Near Elimination of Ventricular Pacing in SafeR Mode Compared to DDD Modes: A Randomized Study of 422 Patients

JEAN-MARC DAVY, M.D., PH.D.,* ELLEN HOFFMANN, M.D.,† AXEL FREY, M.D.,‡ KURT JOCHAM, M.D.,§ STEFANO ROSSI, M.D.,¶ JEAN-MARC DUPUIS, M.D.,** LORENZO FRABETTI, M.D.,†† PASCALE DUCLOUX, M.SC.,‡‡ EMMANUEL PRADES, M.SC.,‡‡ and GAËL JAUVERT, M.D.¶¶

From the *CHU de Montpellier, Montpellier, France; †Städtisches Klinikum Bogenhausen, Munich, Germany; ‡Kardiologische Praxis Prof. Frey, Starnberg, Germany; §Klinikum Memmingen, Memmingen, Germany; ¶Ospedale Generale Provinciale, Saronno (VA), Italy; **CHU d'Angers, Angers, France; ††Policlinico S. Orsola – Malpighi, Bologna, Italy; ‡‡SORIN CRM SAS, Clamart, France; and ¶¶Clinique Bizet, InParys, Paris, France

Aims: *SafeR performance versus DDD/automatic mode conversion (DDD/AMC) and DDD with a 250-ms atrioventricular (AV) delay (DDD/LD) modes was assessed toward ventricular pacing (Vp) reduction.*

Methods: *After a 1-month run-in phase, recipients of dual-chamber pacemakers without persistent AV block and persistent atrial fibrillation (AF) were randomly assigned to SafeR, DDD/AMC, or DDD/LD in a 1:1:1 design. The main endpoint was the percentage of Vp (%Vp) at 2 months and 1 year after randomization, ascertained from device memories. Secondary endpoints include %Vp at 1 year according to pacing indication and 1-year AF incidence based on automatic mode switch device stored episodes.*

Results: *Among 422 randomized patients (73.2 ± 10.6 years, 50% men, sinus node dysfunction 47.4%, paroxysmal AV block 30.3%, bradycardia-tachycardia syndrome 21.8%), 141 were assigned to SafeR versus 146 to DDD/AMC and 135 to DDD/LD modes. Mean %Vp at 2 months was 3.4 ± 12.6% in SafeR versus 33.6 ± 34.7% and 14.0 ± 26.0% in DDD/AMC and DDD/LD modes, respectively ($P < 0.0001$ for both). At 1 year, mean %Vp in SafeR was 4.5 ± 15.3% versus 37.9 ± 34.4% and 16.7 ± 28.0% in DDD/AMC and DDD/LD modes, respectively ($P < 0.0001$ for both). The proportion of patients in whom Vp was completely eliminated was significantly higher in SafeR (69%) versus DDD/AMC (15%) and DDD/LD (45%) modes ($P < 0.0001$ for both), regardless of pacing indication. The absolute risk of developing permanent AF or of remaining in AF for >30% of the time was 5.4% lower in SafeR than in the DDD pacing group (ns).*

Conclusions: *In this selected patient population, SafeR markedly suppressed unnecessary Vp compared with DDD modes. (PACE 2012;1–11)*

ventricular pacing, DDD mode, automatic mode switch, AV delay, AV block, sinus node dysfunction

Introduction

Rarely used because of safety concerns, AAI is the most appropriate pacing mode for a majority of patients suffering from sinus node dysfunction (SND).[1–3] It would also be optimal if combined with a safely ventricular pacing backup in patients presenting with infrequent ventricular pauses due to paroxysmal atrioventricular (AV) conduction disorders. The main advantages of AAI pacing are (1) the preservation of hemodynamic function by enabling spontaneous ventricular activation and (2) sparing of the pulse generator battery. Recent observational and controlled studies in patients with SND have also suggested that ventricular dyssynchrony imposed by right ventricular apical pacing increases the risk of atrial fibrillation (AF), despite the preservation of AV synchrony.[4–9] Related observations were made in the PIPAF (Pacing In Prevention of Atrial Fibrillation) study where, after controlling for the percentage of ventricular pacing (Vp), AF prevention algorithms appeared to alleviate the AF burden only when spontaneous conduction was preserved.[10] The usual practice, nevertheless, consists of (1) implanting a dual chamber pacing system to eliminate the risk of ventricular standstill due to AV block and (2) programming a long AV delay, although the latter

Disclosures: Pr Jean-Marc Davy, Dr. Ellen Hoffmann, Dr. Axel Frey, Dr. Kurt Jocham, Dr. Jacques Victor, and Dr. Gaël Jauvert have received research grants from Sorin CRM SAS. Pascale Ducloux and Emmanuel Prades are Sorin CRM SAS employees.

Address for reprints: Jean-Marc Davy, M.D., Clinique du Coeur et des Vaisseaux – CHU de Montpellier – Hôpital Arnaud de Villeneuve, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier, France. Fax: 33-4-67-33-61-96; e-mail: jm-davy@chu-montpellier.fr

Received March 11, 2011; revised September 30, 2011; accepted November 16, 2011.

doi: 10.1111/j.1540-8159.2011.03314.x

is mostly ineffective and associated with a high rate of pacemaker-mediated tachycardia.[11,12]

Therefore, various pacing modes were developed in recent years to favor spontaneous AV conduction. The SafeR™ pacing mode (SORIN Group CRM SAS, Clamart, France), designed to combine the advantages of AAI with the safety of DDD mode, has been described in detail elsewhere.[13,14] The first recently published clinical application of SafeR in selected pacemaker recipients showed that it was associated with a marked decrease in the percentage of ventricular paced events.

Based on AV delay hysteresis, DDD(R)/automatic mode conversion (DDD/AMC) optimizes the AV delay applied during switch to DDD(R) according to the ambient spontaneous AV conduction times. Its function and clinical applications, also intended to limit the percentage of ventricular paced events, have been detailed previously.[15] The randomized European Spontaneous AtrioVEntricular conduction pReservation (SAVE-R) study was designed to confirm that, in comparison with DDD pacing, SafeR lowers significantly the percentage of ventricular pacing in patients with spontaneous AV conduction (main endpoint) and could decrease the long-term incidence of atrial arrhythmias.

