with high atrial pacing (HR 0.98 [ie, 2% risk decrease for each 1% increase in atrial pacing]; 95% CI 0.97–0.99; $P = .011$); conversely, a higher risk of permanent or persistent AF was associated with patients with higher ventricular pacing (HR 1.03 [ie, 3% risk increase for each 1% increase in ventricular pacing]; 95% CI 1.02–1.05; $P < .001$).

Predictors of ATP efficacy

Univariate and multivariate logistic regression analyses showed that Reactive ATP efficacy was associated with episodes' characteristics such as atrial tachyarrhythmia cycle length and regularity at last ATP attempt and number of atrial tachyarrhythmia rhythm transitions, as described in Table 3.

Of the 19,143 episodes with complete diagnostic data, 12,214 episodes (64%) were treated in 2 or more atrial tachyarrhythmia detection subzones, showing rate or regularity transitions. Importantly, the mean number of detection subzones in which episodes were treated was 1.5 $\pm$ 0.7, 2.4 $\pm$ 0.9, 2.9 $\pm$ 1.0, 3.7 $\pm$ 1.2, and 4.5 $\pm$ 1.4 for episodes' durations comprised between 2 and 15 minutes, between 15 and 30 minutes, between 30 and 60 minutes, between 1 and 6 hours, and $>$6 hours, respectively, showing significant ($P <$ .001) increase as a function of episode duration.

Figure 3 shows the sequence of Reactive ATP attempts (panel A) and the interval plot (panel B) for a specific episode that started fast and irregular, underwent through 24 rate or regularity transitions, and finally became regular and slower and was terminated, after 8.5 hours, at the 63th Reactive ATP attempt, by the second Reactive ATP attempt in the regular atrial tachyarrhythmia window comprised between 300 and 350 ms.

Table 1 Demographic characteristics, medical history, and pacemaker indications

Characteristic	Control DDDR (280 patients)	MVP (268 patients)	DDDRP+MVP (239 patients)	DDDRP+MVP low ATP efficacy (121 patients)	DDDRP+MVP high ATP efficacy (118 patients)	*P* (low vs high ATP efficacy)
Demographic characteristics						
Sex: male	146 (52.1)	131 (48.9)	104 (43.5)	51 (42.1)	53 (44.9)	.666
Age (y)	73 ± 9	74 ± 8	74 ± 9	73 ± 9	74 ± 9	.504
Medical history						
Previous atrial tachyarrhythmia	280 (100.0)	268 (100.0)	239 (100.0)	121 (100.0)	118 (100.0)	
Atrial fibrillation	251 (90.9)	237 (89.8)	207 (87.3)	105 (87.5)	102 (87.2)	.941
Atrial flutter	45 (16.9)	62 (23.8)	47 (20.4)	22 (18.5)	25 (22.5)	.448
Atrial tachycardia	36 (13.4)	41 (15.8)	42 (18.1)	21 (17.6)	21 (18.6)	.853
Persistent atrial tachyarrhythmia	33 (12.3)	28 (10.7)	19 (8.3)	11 (9.4)	8 (7.1)	.815
Paroxysmal atrial tachyarrhythmia	206 (76.9)	205 (78.2)	181 (78.7)	91 (77.8)	90 (79.7)	
Both paroxysmal and persistent atrial tachyarrhythmia	29 (10.8)	29 (11.1)	30 (13.0)	15 (12.8)	15 (13.3)	
Atrial cardioversions	67 (25.2)	73 (28.0)	63 (27.0)	37 (30.8)	26 (23.0)	.179
Hypertension	182 (68.4)	187 (71.4)	172 (74.8)	91 (76.5)	81 (73.0)	.542
Previous stroke/TIA	30 (10.8)	27 (10.2)	26 (11.1)	16 (13.2)	10 (8.8)	.277
Diabetes	53 (19.7)	42 (15.9)	30 (13.0)	18 (15.1)	12 (10.8)	.332
NYHA class > II	18 (6.4)	10 (3.7)	5 (2.1)	4 (4.0)	1 (1.1)	.201
LVEF (%)	57 ± 9	57 ± 10	57 ± 9	56 ± 10	59 ± 10	.325
PR interval (ms)	180 (160–210)	189 (160–210)	180 (160–200)	180 (156–200)	180 (160–200)	.665
$CHADS_2$ score	1.7 (1 · 2)	1.7 ± 1.2	1.7 ± 1.1	1.7 ± 1.1	1.7 ± 1. 1	.911
Baseline medications						
Anticoagulants	141 (50.4)	129 (48.3)	109 (45.8)	60 (50.0)	49 (41.5)	.190
Antiplatelet	93 (33.2)	101 (37.8)	100 (42.0)	51 (42.5)	49 (41.5)	.879
Antiarrhythmic drugs class III	93 (33.2)	83 (31.1)	71 (29.8)	30 (24.8)	41 (34.7)	.100
Antiarrhythmic drugs class IC	45 (16.1)	52 (19.5)	50 (21.0)	23 (19.2)	27 (22.9)	.482
Pacemaker indications						
Sinus node disease	241 (86.1)	228 (85.1)	200 (83.7)	99 (81.8)	101 (85.6)	.810
First- or second-degree AV block	18 (6.4)	14 (5.2)	15 (6.3)	9 (7.4)	6 (5.1)	
Transient complete AV block	4 (1.4%)	8 (3.0)	3 (1.3)	2 (1.7)	1 (0.8)	
Other	17 (6.1)	18 (6.7)	21 (8.8)	11 (9.1)	10 (8.5)	

