SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA | Agencia de Investigación

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

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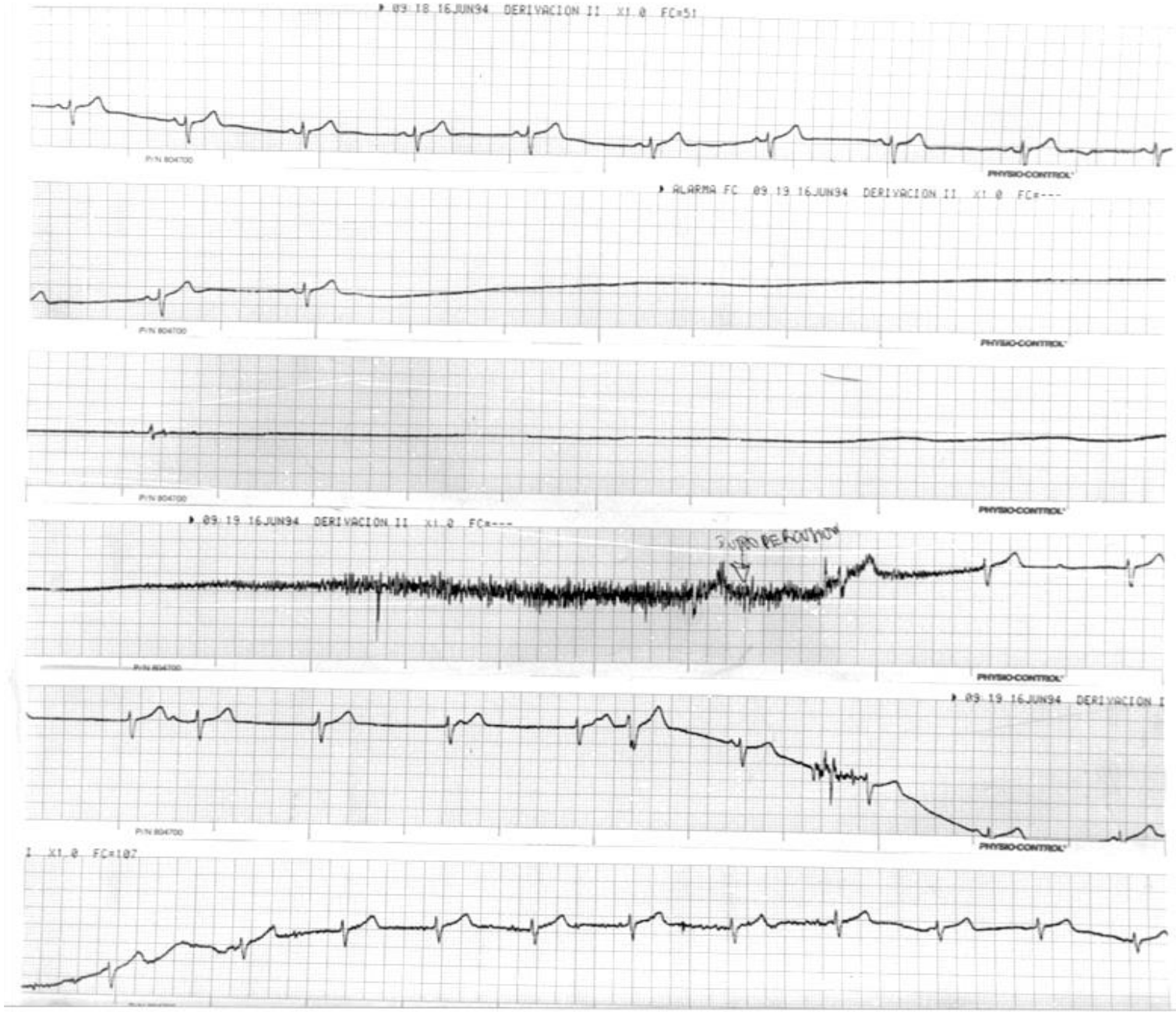
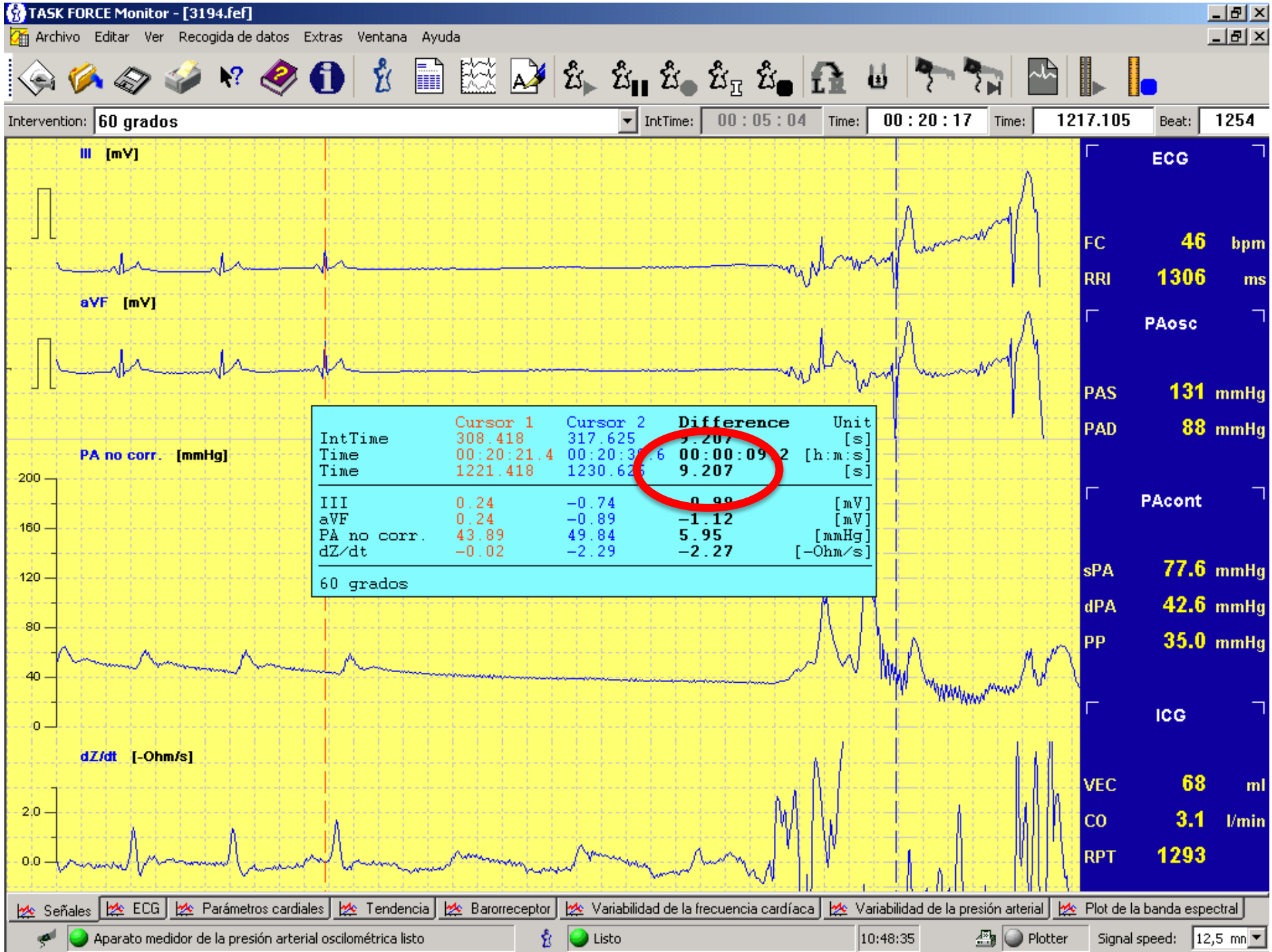
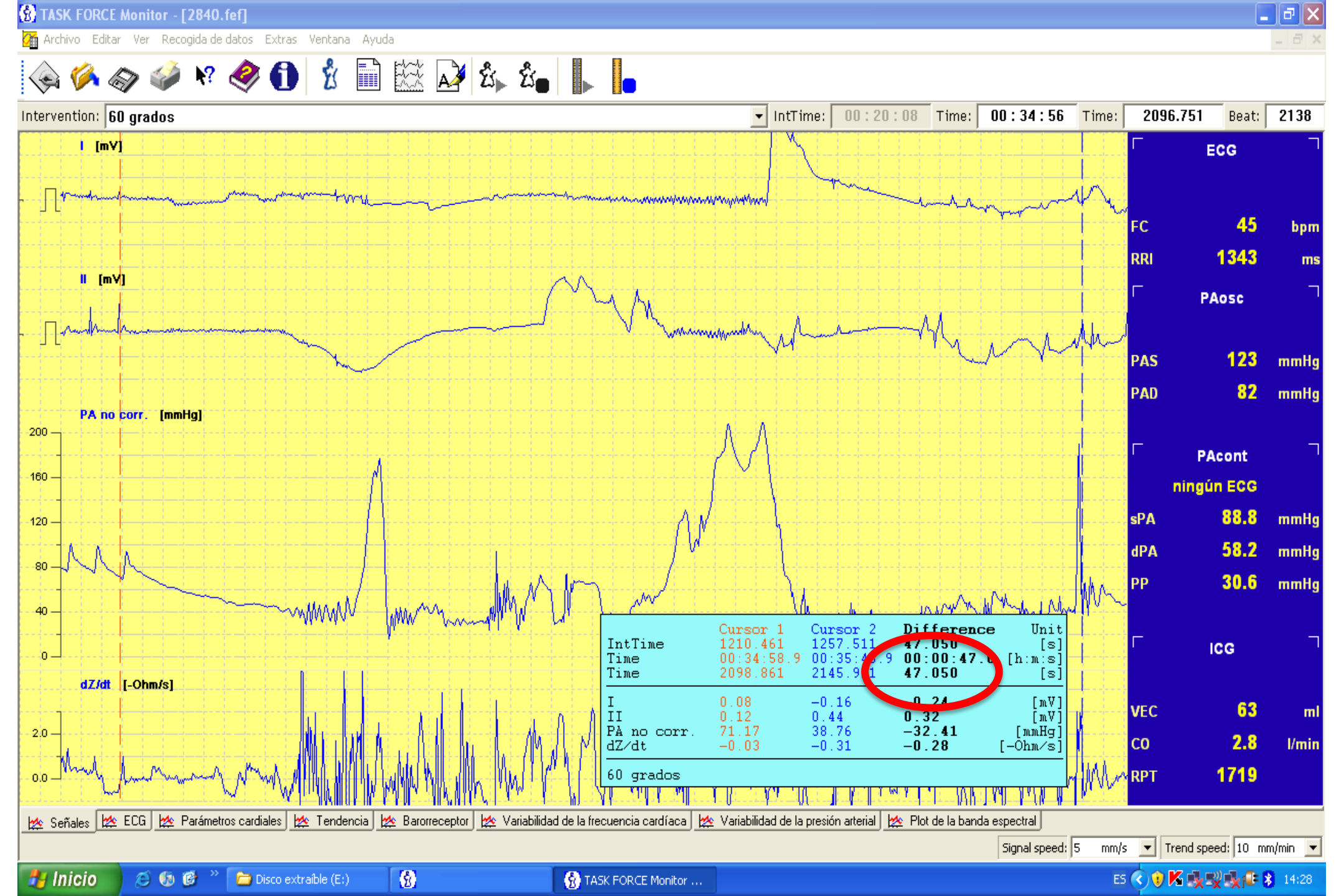
Rafael Romero-Rodriguez MD