Patient Population and Methods

The protocol of SAVE-R was reviewed and approved by the national and, when requested, the institutional Ethics Committees of the enrolling medical centers (Appendix). All patients granted their written informed consent to participate in the trial. The study enrolled 630 patients who had recently undergone the implantation of Symphony® model DR2550 or D2450 pulse generators (SORIN CRM SAS), and satisfied the following criteria: (1) SND, bradycardia-tachycardia syndrome (BTS), or paroxysmal AV block as a pacing indication; and (2) a spontaneous PR interval <250 ms. All right atrial leads were bipolar.

The SafeR Mode

The SafeR mode behaves like an AAI mode in the absence of AV block.[13,14] First- and second-degree AV blocks are tolerated up to a predetermined, programmable limit, and conversion to DDD takes place automatically in response to the following: (i) six consecutive abnormal AR/PR intervals; (ii) three blocked atrial events in the last 12 cycles; (iii) two consecutive blocked atrial events; and (iv) a ventricular pause of programmable duration (between 2 and 4 seconds). While functioning in DDD(R) after an episode of persistent AV block, the device systematically launches a conversion attempt to return to AAI(R) every 24 hours: the device may switch back to AAI provided that AV conduction is restored.

Study Design

After a 1-month run-in phase, the eligible patients were randomly assigned in a 1:1:1 design to one of three study groups and followed for up to 1 year.

Run-In Phase (Phase I)

Before assignment to one of the three study groups, all patients were paced in SafeR mode (with bipolar atrial sensing mandatory) to confirm the proper functioning of the pacing system and the presence of predominant spontaneous AV conduction.

Random Assignment

Following the 1-month run-in phase (phase I), eligible patients were randomly assigned in a single-blind fashion to (a) pacing in SafeR (with a 3-second pause), (b) DDD/AMC, or (c) DDD mode with a 250-ms AV delay after atrial sensing (DDD/LD), or 300-ms AV delay after atrial pacing. The recommended programming included a backup pacing rate at 60 pulses per minute (ppm), rest AV delay at 170 ms and exercise AV delay at 80 ms in SafeR mode, hysteresis at 0%, automatic Fallback Mode Switch (AMS) ON, smoothing OFF, and atrial sensing threshold at 0.6 mV, if possible.

Follow-Up (Phases II and III)

The patients underwent an interim evaluation and interrogation of the pacemaker 2 months after random assignment (phase II), and a final evaluation at 1 year (phase III).

Randomization Criteria

To be eligible for random assignment, the patients had to fulfill the following criteria during the run-in phase: (a) absence of persistent first, second, or third degree AV block, confirmed by the absence of switch to permanent DDD pacing, <5% ventricular pacing and PR < 250 ms or AR < 300 ms; (b) <30% of time spent in AF, manifest as <30% of time spent in AMS, and no need for cardioversion of AF; (c) absence of ventriculoatrial cross-talk and proper atrial sensing at 0.6 mV sensing threshold; and (d) presence of sinus rhythm at the time of randomization. Patients who did not meet all randomization criteria were assigned to the nonrandomized group and followed as described earlier.

Study Outcome Measures

Percent atrial and ventricular pacing was ascertained from device memories at each follow-up. AF episodes were defined as device-stored AMS episodes. All pacemaker devices used in this study have a high specificity and sensitivity for AF measurement. Devices were programmed with atrial sensitivity as low as possible so as to avoid AF under sensing, and connected to an atrial bipolar lead to increase atrial sensing.

Study Objectives

Primary

The main objective of the study was to compare the percent ventricular pacing among the SafeR, DDD/AMC, and DDD/LD modes. The performance and stability of SafeR were evaluated by comparing the mean percent ventricular pacing during sinus rhythm with that measured in the two other groups at (a) the end of phase II and (b) the end of phase III versus phase II.

Secondary

The prespecified secondary objectives of the study were to compare (1) the percent ventricular pacing at the end of phase I versus phase II in patients paced in SafeR mode; (2) the performance of the SafeR mode versus both DDD/AMC and DDD/LD modes (DDD modes) according to the indications for permanent pacing at the end of phase III; and (3) the effects of each pacing mode on the incidence of AF at the end of phase III expressed as (a) the cumulative amount of time in AMS, (b) the overall number of AMS episodes, (c) the number of patients in each study group who remained in AMS for $\geq$30% of the time, (d) the percentage of patients who developed persistent or permanent AF during the study,[16] (e) the percentage of patients who developed AF during the study, and (f) the percentage of patients who were free from atrial arrhythmias at the end of phase III.

Safety Analysis

The incidence of adverse events, and device-related complications observed during the study, were recorded. Major adverse events (MAE) included cardiac and noncardiac deaths, hospitalizations for management of cardiovascular disease, and cardioversion of AF or atrial flutter.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. Multiple comparisons were performed between the three randomized groups. Data were expressed as means $\pm$ standard deviation (SD), or numbers (%) of observations. When normal distribution is not violated, analysis of variance test was used for comparisons of continuous variables. Otherwise the Wilcoxon rank-sum was performed. Fisher's exact test was used for comparisons of categorical data. A P value <0.05 was considered statistically significant.

Results

Study Population

During the recruitment period, 630 patients underwent implantation of dual chamber pacemakers, of whom 141 were randomly assigned to SafeR, 146 to DDD/AMC, and 135 to DDD/LD. Among the 208 patients who did not undergo randomization, 41 were lost to follow-up before randomization and 24 presented with incomplete device memory; 101 did not satisfy the randomization criteria prospectively specified by the protocol, which included PR interval >250 ms in 34 patients, definitive switch to DDD in 66 patients, nonsinus rhythm in 15 patients, and cardioversion in two patients; finally, noncompliance to randomization criteria occurred in 42 patients: 42 patients presented %Vp > 5% and no patients underwent AMS episode for more than 30% of the run-in period. The pacing indications in the 422 patients eligible for random assignment were paroxysmal AV block in 128 (30.3%), BTS in 92 (21.8%), SND in 200 (47.4%), and undetermined in two (0.5%) patients. The baseline characteristics of these 422 patients and of the study groups are summarized in Table I.

