JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 70, NO. 14, 2017
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2017.08.026

Dual-Chamber Pacing With Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope

The SPAIN Study

Gonzalo Baron-Esquivias, MD, PhD,[a,b] Carlos A. Morillo, MD,[c] Angel Moya-Mitjans, MD, PhD,[b,d] Jesus Martinez-Alday, MD, PhD,[b,e,f] Ricardo Ruiz-Granell, MD, PhD,[b,g] Javier Lacunza-Ruiz, MD,[b,h] Roberto Garcia-Civera, MD, PhD,[b,g] Encarnacion Gutierrez-Carretero, MD, PhD,[a,i] Rafael Romero-Garrido, MD[a,b,j]

ABSTRACT

BACKGROUND Pacing in vasovagal syncope remains controversial.

OBJECTIVES The authors evaluated dual-chamber pacing with closed loop stimulation (DDD-CLS) in patients with cardioinhibitory vasovagal syncope.

METHODS This randomized, double-blind, controlled study included Canadian and Spanish patients age ≥40 years, with high burden syncope (≥5 episodes, ≥2 episodes in the past year), and a cardioinhibitory head-up tilt test (bradycardia <40 beats/min for 10 s or asystole >3 s). Patients were randomized to either DDD-CLS pacing for 12 months followed by sham DDI mode pacing at 30 pulses/min for 12 months (group A), or sham DDI mode for 12 months followed by DDD-CLS pacing for 12 months (group B). Patients in both arms crossed-over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

RESULTS A total of 46 patients completed the protocol; 22 were men (47.8%), and mean age was 56.30 ± 10.63 years. The mean number of previous syncopal episodes was 12 (range 9 to 20). The proportion of patients with ≥50% reduction in the number of syncopal episodes was 72% (95% confidence interval [CI]: 47% to 90%) with DDD-CLS compared with 28% (95% CI: 9.7% to 53.5%) with sham DDI mode ($p = 0.017$). A total of 4 patients (8.7%) had events during DDD-CLS and 21 (45.7%) during sham DDI (hazard ratio: 6.7; 95% CI: 2.3 to 19.8). Kaplan-Meier curve was significantly different between groups in time to first syncope: 29.2 months (95% CI: 15.3 to 29.2 months) versus 9.3 months (95% CI: 6.21 months, NA; $p < 0.016$); odds ratio: 0.11 (95% CI: 0.03 to 0.37; $p < 0.0001$).

CONCLUSIONS DDD-CLS pacing significantly reduced syncope burden and time to first recurrence by 7-fold, prolonging time to first syncope recurrence in patients age ≥40 years with head-up tilt test–induced vasovagal syncope compared with sham pacing. (Closed Loop Stimulation for Neuromediated Syncope [SPAIN Study]; NCT01621464) (J Am Coll Cardiol 2017;70:1720–8) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Servicio de Cardiologia y Cirugia Cardíaca, Hospital Universitario Virgen del Rocio, Universidad de Sevilla, Sevilla, Spain; [b]Agencia de Investigación de la Sociedad Española de Cardiologia, Madrid, Spain; [c]Department of Cardiac Sciences, Libin Cardiovacular Institue of Alberta, University of Calgary and Population Health Research Institute-McMaster University, Hamilton, Ontario, Canada; [d]Servicio de Cardiologia, Hospital Universitario Vall d'Hebron, Barcelona, Spain; [e]Hospital Universitario Basurto, Bilbao, Spain; [f]Clínica IMQ Zorrotzaurre, Bilbao, Spain; [g]Servicio de Cardiología, Hospital Universitario Clinico de Valencia, Valencia, Spain; [h]Servicio de Cardiologia, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; [i]CIBER-CV, Centro de Investigación Biomedica en Red de Enfermedades Cardiovasculares, Madrid, Spain; and the [j]Servicio de Cardiologia, Hospital Nuestra Señora de la Candelaria, Tenerife, Spain. The Research Agency of the Spanish Society of Cardiology received an unrestricted research grant from Biotronik Spain. Dr. Martinez-Alday has served as a consultant for and received modest support from Medtronic and St. Jude; and has served as an expert witness for Medtronic. Dr. Ruiz-Granell has received lecture fees from Medtronic and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 9, 2017; revised manuscript received August 9, 2017, accepted August 9, 2017.

Reflex vasovagal syncope (VVS) remains one of the most common causes of recurrent syncope. Despite multiple attempts with a variety of pharmacological options aimed at reducing the recurrence of VVS, less than a handful of evidenced-based options are currently recommended by guidelines (1). Pacemakers were initially met with enthusiasm and backed by several nonrandomized studies and 2 randomized trials, which suggested an almost 70% relative risk reduction (RRR) in the time to first recurrence of syncope (2,3). However, further well-designed randomized trials, in which all patients received a pacemaker and were randomly assigned to pacing versus no pacing, were unable to demonstrate a clinically significant reduction in syncope recurrence, evidencing a large placebo effect (4,5). Only 1 study that included older patients with an asystole recorded by an implantable cardiac monitor demonstrated a 50% RRR in the recurrence of syncope (6). Based on this evidence, recent guidelines provide a Class IIb recommendation (Level of Evidence: C), for pacemaker therapy in patients older than 40 years of age with cardioinhibitory response during head-up tilt testing (HUT) and with recurrent, frequent unpredictable syncope that was refractory to conventional therapy (1).