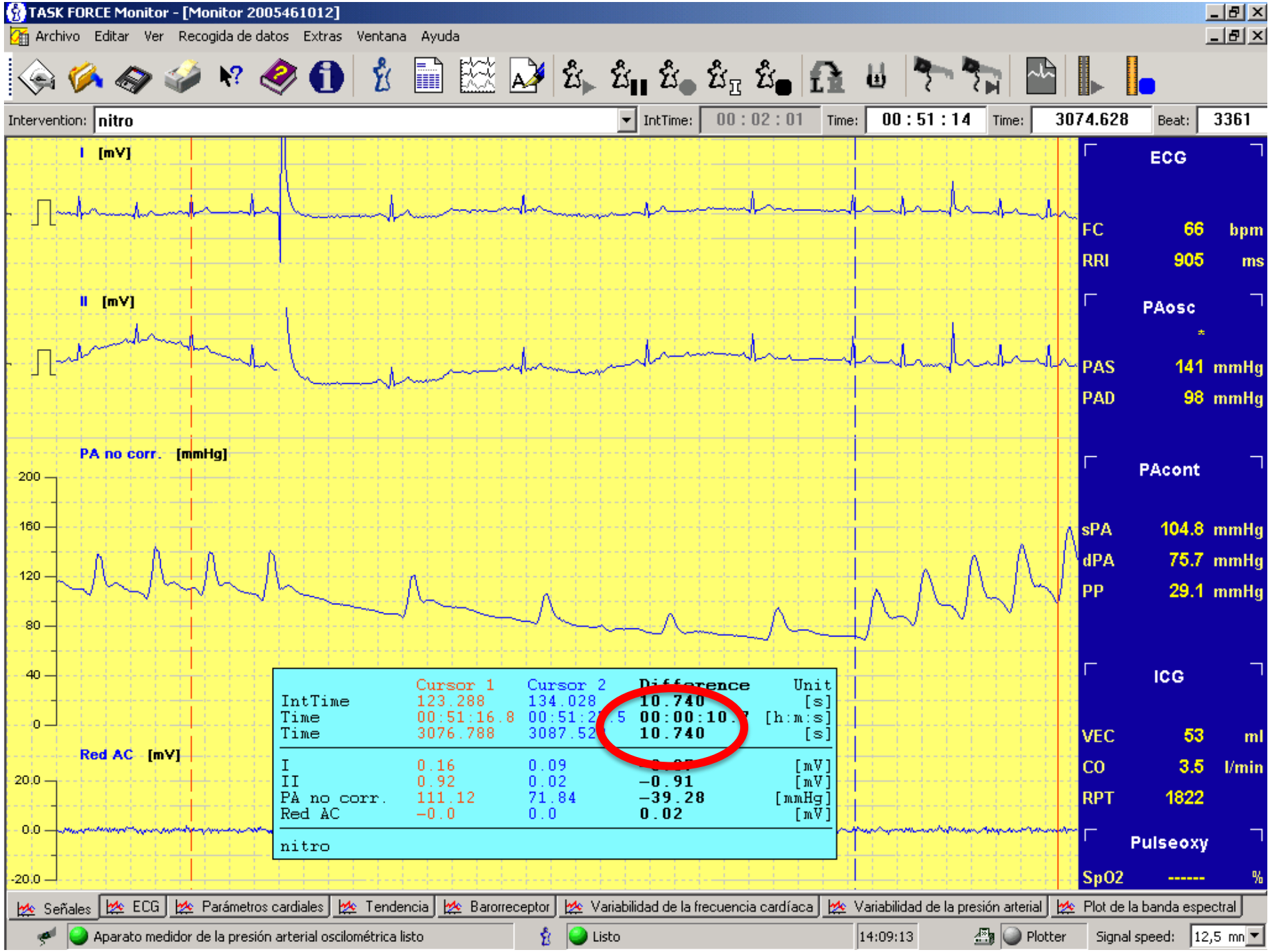
NO CONFLICTS OF INTEREST

30.20 sec


09 18 16JUN94 DERIVACION II X1.0 FC=51
ALARMA FC 09 19 16JUN94 DERIVACION II X1.0 FC=---
09 19 16JUN94 DERIVACION II X1.0 FC=---
09 19 16JUN94 DERIVACION I
I X1.0 FC=107
PHYSIO-CONTROL


TASK FORCE Monitor - [3194.fef]
Archivo Editar Ver Recogida de datos Extras Ventana Ayuda
Intervention: 60 grados
IntTime: 00 : 05 : 04
Time: 00 : 20 : 17
Time: 1217.105
Beat: 1254
III [mV]
aVF [mV]
PA no corr. [mmHg]
dZ/dt [-Ohm/s]
200
160
120
80
40
0
2.0
0.0
Cursor 1 Cursor 2 Difference Unit
IntTime 308.418 317.625 9.207 [s]
Time 00:20:21.4 00:20:30.6 00:00:09.2 [h:m:s]
Time 1221.418 1230.625 9.207 [s]
III 0.24 −0.74 −0.98 [mV]
aVF 0.24 −0.89 −1.12 [mV]
PA no corr. 43.89 49.84 5.95 [mmHg]
dZ/dt −0.02 −2.29 −2.27 [-Ohm/s]
60 grados
ECG
FC 46 bpm
RRI 1306 ms
PAosc
PAS 131 mmHg
PAD 88 mmHg
PAcont
sPA 77.6 mmHg
dPA 42.6 mmHg
PP 35.0 mmHg
ICG
VEC 68 ml
CO 3.1 l/min
RPT 1293
Señales ECG Parámetros cardiales Tendencia Barorreceptor Variabilidad de la frecuencia cardíaca Variabilidad de la presión arterial Plot de la banda espectral
Aparato medidor de la presión arterial oscilométrica listo
Listo
10:48:35
Plotter
Signal speed: 12,5 mm