Values are presented as mean ± SD, as n (%), or as median (Q1–Q3).

No variable showed significant differences either among the 3 randomized groups (control DDDR, MVP, or DDDRP+MVP) or between DDDRP+MVP–low ATP efficacy and DDDRP+MVP–high ATP efficacy groups.

ATP = antitachycardia pacing; AV = atrioventricular; DDDR = dual-chamber pacing; DDDRP = atrial preventive pacing and atrial antitachycardia pacing; LVEF = left ventricle ejection fraction; MVP = minimal ventricular pacing; NYHA = New York Heart Association; Q1–Q3 = first and third quartiles; TIA = transient ischemic attack.

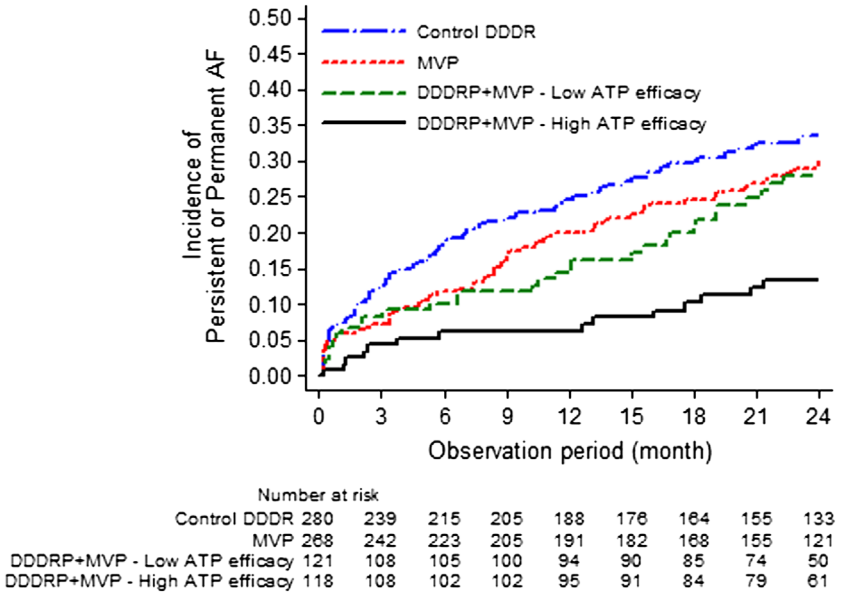

Figure 2 Incidence of permanent or persistent AF in the control DDDR arm, in the MVP arm, and in the DDDRP+MVP arm, which was divided into 2 subgroups—low and high ATP efficacy—as a function of the Reactive ATP efficacy. AF = atrial fibrillation; ATP = antitachycardia pacing; DDDR = dual-chamber pacing; DDDRP = atrial preventive pacing and atrial antitachycardia pacing; MVP = managed ventricular pacing.

