

Early Application of an Implantable Loop Recorder allows Effective Specific Therapy in Patients with Recurrent Suspected Neurally-mediated Syncope

Authors: M. Brignole, *Italy*
R. Sutton, *UK*
C. Menozzi, *Italy*
A. Moya, *Spain*
R. García-Civera, *Spain*
D. Benditt, *USA*
P. Vardas, *Greece*
W. Wieling, *The Netherlands*
D. Andresen, *Germany*

Clinical monitor:
N. Grovale, *Italy*

Statistical analysis:
T. De Santo, *Italy*

Database management:
RDES, *Spain*

Study Overview

- Study: prospective, multicenter
- Centres: 63 in 9 countries
- Duration: 2 yrs recruitment + 1yr follow-up
- Patients: 442
- Start: June 2002
- End: June 2005

Participating hospitals

✓ Italy	24 hospitals
✓ Spain	16
✓ Germany	6
✓ UK	6
✓ The Netherland	6
✓ Greece	2
✓ Austria	1
✓ Denmark	1
✓ USA	1
✓ Total	63

Main objective

To assess the effectiveness of a new strategy:

- risk stratification and diagnosis of NMS based on the Initial Evaluation of the ESC Guidelines on Syncope
- early application of an ILR
- (irrespective of tilt testing and ATP test)
- therapy delayed after ILR documentation of the apparent basis of syncope

Inclusion criteria

- Suspected neurally-mediated syncope at Initial Evaluation (ESC guidelines criteria)*
- ≥ 3 syncopes in the last 2 years
- Severe clinical presentation of syncope requiring treatment initiation
- Age > 30 years
- Absence of carotid sinus syncope

* history, physical exam, ECG & BP supine/upright

Exclusion criteria

- Suspected cardiac syncope
- Orthostatic hypotension
- Non-syncopal loss of consciousness

Study flow



Enrolment

Inclusion/exclusion

CSM (*mandatory*)

Tilt test, ATP test (*recommended*)

ILR implant

Study flow



Enrolment

Inclusion/exclusion
CSM (*mandatory*)
Tilt test, ATP test (*recommended*)

ILR implant

Phase I (diagnosis)

FU 3,6,.....,24 months
First syncope recurrence
First ILR-documented syncope recurrence

Study flow



Enrolment

Inclusion/exclusion
CSM (*mandatory*)
Tilt test, ATP test (*recommended*)

ILR implant

Phase I (diagnosis)

FU 3,6,....,24 months
First syncope recurrence
First ILR-documented syncope recurrence

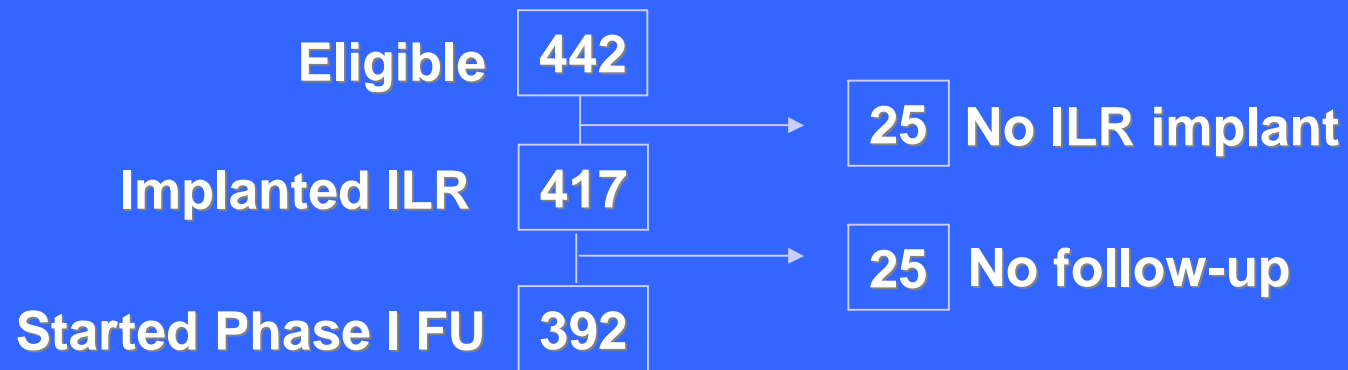
Phase II (therapy)