SEE PAGE 1729

Controversy remains regarding the most efficient pacing mode for the prevention of recurrent cardioinhibitory VVS; only 1 study using rate drop response showed superiority to placebo. The benefits of a physiological pacing algorithm with contractility sensor, known as closed loop stimulation (dual-chamber pacing with closed loop stimulation [DDD-CLS]), has been reported in 2 randomized and 3 observational studies that included patients with asystole during HUT (7–11). We carried out a randomized, prospective, double-blind, controlled, multicenter trial to determine the utility of DDD-CLS pacing in patients with cardioinhibitory refractory VVS.

METHODS

Ethics review committees in all 11 centers (10 in Spain and 1 in Canada) approved the protocol. Patients were eligible if they fulfilled all of the following inclusion criteria: 1) at least 5 previous VVS episodes (at least 2 occurring within the last year); 2) tilt-test with a cardioinhibitory response, defined as a heart rate <40 beats/min for at least 10 s or a >3-s pause; 3) age ≥40 years (based on recent guideline recommendations and previously published trials [1,4,5]); 4) absence of cardiomyopathy and normal 12-lead electrocardiogram; 5) no other indication for a permanent pacemaker; 6) geographical stability and availability to attend follow-up; 7) informed consent; and 8) any of the following contraindications: ß-blocker drug treatment, chronic polyneuropathy and any contraindication to DDD or DDDR pacing. Exclusion criteria included: 1) patients with syncope caused by carotid sinus hypersensitivity, or other cause of syncope; 2) participants in another concurrent trial; and 3) pregnant or breastfeeding women not using contraceptive methods. All patients underwent complete physical examination, including orthostatic test, carotid sinus massage, 12-lead electrocardiogram, 2-dimensional Doppler echocardiography, and 24-h Holter monitoring. HUT was performed using 2 previously reported protocols (12,13). For this trial, we only included patients with a cardioinhibitory response: bradycardia <40 beats/min during >10 s or asystole >3 s, as per the VASIS (Vasovagal Syncope International Study) classification (14).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DDD-CLS = dual-chamber pacemaker with closed loop stimulation

HUT = head-up tilt testing

IQR = interquartile range

RRR = relative risk reduction

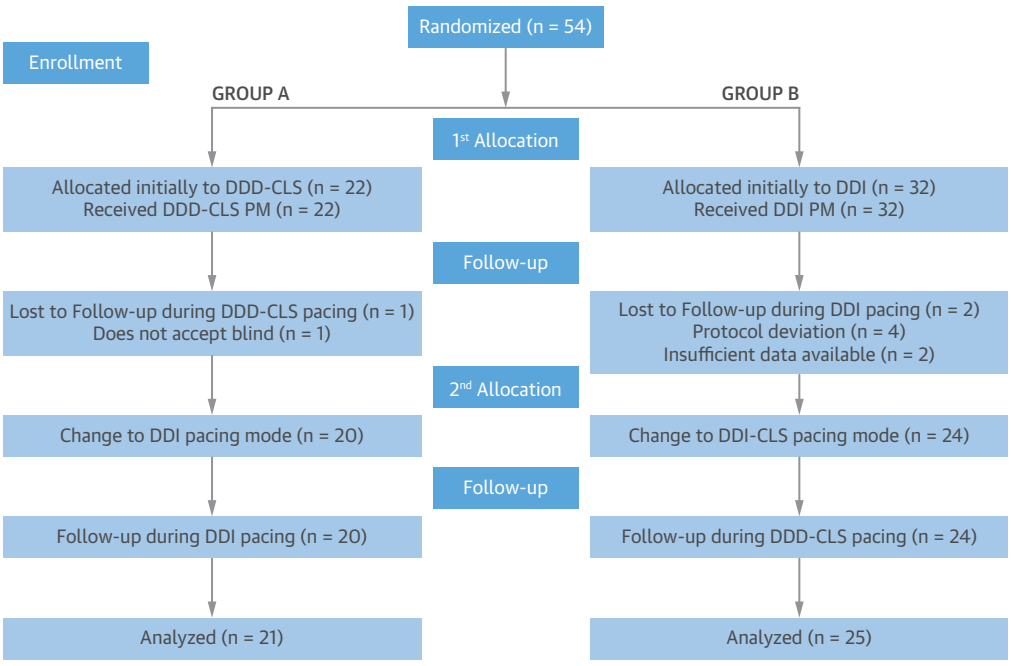
sham DDI = dual-chamber pacemaker implantation but without pacing activity

VVS = vasovagal syncope

RANDOMIZATION AND STUDY TREATMENT. Randomization was performed by an automatic central phone system that allocated patients 1:1 to either group A (DDD pacemaker programmed to DDD-CLS mode for 12 months, after which patients crossed over to a sham DDI mode [30 pulses/min and subthreshold] for the remaining 12 months) or group B (DDI mode [30 pulses/min and subthreshold] for 12 months followed by crossover to active DDD-CLS pacing for the remaining 12 months). Patients in both arms crossed over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

