Randomized Placebo Controlled Trial of Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope. SPAIN Study.

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NO CONFLICTS OF INTEREST
VVS PM Randomized not placebo controlled published studies

**PM vs No Therapy**

**VPS**

*Connolly S.J. et al.*

_JACC 1999;33:16-20_

**PM vs No Therapy**

**VASIS**

*Sutton R. et al.*

_Circ 2000;102:294-99_

**PM vs MED TREAT.**

**SYDIT**

*Ammirati F. et al.*

_Circ 2001;104:52-57_
Long-term outcome of patients with asystole induced by head-up tilt test

Kaplan-Meier analysis of recurrence

PM vs no-PM: p=0.7

Baron-Esquivias G; Eur Heart J, 2002; 23: 483-9
VVS PM Randomized double blinded RCT’s

PM on vs PM off
VPS II (n=100)
Connolly S.J. et al.
JAMA 2003; 289: 2224-9

PM on vs PM off
SYNPACE (n=29)
Raviele A. et al.
Eur Heart J 2004; 25: 1741-8
During VVS:

VV → Venous return → Sympathetic compensatory tone → Inotropic effect → Chronotropic state

- Venous return
- Sympathetic compensatory tone
- Inotropic effect
- Chronotropic state

**Response of Closed Loop Stimulation**

**Closed Loop Stimulation**

**DDD-CLS PM and syncope**

- HEART RATE
- CONTRACTILITY

**NO SYNCOPE**
DDD-CLS in VVS

PM on vs PM off
INVASY
Ochetta E. et al.
Europace 2004; 6: 538-47

DDD-CLS vs DDD convencional

Palmisano P et al.
Europace 2012; 14: 1038-43
DDD-CLS in VVS

DDD-CLS vs DDD convencional

Kanjwal K et al.

DDD-CLS pre vs DDD-CLS on

Bortnik M. et al.
J Cardiovasc Med 2012; 13; 242-5
# Indication for cardiac pacing in patients with undocumented reflex syncope

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2) Tilt-induced cardioinhibitory syncope</strong></td>
<td>IIs</td>
<td>B</td>
</tr>
<tr>
<td>Pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age &gt;40 years after alternative therapy has failed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3) Tilt-induced non-cardioinhibitory syncope</strong></td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5) Tilt-induced cardioinhibitory syncope</strong></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients with cardioinhibitory vasovagal syncope, dual-chamber pacing is the preferred mode of pacing.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eur Heart J 2009; 30: 2631-71
Eur Heart J 2013;34:2281-2329
To determine in a randomized prospective double-blind placebo-controlled cross-over multicentre trial the utility of DDD-CLS pacing in patients with cardioinhibitory refractory neurally reflex VVS.
METHODS
INCLUSION CRITERIA: (Patients must fulfil all those 8 criterias)

1) At least 5 previous neuromediated syncope episodes (at least 2 of them occurring within last year).
2) Positive Tilt-test, cardioinhibitory response: Heart rate <40 bpm for at least 10’’ or > 3’’ pause.
3) ≥ 40 years old.
4) Absence of cardiomyopathy and normal 12-lead electrocardiogram
5) No other type of pacemaker indication.
6) Geographical stability and availability to assist to follow-ups.
7) Signed consent form.
8) None any of the following contraindications: ß-blockers drug treatment, Chronicle polyneuropathy and any contraindication to DDD or DDDR pacing.

EXCLUSION CRITERIA:

1) Patients that not fulfil any of the inclusion criteria described above.
2) Patients with syncope caused by carotid sinus hypersensitivity.
3) Other cause of syncope (known cause and different from neuromediated syncope).
4) Patients that participate in any other investigation study.
5) Pregnant or breast-feeding women that are not making use of at least 2 contraceptive methods.
All patients underwent:

1) Complete physical exam including orthostatic test.
2) Carotid sinus massage.
3) 12-lead electrocardiogram.
4) 2D-Doppler echocardiography
5) 24-h Holter monitoring

All normal

TILT-TABLE TEST

HUT Protocols:

1.- Basal, 60º, 45 minutes

or

2.- Italian (400 µgr nitroglicerin)
Central Randomization
2 blind investigators/centre

Enrollment

GROUP A

1st Allocation

Allocated initially to DDD-CLS

Follow-up

12 months or till 3 syncope in one month

2nd Allocation

Change to DDI-sham pacing mode

Follow-up

12 months or till 3 syncope in one month

Analysis

GROUP B

Allocated initially to DDI-sham

Follow-up

12 months or till 3 syncope in one month

Analysis

Analysis
Primary Efficacy Outcome:

To determine the effect of DDD-CLS in reducing by >50% the overall number of syncope episode compared to the DDI sham placebo mode.