ILR-based specific Rx

FU 3,6,....,24 months
First syncope recurrence
Total syncope burden

Non-specific Rx

FU 3,6,....,24 months
First syncope recurrence
Total syncope burden

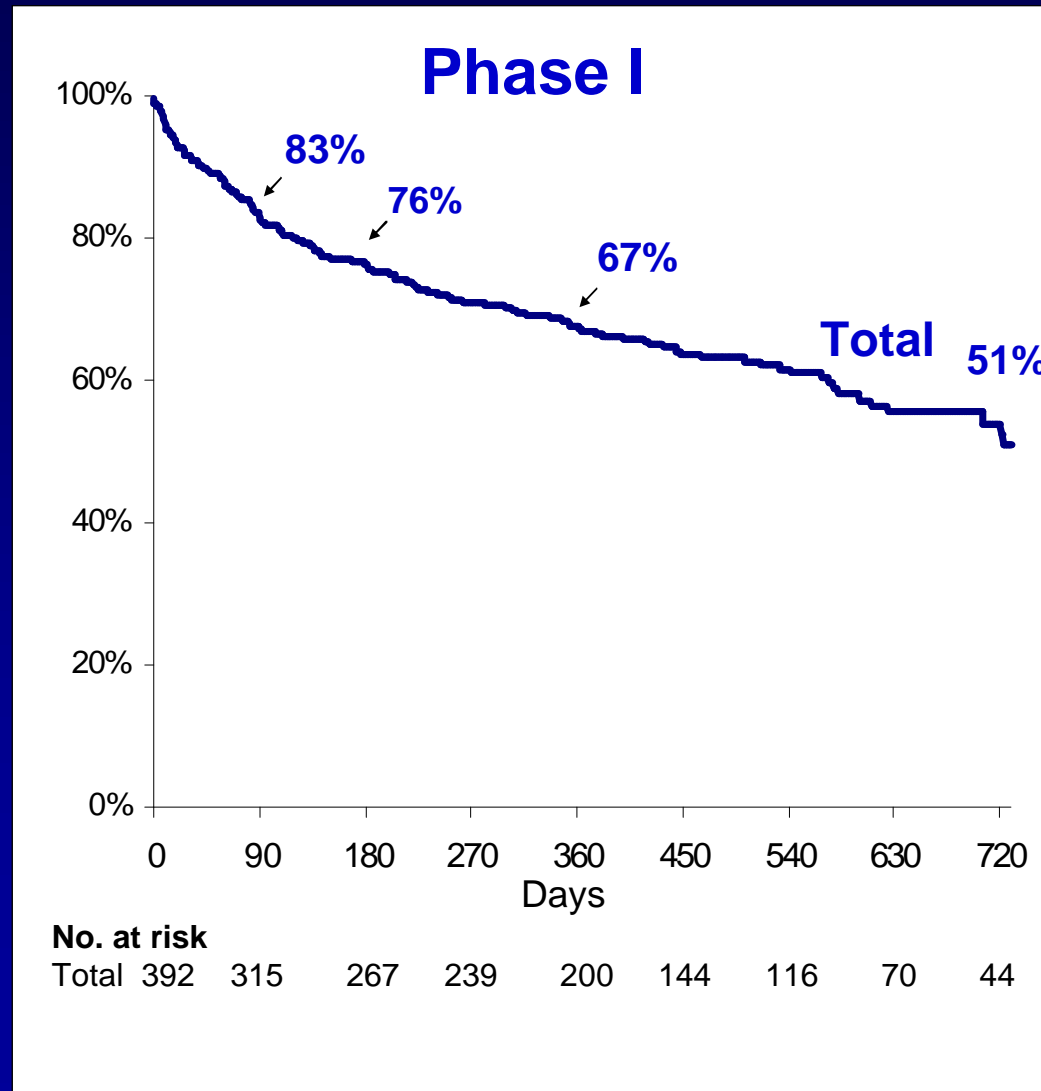


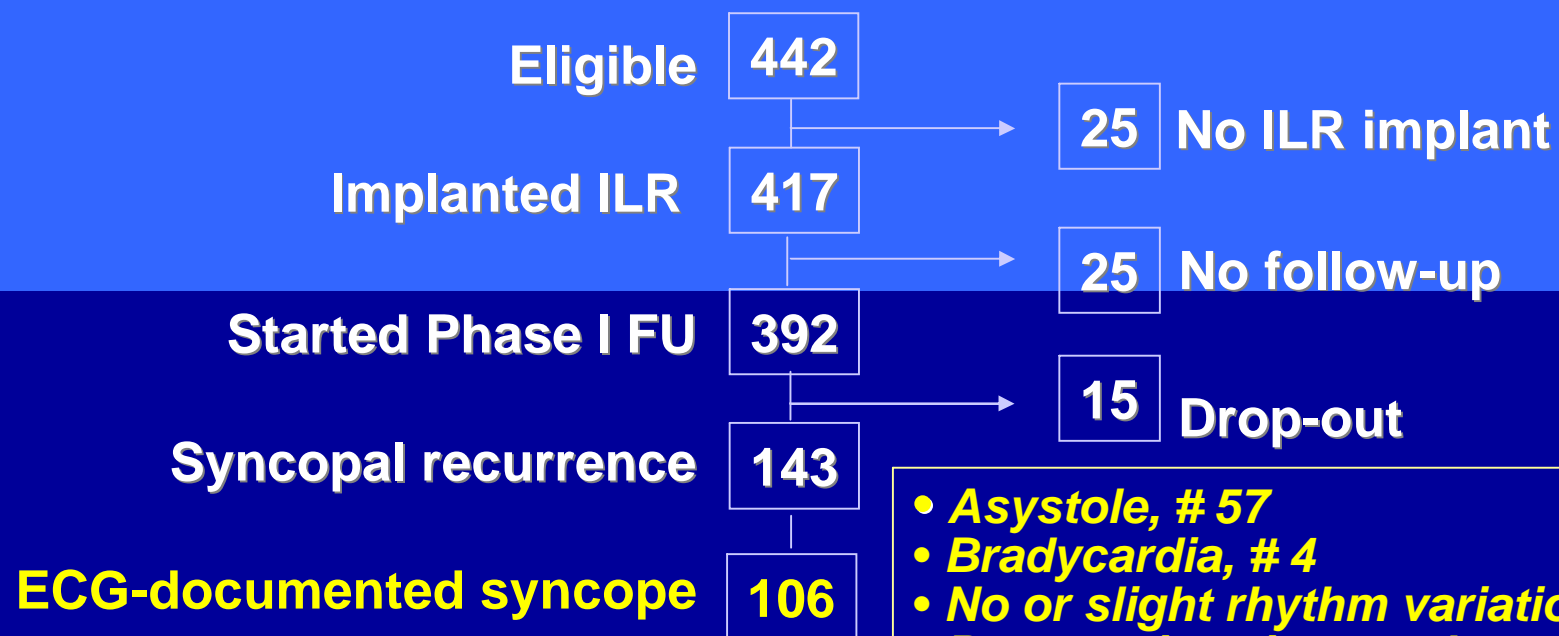
Patient characteristics (n=392)