TASK FORCE Monitor - [2840.fef]
Archivo Editar Ver Recogida de datos Extras Ventana Ayuda
Intervention: 60 grados
IntTime: 00 : 20 : 08
Time: 00 : 34 : 56
Time: 2096.751
Beat: 2138
I [mV]
II [mV]
PA no corr. [mmHg]
200
160
120
80
40
0
dZ/dt [-Ohm/s]
2.0
0.0
ECG
FC 45 bpm
RRI 1343 ms
PAosc
PAS 123 mmHg
PAD 82 mmHg
PAcont
ningún ECG
sPA 88.8 mmHg
dPA 58.2 mmHg
PP 30.6 mmHg
ICG
VEC 63 ml
CO 2.8 l/min
RPT 1719
Cursor 1 Cursor 2 Difference Unit
IntTime 1210.461 1257.511 47.050 [s]
Time 00:34:58.9 00:35:45.9 00:00:47.0 [h:m:s]
Time 2098.861 2145.911 47.050 [s]
I 0.08 -0.16 -0.24 [mV]
II 0.12 0.44 0.32 [mV]
PA no corr. 71.17 38.76 -32.41 [mmHg]
dZ/dt -0.03 -0.31 -0.28 [-Ohm/s]
60 grados
Señales
ECG
Parámetros cardiales
Tendencia
Barorreceptor
Variabilidad de la frecuencia cardíaca
Variabilidad de la presión arterial
Plot de la banda espectral
Signal speed: 5 mm/s
Trend speed: 10 mm/min
Inicio
Disco extraíble (E:)
TASK FORCE Monitor ...
ES
14:28


TASK FORCE Monitor - [Monitor 2005461012]
Archivo Editar Ver Recogida de datos Extras Ventana Ayuda
Intervention: nitro
IntTime: 00 : 02 : 01
Time: 00 : 51 : 14
Time: 3074.628
Beat: 3361
I [mV]
II [mV]
PA no corr. [mmHg]
Red AC [mV]
200
160
120
80
40
0
20.0
0.0
-20.0
ECG
FC 66 bpm
RRI 905 ms
PAosc
*
PAS 141 mmHg
PAD 98 mmHg
PAcont
sPA 104.8 mmHg
dPA 75.7 mmHg
PP 29.1 mmHg
ICG
VEC 53 ml
CO 3.5 l/min
RPT 1822
Pulseoxy
SpO2 ------ %
Cursor 1 Cursor 2 Difference Unit
IntTime 123.288 134.028 10.740 [s]
Time 00:51:16.8 00:51:2 00:00:10. [h:m:s]
Time 3076.788 3087.52 10.740 [s]
I 0.16 0.09 [mV]
II 0.92 0.02 -0.91 [mV]
PA no corr. 111.12 71.84 -39.28 [mmHg]
Red AC -0.0 0.0 0.02 [mV]
nitro
Señales
ECG
Parámetros cardiales
Tendencia
Barorreceptor
Variabilidad de la frecuencia cardíaca
Variabilidad de la presión arterial
Plot de la banda espectral
Aparato medidor de la presión arterial oscilométrica listo
Listo
14:09:13
Plotter
Signal speed: 12,5 mm

VVS PM Randomized not placebo controlled published studies

PM vs No Therapy

VPS

Connolly S.J. et al.

JACC 1999;33:16-20

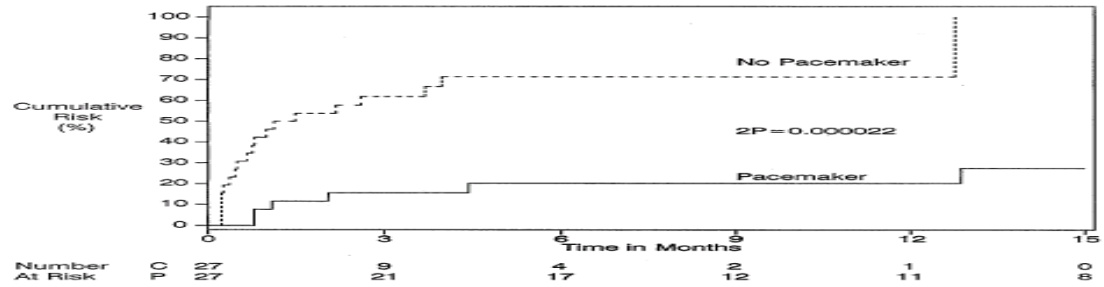


Figure 1. Kaplan-Meier plots of the time to the first recurrence of syncope among 27 patients randomized to receive a pacemaker and 27 patients randomized to not receive a pacemaker by intention-to-treat analysis.

PM vs No Therapy

VASIS

Sutton R. et al.

Circ 2000;102:294-99

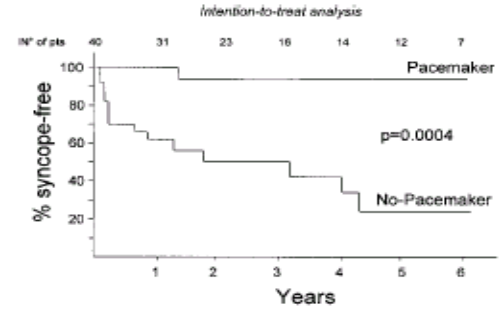


Figure 2. Kaplan-Meier estimates of probability of remaining free of syncopal recurrences in 19 patients in pacemaker arm and 23 patients in no-pacemaker arm in intention-to-treat analysis.

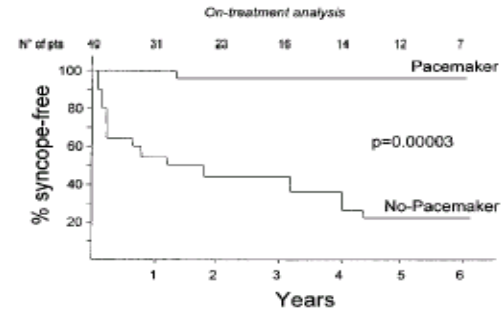


Figure 3. Kaplan-Meier estimates of probability of remaining free of syncopal recurrences in 22 patients in pacemaker arm and 20 patients in no-pacemaker arm in on-treatment analysis.

PM vs MED TREAT.

SYDIT

Ammirati F. et al.

Circ 2001;104:52-57

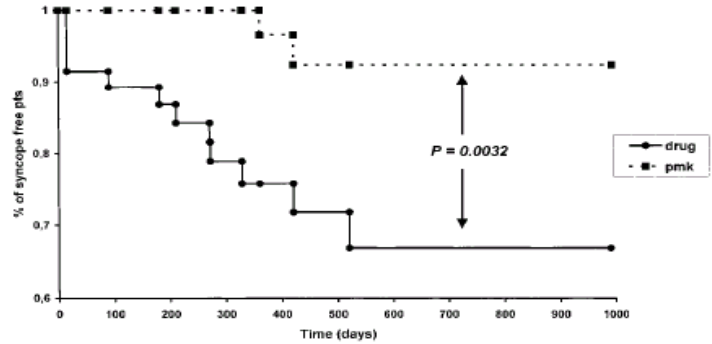
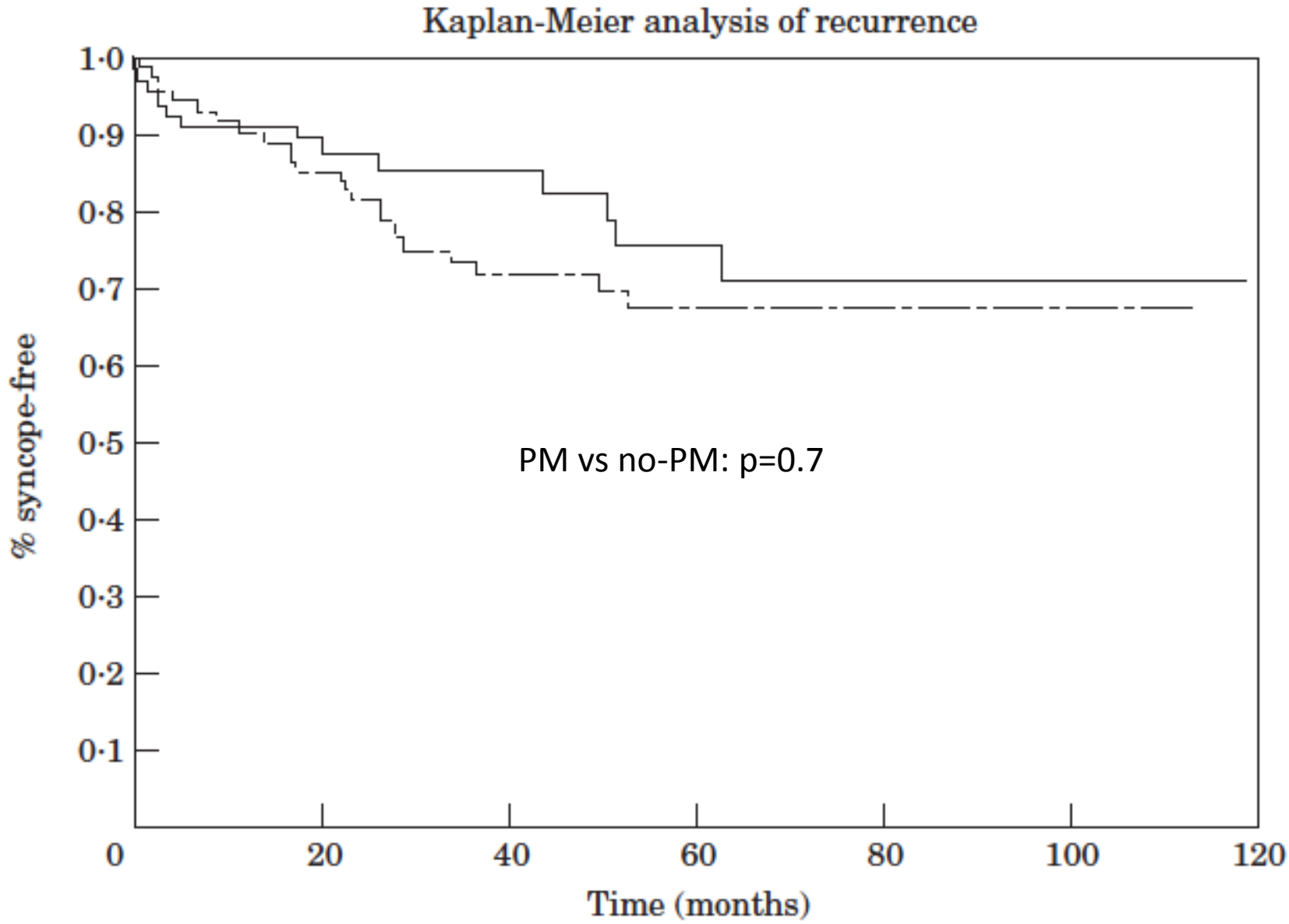


Figure 1. Kaplan-Meier estimates of probability of remaining free of syncopal recurrences in 46 patients (pts) in pacemaker (pmk) arm and 47 patients in pharmacological arm in intention-to-treat analysis.

