

# A Randomized Study to Compare Ramp Versus Burst Antitachycardia Pacing Therapies to Treat Fast Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter Defibrillators

## The PITAGORA ICD Trial

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**Background**—In patients with implantable cardioverter-defibrillators (ICDs), antitachycardia pacing (ATP) is highly effective in terminating fast ventricular tachycardias (FVTs) and lowers the use of high-energy shocks, without increasing the risk of arrhythmia acceleration or syncope.

**Methods and Results**—The aim of the PITAGORA ICD trial was to randomly compare 2 ATP strategies (88% coupling interval burst versus 91% coupling interval ramp, both 8 pulses) in terms of ATP efficacy, arrhythmia acceleration, and syncope. Two hundred six ICD patients (83% male,  $67 \pm 11$  years) were enrolled. FVT episodes with cycle lengths between 240 and 320 ms were treated by 1 ATP sequence and, in the event of failure, by shocks. Over a median follow-up of 36 months, 829 spontaneous ventricular tachyarrhythmia episodes were detected in 79 patients. Episode review identified 595 episodes as true ventricular arrhythmias in 72 patients; devices classified 111 (18.7%) episodes as VF, 216 (36.3%) as FVT, and 268 (45.0%) as VT. Fifty-six patients had 214 treated FVT episodes—2 FVTs self-terminated before ATP release; 44 (79%) of these had at least 1 effective ATP intervention, and 34 (61%) were spared ICD shocks. Burst terminated 100 of 133 (75.2%) FVT episodes, whereas ramp terminated 44 of 81 (54.3%;  $P=0.015$ ). Acceleration occurred in 9 of 214 (4.2%) FVT episodes treated: 6 episodes in 3 ramp patients and 3 episodes in 3 burst patients. Two patients—1 in each group—suffered 1 syncopal event associated to a nonterminated FVT episode.

**Conclusions**—Burst is significantly more efficacious than ramp in terminating FVT episodes. As the first therapy for FVT episodes, ATP carries a low risk of acceleration or syncopal events. (*Circ Arrhythmia Electrophysiol.* 2009;2:146-153.)

**Key Words:** reentry ■ shock ■ burst ■ tachycardia ■ implantable cardioverter defibrillator

Several trials have shown the benefit of implantable cardioverter defibrillators (ICD) in the secondary<sup>1-3</sup> or primary prevention<sup>4-8</sup> of sudden cardiac death.

### Clinical Perspective see p 153

Many arrhythmias that are labeled as ventricular fibrillation (VF) by ICD are clinically rapid monomorphic ventricular tachycardias (VT).<sup>9-10</sup> Several trials have shown that antitachycardia pacing (ATP) can terminate many VT episodes.<sup>10-16</sup> Recently, the PainFREE Rx trials<sup>10,15</sup> have shown that an empirical sequence of burst ATP therapy (8 pulses at 88% coupling interval) is highly effective in terminating fast

ventricular tachycardias (FVT) with cycle lengths (CL) between 240 and 320 ms. These studies have demonstrated that ATP lowers the use of high-energy shocks, without increasing the risk of arrhythmia acceleration or syncope.

Although various ATP schemes have been tested,<sup>10-16</sup> ramp and burst ATP therapies have never been compared in a randomized design on spontaneous FVT episodes. The aim of the PITAGORA ICD (Project for the Investigation and Treatment of Ventricular Arrhythmias: a General Observational Registry on Antitachycardia Pacing Efficacy) trial was to randomly compare the efficacy of 2 different ATP strategies (burst, 8 pulses at 88% coupling interval versus ramp, 8

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**Table 1. FVT Therapy Programming**

Treatment Group: Burst ATP		Treatment Group: Ramp ATP	
1st FVT therapy programming		1st FVT therapy programming	
Therapy 1	ATP	Therapy 1	ATP
Amplitude	8 V	Amplitude	8 V
Pulse width	1.6 ms	Pulse width	1.6 ms
Therapy type	Burst	Therapy type	Ramp
Ventricular pacing	RV	Ventricular pacing	RV
No. of initial pulses	8	No. of initial pulses	8
R-S1 interval (%RR):	88%	R-S1 interval (%RR):	91%
		Interval decrement	10 ms
Minimum interval	200 ms	Minimum interval	200 ms
No. of sequences	1	No. of sequences	1
NID VF	18/24	NID VF	18/24
RNID VF	9/12	RNID VF	9/12

pulses at 91% coupling interval) in terminating FVT in candidates for ICD implantation for the primary or secondary prevention of sudden death.

## Methods

### Multicenter Trial

Two hundred six patients were enrolled in 26 Italian cardiology centers (see Appendix) from December 2003 to June 2006.