Phase II (2-Month Follow-Up)

Percent Ventricular Pacing in SafeR versus DDD/AMC versus DDD/LD

Complete data sets were available at 2 months following randomization in 388 patients, including 134 (34.5%) assigned to SafeR, 132 (34.0%) assigned to DDD/AMC, and 122 (31.4%) assigned to DDD/LD. Mean percent ventricular pacing was 3.4 $\pm$ 12.6% in SafeR, 33.6 $\pm$ 34.7% in DDD/AMC, and 14.0 $\pm$ 26.0% in DDD/LD mode (Table IIA). Ventricular pacing was eliminated in 79% of patients assigned to SafeR, 23% assigned to DDD/AMC ($P < 0.0001$ vs SafeR), and 48% of patients assigned to DDD/LD mode ($P < 0.0001$ vs SafeR). Only 3% of patients assigned to SafeR presented %Vp > 40%, as compared to 39.5% in DDD/AMC ($P < 0.0001$) and 13% in DDD/LD ($P = 0.0125$) (Fig. 1A).

Table I

Baseline Characteristics of the Randomized Population and of the Study Groups

	All Randomized Patients (n = 422)	Random Assignment			P
		SafeR (n = 141)	DDD/AMC* (n = 146)	DDD/LD** (n = 135)	
Age, years	73.2 ± 10.6	73.3 ± 11	73 ± 10.7	73.2 ± 10.1	ns
Men, n (%)	207 (50)	72 (52)	69 (48)	66 (50)	ns
Pacing indications, n (%)					
Atrioventricular block	128 (30.3)	39 (27.7)	47 (32.2)	42 (31.6)	
Bradycardia-tachycardia syndrome	92 (21.8)	32 (22.7)	31 (21.2)	29 (21.8)	ns
Sinus node dysfunction	200 (47.4)	70 (49.7)	68 (46.6)	62 (46.7)	
Undetermined	2 (0.5)	0	0	2	
Other rhythm and conduction disorders, n (%)					
None	232 (55.0)	76 (53.9)	78 (53.4)	78 (57.8)	
Premature atrial complexes	13 (3.1)	5 (3.6)	4 (2.8)	4 (3.1)	ns
Premature ventricular complexes	8 (1.9)	4 (2.9)	2 (1.4)	2 (1.5)	
Atrial tachyarrhythmias	164 (38.8)	59 (41.8)	57 (39)	48 (35.6)	
Ventricular tachyarrhythmias	9 (2.1)	2 (1.4)	6 (4.1)	1 (0.7)	
Underlying heart disease, n (%)					
Coronary artery disease	83 (19.7)	24 (17)	33 (22.6)	26 (19.3)	
Valvular heart disease	30 (7.1)	7 (5)	12 (8.2)	11 (8.2)	ns
Cardiomyopathy	67 (15.9)	27 (19.1)	21 (14.4)	19 (14.1)	
Other	22 (5.2)	7 (5)	7 (4.8)	8 (5.9)	
Concomitant disorders, n (%)					
Hypertension	201 (47.6)	58 (41.1)	80 (54.8)	63 (46.7)	
Diabetes	60 (14.2)	15 (10.6)	25 (17.1)	20 (14.8)	ns
Congestive heart failure	12 (2.8)	5 (3.6)	4 (2.7)	3 (2.2)	
Device programming					
Back up rate (ppm)	60 ± 3	60 ± 3	60 ± 2	59.9 ± 4	
Maximum tracking rate (ppm)	131 ± 15	130 ± 14	132 ± 15	132 ± 15	
AV delay (ms)					
• At rest	170 ± 19	166 ± 16	170.5 ± 14	174 ± 26	
• During exercise	84 ± 25	80 ± 10	82 ± 12	90 ± 41	ns
• Extension	65 ± 7	64 ± 6	65 ± 7	65 ± 6	
Rate response, n (%)					
• NO or LEARN	290	92	103	95	
• DDD-VVIR or AUTO or FIXED	128	49	41	38	
• Undetermined	4	0	2	2	

Values are means ± SD, or numbers (%) of observations in corresponding group.
*DDD/AMC: DDD with automatic mode conversion.
**DDD/LD: DDD with long AV delay.

Phase III (1-Year Follow-Up)

Percent Ventricular Pacing in SafeR versus DDD/AMC versus DDD/LD

Complete data sets were available at 1 year of follow-up in 342 patients, including 113 (33.0%) assigned to SafeR, 115 (33.6%) assigned to DDD/AMC, and 114 patients (33.3%) assigned to DDD/LD. Mean percent ventricular pacing was 4.5 ± 15.3% in SafeR, versus 37.9 ± 34.4% in DDD/AMC, versus 16.7 ± 28.0% in DDD/LD mode (Table IIB). Ventricular pacing was eliminated in 69% of patients assigned to SafeR, 15% assigned to DDD/AMC ($P < 0.0001$ vs SafeR), and 45% of patients assigned to DDD/LD mode ($P < 0.0001$ vs SafeR) (Fig. 1B).

Percent Ventricular Pacing in SafeR between Phases III and II

Significant differences in percent ventricular pacing between the 2-month and the 1-year follow-ups were observed in neither group (Table IIB).

Table II.