Long-term outcome of patients with asystole induced by head-up tilt test



Baron-Esquivias G; Eur Heart J, 2002; 23: 483-9

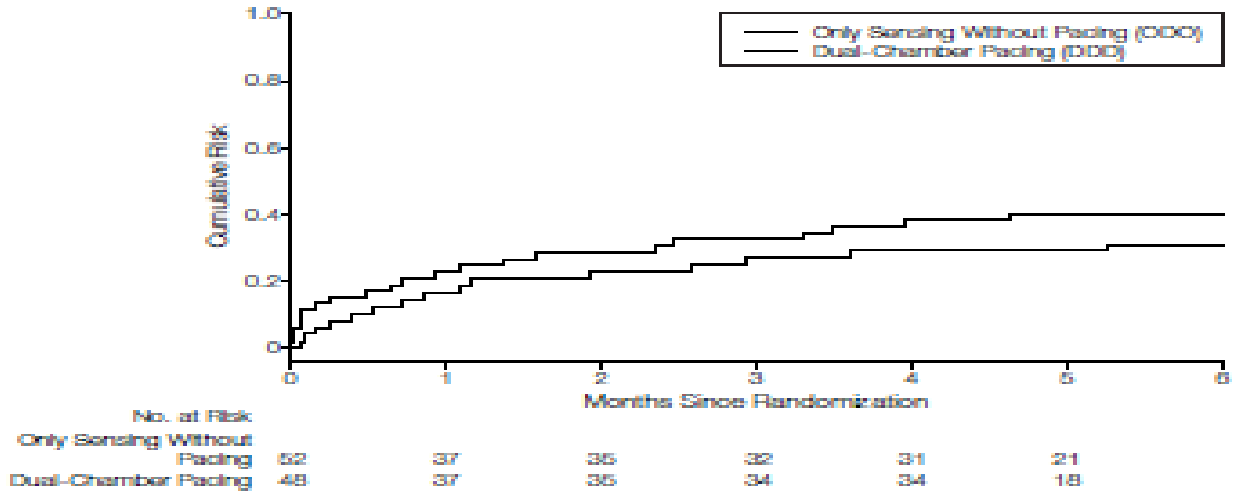
VVS PM Randomized double blinded RCT's

PM on vs PM off

VPS II (n=100)

Connolly S.J. et al.

JAMA 2003; 289: 2224-9



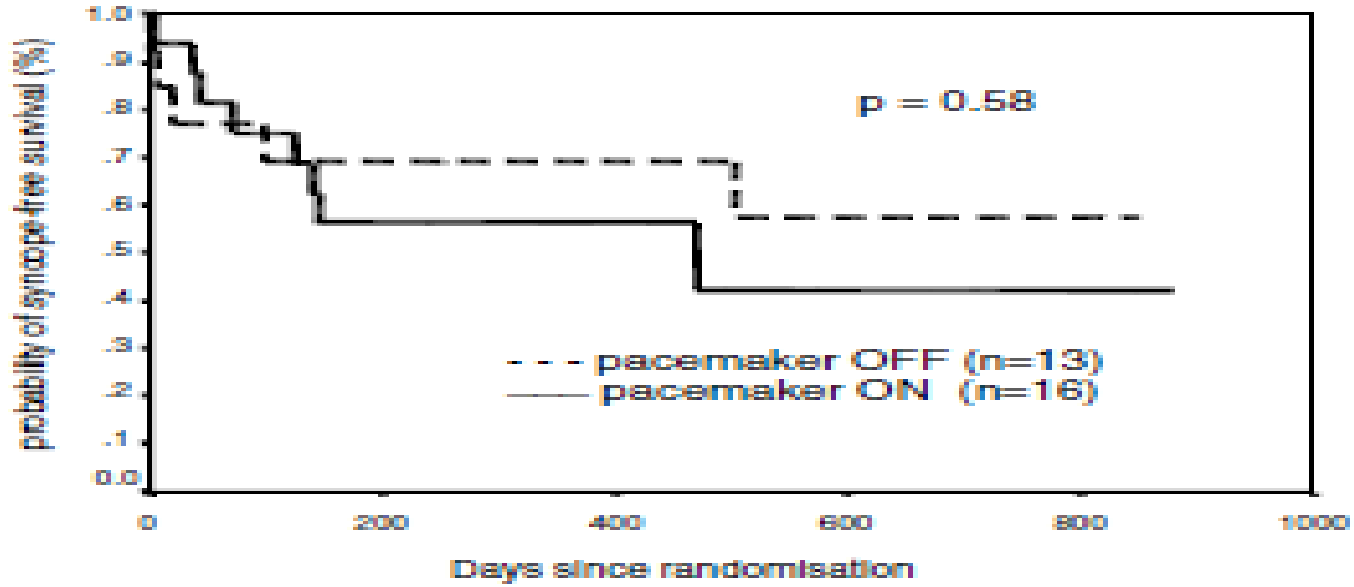
Relative risk reduction of 30.2% (95% confidence interval, −33.2% to 63.4%; log-rank $P=.14$).

PM on vs PM off

SYNPACE (n=29)

Raviele A. et al.

Eur Heart J 2004; 25: 1741-8



DDD-CLS PM and syncope

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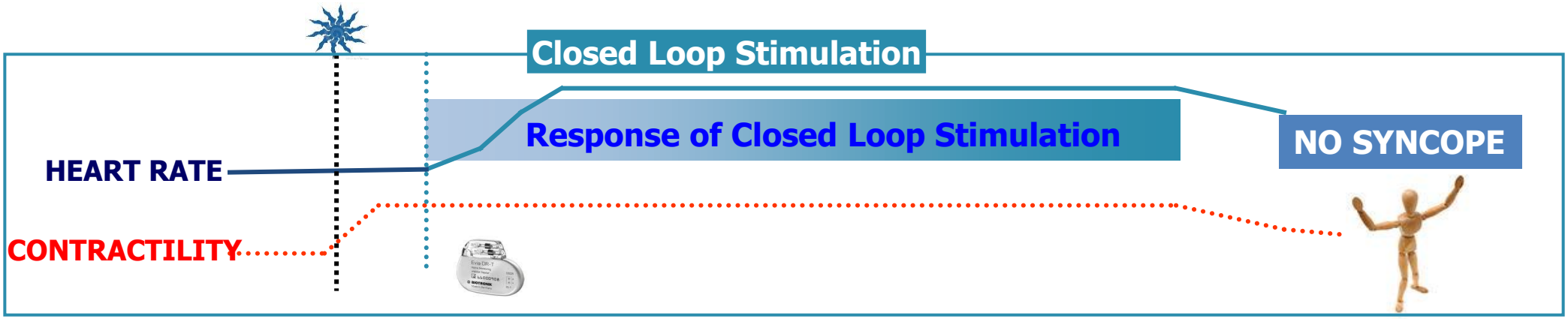
- During VVS:

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



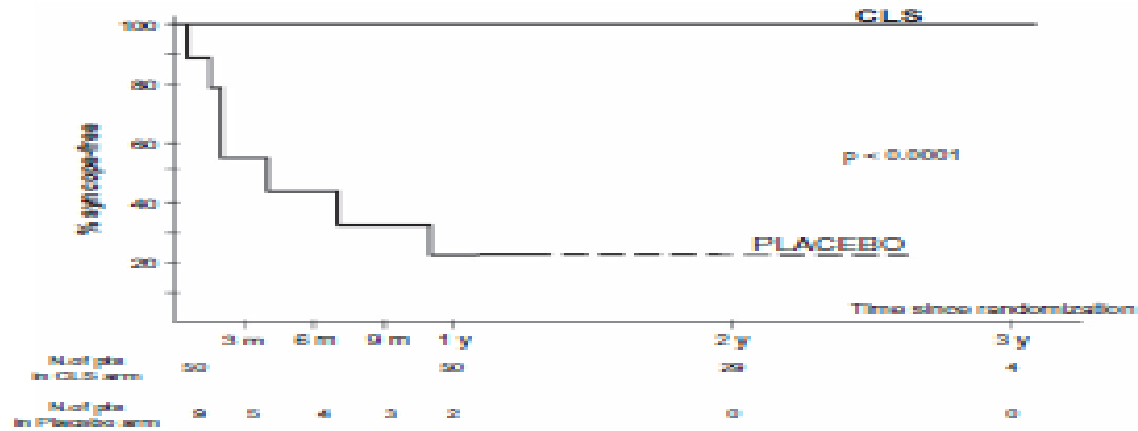
DDD-CLS in VVS

PM on vs PM off

INVASY

Ochetta E. et al.