Mean age – yr	66±14
Male gender	45%
Syncopes – total number	6 (4-10)
Syncopes - last 2 years	4 (3-5)
Syncope duration - yr	7 (4-14)
Age at first syncope -yr	54±20
History of presyncope	54%
Major injuries (fractures, brain concussion)	21%
Minor injuries (bruises, etc)	47%
No warning at the onset	50%
Vasovagal/situational	41%
Atypical presentation	59%

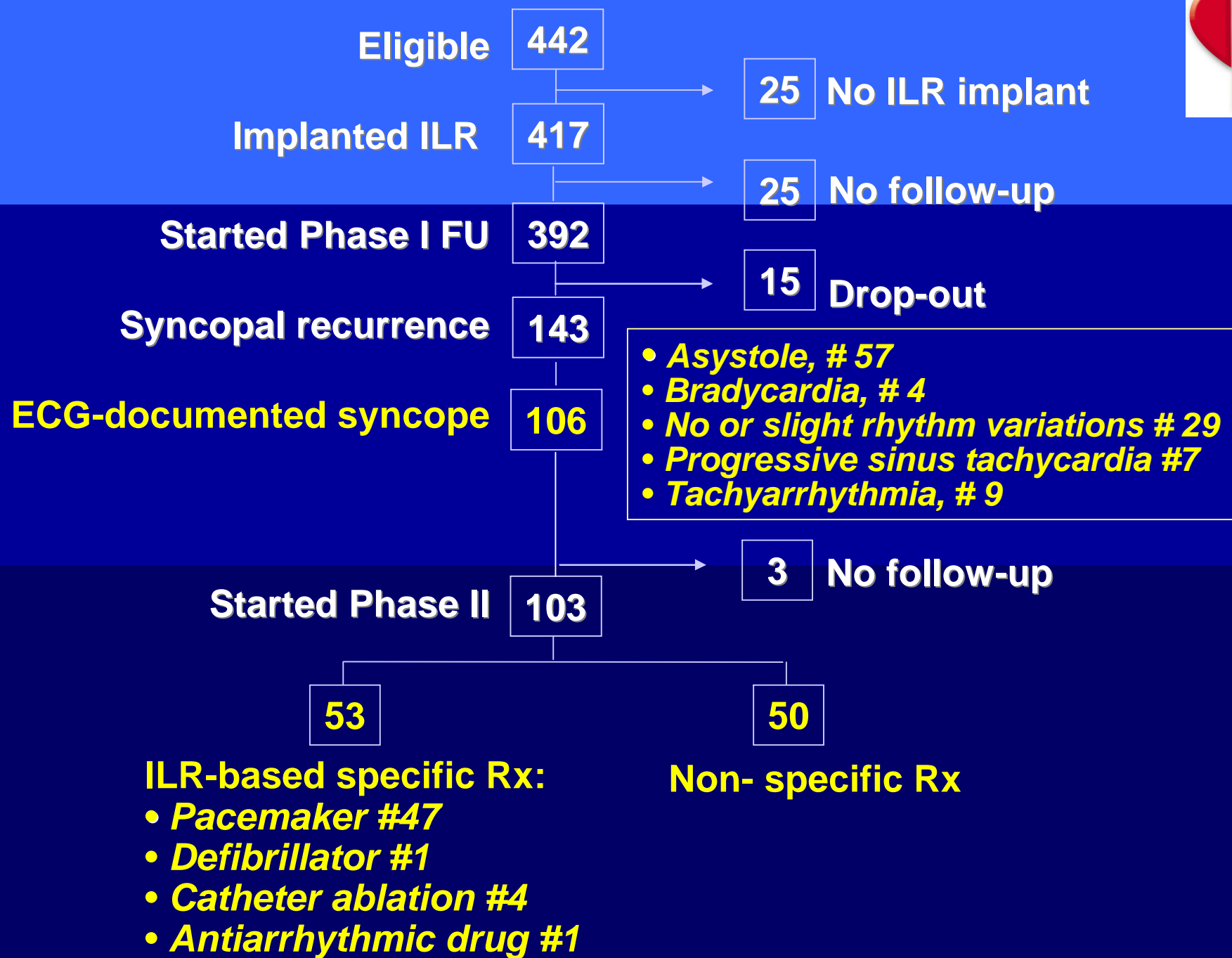
ECG: normal	87%
No structural heart disease	86%
Hypertension	45%
Any neurological disease	9%
Diabetes	8%
Any therapy at the time of enrolment	39%
Antihypertensive drugs	28%
Tilt testing: performed	87%
Tilt testing: positive	48%
ATP test: performed	46%
ATP test: positive	26%

Results: Syncope-free survival





- *Asystole, # 57*
- *Bradycardia, # 4*
- *No or slight rhythm variations # 29*
- *Progressive sinus tachycardia #7*
- *Tachyarrhythmia, # 9*



