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# Closed loop stimulation in prevention of vasovagal syncope. Inotropy controlled pacing in vasovagal syncope (INVASY): a multicentre randomized, single blind, controlled study<sup>☆</sup>

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## KEYWORDS

vasovagal syncope;  
closed loop  
stimulation;  
DDD pacing

**Abstract Objectives** To determine whether dual-chamber rate-adaptive Closed Loop Stimulation (CLS) could prevent recurrence of Vasovagal Syncope (VVS).

**Background** During VVS, an increase in myocardial contractility associated with a reduction of ventricular filling produces an increase in baroreceptor afferent flow and a consequent decrease in the heart rate. The CLS algorithm is a form of rate-adaptive pacing, which responds to myocardial contraction dynamics, by measuring variations in right ventricular intracardiac impedance: during an incipient VVS it could increase paced heart rate and avoid bradycardia, arterial hypotension and syncope.

**Methods** Fifty patients (27 males, mean age  $59 \pm 18$  year) with severe and recurrent vasovagal syncope and positive Head Up Tilt Test (HUTT) with cardioinhibition, received a CLS pacemaker (INOS<sup>2</sup>, Biotronik GmbH Co., Germany). The primary end point was recurrence of two VVSs during a minimum of 1 year of follow-up. Randomization between DDD-CLS and DDI mode (40 bpm) pacing was performed only during the first stage of the study (first year): 9/26 randomized to DDI mode (control group) and 17/26 in DDD-CLS mode. All the 24 patients recruited in the second stage of the study (second year) were programmed in DDD-CLS mode.

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**Results** Of the nine patients randomized to the DDI mode, seven had recurrences of syncope during the first year. At the end of the first year the nine patients were reprogrammed to the CLS mode and no syncope occurred after reprogramming. The 41 patients programmed to CLS had a mean follow-up of  $19 \pm 4$  months: none reported VVS, only four (10%) reported occasional presyncope and their quality of life greatly improved. Positive HUTT at the end of the first year failed to predict the clinical response to CLS pacing.

**Conclusions** The study demonstrates the effectiveness of CLS pacing in preventing cardioinhibitory VVS. A possible placebo effect of pacemaker implantation occurred in 22% of patients.

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## Introduction

In patients with recurrent, severe, cardioinhibitory vasovagal syncope (VVS), significant bradycardia or prolonged asystole (up to more than 60 s) and concomitant hypotension, can produce serious physical injuries and psychological impairment, including a substantial limitation of social and working life [1,2,3].

When VVS is refractory to conventional measures and/or to pharmacological treatment, the implantation of a pacemaker may induce clinical benefits [4,5].

### Closed loop stimulation (CLS) and rationale for its use in vasovagal syncope

During VVS, the diminished venous return stimulates a sympathetic compensatory tone that leads to a positive inotropic effect [6,7]. Since ventricular filling is reduced, the left ventricular systolic pressure may increase participating in a baroreceptor induction of bradycardia [8,9], thereby creating a paradoxical situation: increased inotropic effect associated with decreased chronotropic state. This anomalous situation inhibits sympathetic activity and promotes a vagal effect that causes VVS by increasing peripheral vasodilatation with associated reflex bradycardia [10,11]. Closed Loop Stimulation (CLS) function performed by the model INOS<sup>2</sup> CLS dual-chamber pacemaker (by Biotronik GmbH & Co., Germany) tracks the variations of intracardiac impedance during the systolic phase of the cardiac cycle on a beat-to-beat basis [12]. Changes in intracardiac impedance are closely correlated with both the right and left ventricular  $dP/dt_{max}$ , making this pacing system suitable for the detection of changes in contractility in the early phase of VVS [13,14]. The CLS detection of the increased contractility in the first stage of vasovagal syncope (Fig. 1) could activate atrioventricular (AV) sequential pacing [15,16],

that may anticipate withdrawal of sympathetic tone and counterbalance the increase in vagal tone, thus preventing arterial hypotension, bradycardia and possibly syncope (Fig. 2) [17].