Percent Ventricular and Atrial Pacing in Each Study Group at the End of Phases II and III and Percent Ventricular Pacing According to Pacing Indications

	SafeR	DDD/AMC*	DDD/LD**	P SafeR vs DDD/AMC*	P SafeR vs DDD/LD**
A. Phase II (2 months)	**(n = 134)**	**(n = 132)**	**(n = 122)**		
Percent ventricular pacing	3.4 ± 12.6	33.6 ± 34.7	14.0 ± 26.0	<0.0001	<0.0001
Percent atrial pacing	35.7 ± 29.5	40.8 ± 31.8	35.0 ± 28.3	ns	ns
B. Phase III (1 year)	**(n = 113)**	**(n = 115)**	**(n = 114)**		
Percent ventricular pacing	4.5 ± 15.3	37.9 ± 34.4	16.7 ± 28.0	<0.0001	<0.0001
Percent atrial pacing	33.8 ± 26.2	35.7 ± 28.0	36.9 ± 30.3	ns	ns
C. Percent Vp versus pacing indications (1 year)					
Atrioventricular block (n = 109)	7.2 ± 18.2	47.8 ± 35.7	23.3 ± 33.7	<0.0001	0.02
Sinus node dysfunction (n = 163)	2.7 ± 10.4†	28.8 ± 31.4‡	13.1 ± 20.9	<0.0001	0.004
Bradycardia/tachycardia syndrome (n = 68)	4.9 ± 19.9	45.4 ± 34.8	12.9 ± 28.9	<0.0001	ns

Values are expressed as mean ± SD.
†P = 0.02 versus AV block; ‡P = 0.01 versus SND and P = 0.025 versus BTS; all other among groups differences are statistically nonsignificant.
*DDD/AMC: DDD with automatic mode conversion.
**DDD/LD: DDD with long AV delay.

Percent Atrial Pacing in SafeR versus DDD/AMC versus DDD/LD

Mean percent atrial pacing was 33.8 ± 26.2% in SafeR versus 35.7 ± 28.0% in DDD/AMC and 36.9 ± 30.3% in DDD/LD mode (ns) (Table IIB).

Phase I (Run-In Phase) versus Phase II (2-Month Follow-Up)

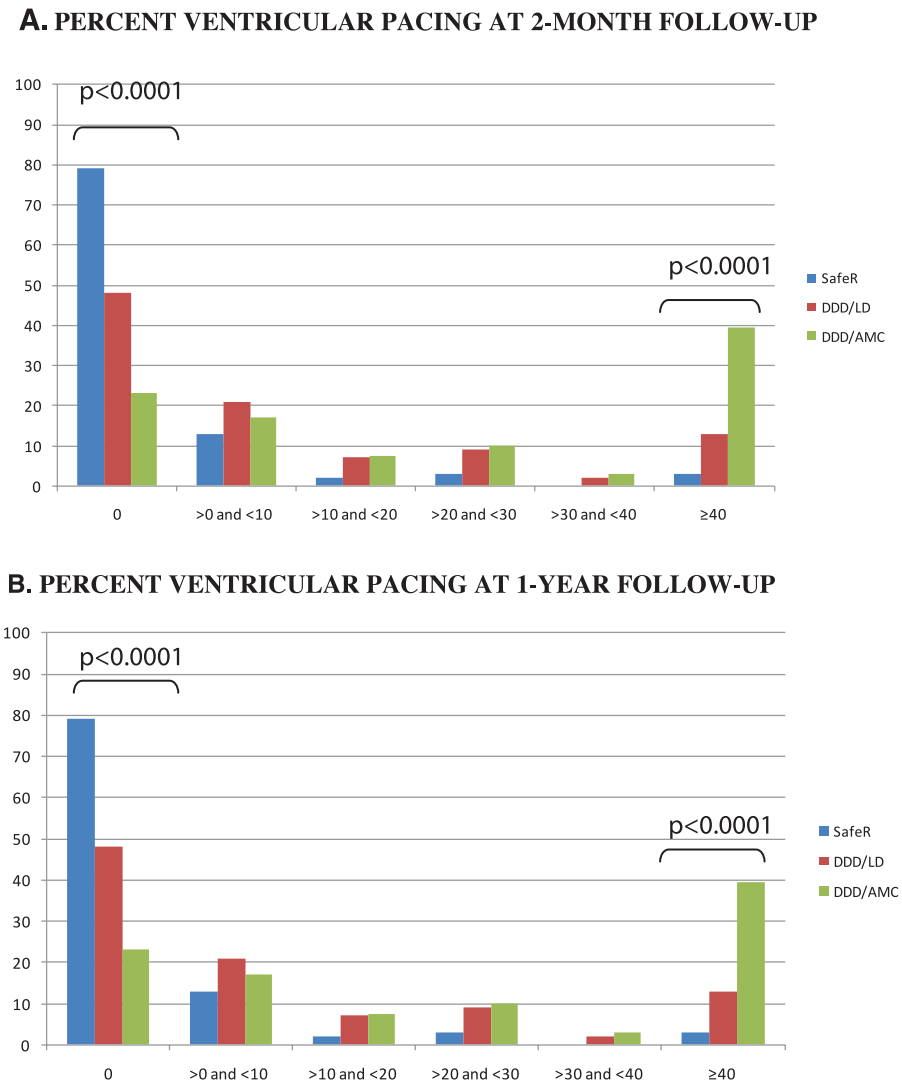
At the end of the run-in phase, complete data sets were available in 417 patients eligible for randomization. Percent ventricular pacing was 0% in 339 patients (81%), and >0% and <10% in the 78 remaining patients (9%). Mean percent ventricular pacing was 0.46 ± 1.0 (range 0–5), similar to that observed in SafeR mode at 2 months after randomization (3.4 ± 12.6%). SafeR completely eliminated ventricular pacing in 81% and 79% of 134 patients who completed the run-in phase and 2-month follow-up, respectively (ns).

Percent Ventricular Pacing at 1 Year of Follow-Up According to Pacing Indications

The pacing indications were known in all but 2 of the 342 patients whose data sets were available at 1 year. The mean (±SD) percent ventricular pacing with each pacing mode at 1 year in 109 patients presenting with AV block, 163 patients with SND, and 68 patients with BTS, is shown in Table IIC. The proportion of patients in whom ventricular pacing was completely eliminated was significantly higher in the group programmed in SafeR than in the groups programmed in DDD/AMC and DDD/LD modes, regardless of the pacing indication (Fig. 2).