Discussion

The main results of our analysis show that high efficacy Reactive ATP is associated with a reduction in the risk of permanent or persistent AF (Figure 2 and Table 2). The progression of atrial disease seems to be prevented or delayed through termination of atrial tachyarrhythmia episodes when they are slow and regular, a condition that can be observed at the onset of the episode or over time; indeed, we observed that long atrial tachyarrhythmia episodes undergo many rhythm transitions, becoming amenable to ATP termination. These results have clinical importance because evolution toward permanent AF is an important prognostic marker for death, stroke, or hospital admissions in primary care.[16–18] The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[16] evaluated 18,201 patients with AF and found that the risk of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF than in those with paroxysmal AF. The Atrial Fibrillation in the Barbanza Area Study[17,18] identified progression to permanent AF as a predictor of

Table 2 Univariate and multivariate models for the risk of permanent or persistent AF

	Univariate model		Multivariate model	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex: male	1.04 (0.49–2.22)	.919		
Age	1.00 (0.96–1.05)	.824		
Persistent AF	1.34 (0.54–3.31)	.525		
Cardioversions	2.54 (1.19–5.43)	.016	2.33 (1.05–5.02)	.038
Hypertension	1.04 (0.44–2.45)	.926		
Stroke/TIA	1.29 (0.45–3.71)	.642		
Diabetes	1.22 (0.37–4.06)	.747		
History of AF hospitalization	2.30 (1.07–4.91)	.032		
LVEF	0.97 (0.91–1.02)	.250		
Spontaneous PR interval >180 ms	1.00 (0.99–1.01)	.387		
Anticoagulants	2.00 (0.93–4.27)	.074		
Antiplatelets	0.47 (0.21–1.08)	.074		
Antiarrhythmic drugs class III	0.59 (0.24–1.47)	.259		
Antiarrhythmic drugs class IC	0.69 (0.26–1.82)	.454		
Mean cycle length* >246 ms	0.86 (0.38–1.95)	.716		
Mean ventricular pacing*	1.04 (1.02–1.05)	<.001	1.03 (1.02–1.05)	<.001
Mean atrial pacing*	0.98 (0.97–0.99)	<.001	0.98 (0.97–0.99)	.011
ATP efficacy* >44.4%	0.38 (0.17–0.87)	.022	0.32 (0.13–0.78)	.012

AF = atrial fibrillation; ATP = antitachycardia pacing; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack.

*Calculated during the first 6 mo of the observation period.

Table 3 Predictors of ATP efficacy among episodes' or patients' baseline characteristics

	Univariate model*		Multivariate model†	
Parameter	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Sex: male	1.12 (0.61–2.03)	.715		
Age	1.01 (0.98–1.04)	.384		
Persistent AF	1.68 (0.84–3.36)	.139		
Hypertension	1.12 (0.63–2.00)	.697		
Stroke/TIA	0.56 (0.18–1.69)	.300		
Diabetes	1.12 (0.50–2.53)	.786		
History of AF hospitalization	1.37 (0.74–2.52)	.318		
NYHA class III-IV	0.70 (0.21–2.36)	.567		
LVEF	0.98 (0.92–1.05)	.598		
Spontaneous PR interval >180 ms	1.84 (0.81–4.16)	.146		
Anticoagulants	1.01 (0.55–1.83)	.980		
Antiplatelets	1.16 (0.64–2.13)	.620		
Antiarrhythmic drugs class III	1.33 (0.71–2.52)	.373		
Antiarrhythmic drugs class IC	0.58 (0.21–1.60)	.295		
Long atrial cycle length‡	3.78 (2.23–6.44)	<.001	4.10 (2.32–7.26)	<.001
Regular rhythm	1.45 (0.93–2.27)	.100	1.72 (1.04–2.86)	.035
No. of transitions	1.23 (1.02–1.49)	.030		

AF = atrial fibrillation; ATP = antitachycardia pacing; CI = confidence interval; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack.

*Logistic regression model for repeated measures.

†Backward selection method (in: $P = .2$; out: $P = .05$).

‡Long atrial arrhythmia cycle length is defined as >210 ms, which was the median of the atrial arrhythmia cycle length at last ATP attempt for the considered tachyarrhythmias.

mortality or hospitalizations in an unselected population with AF.

As expected, atrial pacing was also associated with lower risk of permanent or persistent AF and ventricular pacing with a higher risk of permanent or persistent AF; it is worthwhile to mention that most DDDRP+MVP patients had a ventricular pacing percentage very low (median 2%).