### Study Design

The PITAGORA ICD trial was a prospective, single-blind, parallel, randomized study. Patients were randomly assigned to ramp and burst ATP therapies. Randomization was performed centrally in a 1:1 ratio. Every patient signed an informed consent form approved by each center's ethics committee.

### Study Objectives

The main objective of the PITAGORA ICD trial was to compare the efficacy of FVT termination by 2 different sequences of ATP strategies (burst, 8 pulses at 88% coupling interval versus ramp, 8 pulses at 91% coupling interval).

Main secondary end points were: incidence of ventricular rhythm acceleration after ATP therapy, defined as >10% decrease in arrhythmia cycle length; incidence of syncopal events associated to spontaneous FVT episodes; duration of FVT episodes, ventricular arrhythmia cycle length, deaths, hospitalizations and quality of life, as measured by means of a EuroQol questionnaire, in which patients were asked to score their health status on a scale from 0 to 100.

Inclusion criteria required that patients had received an ICD in accordance with class I and II A indications<sup>17</sup> and, specifically, an ICD capable of detecting FVT episodes via VF and of ATP treatment.

Exclusion criteria were life expectancy less than 1 year because of chronic noncardiac disease; heart transplant expected in <1 year; pregnancy; age <18 years; unwillingness or inability to provide written informed consent; unavailability for follow-up at the study center; ventricular tachyarrhythmias associated with a reversible cause; Brugada syndrome; long-QT syndrome and hypertrophic cardiomyopathy; and the presence of a mechanical tricuspid valve.

### Statement of Responsibility

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Definition of ICD Indications for Primary and Secondary Prevention of Sudden Death

ICD indication for the secondary or primary prevention of sudden death followed indications established by published trials<sup>1-7</sup> and American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology guidelines.<sup>17</sup>

### Implantation and Pacemaker Programming

All patients received a Medtronic ICD system with at least the transvenous endocardial lead positioned at the right ventricular apex.

FVT and VF detection zones were programmed in all patients. VF detection required that 18/24 R-R intervals be  $\leq 320$  ms. A FVT detection zone was programmed within the VF zone (FVT via VF): FVT detection required that 18/24 intervals should have a VTCL between 240 ms and 320 ms and that none of the last 8 R-R intervals be <240 ms. Arrhythmia episodes detected as VF were treated with high-voltage shock, whereas those detected as FVT were first treated by ATP.

According to the randomization, ATP therapies in the FVT zone were programmed as described in Table 1. The choice of the burst ATP coupling interval (88%) was based on the PainFREE trials.<sup>10,15</sup> The ramp coupling interval of 91% was derived from two considerations: (1) the fact that the most commonly used coupling interval in the clinical practice of participating centers was 91% and (2) the fact that the minimum interval between subsequent ATP pulses was set at 200 ms. Setting the coupling interval of the first ATP pulse at 91% of the arrhythmia cycle length therefore enabled the eighth pulse to be delivered at 200 ms or higher for most of the range (240 to 320 ms) of the FVT window. In conclusion, this programming scheme enabled complete 8-pulse ramp ATP to be applied within the FVT window in most episodes.

In the event of failed ATP, a high-energy shock was required, the choice of the energy and configuration of the programmed shock being left to the physician's discretion. Other device features were also programmed at the physician's discretion, according to the patient's characteristics. In dual-chamber ICD, the use of a physiological AV delay long enough to permit supraventricular conduction to take place was recommended.

### Data Collection and Follow-Up

Baseline clinical data were collected on enrollment. Follow-up examinations were performed after 3 and 6 months, and every 6 months thereafter; data on cardiopulmonary symptoms, functional class, ventricular arrhythmia episodes, and cardiac rhythm were collected via a 12-lead ECG, and ICD electric performances were recorded. Specific adverse event forms and episode review forms were used to document clinical events and to assess the appropri-

ateness of detection and termination of episodes classed as ventricular tachyarrhythmias.

### Episode Review and Outcome Committees

Episodes detected as VT, FVT, or VF were classified by an episode review committee of independent expert electrophysiologists. Each episode was also reviewed by electrophysiologists attending follow-up examinations of their own patients. Lack of consensus between these 2 episode reviews triggered a third review by a second group of independent expert electrophysiologists and the final decision was taken on agreement between any 2 reviewers. Episode review was performed in accordance with predetermined criteria: an arrhythmia was classified as VT if it started with a sudden change in heart rate, had regular R–R intervals, and the QRS morphology of the local or far-field EGM during tachycardia was different from that of native ventricular conduction, indicating ventricular origin; an episode was classified as sinus tachycardia on the basis of a continuous heart rate increase and short QRS duration; arrhythmia was classified as atrial fibrillation in the event of irregular R–R intervals (>30 ms change from beat to beat) and short QRS duration; an episode was classified as ventricular fibrillation in the event of heart rate >240 bpm and varying QRS morphology. Episode termination was also classified to confirm device classification of therapy success: any termination that occurred more than 5 beats after therapy was classified as spontaneous, and therapy was consequently defined as unsuccessful.