Atrial Arrhythmias during Follow-Up

Complete reports of AMS episodes were available up to 1 year of follow-up in 110 patients assigned to SafeR, 107 to DDD/AMC, and 87 patients assigned to DDD/LD mode. The mean number of AMS was 10.5 ± 37.8 in SafeR, 14.7 ± 45.7 in DDD/AMC, and 17.9 ± 73.5 in DDD/LD mode (ns), and mean total duration of AMS was 6.2 ± 34.0 days in SafeR mode (ns vs other modes), 5.2 ± 33.0 days in DDD/AMC, and 3.2 ± 16.3 days in DDD/LD mode (P < 0.04 vs DDD/AMC). The proportions of patients who remained in AMS for ≥30% of the time were 15% in SafeR, 24% in DDD/AMC, and 12% in DDD/LD mode, while 7% in SafeR, 10% in DDD/AMC, and 7% of patients in DDD/LD mode developed permanent AF during follow-up. Furthermore, 54%, 50%, and 63% of patients in SafeR, DDD/AMC, and DDD/LD mode, respectively, remained free from AF episodes throughout the follow-up. These among-group differences were statistically nonsignificant.



Figures 1. *Percent ventricular pacing in patients assigned to SafeR compared with DDD/AMC and DDD/LD modes at 2 months (A) and 1 year (B) of follow-up.*

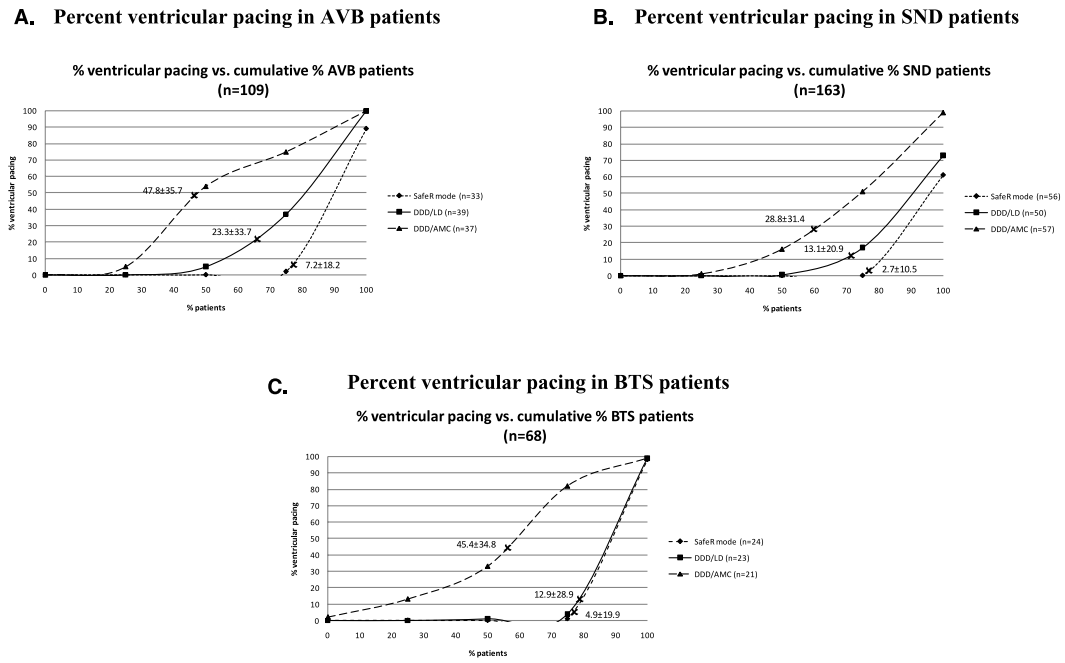
Adverse Clinical Events

Table III details the adverse clinical events observed throughout the study. During the 1-year follow-up, 34 patients (5.4%) suffered an MAE, including 11 patients in SafeR, 15 in DDD/AMC, four in DDD/LD mode (P = 0.56), and four patients in the nonrandomized group. Among a total of 19 deaths (four sudden), seven were due to cardiovascular and 12 to noncardiovascular causes, including malignancy in four and lung disease in three patients. The death rate was similar among the four study groups (P = 0.531). Pacemaker-mediated tachycardia developed in two patients during the run-in phase, which was eliminated by reprogramming of the SafeR mode settings. Finally, two patients in SafeR, five patients in DDD/AMC mode, and two nonrandomized patients suffered syncopal episodes unrelated to pacing (P = 0.076).

Discussion

Main Findings of the SAVE-R Trial

The safety of the SafeR pacing mode has been shown in previous studies,[13,14] as well as its efficacy in selected patients without high-degree AV block.[17] Furthermore, a retrospective analysis from a single center reported a 10 ± 23% ventricular pacing rate in a general population paced in SafeR mode;[18] In this study of patients with preserved AV conduction, SafeR significantly decreased the percentage of ventricular-paced events compared with DDD pacing modes, and



Figures 2. *Percent ventricular pacing in patients assigned to SafeR compared with both DDD/AMC and DDD/LD modes (DDD modes) at 1-year follow-up in AVB (A), SND (B), and BTS (C) patients.*

eliminated ventricular pacing in high proportions of patients paced for paroxysmal AV block, SND, or BTS.

Reducing Unnecessary Ventricular Pacing

AAI has long been considered the optimal pacing mode for patients suffering from SND or BTS.[19] Compared with VVI or DDD with a long AV delay, AAI pacing (1) significantly lowers mortality, healthcare costs, and the incidence of heart failure, stroke, and AF and (2) improves the quality of life.[19–21] However, the AAI mode has not been widely used because (1) it cannot be applied to patients at risk of paroxysmal complete AV block, a risk which, albeit low, is not predictable at the time of device implant[21–23] and (2) patients may suffer from a slow ventricular response during AF.

The new "ADI" modes to prevent ventricular pacing, such as SafeR, were designed to overcome these limitations, while enabling spontaneous AV conduction. In a randomized, crossover trial comparing managed ventricular pacing with DDD with fixed AV delay in unselected dual-chamber implantable cardiac defibrillator (ICD) recipients, mean ventricular pacing decreased from more than 70% during DDD with a long AV delay to less than 5% during managed ventricular pacing.[23] However, it should be noticed that ventricular pacing in DDD with fixed AV delay was overestimated due to the short programmed AV delays (120–180 ms). In another randomized, crossover study in unselected pacemaker recipients, ventricular pacing was decreased from a median of nearly 90% in DDD mode, to less than 2% in the managed ventricular pacing mode through a 1-month follow-up period.[24] A third randomized trial compared VVI versus DDD pacing with AV search hysteresis in a population of ICD recipients and showed a moderated reduction in mean ventricular pacing while extending AV delay extension to 100%.[25] In the present study, we demonstrated a significant reduction in mean ventricular pacing in SafeR (3.4 ± 12.6%) as compared to both DDD modes at 2 months follow-up. Such results may be compared to the mean ventricular pacing reported by Thibault et al.[26] in the CanSaveR study (9.5 ± 23.8%) in a general population of pacemaker patients without permanent AV block. In our study, this reduced ventricular pacing was even lower and sustained over a long-term follow-up of 1 year, regardless of pacing indication.