PACEMAKER IMPLANTATION AND PROGRAMMING. After inclusion and before randomization, all patients had a dual-chamber pacemaker that had the ability to be programmed in the DDD-CLS algorithm mode (Protos DR, Cylos DR, Cylos 990 DR, and Evia, Biotronik GmbH & Co., Berlin, Germany) implanted. In the active intervention arm (DDD-CLS pacing mode), the following programming was performed: lower rate (day/night) 45 pulses/min; upper rate 160 pulses/min; CLS rate 110 pulses/min with dynamic CLS set to "high" and dynamic rate limit set to "off"; atrioventricular interval fixed to 150 ms with atrioventricular hysteresis set to "high"; atrial refractory period 400 ms; pacing polarity set to unipolar and sensing polarity to bipolar; and output adjusted to double atrial and ventricular thresholds. In the "sham" DDI mode, programming was as

FIGURE 1 Patient Flow



Overall, 54 patients were randomized to treatment with DDD-CLS pacemaker. Group A (n = 22): DDD-CLS first for 12 months followed by sham DDI. Group B (n = 32): sham DDI first for 12 months followed by DDD-CLS for the remaining 12 months. After exclusion of 8 patients, 21 and 25 patients were analyzed in groups A and B, respectively. DDD-CLS = dual-chamber pacemaker with closed loop stimulation; sham DDI = dual-chamber pacemaker implantation but without pacing activity; PM = pacemaker.

follows: mode DDI; lower rate (day/night) 30 pulses/min; atrioventricular interval 180 ms; pacing polarity unipolar; sensing polarity bipolar; and atrial and ventricular output set to minimum: 0.1 V at 0.1 ms (subthreshold).

FOLLOW-UP. After discharge, patients were provided with a diary to document all syncopal and pre-syncopal episodes occurring during follow-up. All patients were followed-up at 3, 6, 12, 15, 18, and 24 months by 2 different blinded investigators in each center. A complete clinical evaluation was performed at all visits. After completing the clinical follow-up visit, another investigator, blinded to clinical evolution, interrogated the pacemaker and optimized programming accordingly and switched to the alternative pacing mode as required by the protocol (Figure 1).

STATISTICAL ANALYSIS. The study was powered to address the primary efficacy outcome comparing the effect of pacing mode and the sequence of stimulation. The main efficacy variable was the proportion of patients who reduced their total number of syncopal episodes by ≥50% compared with the year prior to pacing, and a co-primary efficacy outcome based on an on-treatment analysis assessing the time to first syncope recurrence comparing the effect of pacing mode. The null hypothesis was that the difference between both paced groups was >25%. We estimated that 30% of patients who experienced a syncopal recurrence on DDI mode would not have recurrences when programmed to DDD-CLS mode, and only 5% of patients that experienced a recurrence while on DDI would have a recurrence on DDD-CLS. The remaining 60% would not have any change in both programing modes. Based on this hypothesis, we calculated that 50 patients crossing over to both arms would be needed to achieve a 99% power with a 2-sided significance level of 0.025 to detect benefit. Secondary efficacy outcomes were time to first pre-syncope in both pacing mode sequences (group A vs. group B), and response in both pacing modes (DDD-CLS vs. sham DDI). Improvement in quality of life is not reported herein.

The trial was designed, sponsored, and conducted by the syncope working group and the Research Agency of the Spanish Society of Cardiology. All patients, investigators, and care providers were blinded throughout the study. Data was collected and

analyzed by an independent database company, PIVOTAL S.L (Madrid, Spain).

The primary efficacy analysis was based on a modified intention-to-treat-basis (all randomized patients who had a pacemaker implanted and had data for all follow-up visits). To achieve an outcome, patients needed to have at least 1 syncope recurrence or complete the 12 months with the allocated pacing mode. The coprimary efficacy outcome analysis was based on an on-treatment analysis (all patients paced in the randomized mode) of the time to first syncope recurrence. Continuous variables are expressed as median (interquartile range [IQR]) when their distribution was abnormal, and as mean ± SD otherwise after evaluation by Shapiro-Wilk test. These variables were compared by Mann-Whitney *U* test and Wilcoxon (signed rank) or Student *t* test. The Fisher or chi-square test was used for comparison of qualitative data, and McNemar or Q of Cochran when data were couples. To analyze the differences between groups A and B (primary efficacy outcome), the Mainland-Gart and Prescott tests were used. Both tests were used to analyze the possible influence of the order of pacing mode, supported by Freeman approximation and Tukey test if necessary. The cumulative risk of syncope over time (coprimary efficacy outcome) was estimated using the Kaplan-Meier procedure and log-rank test, for correlation between treatment and time to recurrence. A 2-tailed p value < 0.05 was considered significant. Data were analyzed with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Between April 2007 and July 2013, 54 patients were randomized in 11 centers in Spain (10 centers) and Canada (1 center) (see Online Appendix). Four were excluded due to protocol deviations: 2 due to loss to follow-up, and 2 because of insufficient data at follow-up. Overall, 46 patients (22 [47.8%] men, age 56.3 ± 10.6 years) were included in the final analysis (**Figure 1**). The median number of syncopal episodes before randomization was 12 (IQR: 9 to 20 episodes), with a median frequency of 4.5 episodes (IQR: 2 to 7 episodes) during the preceding year. All recruited patients had a positive cardioinhibitory response during HUT: 11 (24%) had bradycardia <40 beats/min, with a mean of 35.9 ± 2.9 beats/min, lasting more than 10 s; and 35 (76%) had an asystole with a median duration of 15 s (IQR: 10 to 26 s). Twenty-one patients were randomized to group A and 25 to group B. There were no significant differences between groups (**Table 1**).