Electrical storms were defined as the occurrence of >3 separate episodes of ventricular tachyarrhythmias within a 24-hour period, each separated by >5 minutes.

Data on major clinical events were obtained during follow-up examinations and, when necessary, by telephone contact. An outcome committee of 2 physicians, who were not involved as study investigators and were blinded to treatment assignment, monitored the data from case report forms and classified syncope and other clinical events as being related or unrelated to ventricular arrhythmias and consequent ICD therapies. Syncope was defined as complete loss of consciousness with loss of postural tone.

### Sample Size and Statistical Analysis

In calculating the sample size, we took the efficacy of the first ATP therapy of each episode in a parallel study design as the end point; we also assumed multiple episodes per patient, and set the estimation of the difference between the ATP efficacy of burst and ramp as the study objective. On the basis of the PainFREE studies,<sup>10,15</sup> we estimated that the enrollment of 200 patients and a 2-year follow-up would result in the collection of more than 400 FVT episodes. This was anticipated to give a 95% confidence interval (CI) of  $\pm 5\%$  in estimating the difference between the ATP efficacy of ramp and that of burst; hypothesizing ramp efficacy to be 77% and burst efficacy to be 87%, we anticipated that the sample would be large enough to estimate the difference between ramp and burst efficacies as  $10\pm 5\%$ .

On enrollment, all patients were programmed in accordance with the randomly assigned ATP therapy. After several ineffective ATP attempts, study investigators were allowed to change the mandatory device programming therapy; thereafter, the patient was regarded as a crossover. Episodes that occurred before the programming changes were considered for statistical analysis.

To adjust ATP efficacy estimation so as to take into account multiple episodes per patient, the generalized estimating equation (GEE) method<sup>18,19</sup>; in particular, we verified that our clustered data were not balanced and had no logical ordering for observations within a cluster, therefore we used an exchangeable correlation matrix.

### Results

Two hundred six patients were randomized—103 to burst and 103 to ramp ATP therapy. Patient characteristics are reported in Table 2 for the overall group and for ramp and burst groups of patients. No baseline characteristics showed statistically significant differences between the 2 groups compared.

**Table 2. Patient Characteristics**

Characteristics	Overall Group (n=206)	Ramp Group (n=103)	Burst Group (n=103)
Age, years	67±11	66±11	67±11
Male gender	167 (81)	81 (79)	86 (84)
NYHA class	2.5±0.7	2.5±0.7	2.6±0.7
NYHA class I	15 (7)	9 (9)	6 (6)
NYHA class II	75 (36)	37 (36)	38 (37)
NYHA class III	110 (53)	55 (53)	55 (53)
NYHA class IV	6 (3)	2 (2)	4 (4)
QRS width, ms	119±38	120±36	119±39
Left bundle-branch block	80 (39)	44 (43)	36 (35)
LVEF, %	32±13	30±10	33±15
Ischemic disease	129 (63)	59 (57)	70 (68)
Heart failure	97 (47)	50 (49)	47 (46)
Hypertension	100 (49)	50 (49)	50 (49)
Diabetes	56 (27)	32 (31)	24 (23)
Sudden death secondary prevention	98 (48)	42 (41)	56 (54)
Atrial arrhythmias	53 (26)	24 (23)	29 (28)
Diuretics	167 (81)	85 (83)	82 (80)
Digitalis	20 (10)	8 (8)	12 (12)
Class III antiarrhythmic agents	100 (49)	48 (47)	52 (50)
ACE inhibitors	145 (70)	73 (71)	72 (70)
$\beta$ -blockers	146 (71)	72 (70)	74 (72)
Statins	122 (59)	57 (55)	65 (63)
Antiplatelet agents	113 (55)	49 (48)	64 (62)
Anticoagulant agents	54 (26)	29 (28)	25 (24)

Data are presented as mean±SD or n (%). NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.

Median (25th to 75th interquartile range) follow-up duration was 36 (25 to 44) months. One hundred ninety-six patients underwent at least 1 follow-up examination, of which a small percentage (3%) of patients underwent only 1 follow-up examination, whereas 50% of patients had a total of 8 follow-up examinations. During the study, 14 patients died and 8 were lost to follow-up.

### Spontaneous Ventricular Tachyarrhythmia Episodes

In 79 patients, the ICD detected 829 spontaneous ventricular tachyarrhythmia episodes with complete electrogram data. In 3 patients (1 ramp group and 2 burst group) episode data were not collected, owing to incomplete interrogation or cleared memory.