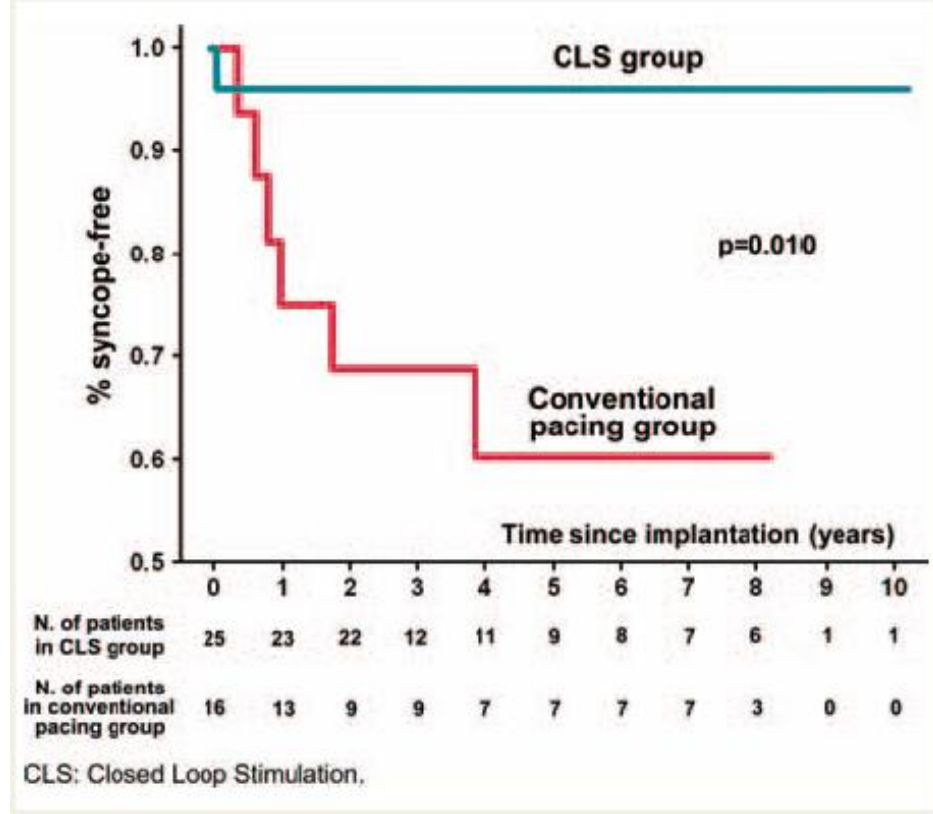
Europace 2004; 6: 538-47



DDD-CLS vs DDD convencional

Palmisano P et al.

Europace 2012; 14: 1038-43

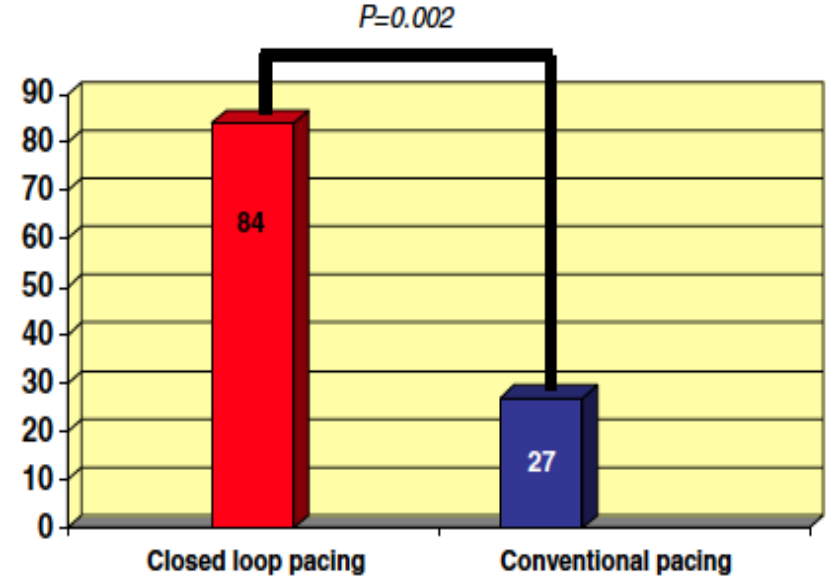


DDD-CLS in VVS

DDD-CLS vs DDD convencional

Kanjwal K et al.

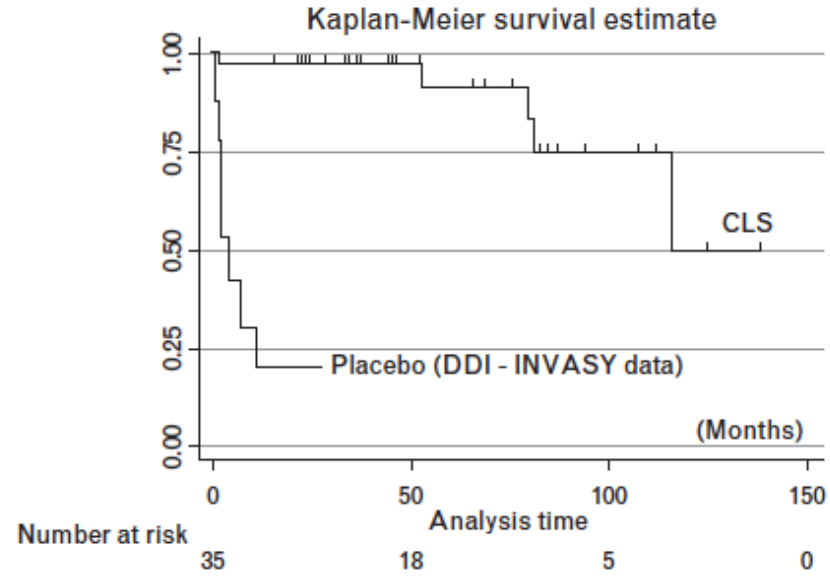
J Interv Card Electrophysiol 2010; 27: 69-73



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	Class	Level
2) Tilt-induced cardioinhibitory syncope Pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age >40 years after alternative therapy has failed	IIb	B
3) Tilt-induced non-cardioinhibitory syncope Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex	III	B
5) Tilt-induced cardioinhibitory syncope In patients with cardioinhibitory vasovagal syncope, dual-chamber pacing is the preferred mode of pacing.	I	C

Eur Heart J 2009; 30: 2631-71

Eur Heart J 2013;34:2281-2329

OBJECTIVE

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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)

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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:

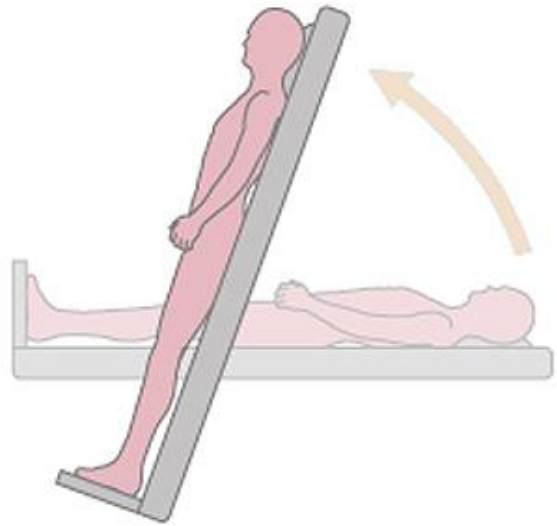
1) Patients that not fulfil any of the inclusion criteria described above.
2) Patients with syncope caused by carotid sinus hypersensitivity.
3) Other cause of syncope (known cause and different from neuromediated syncope).
4) Patients that participate in any other investigation study.
5) Pregnant or 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