Detrimental Effect of Unnecessary Ventricular Pacing

Recent studies have reported that frequent right ventricular pacing may have long-term adverse effects including an increased risk in AF and congestive heart failure, confirming the

Table III

Adverse Clinical Events Observed between Study Enrollment and 1 Year of Follow-Up in Each Study Group

	All Patients (n = 630)	Nonrandomized (n = 208)	SafeR (n = 141)	DDD/AMC* (n = 146)	DDD/LD** (n = 135)	P***
Deaths	19	3	6	7	3	0.531
• Cardiac	7	3	0	3	1	0.276
• Noncardiac	12	0	6	4	2	0.383
Hospitalizations†	22 (19)	3	2	9 (6)	8	0.137
Cardioversions‡	1	1	0	0	0	/
All major adverse events	34	4	11	15	4	0.560
Pacemaker-mediated tachycardia	2	0	0	0	2	/
Lead dislodgement	17 (16)¶	3	2	4 (3)	8¶	0.092
• Atrial	13	2	0	3	6	0.026
• Ventricular	6	1	2	1	4	0.267
Oversensing	2 (1)	0	2 (1)	0	0	/
Loss of pacing capture	3	2	0	0	1	/
Pacing system explantation	5	1	2	0	2	/
Atrial arrhythmias	14 (12)	5 (4)	3	4 (3)	2	1
Ventricular arrhythmias	7	2	0	1	4	/
Syncope	10 (9)	3 (2)	2	5	0	0.076
Congestive heart failure	6	3	2	1	0	/
Miscellaneous	31 (27)	7 (6)	10 (9)	9 (8)	5	0.596

The values are expressed as number of events (number of patients when different).
*DDD/AMC: DDD with automatic mode conversion.
**DDD/LD: DDD with long AV delay mode.
***Among three study groups differences.
†Hospitalization for management of cardiovascular disorder.
‡Cardioversion of AF or flutter.
¶Dislodgment of both A and V leads is counted as a single event in two patients.

negative clinical effects of ventricular pacing that were suspected in the DAVID (Dual chamber And VVI Implantable Defibrillator) trial.[27] The randomized Search AV Extension and managed ventricular pacing for Promoting Atrioventricular Conduction (SAVE-PACe) trial showed that the prevention of unnecessary ventricular pacing was associated with a significant decrease in the development of persistent AF.[28] However, it should be noted that in this study, the conventional dual chamber arm presented an average of 99% ventricular pacing. The recent long-MinVPACE (Minimal Ventricular PACing) study showed that the different dual-chamber algorithms, designed to reduce ventricular pacing as SafeR, resulted in a significantly reduced AF burden in the minimized ventricular pacing arm after a 1.4 years follow-up.[29]

The SAVE-R trial could not confirm these results, as other studies which could not find any association, maybe due to a relatively low mean ventricular pacing percentage in the conventional dual-chamber arms (16.7 ± 28.0% in DDD with long AV delay mode and 37.9 ± 34.4% in DDD/AMC mode) and a too short follow-up period (1 year). The MinVPACE study[29] published in 2010 by Veasey et al. did not show any significant impact of minimized ventricular pacing toward AF on a short-term follow-up of 2 months, despite a big difference in ventricular pacing percentage (86% in the conventional dual chamber arm vs 2% in the minimized ventricular pacing arm). Likely this period was too short. The effect of ventricular pacing on the development of AF and heart failure may be delayed by 1–2 years,[8] which was recently confirmed by the recent long-MinVPACE study results which highlighted the fact that significant difference in AF burden only emerged after 9 months.[30] Trials are in progress to further evaluate the clinical benefits of SafeR on a longer follow-up (3 years). Finally, the recent Danpace study[31] revealed an unexpected detrimental impact of preserved AV conduction in sick sinus syndrome patients. In this study, patients with sick sinus syndrome presented a higher incidence of paroxysmal AF in AAIR versus DDDR pacing. The reason for this increased risk may be the prolonged average AV conduction

time observed in AAIR pacing. Our data may support this concept. However, it is noteworthy that the mean percent ventricular pacing in the group assigned to DDDR was only 65% in the Danpace study, perhaps explaining the relatively low incidence of AF observed with dual chamber pacing. A closer scrutiny of these results is awaiting their full-length, peer-reviewed presentation.

Study Limitations

The run-in phase in SafeR mode may bias the results on adverse clinical events in favor of the SafeR group as it may result in earlier occurrence in this group than that in the two other groups.

Only 422 patients randomized out of the 630 included patients, and this is a limitation that must be taken into account when interpreting the results. Owing the strong randomization criteria required, 16% of the patients (n = 101) who performed the run-in phase were not randomized, and 7% (n = 42) were randomized while noncompliant. Finally, 10% of the patients (n = 65) were either lost to follow-up (n = 41) or incorrectly programmed (n = 24) before randomization. Moreover, complete sets of data at 1 year were available in 342 out of 422 included patients (19% drop outs).

Study drop outs may have limited the power of the study to detect a significant effect of the pacing modes on AF burden.

The absence of Holter monitoring, and the total reliance on pacemaker diagnostics for ventricular pacing assessment and using mode switch episodes as a surrogate for AF, is a weakness of the study. The authors acknowledge that in this group of patients who were selected on the basis of preserved AV conduction, % ventricular pacing as recorded by the device may not be the same as ventricular depolarization due to pacing.

Finally, information on drugs is not available and represents a limitation of the study.