Two hundred twenty-three episodes in 36 (17.5%) patients were deemed to have been inappropriately detected. In 11 episodes, reliable classification was not possible; thus, 595 detected episodes were true ventricular arrhythmias; 111 (18.7%) were classified as VF, 216 (36.3%) as FVT, and 268 (45.0%) as VT. Consequently, 216 of 327 (66.1%) ventricular arrhythmias were detected as FVT via VF; on traditional ICD programming, these would have been detected as VF.

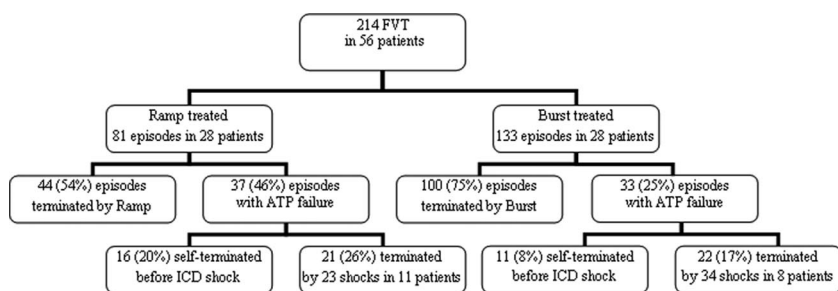


Figure 1. Reviewer classification of episodes detected by ICD as spontaneous FVT episodes and saved with complete electrograms.

**Primary End Point**

The dataset for primary end point analysis was composed of 214 FVT episodes because expert electrophysiologists, who reviewed arrhythmia data stored in device memory, stated that 2 FVT episodes were terminated before the release of the ATP therapy. As shown in Figure 1, FVT episodes were treated in 56 patients: 81 episodes in 28 ramp patients and 133 episodes in 28 burst patients. Burst terminated 100 of 133 (75.2% unadjusted, 72.7% GEE-adjusted; 95% CI, 59.2% to 85.1%) FVT episodes, whereas ramp terminated 44 of 81 (54.3% unadjusted, 52.1% GEE-adjusted; 95% CI, 36.7% to 67.5%) FVT episodes ( $P=0.015$ ). The difference in ATP efficacy between the 2 arms was 20.9%, with a 95% confidence interval between 7.9% and 35.8%.

Of 56 patients with treated FVT episodes, 44 (79%) had at least 1 effective ATP intervention and 34 (61%) were spared ICD shocks. Of 214 FVT episodes, 171 (80%) were spared ICD shocks, thanks to ATP-induced or self-termination.

Overall, 44 of 206 (21.4%) patients received shocks, 30 of 206 (14.6%) received appropriate shocks, and 22 of 206 (10.7%) received inappropriate shocks.

Class III antiarrhythmic agents were administered to almost half of the study population. ATP efficacy in terminating FVT episodes did not differ significantly between patients taking these agents and those not taking them (42/69 [61%] versus 102/145 [70%];  $P=NS$ ). The difference between burst and ramp efficacy was independent of whether patients were treated with antiarrhythmic drugs. Indeed, in patients not taking Class III antiarrhythmic drugs, burst terminated 70 of 89 (79%) FVT episodes, whereas ramp terminated 32 of 56

(57%;  $P=0.005$ ); in patients on Class III antiarrhythmic drugs burst terminated 30 of 44 (68%) FVT episodes, whereas ramp terminated 12 of 25 (48%;  $P=0.09$ ).

ATP efficacy did not significantly vary as a function of ICD indication; the unadjusted efficacy values were 62% in primary and 65% in secondary prevention patients.

Figure 2 shows the distribution of VF, FVT, and VT episodes as a function of arrhythmia cycle length.

The efficacy of ATP in dealing with FVT episodes did not change significantly as a function of VT cycle length. Because the median value of VT cycle length (VTCL) for FVT episodes was 290 ms, we estimated ATP efficacy for episodes with  $VTCL \leq 290$  ms and  $VTCL \geq 300$  ms, respectively. Burst ATP efficacy was 48 of 69 (70%) for  $VTCL \leq 290$  ms and 52 of 64 (81%) for  $VTCL \geq 300$  ms. Ramp ATP efficacy was 16 of 35 (46%) for  $VTCL \leq 290$  ms and 28 of 46 (61%) for  $VTCL \geq 300$  ms.