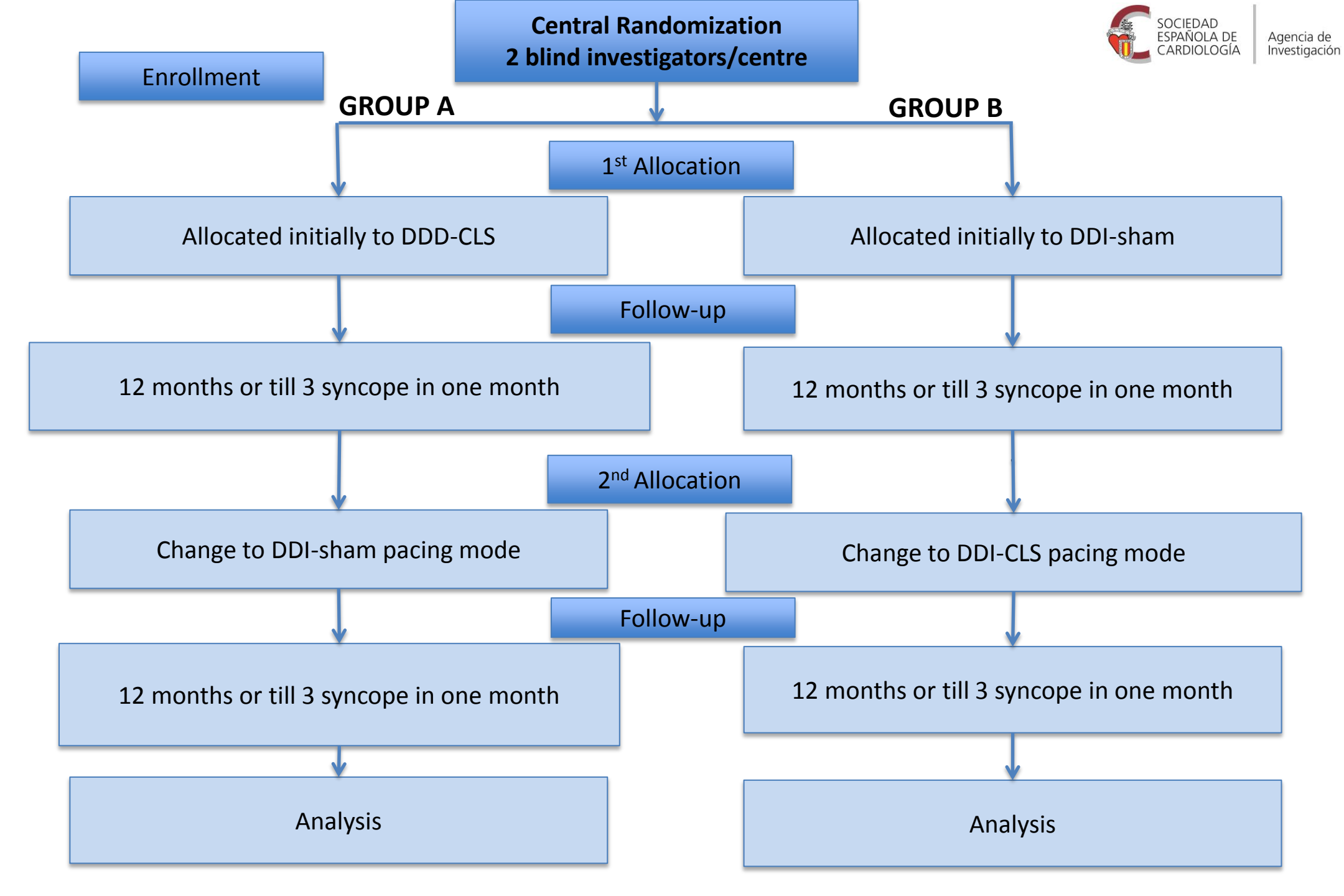


HUT Protocols:

1.- Basal, 60º, 45 minutes

or

2.- Italian (400 µgr nitroglicerin)


Central Randomization
2 blind investigators/centre
Enrollment
GROUP A
GROUP B
1st Allocation
Allocated initially to DDD-CLS
Allocated initially to DDI-sham
Follow-up
12 months or till 3 syncope in one month
12 months or till 3 syncope in one month
2nd Allocation
Change to DDI-sham pacing mode
Change to DDI-CLS pacing mode
Follow-up
12 months or till 3 syncope in one month
12 months or till 3 syncope in one month
Analysis
Analysis
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OUTCOME

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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).

STATISTICAL ANALYSIS

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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.

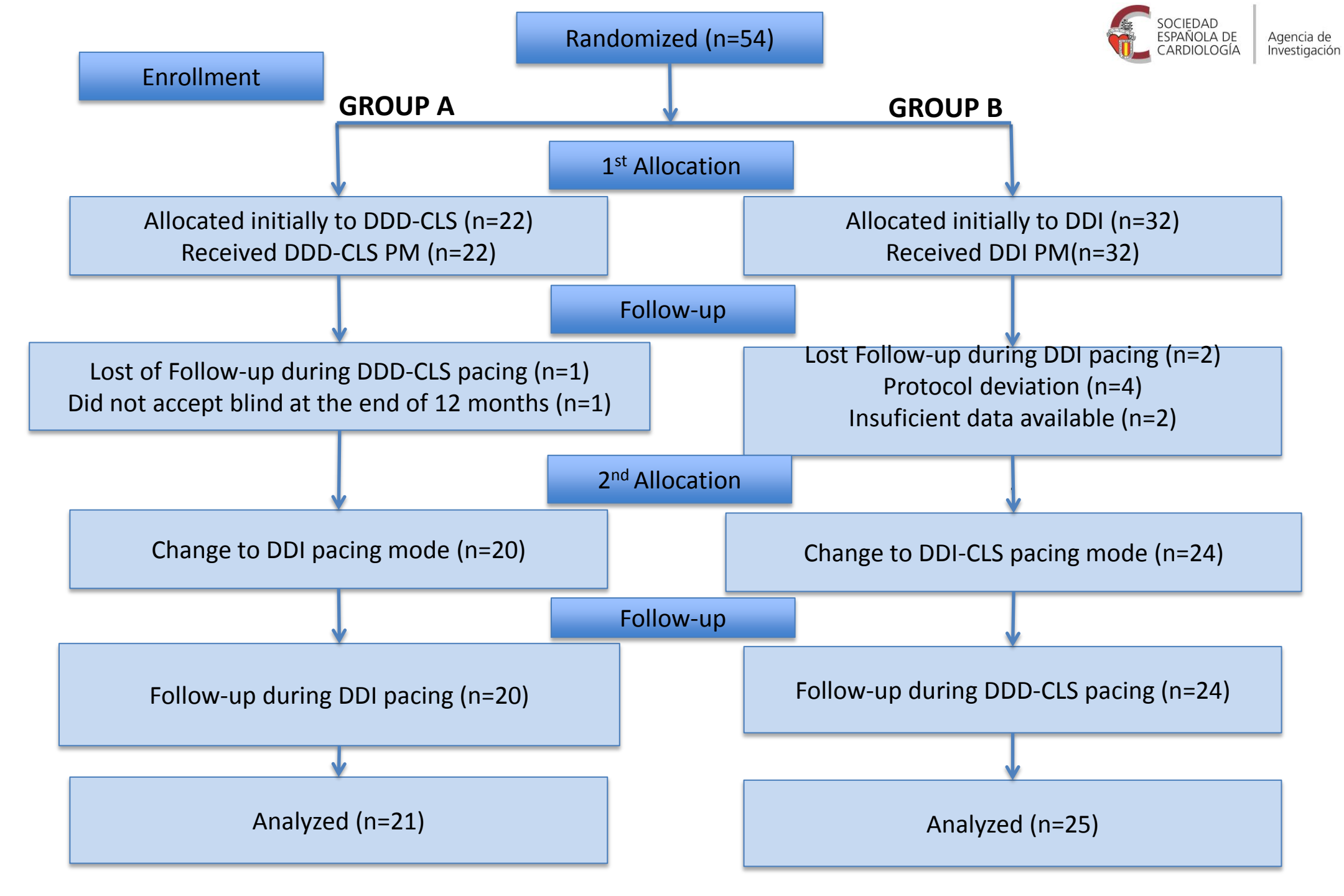
To analyse the primary efficacy endpoint, differences between groups A and B, **Mainland-Gart** and **Prescott** test were used.

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. Preespecified number of patients: 50

Data were analysed with version 9.4 of SAS® software.