The promising results of the CLS Pre-INVASY registry [18] justified a larger prospective randomized controlled study. Thus, the INVASY study was designed to investigate whether CLS pacing may be more effective in preventing syncope than a placebo pacemaker implantation programmed in DDI back-up mode.

## Methods

### Study protocol

INVASY was a prospective, controlled, randomized, single blind, multicentre study: DDD-CLS versus DDI pacing mode, with crossover after the second recurrence of syncope. The tested hypothesis was that the implantation of a DDD-CLS pacemaker would reduce the recurrence of syncope by at least 50% compared with the placebo implantation of a similar pacemaker programmed in DDI mode at 40 ppm.

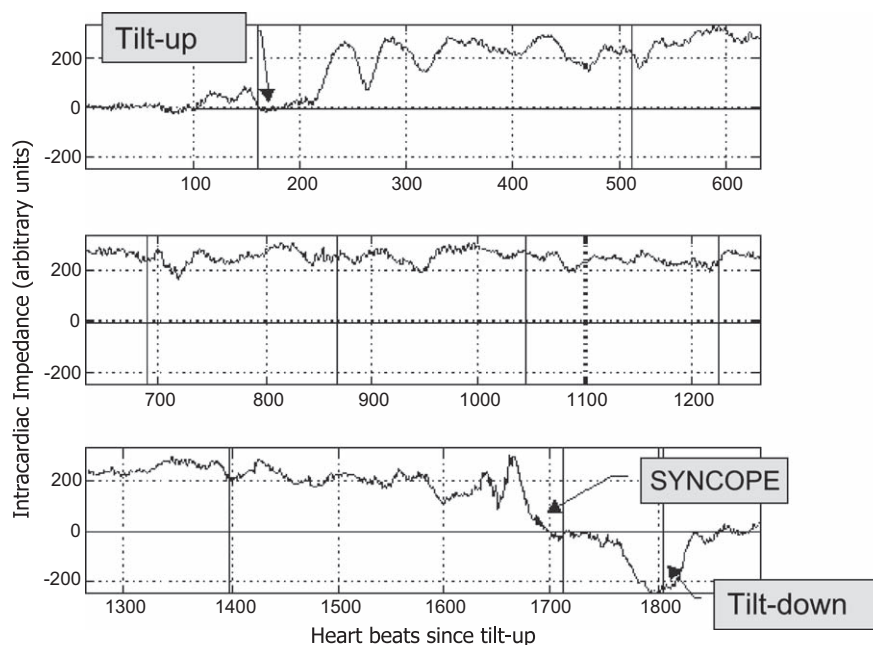
The ethics committee of the institution of the principal investigator approved the study protocol. Because of the clinical characteristics of the enrolled patients (several syncopal recurrences and cardioinhibitory response to head up tilt test), the ethics committee did not allow programming of ODO mode.

All enrolled patients gave their written, informed consent.

### Patient eligibility

Patients had to meet the following criteria for inclusion in the study:

- more than five syncopal episodes and/or >2 in the last year before enrolment;



**Figure 1** Course of intracardiac impedance (contractility) during head up tilt test in a patient with an implanted INOS<sup>2</sup> CLS pacemaker programmed to DDD mode (CLS function OFF – base rate 70 bpm). The impedance signal increases at the beginning of the head up tilt test (tilt-up), sudden falls corresponding with the onset of syncope, and increases again on tilt-down. Impedance signal was downloaded via the pacemaker real-time telemetry and processed by a laptop computer.

- positive type 2A or 2B (in accordance with the VASIS classification) cardioinhibitory response to Head Up Tilt Test (HUTT) [19];
- age > 18 years;
- proven refractoriness to conventional drug therapy and tilt training (when performed).

The diagnosis of VVS was based on a positive tilt test, after exclusion of other possible causes of syncope by complete systematic cardiac and neurological evaluation [20]. Exclusion criteria included: previous myocardial infarction; congestive heart failure and concomitant severe chronic diseases (e.g., neurological disorders, metabolic diseases, neoplasm and life expectancy < 1 year).