The occurrence of FVT episodes was slightly unbalanced between the 2 groups: 133 episodes in the burst group and 81 episodes in the ramp group. In the burst group, 10 patients had only 1 episode, 10 patients had between 2 and 5 episodes, 5 patients had between 6 and 10 episodes, and 3 patients had >10 episodes (ie, 14, 15, and 22). In the ramp group, 11 patients had only 1 episode, 14 patients had between 2 and 5 episodes, 1 patient had 8 episodes, 1 patient had 11 episodes, and 1 patient had 13 episodes. The median (25th to 75th quartile range) number of FVT episodes was 2 (1 to 7) in the burst group and 2 (1 to 3) in the ramp group. The mean number of FVT episodes per patient was 4.8 and 2.9 in the burst and ramp groups, respectively. This difference was not statistically significant, nor did it affect primary end point analysis,

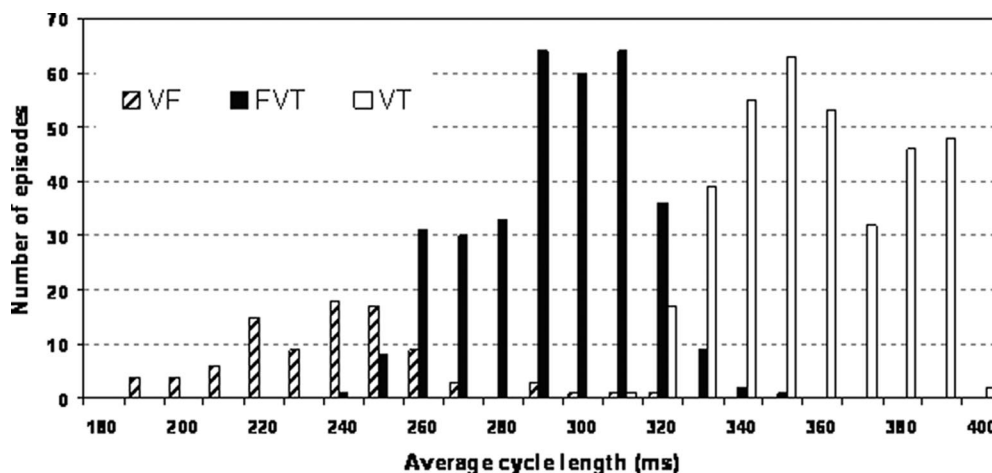


Figure 2. Distribution of VF, FVT, and VT episodes as a function of arrhythmia cycle length.

which was corrected by means of the GEE method<sup>18,19</sup> to take into account multiple episodes per patient.

### Safety End Points

The relative safety of the 2 ATP strategies was assessed by comparing FVT episode duration, incidence of acceleration, incidence of syncope, first shock efficacy, and death between the treatment arms.

The median duration of treated FVT episodes was 6 seconds in the burst arm (25th to 75th quartile interval: 6 to 12 seconds) and 9 seconds in the ramp arm (25th to 75th quartile interval: 7 to 16 seconds).

Acceleration occurred in 9 of 214 (4.2%) treated FVT episodes in 6 of 55 (10.9%) patients. Specifically, in 3 burst group patients, acceleration occurred in 3 FVT episodes (2.3% of all FVT episodes treated by burst); 2 of these episodes required shocks, whereas 1 self-terminated. In 3 ramp group patients, acceleration occurred in 6 FVT episodes (7.4% of all FVT episodes treated by ramp;  $P=0.085$  versus burst); 4 episodes required shocks, whereas 2 self-terminated. Episode acceleration in 1 ramp patient prompted crossover to the burst group, whereas 1 burst group patient crossed over to the ramp group owing to ineffective ATP.

Five patients experienced 1 syncope each: 3 in the burst arm and 2 in the ramp arm. In 1 patient, the syncopal episode was nonarrhythmic; in 2 patients, syncopes were associated to sustained VT episodes with cycle lengths of 330 and 390 ms, respectively; 2 patients, one in each arm of the study, experienced syncopes associated to ineffective ATP treatment for FVT. The incidence of FVT-related syncope was therefore 2 of 206 (0.97%).

Ten patients experienced electrical storms. Electrical storms were composed of VF episodes in 1 patient, VT episodes in 3 patients, and FVT episodes in 6 patients; of these 6, 3 were in the ramp group and 3 in the burst group.

Fourteen patients died during the study: 6 in the burst arm and 8 in the ramp arm. Most deaths occurred at home; in these cases, it was not possible to classify the deaths reliably.

### Quality of Life

The EuroQoL questionnaire was completed by all patients at the baseline and during all follow-up examinations. Mean scores were  $52 \pm 14$  at the baseline in both the burst and ramp groups and  $64 \pm 15$  and  $64 \pm 16$  for the burst and ramp groups, respectively, on 12th month follow-up examination. This increase between baseline and follow-up examinations was statistically significant ( $P < 0.01$ ) and was maintained at the 24th month follow-up examination. In patients who experienced ICD shocks, the EuroQoL score was  $50 \pm 16$  at the baseline and  $53 \pm 20$  at the first follow-up examination after ICD firing. This mean was significantly lower ( $P < 0.03$ ) than the mean of  $64 \pm 14$  calculated at the first follow-up examination of patients who received no shocks.