TABLE 1 Baseline Characteristics of the Patients

	Total (N = 46)	Group A DDD-CLS → DDI (n = 21)	Group B DDI → DDD-CLS (n = 25)	p Value
Age, yrs	56.3 ± 10.6	56.9 ± 10.3	55.9 ± 11.8	0.7
Weight, kg	72 (62–85)	74.0 (66.2–90.5)	67.5 (61–83)	0.3
Height, cm	164.8 ± 9.3	164.0 ± 10.8	164.7 ± 8.2	0.9
Male	22 (48)	9 (43)	13 (52.0)	0.5
HBP	14 (30.0)	6 (28.0)	8 (32.0)	0.7
Diabetes	1 (2.0)	1 (4.0)	0 (0.0)	0.4
Previous syncopal episodes	12 (9–20)	12 (10–20)	10 (8–20)	0.8
Previous syncopal episodes during the last 12 months	4.5 (2–7)	4.5 (3.0–7.5)	4.5 (2–6)	0.5
Orthostatic test, mm Hg				
Supine systolic BP	129 ± 16	133 ± 17	125 ± 14	0.1
Supine diastolic BP	77 ± 9	77 ± 10	77 ± 9	0.8
Orthostatic systolic BP	128 ± 17	129 ± 19	127 ± 16	0.8
Orthostatic diastolic BP	77 ± 11	78 ± 13	76 ± 8	0.5
Asystole in HUT	35 (76.0)	16 (79.0)	19 (76.0)	1.0
Asystole duration, s	15 (10–26)	14.3 (7–29)	15 (10–22)	0.9

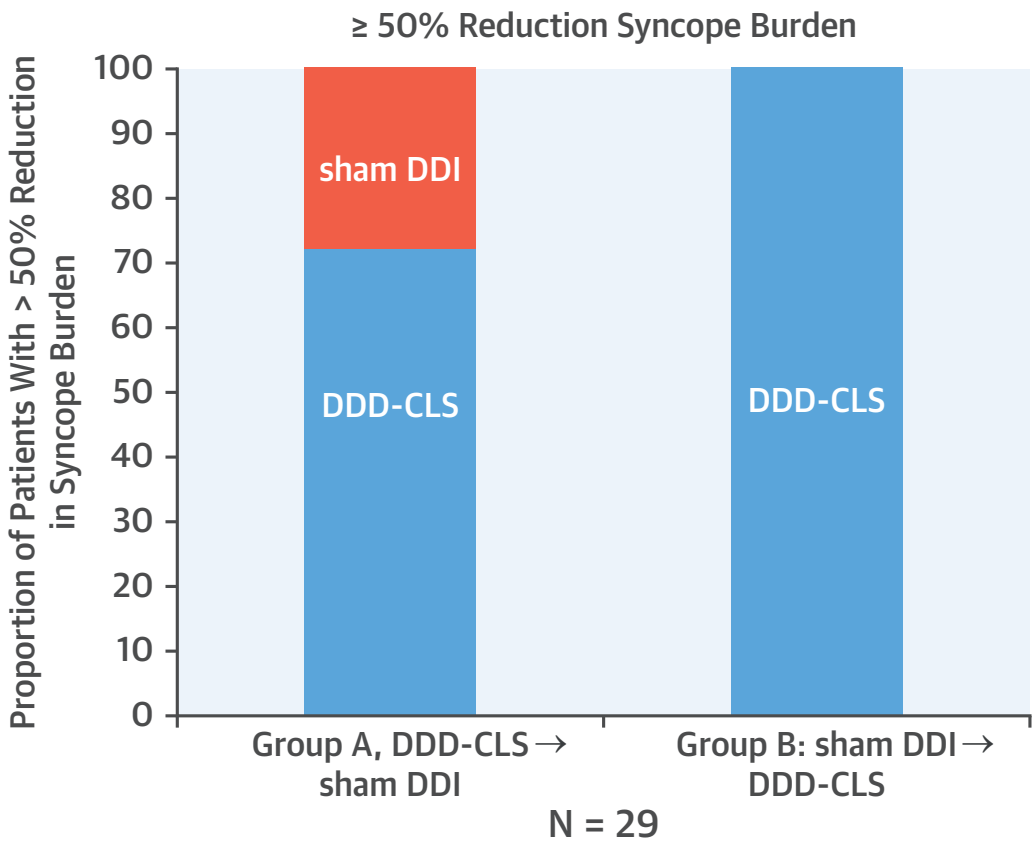
Values are mean ± SD, median (interquartile range), or n (%).

BP = blood pressure; DDD-CLS = dual-chamber pacemaker with closed loop stimulation; DDI = dual-chamber pacemaker implantation but without pacing activity; HBP = high blood pressure; HUT = head-up tilt testing.