### Tilt test protocol

The end point of the HUTT was syncope.

First the Westminster protocol [21,22] (tilting to 60° for 45 min) was used. The blood pressure was measured every minute. If the response was negative at the end of 45 min, 300 µg sublingual nitroglycerine was administered [23] with continued tilt.

Fourteen patients (11 in the CLS arm and three in the placebo arm) were enrolled following a positive response to nitroglycerine. Only patients with a cardioinhibitory positive response, i.e. the type 2

of the VASIS classification [19] were eligible for inclusion.

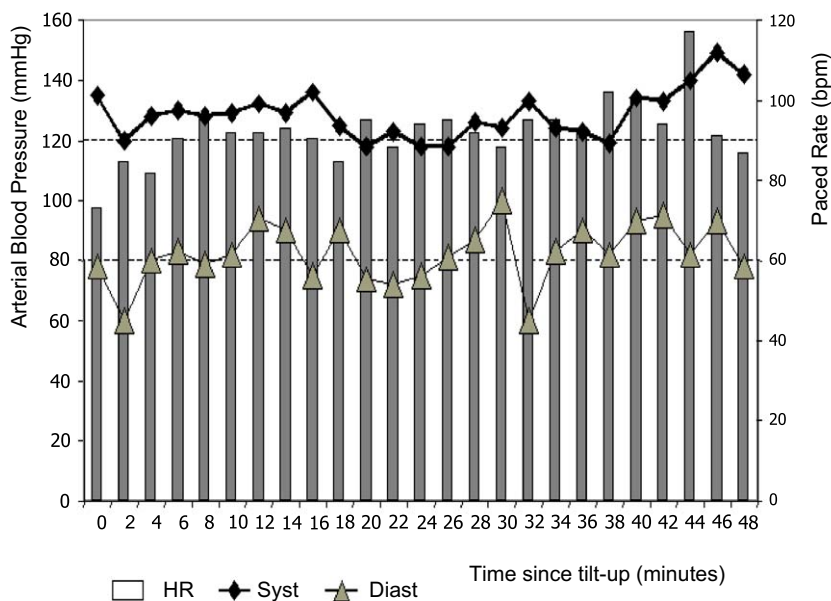
### Study design

Patients were assigned to two study arms according to a central computer-generated 2:1 (DDD-CLS to DDI ratio) randomization list. This kind of randomization was chosen after the positive results observed in the previous CLS Pre-INVASY registry [18].

All patients received an INOS<sup>2</sup> CLS pacemaker. Patients were not informed of the pacemaker's programme, in accordance with a single blind method.

In the CLS arm the device was programmed in DDD-CLS mode. Since the response of the CLS algorithm is self adjusting on intracardiac impedance variations, the parameters programmed by the physician were:

- (1) the maximum sensor driven pacing rate at a value of at least 100 ppm (programmed range 100–120 bpm), in accordance with the experience achieved during the registry and with patient tolerance;
- (2) the maximum sinus tracking rate (programmed range 140–160 bpm) to avoid interference with sinus rate during exercise and emotion;



**Figure 2** Course of systolic and diastolic blood pressure and heart rate histogram during head up tilt test in a patient (same as in Fig. 1) implanted with an INOS<sup>2</sup> CLS pacemaker and programmed in DDD-CLS mode (base rate 60 bpm, upper rate 120 bpm). Few minutes after tilt-up the paced rate becomes dominant (90–100–120 bpm) and syncope does not occur during the test. The fall in diastolic pressure at 30 min from tilt-up is possibly the marker of the height of the vasovagal spell.

(3) the optimal dynamic AV interval at rest (programmed range 120–160 ms) to allow persistent ventricular pacing and intraventricular impedance detection.

In the control group the devices were programmed in DDI mode, (lower rate 40 bpm and AV interval of 150 ms).

Unfortunately, the diagnostic memory of the device used had no capability to store data about syncopal episodes requiring pacing.