### Hospitalizations

During the observation period, 20 patients underwent hospitalization for the following causes: heart failure in 9 patients, lead-related issues in 4 patients, syncope in 3 patients, AF in

2 patients, respiratory problems in 1 patient, and kidney dysfunction in 1 patient.

### Episode Classification and ICD Indication

Episode classification as a function of ICD indication (primary versus secondary) showed some differences. In primary prevention patients, devices classified 91 (26.8%) episodes as VF, 92 (27.1%) as FVT, and 157 (46.2%) as VT. In secondary prevention patients, devices classified 20 (7.8%) episodes as VF, 124 (48.6%) as FVT, and 111 (43.5%) as VT.

### Discussion

Several ICD studies<sup>10–15</sup> have consistently demonstrated that ATP therapies can terminate  $\approx 75\%$  to 90% of VT with CL  $< 320$  ms and carry a low risk of acceleration or syncope. Efforts to avoid painful high-energy shocks and keep up the patient's quality of life require optimization of the VT/VF detection window, the number of intervals to be detected, and the ATP scheme. In particular, our study addressed the relevant clinical question of whether burst is better than ramp ATP in terminating FVT episodes.

### Main Study Results

The 3 main findings of the present study are that (1) burst (8 pulses at 88% coupling interval) was significantly more effective (72.7% versus 52.1% GEE-corrected efficacy) than ramp (8 pulses at 91% coupling interval) in terminating spontaneous FVT episodes, (2) the strategy of FVT detection and ATP enabled 81% of FVT episodes to be terminated before shock intervention, and (3) quality of life was significantly impaired by ICD shocks.

### Comparison of Ramp and Burst ATP Therapy Efficacy

Only 3 studies have compared the effect of burst and ramp on spontaneous fast VT, and those were nonrandomized. In the study by Gillis et al,<sup>11</sup> ATP efficacy proved to be 86% for burst and 38% for ramp ( $P < 0.05$ ). In the study by Schaumann et al,<sup>20</sup> ATP efficacy was 86% for burst and 77% for ramp ( $P < 0.05$ ). More recently, Peters et al<sup>21</sup> found that ramp was less effective and associated with more frequent accelerations.

For the first time within a randomized controlled trial design, our data show the superiority of burst in terminating episodes with VTCL  $\leq 320$  ms. With regard to ATP safety, burst was associated with fewer accelerations than ramp (2.3% versus 7.4% of cases), though this difference was not statistically significant ( $P = 0.085$ ). Ramp was more aggressive than burst, with the last ramp pulse delivered at a higher rate than the last burst pulse, the difference being 10 ms for VTCL of 240 ms and 60 ms for VTCL  $\geq 300$  ms. Further studies should be performed to explain the superiority of burst in terms of its interaction with ventricular refractoriness, excitable gap, and conduction time to the circuit.<sup>22–23</sup>

Finally, both burst and ramp ATP efficacies were lower than expected on the basis of the PainFREE studies.<sup>10,15</sup> In our view, this finding can be explained by the different characteristics of the populations enrolled. Indeed, we enrolled a higher number of nonischemic HF and primary prevention patients than previous ICD trials; the episodes

presented by such patients generally have shorter cycle lengths<sup>24</sup> and are therefore more likely to persist after ATP attempts.

### Optimizing Programming to Prevent ICD Shocks

The strategy adopted in our study, ie, FVT detection, ATP as first therapy, and prolonged number of intervals to detect (NID), enabled 81% of FVT episodes to be terminated before shock intervention. The efficacy of this strategy stems from several factors. The first is the percentage of arrhythmias detected as FVT, which would be construed as ventricular fibrillation by traditional ICD programming and therefore shocked. This percentage was 93% in the PainFREE Rx study,<sup>10</sup> which enrolled 220 ICD patients with coronary artery disease, 76% in the PainFREE Rx II trial,<sup>15</sup> which enrolled 634 ischemic and nonischemic ICD patients, and 66% in our study. Slight differences among these trials may be partially explained by the evolution of ICD indications toward primary prevention. Indeed, Wilkoff et al<sup>24</sup> found that, in primary prevention patients, episodes had shorter cycle lengths than in secondary prevention patients and were more likely to be classified as VF and thus receive shock therapy. A recent publication by Sweeney et al<sup>25</sup> also reported differences between primary and secondary prevention patients in the incidence of VF episodes and of shocks delivered.