PRIMARY EFFICACY OUTCOME. After a mean 22.2 ± 5.1 months of follow-up, of the 46 patients randomized, 29 (63.04%) reached the primary outcome and had complete data for this analysis. The proportion of patients that had a ≥50% reduction in the number of syncopal episodes was 72.22% (95% CI: 47% to 90%) with DDD-CLS mode compared with 28% (95% CI: 9.7% to 53%) paced in sham DDI mode ($p = 0.017$). Syncope recurred after crossing over to the sham DDI mode in 6 (29%). All the patients in group B had a ≥50% reduction in the number of syncopal episodes once they crossed over from sham DDI mode to DDD-CLS mode during the second year, $p = 0.0003$, Mainland-Gart, (**Central Illustration**). An association between sequence of stimulation (groups A and B) was confirmed by a Prescott analysis, detecting a significant difference between sequence of stimulation and syncopal recurrence reduction ($p = 0.0003$).

In group A, 9 patients had a syncopal recurrence: syncope occurred in 3 patients when in DDD-CLS mode and in the remaining 6 patients when in sham DDI mode, 3 of which reported 3 syncopal episodes within 1 month after randomization to sham DDI mode and, therefore, reached the primary outcome. In group B, 16 patients had syncopal recurrences: 15 were randomized to sham DDI mode, 8 of which reported 3 syncopal episodes within 1 month and crossed over to the DDD-CLS mode; and only 1 patient had syncope recurrence while being paced in the DDD-CLS mode.

CENTRAL ILLUSTRATION **Closed Loop Stimulation in Vasovagal Syncope: Primary Efficacy Outcome**



Baron-Esquivias, G. et al. J Am Coll Cardiol. 2017;70(14):1720–8.

Proportion of patients with ≥50% reduction in syncope burden according to allocated pacing mode. Group A (DDD-CLS × 12 months crossed to sham DDI × 12 months): 72% (95% confidence interval [CI]: 47 to 90) with the DDD-CLS mode **(blue)** compared to 28% (95% CI: 10 to 53) paced in the sham DDI mode **(orange)** reached the primary efficacy outcome ($p = 0.0172$, Mainland-Gart). Group B: (Sham DDI x 12 months crossed to DDD-CLS x 12 months) 0% sham DDI versus 100% (95% CI: 40 to 100) DDD-CLS ($p = 0.003$, Mainland-Gart). DDD-CLS = dual-chamber pacemaker with closed loop stimulation; sham DDI = dual-chamber pacemaker implantation but without pacing activity.

COPRIMARY EFFICACY OUTCOME. For the analysis of the time to first recurrence according to the pacemaker programming mode, only patients that had complete data for all follow-up visits were included ($n = 46$). Mean follow-up was significantly longer in group A compared with group B (29 ± 2.9 months vs. 21 ± 6 months, respectively; $p = 0.02$). Kaplan-Meier model by treatment sequence estimated a median onset to first syncope in group A of 29 months (95% CI: 15 to 29 months) compared with 9.3 months (95% CI: 6.2 to NA months) in group B ($p = 0.016$) (Figure 2). To determine the overall efficacy of pacing mode, we assessed the recurrence of syncope during 11 ± 3.5 months of follow-up of the 46 patients during both DDD-CLS and sham DDI pacing modes. Only 4 (8.7%) patients suffered syncopal events in 46 patients while they were stimulated with DDD-CLS, compared to 21 (46%) randomized to the sham DDI mode. The Kaplan-Meier model by treatment arm could not estimate the median time until first syncope in the DDD-CLS mode, because no events were recorded in one-half of them. In patients randomized to the sham DDI mode, the median estimate was 9.30 months (95% CI: 6.6 to 19.0 months) from the initiation of treatment (log-rank test; $p < 0.0001$) (Figure 3). Pacing mode had a strong effect in favor of DDD-CLS, with an RRR of 89%, odds ratio: 0.11 (95% CI: 0.03 to 0.37; $p < 0.0001$) (Figure 3),

an absolute risk reduction of 37%, and a number needed to treat with DDD-CLS of 2.7 to prevent 1 recurrence of syncope.

SECONDARY EFFICACY OUTCOME. Time to first pre-syncope in both pacing mode sequences (group A vs. group B) and response in both pacing modes (DDD-CLS vs. sham DDI) were not significantly different. Pre-syncope was quantified by a graded scale of pre-syncope episodes: 0, ≤5, 6 to 10, 11 to 15, and >15. Overall, 46.67% of patients had pre-syncopal recurrences in group A compared with a 53.33% recurrence rate in group B ($p = 0.5692$ by Mainland-Gart).

ADVERSE EVENTS. There were 4 minor complications during pacemaker implantation in the 46 patients: 3 atrial transitory arrhythmias and 1 atrial lead dislodgment.