Patient characteristics

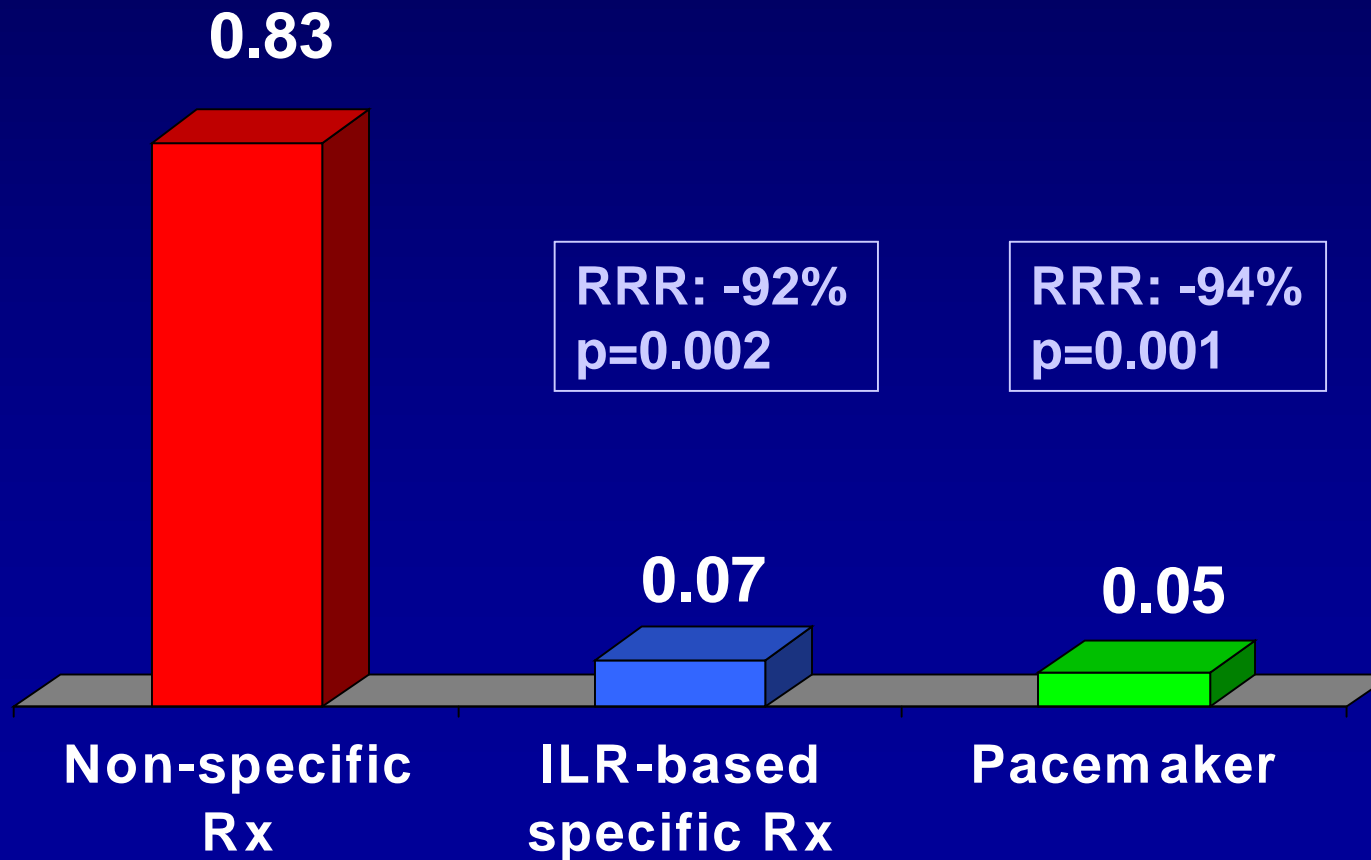
	Therapy	No therapy	
Mean age – yr	69 ±13	64±15	ns
Male gender	38%	50%	ns
Syncopes – total number	5 (4-8)	6 (4-14)	ns
Syncopes - last 2 years	4 (3-5)	4 (3-7)	ns
Syncope duration - yr	6 (4-14)	6 (4-12)	ns
Age at first syncope -yr	59 ±18	54±19	ns
History of presyncope	38%	46%	ns
Major injuries	25%	16%	ns
Minor injuries	51%	52%	ns
No warning at the onset	45%	48%	ns
Vasovagal/situational	26%	42%	ns
Atypical presentation	74%	58%	ns