Co-Primary efficacy outcome:

- Time to first recurrence of syncope in both pacing mode sequences: Group A vs Group B.

- Time to first recurrence in both groups (DDD-CLS vs DDI).
DATA

Data was collected and analysed by an independent database company, PIVOTAL S.L.

Continuous variables were expressed as median [interquartile range IQ] when their distribution was not normal, and as mean ± SD otherwise **Shapiro-Wilk** test, and these variables were compared by **Mann–Whitney** 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 analyse the primary efficacy endpoint, differences between groups A and B, **Mainland-Gart** and **Prescott** test were used.

The cumulative risk of syncope over time was estimated using the **Kaplan–Meier** procedure and **long-Rank** test, for correlation between treatment and time to recurrence.

A two-tailed P value<0.05 was considered significant. Predefined number of patients: 50

Data were analysed with version 9.4 of SAS® software.
RESULTS
Enrollment

GROUP A

Randomized (n=54)

1st Allocation

Allocated initially to DDD-CLS (n=22)
Received DDD-CLS PM (n=22)

Follow-up

Lost of Follow-up during DDD-CLS pacing (n=1)
Did not accept blind at the end of 12 months (n=1)

2nd Allocation

Change to DDI pacing mode (n=20)

Follow-up

Follow-up during DDI pacing (n=20)

Analyzed (n=21)

GROUP B

Allocated initially to DDI (n=32)
Received DDI PM (n=32)

Follow-up

Lost Follow-up during DDI pacing (n=2)
Protocol deviation (n=4)
Insufficient data available (n=2)

2nd Allocation

Change to DDI-CLS pacing mode (n=24)

Follow-up

Follow-up during DDI-CLS pacing (n=24)

Analyzed (n=25)
### CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=46</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$56 \pm 10.6$ y.o.</td>
</tr>
<tr>
<td>Males</td>
<td>47.8%</td>
</tr>
<tr>
<td>Previous syncopal episodes (SE)</td>
<td>12 [IQ9, IQ20]</td>
</tr>
<tr>
<td>Previous SE during last 12 months</td>
<td>4.5 [IQ2, IQ7]</td>
</tr>
<tr>
<td>Asystole during HUT (%)</td>
<td>35 (76)</td>
</tr>
<tr>
<td>Asystole duration (sec)</td>
<td>15 [IQ10, IQ26]</td>
</tr>
</tbody>
</table>
## CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Group A: DDD-CLS $\rightarrow$ DDI (n=21)</th>
<th>Group B: DDI $\rightarrow$ DDD-CLS (n=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y.o.)</td>
<td>56.9 ± 10.3</td>
<td>55.9 ± 11.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 [IQ66, IQ90]</td>
<td>67 [IQ61, IQ83]</td>
<td>0.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 ± 10.8</td>
<td>164.7 ± 8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>9 (42.8)</td>
<td>13 (52)</td>
<td>0.5</td>
</tr>
<tr>
<td>High Blood Pressure (%)</td>
<td>6 (28)</td>
<td>8 (32)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Previous Syncopal Episodes (SE)</td>
<td>12 [IQ10, IQ20]</td>
<td>10 [IQ8, IQ20]</td>
<td>0.8</td>
</tr>
<tr>
<td>Previous SE during last 12 months</td>
<td>4.5 [IQ3, IQ7.5]</td>
<td>4.5 [IQ2, IQ6]</td>
<td>0.5</td>
</tr>
<tr>
<td>Orthostatic test</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Asystole in HUT (%)</td>
<td>16 (79)</td>
<td>19 (76)</td>
<td>1.0</td>
</tr>
<tr>
<td>Asystole duration (sec)</td>
<td>14.3 [IQ7, IQ29]</td>
<td>15 [IQ10, IQ22]</td>
<td>0.9</td>
</tr>
</tbody>
</table>
## Primary Efficacy Outcome