DISCUSSION

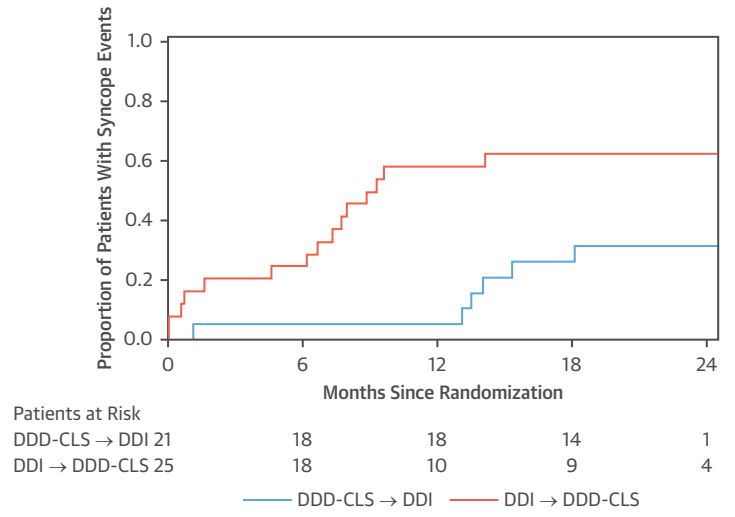
Our major finding is that DDD-CLS pacing mode was superior to sham DDI mode in reducing the burden of syncope by ≥50% of syncopal episodes in over 70% of patients with recurrent VVS. Furthermore, there was a strong effect based on the stimulation sequence, with an impressive 37% absolute risk reduction in time to first recurrence of syncope determining a number needed to treat of only 2.7 to prevent a syncope relapse. Finally, time to first relapse was also significantly prolonged by over 2 years by the DDD-CLS mode compared with sham pacing.

Previous trials testing the usefulness of pacing in patients with recurrent VVS have had mixed and controversial results (2,3). Earlier randomized studies in which all patients were paced, such as VPS II (Second Vasovagal Pacemaker Study), SYNPACE (Vasovagal Syncope and Pacing Trial), and ISSUE 3 (Third International Study on Syncope of Uncertain Etiology), recruited a different population than North American studies, usually including younger patients than our population (4-6). The burden of syncope appears to be comparable among these studies, with a median around 15 episodes in previous studies compared with 12 in the current trial. ISSUE-3, which initially screened 511 patients who had an implantable cardiac monitor inserted but randomized only 79 patients, compared pacing versus no pacing in an older population with either syncope with documented asystole >3 s or an asymptomatic asystole >6 s (6). This trial showed a similar effect to that seen in our trial, although our patients had to fulfill strict HUT criteria to be included. Of note, this is the first trial to demonstrate a strong beneficial effect related to the pacing algorithm in patients with a cardioinhibitory response during HUT. Our findings contrast with a post hoc analysis of ISSUE 3, in which patients with documented asystolic neurally mediated reflex syncope documented by an implantable cardiac monitor and a HUT with a cardioinhibitory response who received a pacemaker did not have a significant reduction in syncope recurrence (15). The reason for this difference is unclear and may be attributed to multiple causes, such as pacing mode, age of patients, and the fact that our study only included HUT cardioinhibitory pre-defined responses. Further studies are clearly needed to better understand this discrepancy.

We did not have enough events to determine if there were any differences between those patients who experienced an asystole or a bradycardia during HUT and their response to pacing mode. An ongoing trial, BIOSYNC (Benefit of Dual Chamber Pacing With Closed Loop Stimulation in Tilt-Induced cardioinhibitory Reflex Syncope), may provide further information to answer this question (16).

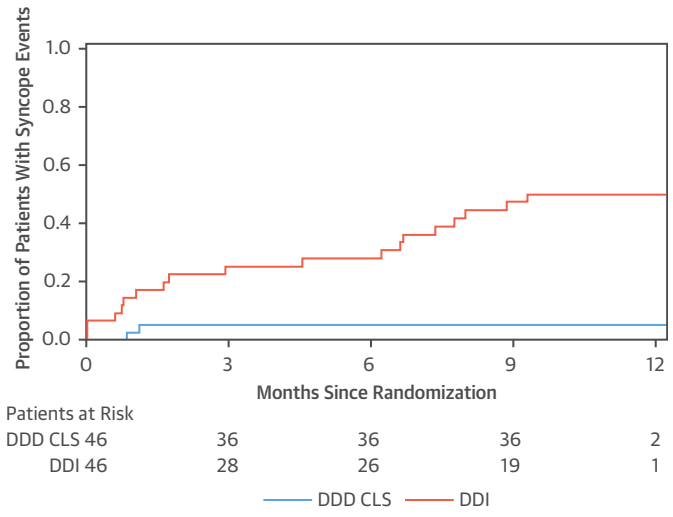
There is evidence of a strong placebo or "expectation" effect in patients with recurrent VVS who undergo interventions, such as receiving a pacemaker; this is particularly true in trials that have not been double-blinded (2,3). Our design was based on a

FIGURE 2 Coprimary Efficacy Outcome in Group A Versus Group B



Time to first recurrence of syncope in both pacing mode sequences. Group A (DDD-CLS first → sham DDI) versus group B (sham DDI → DDD-CLS). During a mean of 22.2 ± 5.1 months of follow-up, in an intent-to-treat analysis, the Kaplan-Meier model by treatment sequence estimated a longer median onset to first syncope in group A compared with group B (29.15 months vs. 9.30 months; $p = 0.0158$). Abbreviations as in Figure 1.