Conclusions

This randomized trial confirmed the superiority of SafeR in the prevention of ventricular pacing in patients without fixed high-degree AV block compared with DDD pacing. The beneficial effects of preventing ventricular pacing on the long-term incidence of AF and on cardiac function are being further examined in the ongoing Canadian randomized CAN-SAVE-R trial, in selected and unselected recipients of dual-chamber pacemakers.

Acknowledgments: The authors thank Rodolphe Ruffy, M.D., for reviewing the manuscript and Anne Rousseau-Plasse, Ph.D., for editorial assistance.

References

1. Leclercq C, Gras D, Le Helloco A, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995; 129:1133–1141.
2. Rosenqvist M, Isaaz K, Botvinick E, Dae MW, Cockrell J, Abbott JA, Schiller NB, et al. Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991; 67:148–156.
3. Andersen HR, Nielsen JC. Pacing in sick sinus syndrome—Need for a prospective, randomized trial comparing atrial with dual chamber pacing. Pacing Clin Electrophysiol 1998; 21:1175–1179.
4. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003; 107:2932–2937.
5. Kristensen L, Nielsen JC, Mortensen PT, Pederden OL, Pedersen AK, Andersen HR. Incidence of atrial fibrillation and thomboembolism in a randomized trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome. Heart 2004; 90:661–666.
6. Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006; 113:2082–2088.
7. Israel CW. The role of pacing mode in the development of atrial fibrillation. Europace 2006; 8:89–95.
8. Lamas GA, Lee KL, Sweeney M, Silverman R, Leon A, Yee R, Marinchak RA, et al. for the Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346:1854–1862.
9. Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G. Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. Am J Cardiol 1990; 65:729–735.
10. Blanc JJ, De Roy L, Mansourati J, Poezevara Y, Marcon JL, Schoels W, Hidden-Lucet F, et al. for the PIPAF Investigators. Atrial pacing for prevention of atrial fibrillation prevention: Assessment of simultaneously implemented algorithms. Europace 2004; 6:371–379.
11. Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. Programming a fixed long atrioventricular delay is not effective in preventing ventricular pacing in patients with sick sinus syndrome. Europace 1999; 2:113–120.
12. Calfee RV. Pacemaker-mediated tachycardia: engineering solutions. Pacing Clin Electrophysiol 1988; 11:1917–1928.
13. Fröhlig G, Ducloux P, Victor J, Mabo P, Galley D, Savouré A, Jauvert G, et al. Use of a new cardiac pacing mode designed to eliminate unnecessary ventricular pacing. Europace 2006; 8:96–101.
14. Savouré A, Fröhlig G, Galley D, Defaye P, Reuter S, Mabo P, Sadoul N, et al. A new dual-chamber pacing mode to minimize ventricular pacing. Pacing Clin Electrophysiol 2005; 28(Suppl. 1):S43–S46.
15. Girodo S, Ritter P, Pioger G, Lamaison D, Malherbe O. Improved dual chamber pacing mode in paroxysmal atrioventricular conduction disorders. Pacing Clin Electrophysiol 1990; 13(Part II):2059–2064.
16. Gallagher MM, Camm AJ. Classification of atrial fibrillation. Pacing Clin Electrophysiol 1997; 20:1603–1605.
17. Davy JM, Gras D, Thia A. Determining the optimal pacing mode to prevent ventricular pacing: SAVE R study results. Heart Rhythm 2006; 3(Suppl. 5):S2–S94.
18. Pioger G, Leny G, Nitzsché R, Ripart A. AAIsafeR limits ventricular pacing in unselected patients. Pacing Clin Electrophysiol 2007; 30(Suppl. 5):S66–S70.
19. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: Echocardiographic and clinical outcome. J Am Coll Cardiol 2003; 42:614–623.

20. Sgarbossa EB, Pinski SL, Maloney JD, Simmons TW, Wilkoff BL, Castle LW, Trohman RG. Chronic atrial fibrillation and stroke in paced patients with sick sinus syndrome. Relevance of clinical characteristics and pacing modalities. Circulation 1993; 88:1045–1053.
21. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. . Long-term follow-up of patients from a randomized trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997; 350:1210–1216.
22. Rosenqvist M, Brandt J, Schüller H. Long-term pacing in sinus node disease: Effects of stimulation mode on cardiovascular morbidity and mortality. Am Heart J 1988; 116:16–22.
23. Sweeney MO, Ellenbogen KA, Casavant D, Betzold R, Sheldon T, Tang F, Mueller M, et al., for the Marquis MVP Download Investigators. Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. J Cardiovasc Electrophysiol 2005; 16:811–817.
24. Gillis AM, Purerfellner H, Israel CW, Sunthorn H, Kacet S, Anelli-Monti M, Tang F, et al. Reducing unnecessary ventricular pacing with the managed ventricular pacing mode in patients with sinus node disease and AV block. Pacing Clin Electrophysiol 2006; 29:697–705.
25. Olshansky B, Day J, McGuire M, Hahn S, Brown S, Lerew DR. Reduction of right ventricular pacing in patients with dual-chamber ICDs. Pacing Clin Electrophysiol 2006; 29:237–243.
26. Thibault B, Simpson C, Gagne CE, Blier L, Senaratne M, MacNicoll S, Stuglin C, et al. Impact of AV conduction disorders on SafeR mode performance. Pacing Clin Electrophysiol Proceedings 2009; 32:S231–S235.
27. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The dual chamber and VVI implantable defibrillator (DAVID) Trial. JAMA 2002; 288:3115–3123.
28. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus node disease. N Engl J Med 2007; 357:1000–1008.
29. Veasey RA, Arya A, Freemantle N, Silberbauer J, Patel NR, Lloyd GW, Sulke AN. . The usefulness of minimal ventricular pacing and preventive AF algorithms in the treatment of PAF: the 'MinVpace' study. J Interv Card Electrophysiol 2010; 28: 51–57.
30. Veasey RA, Arya A, Silberbauer J, Sharma V, Lloyd GW, Patel NR, Sulke AN. . The relationship between right ventricular pacing and atrial fibrillation burden and disease progression in patients with paroxysmal atrial fibrillation: The long-MinVPACE study. Europace 2011; 13:765–767.
31. Nielsen JC, Thomsen PEB, Højberg S, Møller M, Vesterlund T, Dalsgaard D, Mortensen LS, et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J 2010; 32:686–696.