### Mailand-Gard Test (CI 95%)

<table>
<thead>
<tr>
<th></th>
<th>1st period of treatment</th>
<th>2nd period of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% reduction in the number of syncopal episodes</td>
<td>72.22 (95%CI 46.52, 90.31)</td>
<td>0.00</td>
</tr>
<tr>
<td>≥ 50% reduction in the number of syncopal episodes</td>
<td>27.78 (95%CI 9.69, 53.48)</td>
<td>100 (95%CI 39.76, 100.00)</td>
</tr>
</tbody>
</table>

\[ p = 0.0172 \]

### Prescott analysis

<table>
<thead>
<tr>
<th></th>
<th>Prefers the 1st period (n=18)</th>
<th>Prefers the 2nd period (n=4)</th>
<th>Does not have preference (n=7)</th>
<th>Total (n=29)</th>
<th>Fisher test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: DDD-CLS&lt;&lt;DDI</td>
<td>13 (72.22)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>13 (44.83)</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>Group B: DDI&gt;&gt;DDD-CLS</td>
<td>5 (27.78)</td>
<td>4 (100.00)</td>
<td>7 (100.00)</td>
<td>16 (25.17)</td>
<td></td>
</tr>
</tbody>
</table>
**Primary Efficacy Outcome**

> 50% Reduction Syncope Burden

- **Group A**: DDD-CLS --> DDI Sham
- **Group B**: DDI Sham --> DDD-CLS

**Mailand-Gard Test**
- $p = 0.0172$

**Prescott analysis**
- $p = 0.0003$

Proportion of patients with > 50% reduction in syncope burden
**Co-Primary Efficacy Outcome (DDD-CLS vs DDI)**

**Number of patients suffering syncopal recurrence**

<table>
<thead>
<tr>
<th></th>
<th>DDD-CLS (n=46)</th>
<th>DDI-SHAM (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients without syncope</strong></td>
<td>42 (91.30%)</td>
<td>25 (54.35%)</td>
</tr>
<tr>
<td><strong>Patients with syncope</strong></td>
<td>4 (8.70%)</td>
<td>21 (45.65%)</td>
</tr>
</tbody>
</table>

**DDD-CLS pacing mode**

- Number of patients: 46
- Number of patients without events: 42 (91.30%)
- Number of patients with events: 4 (8.70%)
Co-Primary Efficacy Outcome (Group A vs B)

Group B: 9.30 months (95% CI: 6.21 to NA)  
Group A: 29.15 months (95% CI: 15.34 to 29.19)  
p = 0.0158
Co-Primary Efficacy Outcome (DDD-CLS vs DDI)

**DDD-CLS pacing mode**: Not applicable

**DDI pacing mode**: 9.30 months (95% CI, 6.61, 19.074) Log-rank test: p <0.0001

![Graph showing syncope event rates over months since randomization](image-url)
## Co-Primary Efficacy Outcome (DDD-CLS vs DDI)

<table>
<thead>
<tr>
<th>Time to first syncope (Median (95%CI))</th>
<th>DDD-CLS pacing mode</th>
<th>DDI sham pacing mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA (12.99, NA)</td>
<td>9.30 (6.61, 19.07)</td>
<td></td>
</tr>
</tbody>
</table>

| IQ25% - 75%                             | 14.04 - NA           | 2.91 – 14.14         |

| Odds Ratio                              | 0.1133 (95% CI 0.034897, 0.368361) | p= 0.0001             |

| Risk of Syncopal Recurrence (1/OR)      | 8.82                             |
| (times greater DDI than DDD-CLS)        |                                  |

| Absolute Risk Reduction                  | 37%                              |
| (45.65% – 8.70%= 37%)                    |                                  |

| NNT = (1/ARR) * 100                     | 2.7                              |

| Cox model over time to event            | Hazard ratio (95% CI)            |
| DDI vs DDD-CLS                          | 6.7281 (95%CI 2.2905, 19.7630)   | p=0.0005}
CONCLUSION

DDD-CLS pacing compared to sham pacing in patients ≥40 yo with cardio-inhibitory refractory reflex VV syncope:

✓ Significantly reduced syncope burden.

✓ 7-fold reduction in the recurrence of syncope.

✓ Significantly prolonged time to 1st syncope recurrence.
AKNOWLEDGMENTS

INSTITUTIONS & INVESTIGATORS

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