A second factor influencing shock prevention is episode termination by ATP. Burst ATP efficacy was 85% in the PainFREE Rx trial,<sup>10</sup> 81% in the PainFREE Rx II trial,<sup>15</sup> and 75% in our study. A third factor contributing to shock prevention is the use of a long NID. In our study, we programmed an 18/24 NID, which was longer than the NID (12/16) used in clinical practice in Italy. The delay resulting from the 18/24 NID, time to deliver ATP, and redetection time resulted in self-termination and consequent shock prevention in 30 of 70 (43%) FVT episodes that were ineffectually treated with ATP. In the PainFREE Rx II<sup>15</sup> trial, 33% of FVT episodes detected in the shock arm self-terminated during capacitor charging. The effect of longer detection times on the suppression of shocks for self-terminating rapid VTs has recently been shown in 2 controlled observational evaluations.<sup>26–27</sup>

The safety of the PainFREE strategy was measured by evaluating the incidence of syncope, the incidence of FVT episodes accelerated after ATP treatment, and the median duration of FVT episodes. FVT-associated syncope occurred in 2 of 220 (0.91%) patients in the PainFREE Rx study,<sup>10</sup> in 2 of 313 (0.64%) in the PainFREE II trial,<sup>15</sup> and in 2 of 206 (0.97%) in our study, despite the much longer follow-up of this last. The incidence of FVT acceleration (4.3% of treated episodes) in our study also compares favorably with those of previous studies.<sup>10,11,15</sup> Burst ATP caused fewer accelerations than ramp (2.3% versus 7.4%;  $P=0.089$ ). The median duration of FVT episodes—including failed therapies and spontaneously terminating episodes—was 10 seconds in the PainFREE Rx II, both in the ATP and in the shock arm, whereas in the PITAGORA ICD study it was 6 and 9 seconds in the Burst and ramp arms, respectively.

### Quality of Life and Hospitalizations

Quality-of-life scores of the overall population showed a significant increase as a function of time after ICD implantation. In the subgroup of patients with ICD shocks, however, scores were significantly depressed when evaluated at the first examination after ICD firings. These data resemble the CIDS trial results,<sup>28</sup> which showed that emotional and physical health scores improved significantly as a function of time in the overall ICD group but did not improve in the subgroup of ICD patients who received  $\geq 5$  shocks from their device. Other studies<sup>29–30</sup> have also shown that quality of life is significantly affected by the occurrence of shocks, owing to the pain caused and anxiety over the next shock.

Shock therapy has a considerable impact on the use of hospital resources. Indeed, a recent trial<sup>31</sup> revealed that the principle cause (26%) of hospitalization among ICD patients in a 12-month observation period was shock delivery after appropriate detection of VT/VF. In our study, the fact that no hospitalizations were attributable to ICD shocks may be interpreted as indirect confirmation of the ability of ATP therapy to significantly reduce the incidence of shocks.<sup>15</sup>

### Study Conclusions and Clinical Implications

The widespread adoption of ATP treatment as the first therapy for FVT episodes, as proposed by the PainFREE trials,<sup>10,15</sup> has raised relevant clinical questions regarding the best programming of ATP therapies. PITAGORA ICD, a trial with a prospective, parallel, randomized design, shows that burst (8 pulses at 88% coupling interval) is more effective than ramp (8 pulses at 91% coupling interval) in terminating FVT in candidates for ICD implantation for the primary or secondary prevention of sudden death. The study also confirms the safety of ATP therapy for FVT episodes in that it documented a low incidence of syncope and rhythm acceleration after ATP treatment. Finally, the study adds new data on the impairment of quality of life caused by ICD shocks.

### Study Limitations

Despite the 36-month follow-up period, the number of appropriately detected FVT episodes was less than expected. On average, we collected 3.9 FVT episodes per patient (216 in 56 patients), which is lower than the 4.4 FVT episodes per patient (431 in 98 patients) recorded over a mean 11-month follow-up in the PainFREE II trial.<sup>15</sup> This lower incidence was probably attributable to the evolution of ICD indications; indeed, most primary prevention patients in PainFREE II<sup>15</sup> had MADIT<sup>4</sup> or MUSTT<sup>5</sup> indication, whereas most of ours had MADIT II<sup>6</sup> or SCD-HeFT<sup>8</sup> indication. Moreover, we enrolled a higher number of nonischemic patients (37%) than the PainFREE II<sup>15</sup> study (15%), and it is known that patients with nonischemic HF and primary prevention indication for an ICD generally present a lower incidence of ventricular tachyarrhythmias.<sup>5</sup> The low FVT incidence, however, did not prevent us from finding a significant difference in ATP efficacy between burst and ramp, because the relative difference between therapies was greater than that hypothesized for sample size evaluation.