Patient characteristics

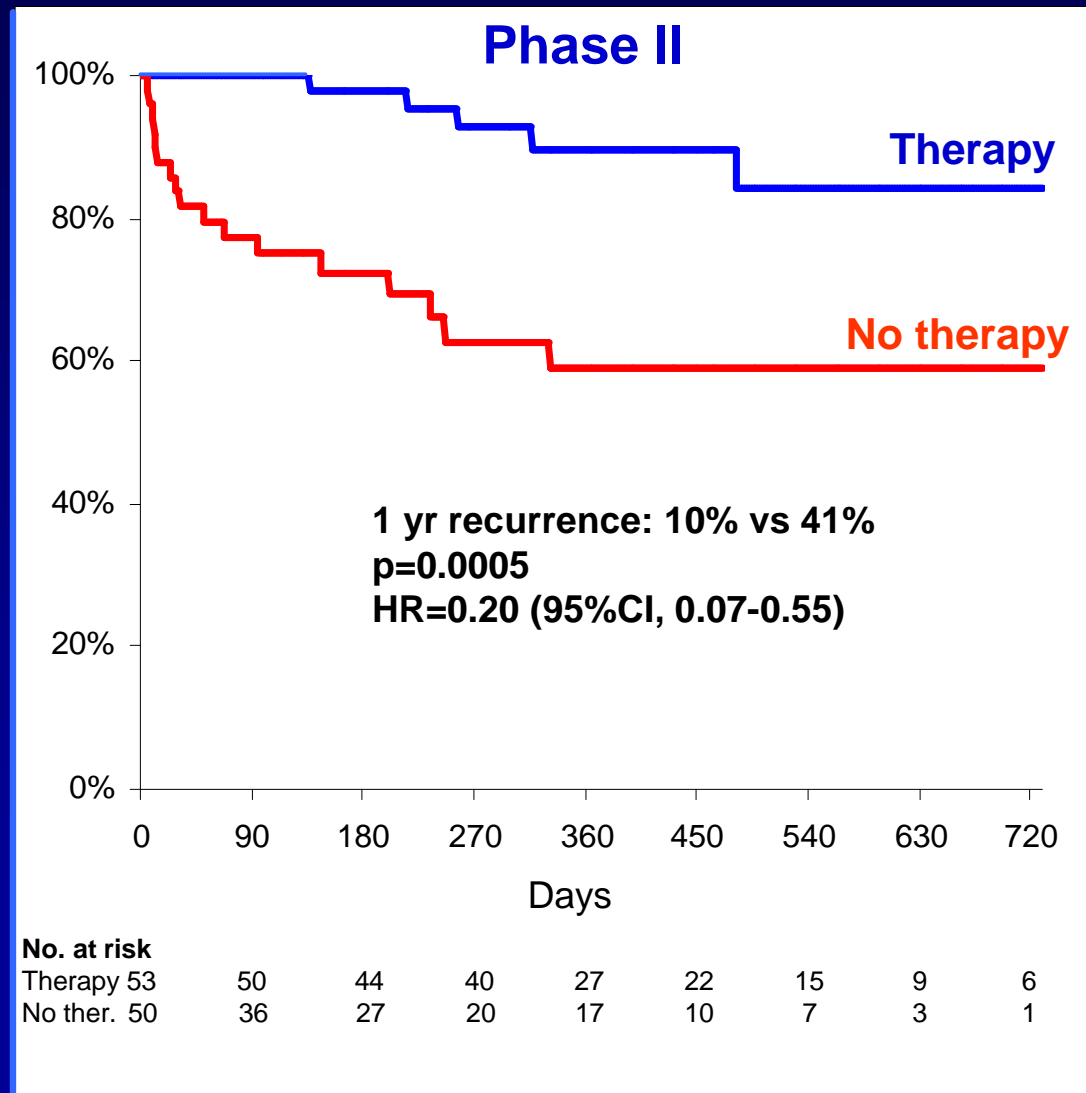
	Therapy	No therapy	
ECG: normal	87%	90%	ns
No SHD	91%	86%	ns
Hypertension	45%	48%	ns
Any neurological disease	38%	12%	ns
Diabetes	13%	4%	ns
Any therapy	38%	52%	ns
Antihypertensive drugs	28%	34%	ns
Tilt testing: performed	77%	98%	ns
Tilt testing: positive	37%	45%	ns
ATP test: performed	42%	58%	ns
ATP test: positive	32%	28%	ns