RESULTS


Randomized (n=54)
Enrollment
GROUP A
GROUP B
1st Allocation
Allocated initially to DDD-CLS (n=22)
Received DDD-CLS PM (n=22)
Allocated initially to DDI (n=32)
Received DDI PM(n=32)
Follow-up
Lost of Follow-up during DDD-CLS pacing (n=1)
Did not accept blind at the end of 12 months (n=1)
Lost Follow-up during DDI pacing (n=2)
Protocol deviation (n=4)
Insuficient data available (n=2)
2nd Allocation
Change to DDI pacing mode (n=20)
Change to DDI-CLS pacing mode (n=24)
Follow-up
Follow-up during DDI pacing (n=20)
Follow-up during DDD-CLS pacing (n=24)
Analyzed (n=21)
Analyzed (n=25)

CLINICAL CHARACTERISTICS

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n=46	
Age	56 ± 10.6 y.o.
Males	47.8%
Previous syncopal episodes (SE)	12 [IQ9, IQ20]
Previous SE during last 12 months	4.5 [IQ2, IQ7]
Asystole during HUT (%)	35 (76)
Asystole duration (sec)	15 [IQ10, IQ26]

CLINICAL CHARACTERISTICS

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	Group A: DDD-CLS→DDI (n=21)	Group B: DDI→DDD-CLS (n=25)	p
Age (y.o.)	56.9 ± 10.3	55.9 ± 11.8	0.7
Weight (kg)	74 [IQ66, IQ90]	67 [IQ61, IQ83]	0.3
Height (cm)	164 ± 10.8	164.7 ± 8.2	0.9
Male (%)	9 (42,8)	13 (52)	0.5
High Blood Pressure (%)	6 (28)	8 (32)	0.7
Diabetes (%)	1 (4)	0 (0)	0.4
Previous Syncopal Episodes (SE)	12 [IQ10, IQ20]	10 [IQ8, IQ20]	0.8
Previous SE during last 12 months	4.5 [IQ3, IQ7,5]	4.5 [IQ2, IQ6]	0.5
Orthostatic test			0.8
Asystole in HUT (%)	16 (79)	19 (76)	1.0
Asystole duration (sec)	14.3 [IQ7, IQ29]	15 [IQ10, IQ22]	0.9

Primary Efficacy Outcome

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Mailand-Gard Test (CI 95%)

	1st period of treatment	2nd period of treatment
≥ 50% reduction in the number of syncopal episodes	72.22 (95%CI 46.52, 90.31)	0.00
≥ 50% reduction in the number of syncopal episodes	27.78 (95%CI 9.69, 53.48)	100 (95%CI 39.76, 100.00)

p= 0.0172

Prescott analysis

	Prefers the 1st period (n=18)	Prefers the 2nd period (n=4)	Does not have preference (n=7)	Total (n=29)	Fisher test
Group A: DDD-CLS<<DDI	13 (72.22)	0 (0.00)	0 (0.00)	13 (44.83)	p=0.0003
Group B: DDI>>DDD-CLS	5 (27.78)	4 (100.00)	7 (100.00)	16 (25.17)	

Primary Efficacy Outcome

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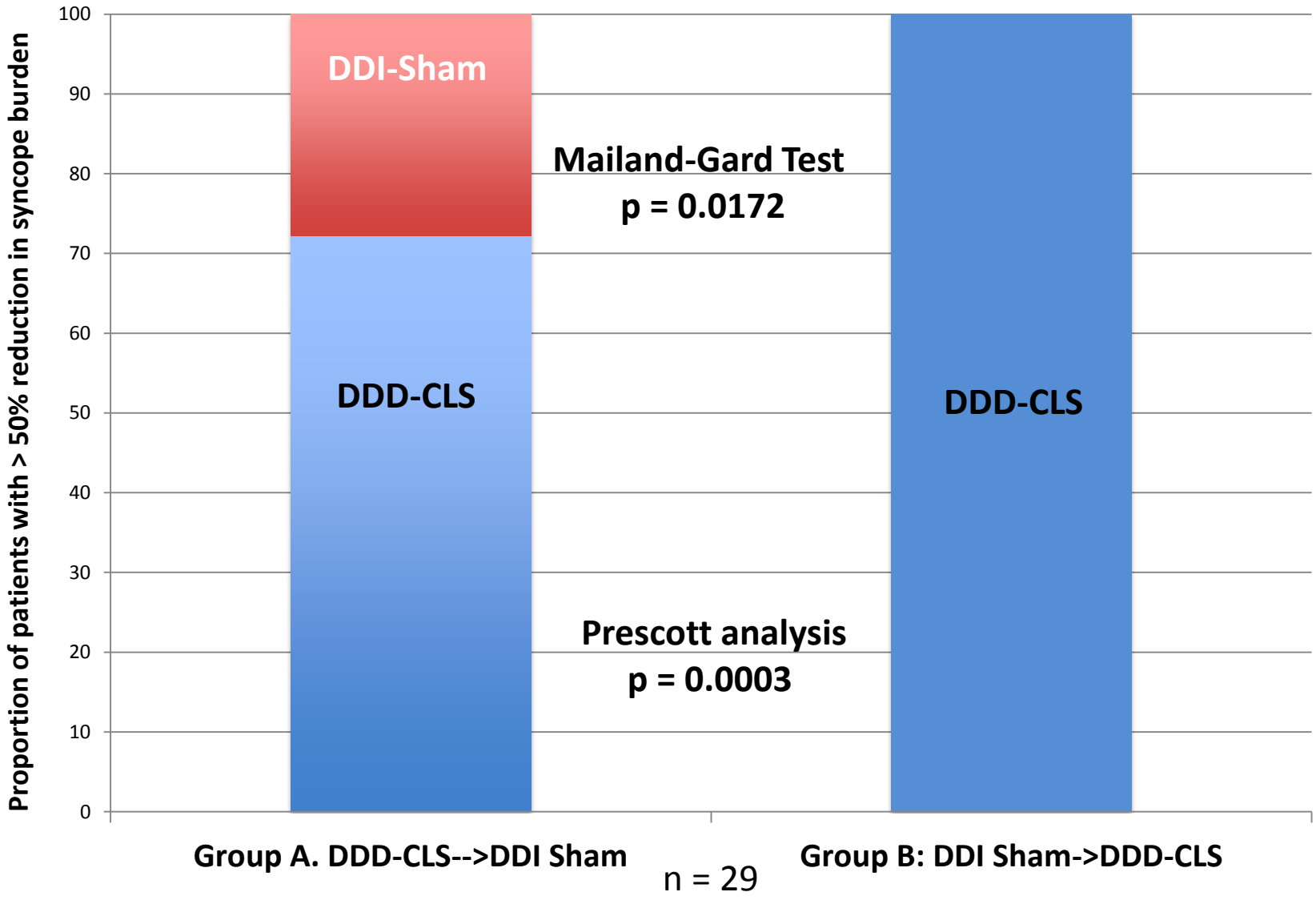
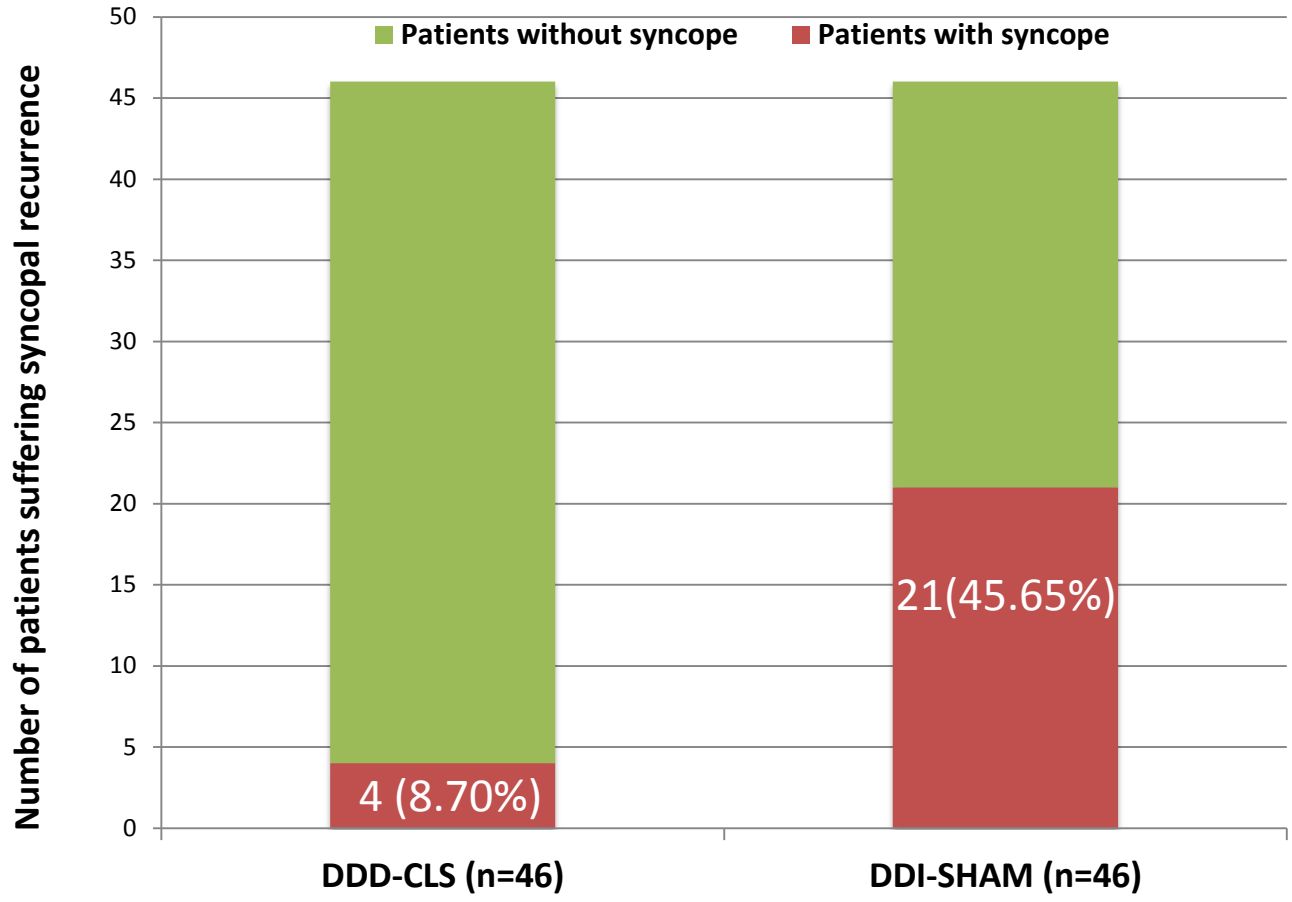
≥ 50% Reduction Syncope Burden