Patients in both groups received no medication for syncope. Other drug treatments in progress were continued in both groups without dosage modification.

Patients were followed every 6 months with the same pre-defined protocol. A HUTT was performed after each recurrence of syncope or at the end of the first year.

The *primary end point* of the study was the recurrence of the second syncopal spell.

*Secondary end points included:*

- the predictive value of HUTT for VVS recurrence;
- the effectiveness of CLS pacing during HUTT (time-to-syncope);
- the quality of life [24,25] at 1 year: the quality of life questionnaire included a total of 35 areas, covering health, psychological, physical and lifestyle feelings of the patient. The

evaluation of the answers was based on attributing low and high scores to responses reflecting negative/worsening and positive/improving status, respectively (score range 35–105). All patients were asked to fill the questionnaire at the time of recruitment and at the end of the study.

## Statistical methods

The original assumption to calculate the power of the study was that the CLS paced arm would have a cumulative risk of recurrence of syncope 50% lower than the control group, and that only 75% of the patients included in this latter group would have a recurrence of syncope during the first year of observation.

We anticipated that a total of 100 patients would have to be followed for 1 year to yield a statistically significant reduction in the risk of recurrence of syncope in the CLS paced arm ( $P \leq 0.05$ ).

For the primary analysis, all outcomes were analyzed on the intention-to-treat principle. The time to first syncopal recurrence in the two treatment groups was analyzed by means of Kaplan-Meier event-free curves.

The secondary end points were analyzed by means of the chi-square test (HUTT predictive value) and *t* test for combined estimation of variance (time-to-syncope and quality of life score).

Data are reported as mean  $\pm$  standard deviation, unless otherwise specified.

## Results

### Patient characteristics

Fifty patients were enrolled between May 2000 and June 2002 in 19 Italian hospitals and all were followed for a minimum of 12 months and a maximum of 36 months ( $18.9 \pm 4.2$  months).

Twenty-six patients were enrolled between May 2000 and June 2001. Seventeen in this group were included in the CLS group and nine in the control group. During this period no patients randomized to CLS pacing had syncope, but seven patients in the DDI group experienced at least one syncopal spell.

For this reason the steering committee decided to discontinue randomization in July 2001.

From August 2001 to June 2002 all 24 patients were enrolled only in the CLS arm.

The baseline characteristics of patients in the three groups are summarized in Table 1.

The CLS programmed patients had slightly, but insignificantly, fewer syncopal episodes in the last year before enrolment, than the control group patients. A cardioinhibitory response HUTT with asystole of  $> 3$  s (VASIS 2B) was present in 37 of 41 patients in the CLS group (90%) and in seven of nine patients (78%) in the control group.

As the clinical characteristics of the three groups of patients did not significantly differ, the 41 patients who received CLS therapy were combined in the analysis, versus nine patients in the control group (pacemaker programmed in DDI) (Table 2).

### Primary end point

During the follow-up period (mean  $18.9 \pm 4.2$  month/patient; range 12–36 months), none of

the 41 patients in the CLS arm experienced syncope (0%); four out of 41 patients (9.7%) reported rare mild presyncopal symptoms and two (4.9%) reported rare brief dizziness, without any impairment of daily life. In three patients the pacemaker upper rate was reprogrammed to a lower value because of palpitations. No other clinical complications occurred.

In the control arm, four of nine patients (44%) had two syncopal spells before the end of the first year (mean time to first recurrence 1.5 months; range 0.5–2 months) and they were crossed over to the CLS pacing group after the second spell; three patients (33%) had one syncopal recurrence in the first year (mean time to recurrence 7.3 month; range 4–11 months) and were crossed over to the CLS pacing group at the end of the study period; two patients (22%) experienced only presyncopal symptoms.

The Table 2 summarizes the primary end point data and Fig. 3 shows the Kaplan-Meier actuarial estimation of first recurrence of syncope for the two groups.

The seven patients crossed over to CLS pacing were followed until June 2003 and none of them reported syncope after device reprogramming.