Appendix

The following Investigators and Institutions participated in the SAVE-R study:

Principal Investigator: Jean-Marc Davy, M.D., Ph.D., CHU Montpellier, Montpellier, France

Coinvestigators:

France: D Galley, M.D., CHG d'Albi, Albi; JL Rey, M.D., Hopital sud, Amiens; J Victor, M.D., J M Dupuis M.D., CHRU Angers, Angers; JL Marcon, M.D., CHG Annonay, Annonay; P Scanu, M.D., CHU de la côte de Nacre, Caen; P Chavernac, M.D., CHG Inter. Castres-Mazamet, Castres; D Lamaison, M.D., CHRU Gabriel Montpied, Clermont-Ferrand; P Defaye, M.D., CHRU A. Michallon, Grenoble; S Kacet, M.D., C Guedon, M.D., D Klug, M.D., C Marquie, M.D., CHRU Hôpital cardiologique, Lille; C d'Ivernois, M.D., CHRU Dupuytren, Limoges; R Luccioni, M.D., Clinique Clairval, Marseille; JM Davy, M.D., F Raczka, M.D., JL Pasquié, M.D., CHRU Arnaud de Villeneuve, Montpellier; J Levy, M.D., CH E Muller, Mulhouse; N Sadoul, H Blangy M.D., CHRU de Brabois, Nancy; L Kubler, M.D., Polyclinique de Gentilly, Nancy; H Le Marec, G Lande, M Burban, M.D., CHRU Laennec, Nantes; D Gras, Cebron, M.D., Nouvelles Cliniques Nantaises, Nantes; JP Camous, M.D., F Raybaud, M.D., I Lesto, M.D., CHRU Pasteur, Nice; M Proult, M.D., JF Guidicelli, M.D., Clinique des Fleurs, Ollioules, France; G Jauvert, M.D., L Henry, M.D., Clinique Bizet, Paris; P Mabo , M.D., C Crocq, M.D., B Vaquette, M.D., A Le Helloco, M.D., D Pavin, M.D., CHRU Pontchaillou, Rennes; F Anselme, M.D., A Savoure, M.D., CHRU C. Nicolle, Rouen; C Alonso, M.D., Clinique du Val D'or, Saint Cloud; S. Boveda, M.D., clinique Pasteur, Toulouse.

Germany: E Bub, M.D., Holzminden; R Zarhorsky, M.D., R Rüppel, M.D., Kardiolog. Gem. Praxis Zahorsky, Hamburg; K Schwabe, M.D., Segeberg Klinikum GmbH, Bad Segeberg; I Assmann, M.D., Klinikum Erfurt GmbH, Erfurt; K. Jocham, M.D., Klinkum Memmingen, Memmingen; I Hoffmann, M.D., Krankenhaus München-Bogenhausen, München; G Tsogias, M.D., Gemeinschaftspraxis Nienburg, Nienburg; M Bitar, M.D., Praxis Bitar, Peine; S Schade, M.D., Praxis für Innere Medizin, Berlin; A Frey, M.D., Kardiol. Praxis Prof. Frey, Starnberg; U Wiegand, M.D., Univ. Lübeck, Lübeck; E Himmrich, M.D., Univ. Mainz, Mainz; C Wollmann, M.D., Univ. Münster, Münster; A Bauer, M.D., Universitätsklinik Heidelberg, Heidelberg; F Richter, M.D., Kreiskrankenhaus Wolgast, Wolgast.

Italy: Roberto Cazzin, M.D., Gianni Pastore, M.D., Portogruaro (VE); Ezio Aimè, M.D., IRCCS Policlinico San Donato, S Donato (MI); Alessandro Vaglio, M.D., Venezia; Gianpietro Marinoni, M.D., Voghera (PV); Stefano Rossi, M.D., Maurizio Bisioli, M.D., Saronno (VA); Lorenzo Frabetti, M.D., Policlinico S. Orsola, Bologna; Alfredo Vicentini, M.D., Peschiera del Garda (VR); Claudio Orvieni, M.D., Massimo Romanò, M.D., Vigevano (PV); Elena Marras, M.D., Eugenio Moro, M.D., Conegliano Veneto (TV); Marco Ridarelli, M.D., Stefano Nardi, M.D., Terni; Ruggero Manfredini, M.D., Pietro Broglia, M.D., Francesco Ambrosini, M.D., Ospedale Maggiore Policlinico, Milano; Giulio Molon, M.D., Alessandro Costa, M.D., Ospedale Sacro Cuore, Negrar (VR); Giuseppe Mantovani, M.D., Patrizia Bertocchi, M.D., Desio (MI); Claudio Gentilini, M.D., Marco Lorini, M.D., Ospedale Mellini, Chiari (BS); Ezio Calosso, M.D., Ospedale San Paolo, Milano; Riccardo Bana, M.D., Garbagnate (MI); Franco Ferrari, M.D., Fabio Locati, M.D., Rho (MI); Cesare Storti, M.D., CdC

Città di Pavia, Pavia; Girolamo Spitali, M.D., Corrado Tomasi, M.D., Ida Rubino, M.D., Ravenna; Selina Argnani, Faenza (RA).

The Netherlands: G.M.G. Paulussen, M.D., Atrium Medisch Centrum, Heerlen; S.A.M. Saïd, M.D., Streekziekenhuis Midden Twente, Hengelo; A.J.M. Timmermans, M.D., Medisch Spectrum Twente, Enschede.

Belgium: D. El Allaf, M.D., Centre Hospitalier Hutois, Huy; C. Dubois, M.D., M. Bertholet, M.D., CHC Clinique St Joseph, Hermalle sous Argenteau; J. P. Salembier, M.D., Clinique Ste Elisabeth, Namur.

United Kingdom: R. Thomas, M.D., William Harvey Hospital, Ashford; K. Ward, M.D., Queens Hospital, Burton.