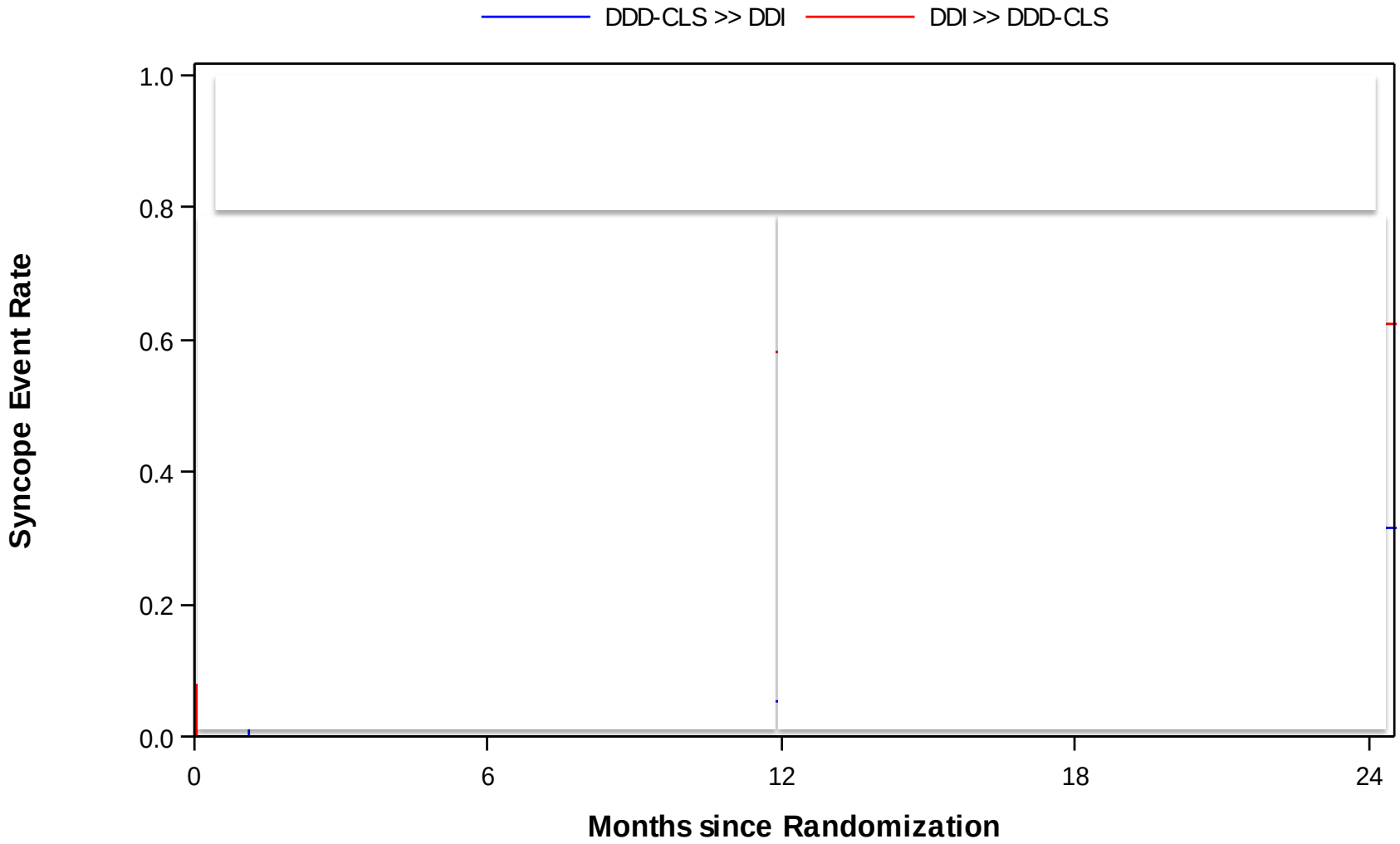


Co-Primary Efficacy Outcome (DDD-CLS vs DDI)



	DDD-CLS pacing mode	DDI sham pacing mode
Number of patients	46	46
Number of patient without events	42 (91.30%)	25(54.35%)
Number of patients with events	4(8.70%)	21 (45.65%)

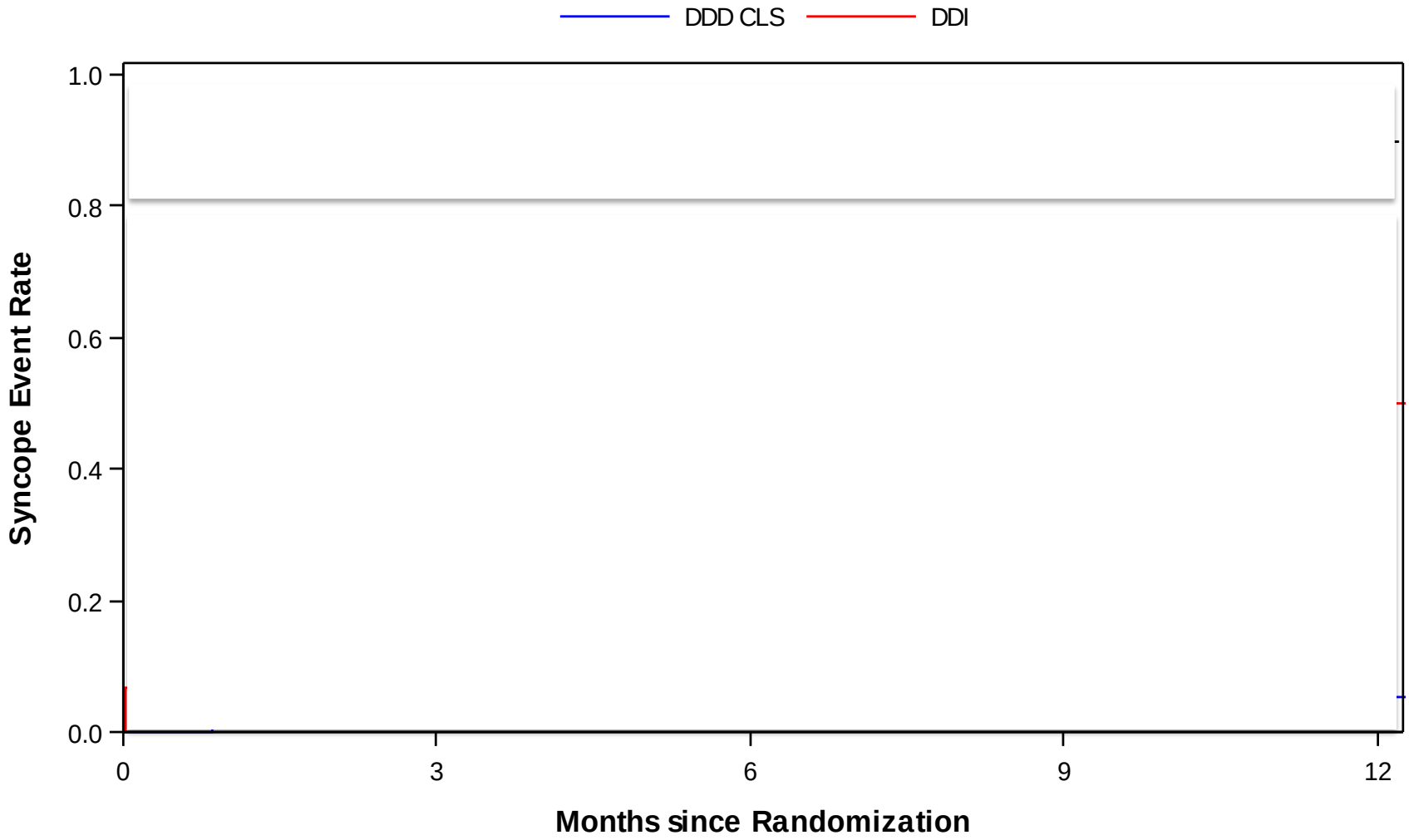
Co-Primary Efficacy Outcome (Group A vs B)



Patients at Risk

DDD-CLS >> DDI	20	18	18	14	1
DDI >> DDD-CLS	25	18	10	9	4

Co-Primary Efficacy Outcome (DDD-CLS vs DDI)



Patients at Risk

DDD CLS	46	36	36	36	2
DDI	46	28	26	19	1

Co-Primary Efficacy Outcome (DDD-CLS vs DDI)

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	DDD-CLS pacing mode	DDI sham pacing mode
Time to first syncope (Median (95%CI)	NA (12.99, NA)	9.30 (6.61, 19.07)
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

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DDD-CLS pacing compared to DDI-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.

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