The two remaining patients in the control group were reprogrammed to CLS pacing: one immediately after the end of the study and the second at the 18-month follow-up because of frequent episodes of presyncope.

### Secondary end points

#### Predictive value of HUTT

At the end of the first year, or just before pacing mode crossover, a HUTT was performed in 39/50 patients (30 in CLS and nine in control group) without reprogramming the pacemaker. Eleven patients (all CLS) refused testing.

**Table 1** Baseline clinical characteristics of study population

Clinical Characteristics	Randomized phase		Non-randomized phase
	Control ( <i>n</i> = 9)	CLS ( <i>n</i> = 17)	CLS ( <i>n</i> = 24)
Age (years)	58.3 $\pm$ 16.3	59.2 $\pm$ 19.3	58.8 $\pm$ 18.9
Male, <i>n</i> (%)	5 (55)	10 (53)	12 (50)
Syncopal episodes in last year, median (range)	4 (2–10)	3 (2–7)	3 (2–6)
Trauma secondary to syncope, <i>n</i> (%)	5 (55)	11 (65)	15 (63)
Previous drug treatment, <i>n</i> (%)	3 (33)	6 (35)	8 (33)
Previous tilt training, <i>n</i> (%)	2 (22)	2 (12)	3 (13)
Baseline HUTT			
Type 2A response, <i>n</i> (%)	3 (33)	7 (41)	9 (38)
Type 2B response, <i>n</i> (%)	6 (67)	10 (59)	15 (62)
Asystole $> 3$ , <i>n</i> (%)	8 (89)	16 (94)	21 (88)

*P* = not significant for all groups of data.

**Table 2** Primary outcome events by group (DDD-CLS versus control DDI)

Outcome event	Control	CLS
Patients in analysis, <i>n</i>	9	41
Syncopal recurrence, <i>n</i> (%)	7 (78)	0 (0)
Syncopal episodes		
Total number of episodes, <i>n</i>	11	0
Mean per patient, <i>n</i> ± SD	1.2 ± 0.8	0
Median time to first recurrence, months (range)	4 (0.5–11)	–
Cumulative follow-up (years)	7.25	68.2
Rate of recurrence per year	1.52	0

The protocol was identical to that used at recruitment.

Group I: 15 HUTTs (38%) produced a response concordant with the clinical picture during follow-up – seven were positive (all in the placebo arm and before crossing over) and eight negative (all CLS arm).

Group II: the remaining 24 HUTTs (62%) – 22 CLS arm and two syncope-free in the DDI arm had a positive response with hypotensive presyncopal symptoms, but without asystole because of pacing support.

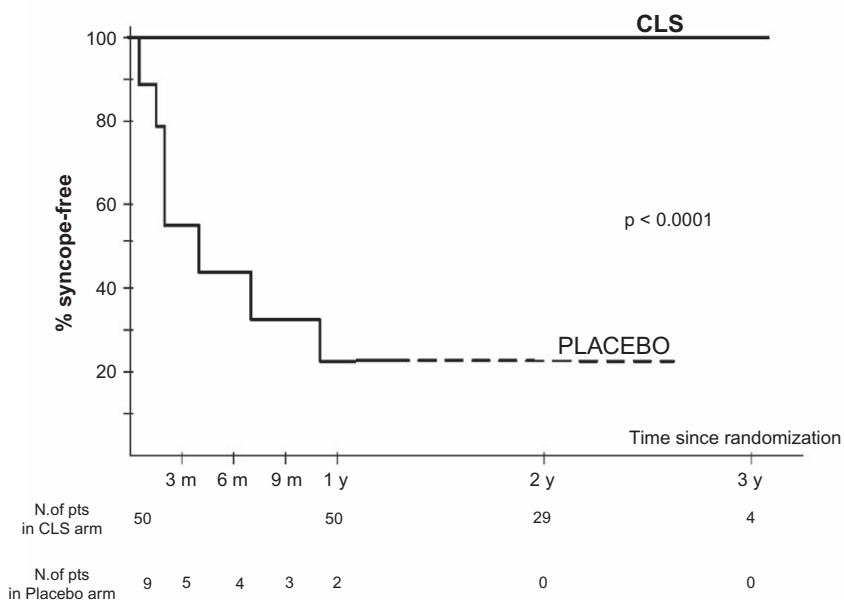
For the 22 patients in the CLS arm the early increase in pacing rate was insufficient to avoid a fall in systolic blood pressure of at least 30% relative to the basal value. None of these patients had reported syncopal spells during follow-up. The