Mechanism of the impact of reactive ATP

Although most (86%) of our patients had a history of AF at baseline and only 20% had a history of atrial flutter and 17% had a history of atrial tachycardia, many atrial arrhythmia episodes had quite slow rates at onset, with a median of 244 beats/min, as estimated by the device. In our patient population, ATP probably terminated many reentrant atrial tachyarrhythmias.[7–10]

ATP cannot terminate true AF, but it can terminate atrial tachyarrhythmia episodes—even if they start fast and irregular—whenever the rhythm stabilizes and/or slows down. We observed that many (64%) atrial tachyarrhythmia episodes underwent rhythm and regularity transitions. Our data suggest that even after hours of atrial tachyarrhythmia, when most cardiologists would expect AF to be stably irregular and fast, transitions toward more regular or slower rhythms occur, thus making the arrhythmia amenable to ATP termination (Figure 3). Indeed, we observed that the number of rate and regularity transitions increased as a function of episode duration and that ATP efficacy was higher in episodes with long cycle length, in episodes with many rhythm transitions, and in episodes with regular rhythm (Table 3).

Before the MINERVA trial, the impact of atrial ATP therapies was not widely recognized,[5,6] since previous studies had yielded contradictory findings.[8,9] Indeed, the Atrial Therapy Efficacy and Safety Trial (ATTEST) randomized parallel trial[8] tested atrial preventive and ATP therapies in 368 patients with pacemaker and found no significant reduction in atrial tachyarrhythmia burden or frequency despite a median ATP efficacy of 54%. Conversely, Gillis et al[9] described a significant impact of atrial ATP therapy on atrial tachyarrhythmia burden in the subgroup of patients with high ATP efficacy (≥60%). The fact that previous studies on ATP did not yield convincing results can be explained by the fact that the devices used in previous trials only featured standard ATP therapies, which attempt atrial tachyarrhythmia termination after detection but give up after a maximum of 30 ATP attempts, that is, after about 10–15 minutes. Standard ATP therapies fail to take advantage of rhythm changes and are unable to terminate long-lasting atrial tachyarrhythmia. By contrast, Reactive ATP continues to monitor atrial rhythm, watches for any change in rate or regularity, and then opportunistically applies ATP when the episode is most amenable to termination by pacing. Consequently, Reactive ATP also treats long episodes and, when effective, prevents them from being sustained for hours or days.

Clinical implications

The new results reported here of the MINERVA trial for the first time convincingly indicate that Reactive ATP is an effective means of preventing AF disease progression. Reducing the risk of persistent and permanent AF have clinical and economic relevance in terms of improved patient care, by lowering the risk of stroke and heart failure,[16–20] and of reduced health care resources and costs.[15,21] Indeed, the importance of new therapies