FVT episodes were not balanced between the 2 study groups (133 in the burst arm and 81 in the ramp arm). We

believe this finding is attributable to the play of chance and that it does not undermine the results because, more importantly, the number of patients with FVT episodes was perfectly balanced (28 in each arm). Moreover, the GEE method<sup>18,19</sup> allowed us to correct our estimation of ATP efficacy by taking into account the fact that some patients, especially in the burst arm, had multiple episodes.

The study design, which was randomized and parallel, prevented us from evaluating which ATP therapy (ramp or burst) might be more effective in each single patient. We cannot therefore exclude the possibility that ramp may be more effective than burst in specific patients. Tailoring ATP therapies, to determine the most appropriate and effective ATP therapy for each patient, may result in a further reduction of high-energy shocks. This could improve patients' quality of life, increase device longevity, and reduce shock-induced hospitalizations.

Arrhythmia episode review was not blinded with regard to the ATP programmed.

## Appendix

### List of Active Study Sites and Investigators Involved in the PITAGORA ICD Study

Ospedale Civico E Benfratelli, Palermo, Sammartano-Giordano-Piraino-Andolina; Ospedale Civile S. Antonio Abate, Trapani, Puntarello; Ospedale Umberto I, Enna, Vasco-Battaglia-Privitera; Ospedale G. Rummo, Benevento; Scherillo-Capobianco-Polcino-Nocerino, Ospedale Perrino, Brindisi, Scianaro; Ospedale Villa Sofia, Palermo, Pensabene; Ospedale S. Sebastiano, Caserta, Mascia-Golino-Viscusi-Ricciardiello; Ospedale S. Elia, Caltanissetta, Giglia; Azienda Ospedaliera Muscatello, Augusta, Chiarandà-Muscio; Ospedale S. Giovanni Di Dio, Agrigento, Vaccaro-Catalano; Ospedale Garibaldi, Catania, Mangiameli-Doria; Ospedale S. Giuseppe Moscati, Avellino, De Fabrizio-Rotondi-Candelmo; Jazzolino Di Vibo Valenzia, Vibo Valenzia, Comito; Ospedale Monaldi, Napoli, Santangelo; Ospedale Vittorio Emanuele II, Catania, Virgilio-Tosto; Ospedale Civile, Piacenza, Capucci; Az. Osp. Pugliese E Ciaccio, Catanzaro, Cicone-Ceravolo-Attana; Clinica Mediterranea, Napoli, Nocerino; Ospedale S. Raffaele, Cefalù, Giannola; Ospedale Cannizzaro, Catania, Lisi-Liberti; Garibaldi Nesima, Catania, Gulizia-Francesco-Mangiameli; Ospedale Pardo, Messina, Busà-Patanè-Donato-Grassi; Ferrari, Castrovillari, Bisignani-Sanpasquale; Civile, Milazzo, Vasquez-Badessa-Pizzimenti; Asl 10, Polistena, Polimeni; Ospedale Civile, Ragusa, Spadola-Piccione.

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## Disclosures

Drs Corrao, Santi, and Grammatico are employees of Medtronic Inc.

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### CLINICAL PERSPECTIVE

Randomized trials have established that the prophylactic use of implantable cardioverter-defibrillators (ICDs) prolongs survival in patients with left ventricular dysfunction that is attributable to myocardial infarction or other causes. Unfortunately, the mortality benefit is obtained by ICD shocks, which may also cause pain and worsen quality of life. For this reason, several trials have been designed to test the best ICD programming to avoid unnecessary shocks and improve patient quality of life. The PITAGORA ICD trial is the first prospective, single-blind, randomized study to show that burst antitachycardia pacing (ATP) strategy (8 pulses at 88% coupling interval) is significantly more effective than ramp ATP (8 pulses at 91% coupling interval) for fast ventricular tachycardia (FVT) termination. The PITAGORA trial also showed that FVT detection and ATP delivery allowed 81% of FVT episodes to terminate before shock intervention. Quality of life was measured as a function of time, ATP programming, and shock occurrence and significantly and negatively correlated with ICD shocks, confirming the importance to improve ICD programming. After the programming indications defined by the PainFREE trials, the PITAGORA ICD results represent a confirmation and a guide for physicians when programming FVT detection, as separate from ventricular fibrillation detection, and ATP burst as first ICD therapy on FVT episodes to avoid, as much as possible, painful therapies for the patients, ameliorating quality of life, and improving devices and battery performances.



## A Randomized Study to Compare Ramp Versus Burst Antitachycardia Pacing Therapies to Treat Fast Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter Defibrillators: The PITAGORA ICD Trial

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on behalf of PITAGORA ICD Study Investigators

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