chi-square test performed on these data confirm that HUTT is an unreliable predictor of clinical recurrence of VVS in CLS treated patients ( $P < 0.0001$ ).

**Effect of CLS pacing during HUTT at 1 year of follow-up**

The time from tilt-up to the development of presyncope was measured in 22 patients in the CLS arm in Group II who exhibited a positive response to HUTT at the end of the first year. This time was compared with that recorded during HUTT at recruitment.

The mean time-to-syncope/presyncope was  $19.7 \pm 3.8$  min (range 8–31 min) at 1 year, compared with  $13.9 \pm 4.2$  min (range 5–22 min) at recruitment, a median increase of 42% ( $P < 0.001$ ).



**Figure 3** Probability of remaining free of syncopal recurrences (Kaplan-Meier estimation) in 41 patients in CLS arm and nine patients in the control group.

Further attempts to persuade these patients to undergo additional HUTT with different pacemaker programming failed.

### Quality of life

At recruitment, the QoL score for all patients showed a median of 49 (range 35–57).

After 1 year of CLS therapy, the median QoL score for the 41 treated patients was 85 (range 72–101), with an improvement from 46% to 81% in a normalized scale of QoL.

QoL scores of the two syncope-free patients in the control arm were 44 versus 66 and 51 versus 74, at recruitment and follow-up, respectively.

## Discussion

This study shows that dual-chamber CLS pacing prevents recurrence of vasovagal syncope in patients with a cardioinhibitory response to HUTT. Zero recurrence of syncope during CLS treatment is in accordance with the data achieved in the Pre-INVASY registry [18]. This benefit is maintained for up to 2 years, in the present INVASY study, but it may extend to over 5 years as the results of the Pre-INVASY registry suggest.

Despite this relatively long follow-up, it cannot be excluded that patients implanted with INOS<sup>2</sup> CLS pacemakers could experience some recurrence of syncope during their lives. It is generally accepted that the natural history of VVS is variable with long periods free of recurrences: follow-up for decades would be required to confirm definitively the clinical benefit.

Syncopal history before enrolment and selection criteria were basically similar in all the previous studies (Table 1).

The mean age of treated patients in the INVASY study (59 years) (Table 1) was higher than of those enrolled in VPS-1 (43 years) and VPS-2 (50.8 years) [26,27], similar to those of SYDIT (58.1 years) [28], and lower than those in the VASIS study (64 years) [19].

The follow-up periods (Table 3) are quite variable (range 6–44 months) and may have influenced the outcome of the treated groups.

It appears that the better results of the INVASY study compared with VPS-2 [27] may be related to a different pacing algorithm rather than differences in the length of follow-up or patient age.

In cardioinhibitory vasovagal syncope (VASIS Type 2A and 2B during HUTT) bradycardia/asystole and the associated hypotension develop almost simultaneously, but neuroendocrine mechanisms in the two events are different and somewhat

independent. When a conventional dual-chamber pacemaker, which intervenes on the basis of falling heart rate (as in all studies except INVASY), prevention of syncope may not be optimal. Since the pacemaker must detect the onset and stability of bradycardia (DDD with Rate Drop Response (RDR) algorithm in VPS, VPS II and SYDIT studies) [29,30] or wait until it reaches the hysteresis rate (DDI with Rate Hysteresis in the VASIS study) [19], pacing may be inadequate to prevent syncope as delay allows hypotension to become prominent.