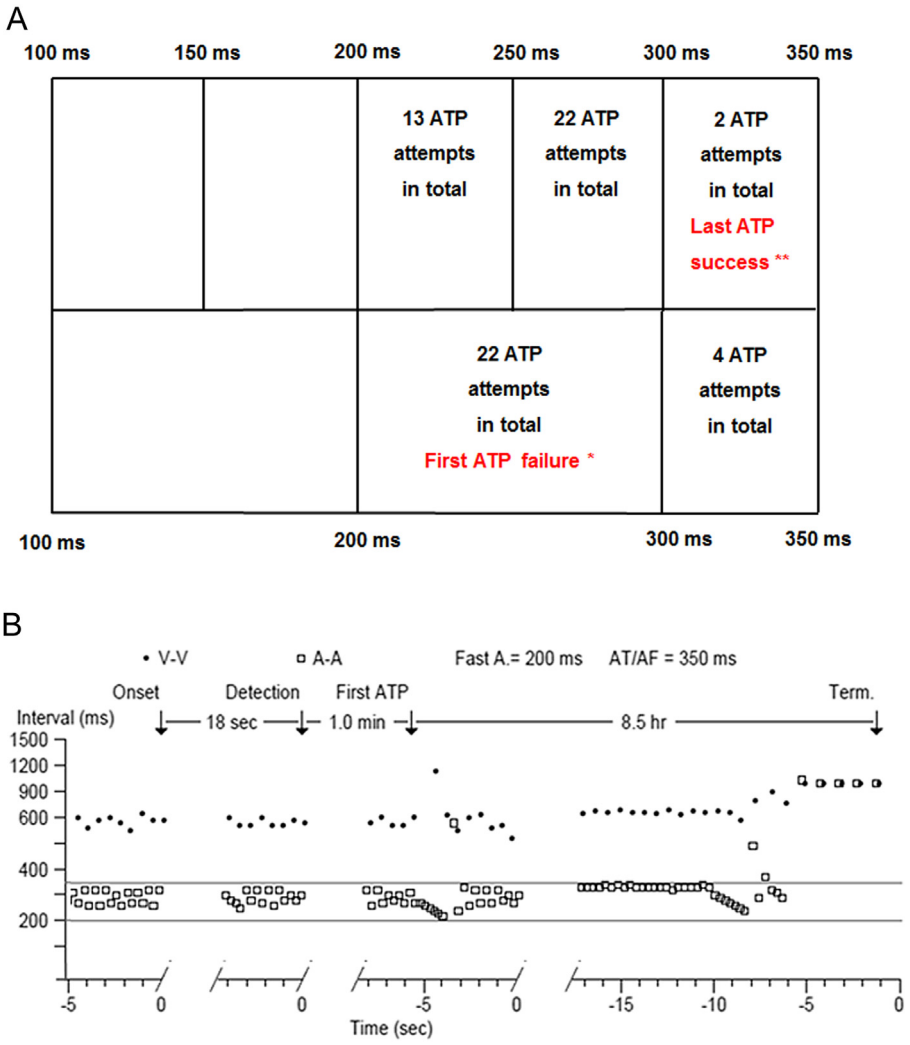

Figure 3 Number of Reactive ATP attempts in the atrial tachyarrhythmia detection subzones (**A**) and interval plot (**B**) for a specific atrial tachyarrhythmia episode that was successfully terminated by Reactive ATP after about 8.5 hours from episode onset. The episode started with an irregular rhythm and a cycle length of 290 ms and was first treated in the irregular atrial tachyarrhythmia window comprised between 200 and 300 ms. After the first unsuccessful attempt, the episode underwent several rate or regularity transitions and was treated in 5 atrial tachyarrhythmia windows, 3 regular windows, and 2 irregular windows. Finally, the episode transitioned to a regular rhythm and a slower rate, with a cycle length of 330 ms and was terminated at the 63th attempt, in the regular window comprised between 300 and 350 ms. Panel B shows that the episode was treated by first ATP after 1 minute from detection when the episode was irregular and that after about 8.5 hours the episode became slower and regular, was treated, and terminated within 4 ventricular beats. AF = atrial fibrillation; AT = atrial tachyarrhythmia; ATP = antitachycardia pacing.

for AF is confirmed by the fact that AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances and is displaying a clear upward trend worldwide.[22–25]

Study limitations

The study was single blind; therefore, the investigators were aware of device programming. To limit the possibility to bias the ascertainment of study end points, permanent AF diagnoses and cardiovascular hospitalization decisions, performed by study investigators according to predefined conditions, were validated by an independent event adjudication committee on the basis of patients' data and hospital admissions letters and according to guidelines. Occurrence of persistent AF was derived by device diagnostics and therefore by definition unbiased by investigator awareness of each patient therapy programming. The lower occurrences of atrial cardioversions, of emergency department visits, and of AF-related hospitalizations[15] in the DDDRP+MVP arm were reassuring about the fact that investigators did not influence the study results and the end point definition. Findings from the described trial cannot be generalized for all patients implanted with dual-chamber pacemakers, but rather to patients included in the trial, that is, patients with indication to DDDR—but without complete AV block—and with paroxysmal or persistent atrial tachyarrhythmias, treated by Reactive ATP.

Conclusion

In patients with bradycardia, DDDRP+MVP delays AF disease progression, with Reactive ATP efficacy being an independent predictor of permanent or persistent AF risk

reduction. While most patients had a history of AF at baseline, pacemaker diagnostics showed that most atrial arrhythmias started with relatively long cycle lengths or, over time, underwent rate or regularity transitions, thus becoming amenable to termination by pacing. Reactive ATP provides the opportunity to treat atrial tachyarrhythmias when they spontaneously organize or slow down.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2015.04.015.

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CLINICAL PERSPECTIVES

This analysis of the MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure clinical trial provides new evidence about the fact that in patients with history of atrial fibrillation, after pacemaker implant, many atrial arrhythmias are relatively slow or, over time, undergo rate or regularity transitions. The study results show that the use of a new atrial antitachycardia pacing (Reactive ATP) prevent the progression of AF to permanent or persistent AF because this new feature is able to monitor atrial tachyarrhythmias and treat them when they spontaneously organize or slow down, thus becoming amenable to termination by pacing. Patients with indication to pacing for bradycardia and history of atrial fibrillation may therefore benefit by a systematic use of atrial antitachycardia pacing.