FIGURE 3 DDD-CLS in 46 Patients Versus Sham DDI in 46 Patients



Time to first recurrence of syncope per pacing mode (DDD-CLS vs. DDI) was significantly different during 11 ± 3.5 months of follow-up ($p < 0.0001$). Odds ratio: 0.11; relative risk reduction: 89% in favor of DDD-CLS; absolute risk reduction: 37%; and a number needed to treat with DDD-CLS of 2.7 to prevent 1 recurrence of syncope. Abbreviations as in Figure 1.

double-blind, cross-over design; all patients received a pacemaker and to maximize the understanding on the potential effects of the specific algorithm tested (DDD-CLS) compared with sham pacing. All patients received a pacemaker and crossed over after 12 months or after reaching the primary efficacy outcome. Although a smaller sample contributed data for the primary efficacy outcome of at least a 50% reduction in burden of syncope, the effect was clear and highly significant, indicating that DDD-CLS pacing is highly beneficial in a population of patients with recurrent, high-burden VVS. This benefit was further supported by the highly significant effect (89% RRR) in the time to first recurrence of syncope. Time to first recurrence of syncope correlates well with frequency of syncope, which may be more clinically relevant from the patient's perspective and for health care resource utilization (17). Interestingly, our recurrence rate in the sham mode may have been higher than previously reported, and a "nocebo" effect of sham pacing cannot be completely ruled out.

The objective of pacing in patients with severe cardioinhibitory VVS is to pace at the onset of the episode, in an attempt to abort or minimize the progression of symptoms and loss of consciousness. DDD-CLS pacing is a rate-responsive mode that uses intracardiac impedance as a surrogate of cardiac contractility to adapt heart rate to patient needs. Impedance is measured between the ventricular electrode tip and the pacemaker case during the systolic phase of the cardiac cycle on a beat-to-beat basis. Variations in impedance are transformed into variations in heart rate (18). It has been suggested that an increase in cardiac contractility occurs when VVS is impending; once detected by this algorithm, it triggers an increase in rate (probably when the heart rate is still inhibited by spontaneous rhythm). As the patient's heart rate starts to drop due to the cardioinhibitory reflex, the pacemaker's escape rate is already set at a higher rate, thereby preventing bradycardia, asystole, and consequently, syncope.

The utility of the DDD-CLS algorithm was described in 1998, but there are no well-conducted, randomized, double-blind trials supporting its efficacy in recurrent VVS. Five studies suggesting that DDD-CLS mode reduces VVS recurrence have been reported. INVASY (INotropy controlled pacing in Vasovagal SYncope) was a prospective, controlled, randomized, single-blind, multicenter study that compared DDD-CLS and DDI pacing mode, with crossover after the second recurrence of syncope in patients with a cardioinhibitory response to HUT. DDD-CLS pacing was more effective than DDI in preventing VVS recurrence during a mean follow-up of 19 months, and no recurrences were observed in the DDD-CLS-paced group (7). In another single-center, retrospective, North American study including 35 patients, 12 received a standard pacing mode (rate drop or rate hysteresis response), and 32 were paced with a DDD-CLS unit. The recurrence was lower: 83% versus 59%, and the reduction in syncope burden was also higher: 25% versus 84% ($p = 0.002$), in those paced with a DDD-CLS device (8). Bortnik et al. (9), in a prospective study that included 35 patents with VVS, reported that 83% were rendered asymptomatic when paced in the DDD-CLS mode. In a single-center, retrospective study that included 41 patients (25 with DDD-CLS pacing and 16 with DDD with rate-drop response), only 1 patient (4%) in the DDD-CLS group had syncope recurrences, compared with 6 (38%) in the conventional pacing group (10). Finally, a recent prospective, randomized, single-blind, multicenter study, designed as an intrapatient comparison, enrolled 30 patients with HUT-induced cardioinhibitory VVS (11). Two HUTs were performed 1 week apart: 1 during DDD-CLS pacing, and the other during DDD pacing. Patients were randomly and blindly assigned to 2 groups: in 15 patients, the first HUT was performed with the pacemaker programmed to DDD-CLS, and in another 15 patients, their first HUT was programmed to DDD. DDD-CLS significantly

reduced the occurrence of syncope induced by HUT (30.0% vs. 76.7%; $p < 0.001$). Our trial did not directly compare DDD-CLS pacing mode with other dual-chamber pacing modes (DDI with hysteresis, DDD with rate drop response, and so on) that have had limited success in preventing recurrence of VVS (4,5). Therefore, further testing is needed to determine which DDD pacing mode should be recommended to patients with VVS and develop a pacing indication.

Our study showed that DDD-CLS pacing significantly reduced syncopal recurrence both during the first 12 months when initially allocated to DDD-CLS, and after crossover to DDD-CLS when the initial pacing mode was DDI. Furthermore, the benefits were maintained by reducing the burden of syncope prior to randomization, as well as time to first recurrence when comparing the pacing mode sequence, further minimizing a placebo or "carry on" effect of DDD-CLS pacing. Previous studies using HUT response to select patients with a cardioinhibitory response for pacing have failed to show benefit. This has steered investigators to document spontaneous, asystolic, neutrally-mediated reflex VVS by an implantable cardiac monitor, as the guideline recommendations suggest, prior to indicating pacemaker therapy in VVS (1,4–6,17). Overall, pre-syncopal episodes did not differ between groups and were not modified by programming mode. These findings are consistent with previously published data, suggesting that pacing may prevent syncope, but not pre-syncope (4).