Results: Syncope burden

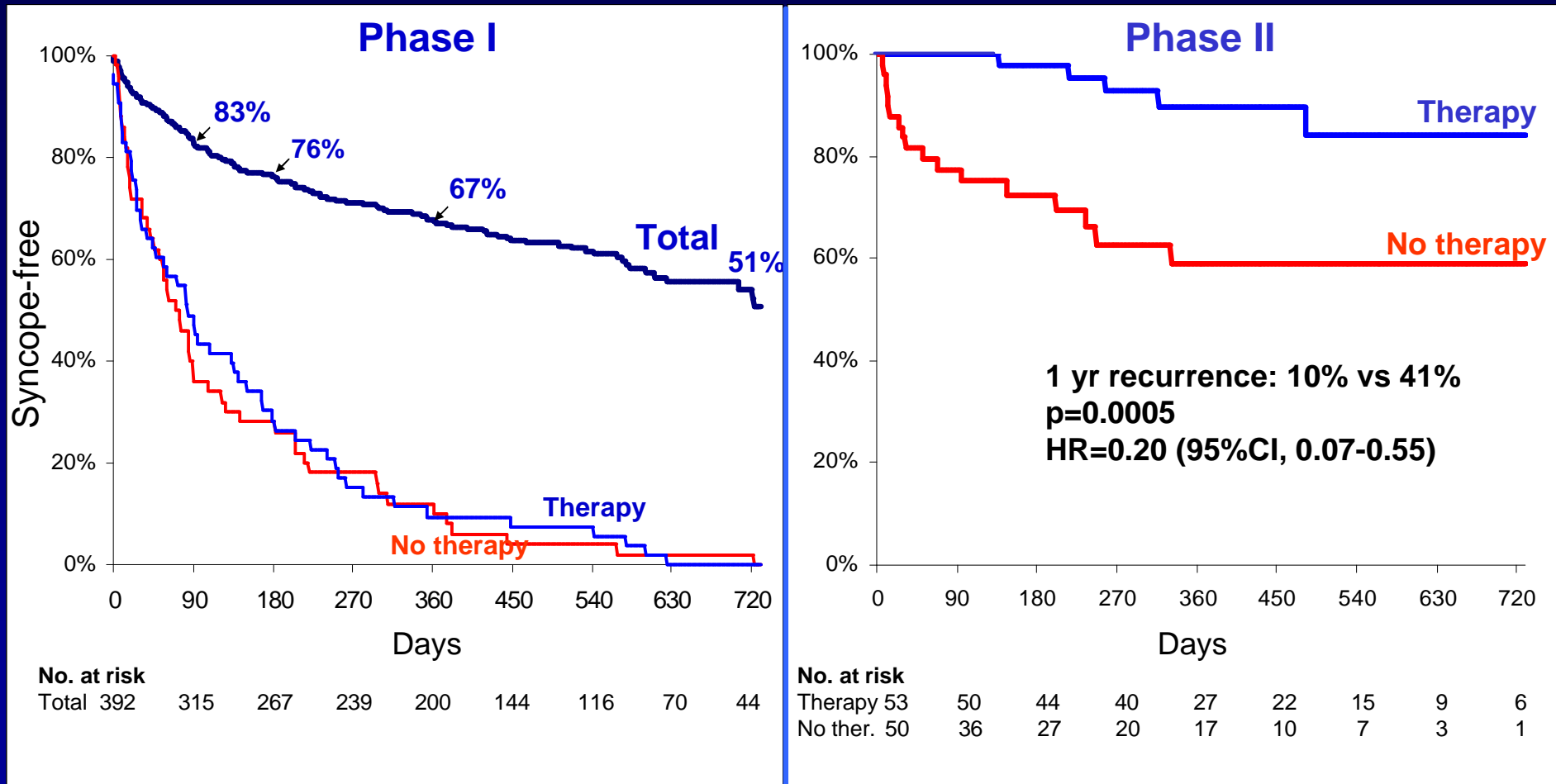
Episodes per patient/year



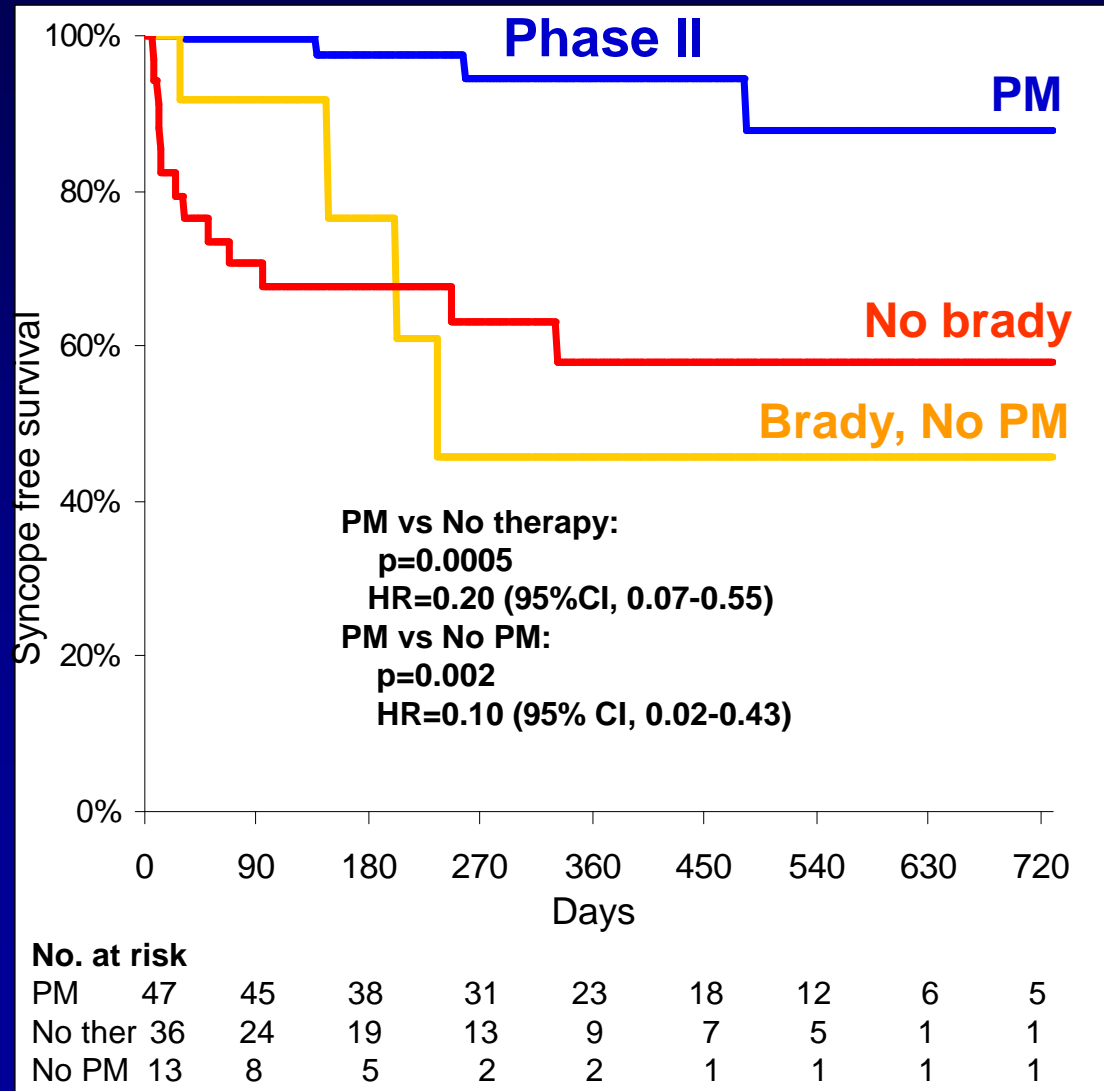