In contrast, CLS detects variations in myocardial contractility at the beginning of vasovagal syncope and reacts quickly with a rate increase after a mean of 4 min from the beginning of the HUTT [31,32], while the mean time for syncope to occur is about 14 min. This timely intervention suppresses the resultant bradycardia and counterbalances the hypotension of decreased venous return by maintaining cardiac output. In patients with dominant vasodepression, syncopal symptoms at the peak of the reflex may occur despite CLS pacing.

These positive results were also documented in other smaller studies in which INOS<sup>2</sup> CLS pacemaker was used to prevent VVS [15,32,33].

### Placebo effect

Our patients in the control group had a percentage of VVS recurrences (78%) higher than that previously reported.

Even if the number of these patients is small, their baseline clinical characteristics were similar to those randomized to CLS stimulation; and clinical recurrence of syncope during follow-up in this group was in accordance with the statistical hypothesis.

The most probable reason for this should be sought in the study protocol. In order to avoid inconsistencies in the data and to assess the efficacy of CLS, or the real influence of the placebo effect of surgery, any pharmacological therapy to suppress or attenuate vasovagal symptoms was not allowed in both groups.

While in other studies,  $\beta$ -blockers were used in SYDIT [28] in the control group and in VASIS [19], VPS-1 [26] and VPS-2 [27] medication was permitted to continue during these studies (Table 3).

### Psychological considerations

The placebo effect of pacemaker implantation is a crucial question raised by the VPS-2 study [27]. Because VVS is neurally-mediated, its occurrence

**Table 3** Syncopal recurrences in major studies on pacing for vasovagal syncope

Study (pacing mode)	F-U (mo.)	Treated group		Control group		P	Treatment in control group
		n	VVS recurrence, n (%)	n	VVS recurrence, n (%)		
VPS study [26] (DDD-RDR) <sup>a</sup>	> 12	27	5 (18.5)	27	16 (59.7)	<0.0001	No pacemaker – drug therapy could be maintained
VASIS study [19] (DDI with hysteresis)	44.4	19	1 (5.2)	23	14 (60.9)	0.0006	No pacemaker – drug therapy could be maintained
SYDIT study [28] (DDD-RDR) <sup>a</sup>	17.3	45	2 (4.4)	46	12 (26.1)	0.004	No pacemaker – β-blocker
VPS II study [27](DDD-RDR) <sup>a</sup>	6	48	16 (33)	52	22 (42)	0.14	Placebo pacemaker (ODO mode) – drug therapy
INVASY study (DDD-CLS)	18.9	41	none (0)	9	7 (78)	<0.0001	Placebo pacemaker (DDI mode) – no drug therapy

<sup>a</sup> RDR, Rate Drop Response algorithm (by Medtronic, Inc., Minneapolis, MN).

in some patients may be influenced by psychological factors. The VPS-2 study showed that in patients with a DDD-RDR device the placebo effect may be important, because the cumulative risk of syncope at 6 months was 31% in the paced group versus 40% in the placebo group (relative risk reduction 30% – not statistically significant). Remarkably, the INVASY study showed that the cumulative risk of syncope at 12 months in patients with the pacemaker programmed in DDI (without medication) was 78%, while the risk dropped to zero in the treated CLS group.

### Head up tilt

The value of HUTT in vasovagal syncope remains controversial [21–23,34]. The INVASY and other studies have demonstrated the inability of tilt testing to predict adverse events in syncopal patients treated with pacing [19,26]. A positive HUTT, but no spontaneous recurrence of syncope during follow-up, was the most frequent result in our study (62%).

During vasovagal syncope induced by HUTT, CLS showed some possible effectiveness in increasing the time-to-syncope by 42% compared with that at enrolment. The two tests were performed 1 year apart so that the influence of a tilt training effect is unlikely. The effect of CLS pacing in the prevention of vasovagal syncope induced by HUTT was recently confirmed by Griesbach et al. in a group of 22 syncopal patients using a particularly aggressive three step tilt protocol [32].