STUDY LIMITATIONS. A systematic approach using pharmacological interventions was not required in this trial. However, no single pharmacological intervention has been proven to benefit patients with HUT-induced cardioinhibitory VVS. It is unclear whether the spontaneous cause of syncope was due to significant bradycardia and asystole. However, based on the 86% positive predictive value of asystolic responses during HUT reported in the ISSUE 3 trial, we assumed that this was the case in our trial. We selected a ≥50% reduction in syncope frequency as the primary efficacy outcome, but only 29 patients reached the primary efficacy endpoint, potentially limiting our findings. However, time to first recurrence of syncope has been shown to correlate well with syncope burden (19), and this outcome demonstrated a 37% absolute risk reduction favoring the DDD-CLS pacing mode. Finally, our study did not compare the DDD-CLS pacing mode to other DDD pacing modes; therefore, we cannot conclude that DDD-CLS is superior to other DDD pacing modes in patients with refractory reflex VVS.

CONCLUSIONS

DDD-CLS pacing reduced syncope burden and time to first recurrence by 7-fold, and prolonged time to first syncope recurrence in patients age ≥40 years with tilt-induced cardioinhibitory vasovagal syncope compared with sham pacing.

ADDRESS FOR CORRESPONDENCE: Dr. Gonzalo Baron-Esquivias, Servicio de Cardiologia y Cirugia Cardíaca, Hospital Universitario Virgen del Rocio, Universidad de Sevilla, Avenida de Portugal, 19, 41004 Seville, Spain. E-mail: gonzalo.baron.sspa@juntadeandalucia.es.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Asystole and severe bradycardia triggered during HUT correlate with spontaneous asystole documented by implantable cardiac monitors, and should be prevented in patients with recurrent reflex VVS.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a randomized trial, patients with recurrent cardioinhibitory reflex VVS significantly improved with the implantation of a DDD-CLS pacemaker.

TRANSLATIONAL OUTLOOK: Although this is a relatively short-term study (median 2 years), a marked clinical improvement was shown, and further long-term studies are needed to determine the effect and sustainability of this treatment.

REFERENCES

1. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2017;70:620–63.

2. Ammirati F, Colivicchi F, Santini M, for the Syncope Diagnosis and Treatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. Circulation 2001;104:52–7.

3. Sutton R, Brignole M, Menozzi C, et al., for the Vasovagal Syncope International Study (VASIS) Investigators. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. Circulation 2000;102:294–9.

4. Connolly SJ, Sheldon R, Thorpe KE, et al., for the VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. JAMA 2003;289:2224–9.

5. Raviele A, Giada F, Menozzi C, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J 2004;25:1741–8.

6. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. Circulation 2012; 125:2566–71.

7. Ochetta E, Bortnik M, Audoglio R, et al., for the INVASY Study Investigators. Closed loop stimulation in prevention of vasovagal syncope. Inotropic Controlled Pacing in Vasovagal syncope (INVASY): a multicentre randomized, single-blind, controlled study. Europace 2004;6:538–47.

8. Kanjwal K, Karabin B, Kanjwal Y, Grub BP. Preliminary observations on the use of closed-loop cardiac pacing in patients with refractory neurocardiogenic syncope. J Interv Card Electrophysiol 2010;27:69–73.

9. Bortnik M, Occhetta E, Dell'Era G, et al. Long-term follow-up of DDDR closed-loop cardiac pacing for the prevention of recurrent vasovagal syncope. J Cardiovasc Med 2012;13:242–5.

10. Palmisano P, Zaccaria M, Luzzi G, Nacci F, Anaclerio M, Favale S. Closed-loop cardiac pacing vs. conventional dual-chamber pacing with specialized sensing and pacing algorithms for syncope prevention in patients with refractory vasovagal syncope: results of a long-term follow-up. Europace 2012;14:1038–43.

11. Palmisano P, Dell'Era G, Russo V, et al. Effects of closed-loop stimulation vs. DDD pacing on haemodynamic variations and occurrence of syncope induced by head-up tilt test in older patients with refractory cardioinhibitory vasovagal syncope: the Tilt test-Induced REsponse in Closed-loop Stimulation multicentre, prospective, single blind, randomized study. Europace 2017 April 12 [E-pub ahead of print].

12. Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. J Am Coll Cardiol 1991;17:125–30.

13. Bartoletti A, Alboni P, Ammirati F, et al. 'The Italian protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace 2000; 2:339–42.

14. Brignole M, Menozzi C, Del Rosso A, et al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. Europace 2000;2: 66–76.

15. Brignole M, Donateo P, Tomaino M, et al. Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative: an analysis from the third International Study on Syncope of Uncertain Etiology (ISSUE-3). Circ Arrhythm Electrophysiol 2014;7:10–6.

16. Brignole M, Tomaino M, Aerts A, et al. Benefit of dual-chamber pacing with closed loop stimulation in tilt-induced cardio-inhibitory reflex syncope (BIOSync trial): study protocol for a randomized controlled trial. Trials 2017;18: 208.

17. Sud S, Massel D, Klein GJ, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. Am J Med 2007;120:54–62.

18. Schaldach M, Hutten H. Intracardiac impedance to determine sympathetic activity in rate responsive pacing. Pacing Clin Electrophysiol 1992;15:1778–86.

19. Malik P, Koshman ML, Sheldon R. Timing of first recurrence of syncope predicts syncopal frequency after a positive tilt table test result. J Am Coll Cardiol 1997;29:1284–9.

KEY WORDS asystole, pacemaker, syncope, tilt table testing

APPENDIX For a complete list of participating centers, please see the online version of this article.