Results: Syncope-free survival



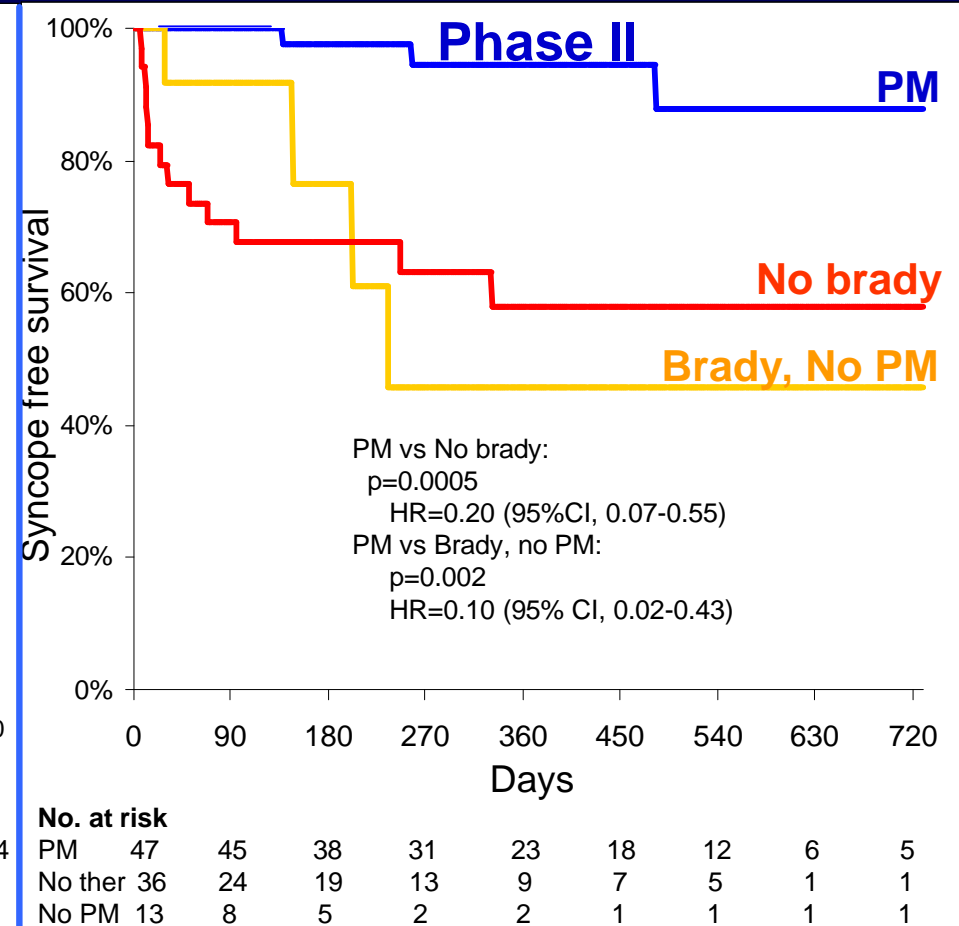
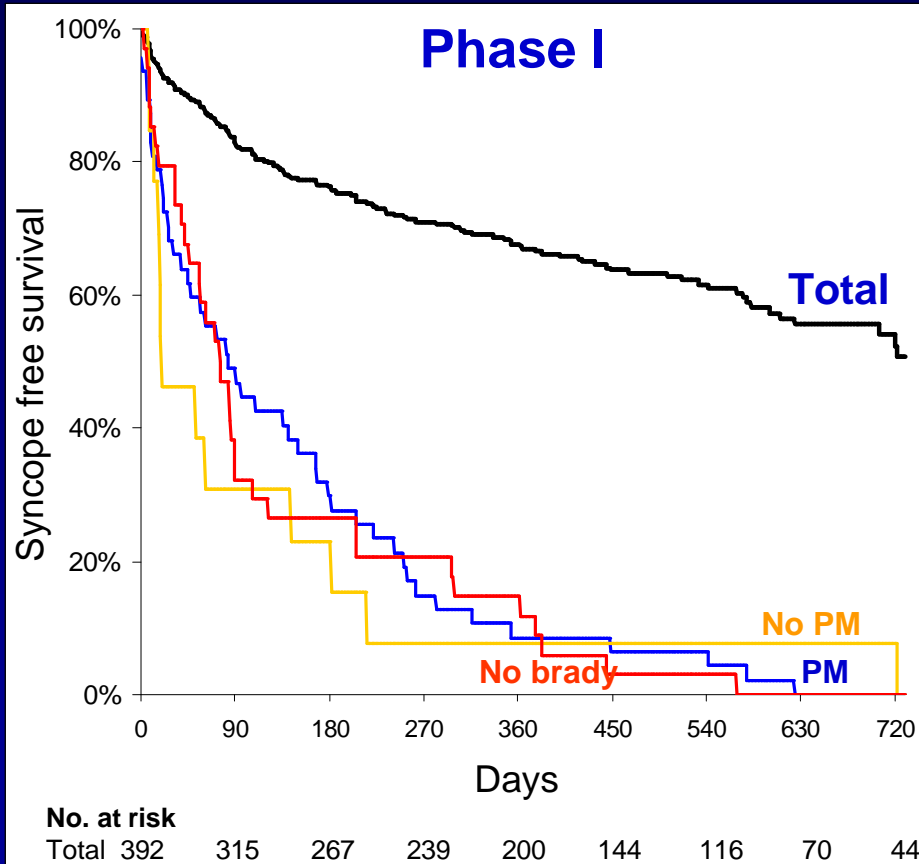
Results: Syncope-free survival