### Quality of life

The improvement of the quality of life in the CLS paced patients was great and in accordance with the clinical outcome. The possible placebo effect of surgery significantly and positively influenced the quality of life of the two patients in the control arm that did not experienced syncopal recurrence during follow-up.

### Study limitations

The decision of the steering committee to prematurely to discontinue the randomization, forced by the relevant number of syncopal recurrences in the control group, caused the low number of control subjects, which represents the main limitation of the study.

The total population enrolled in the study was relatively low because a substantial number of



eligible patients were included in the Pre-INVASY registry.

Moreover, screening logs were not maintained throughout the study recruitment period to calculate the total of potentially eligible patients. Recurrences of presyncope and dizziness were not collected at enrolment, because they are difficult to evaluate and because patients are more likely to remember syncope rather than dizziness.

Finally, as the two syncope-free patients in the control arm were crossed over early to CLS pacing, the follow-up of patients in DDI mode is limited to 1 year.

## Conclusions

The INVASY study, supported by the Pre-INVASY registry, has yielded favourable long-term results, using Closed Loop Stimulation, whose rate response is driven by variations in myocardial contractility, in prevention of vasovagal syncope.

Patients paced with Closed Loop Stimulation did not exhibit any recurrence of syncope and had an improved quality of life. Further follow-up is required to confirm lifetime benefit.

## Appendix

### Pre-INVASY registry and INVASY study Participating Centers and Investigators

Ospedale Civile, Acqui Terme: Pierluigi Roncarolo; Ospedale S.M. Annunziata, Bagno a Ripoli: Leandro Chiodi; Ospedale degli Infermi, Biella: Marco Marcolongo, Davide Torta; Ospedale S.S. Trinità, Borgomanero: Marco Zanetta; Policlinico S. Orsola, Bologna: Giuseppe Boriani; Ospedale S. Giovanni, Cagliari: Raimondo Pirisi; Ospedale Civile, Chivasso: Antonio Mazza; Ospedale Careggi, Firenze: Paolo Marconi; Ospedale Civile, Legnago: Diran Igidbashian; Ospedale Policlinico, Milano: Salvatore Romano, Ruggero Manfredini; Centro Cardiologico Monzino, Milano: Claudio Tondo; Policlinico, Monza: Massimo Arlotti, Marcello Chimienti; Ospedale Monaldi, Napoli: Luigi Zamparelli, Luciano Cioffi; Azienda Ospedaliera, Parma: Angelo Carboni; Ospedale di Cisanello, Pisa: Maria Grazia Bongiorno; Ospedale S. Maria degli Ungheresi, Polistena: Rocco Polimeni;

Ospedale degli Infermi, Rimini: Sergio Sermasi; Ospedale S. Giovanni-Addolorata, Roma: Giovanni Del Giudice; Ospedale Generale Provinciale, Saronno: Adriano Croce; Ospedale S.S. Annunziata, Sassari: Giovanni Battista Tola, Pierfranco Terrosu; Ospedale San Paolo, Savona: Paolo Bellotti, Massimo Gazzarata; Ospedale Maggiore, Torino: Luigi Libero, Marcella Jorfida; Ospedale Giovanni Bosco, Torino: Mauro Bensoni; Ospedale Galmarini, Tradate: Daniela Barbieri, Sergio Lombroso; Ospedale Panico, Tricase: Antonio Galati; Ospedale di Circolo, Varese: Jorge Salerno, Salvatore Caico; Stabilimento Ospedaliero, Verbania: Enzo Maria Bianchi, Renato Glenzer; Ospedale Civile, Vigevano: Francesco Zolezzi, Roberto Negro; Ospedale Belcolle, Viterbo: Massimo Sassara, Fernando De Luca.

### Organizing Committee (Steering Committee)

E. Occhetta (Chairman), R. Audoglio, M.G. Bongiorno, L. Chiodi, S. Favale, S. Romano.

### External Monitoring and Safety Committee

A. Malliani and R. Furlan.

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