Results: Pacemaker therapy



Results: Pacemaker therapy



Phase II: Predictors of syncope recurrence (univariate)

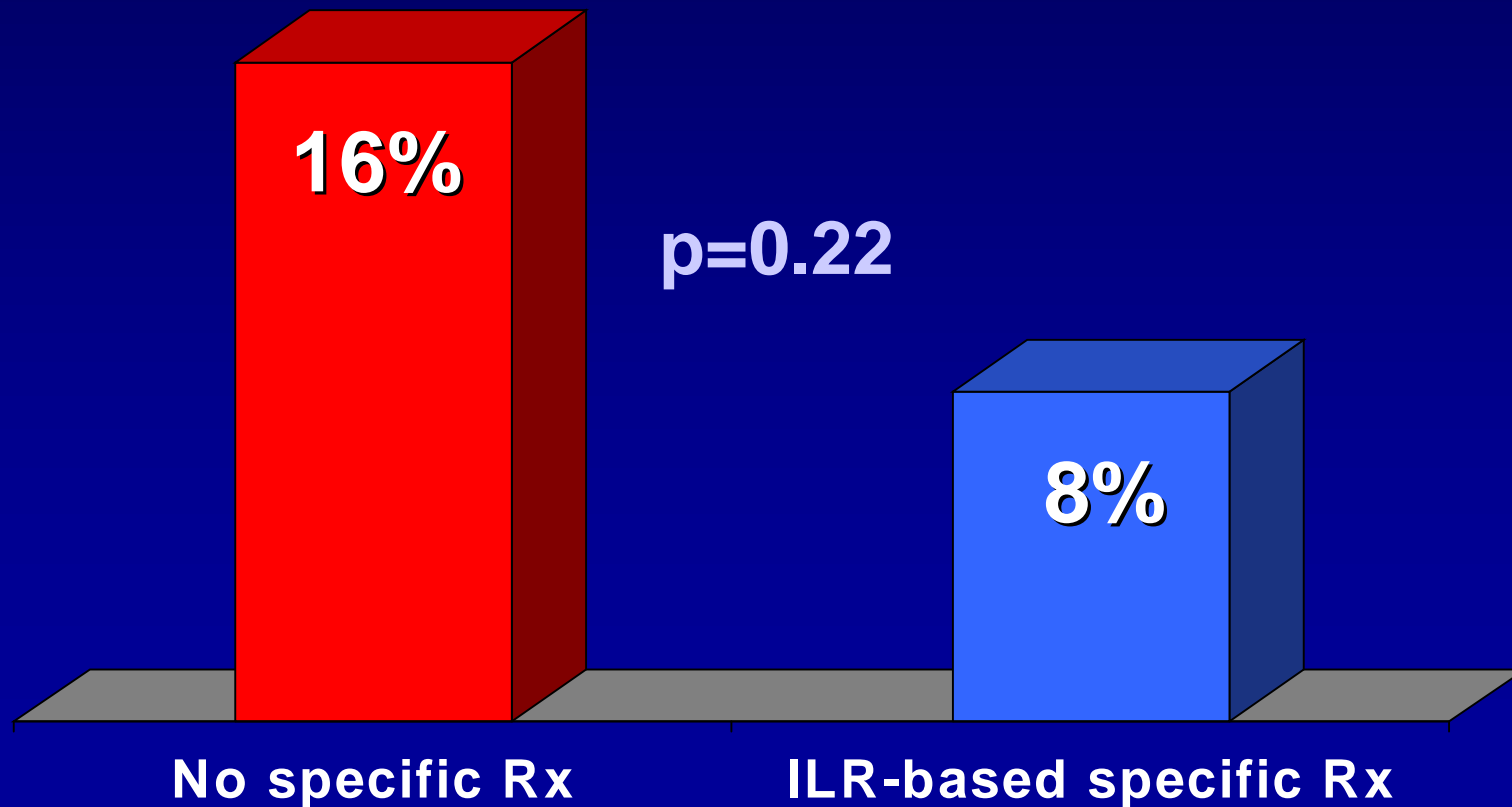
Increasing age – yr	0.024	ECG: normal	
Male gender		No structural heart disease	
Syncope – total number		No hypertension	0.035
Syncope – >4 last 2 years	0.007	Any neurological disease	
Syncope duration - yr		Diabetes	
Age at first syncope -yr		Any therapy	
History of presyncope		Antihypertensive drugs	
Major injuries (fractures, brain concussion)		Tilt testing: performed	
Minor injuries (bruises, etc)		Tilt testing: positive	
No warning at the onset		ATP test: performed	
Vasovagal/situational		ATP test: positive	
Atypical presentation		No specific therapy	0.002
		No pacemaker	0.002

Phase II: Predictors of syncope recurrence (multivariate)

	Hazard ratio	P value
Mean age – yr	0.92 (0.86-1.00)	0.024
Hypertension	0.21 (0.06-0.67)	0.009
No pacemaker therapy	26 (3.14-217)	0.003

Results: Pre-syncope

% patients



Results: Safety

Syncope-related events

	Phase I	Phase II
Severe trauma	7 (2%)	0
Mild trauma	16 (4%)	0
Death	0	0

Conclusions

A new strategy of risk stratification and diagnosis of NMS based on simple initial evaluation, early application of diagnostic ILR and therapy delayed until documentation of syncope is:

- **safe and**
- **allows effective specific therapy**

Discussion

ISSUE-2 population

Features:

- Mean age >65 years
- History of recurrent syncopes beginning in middle or older ages
- Severe clinical presentation requiring treatment (high risk and/or high frequency)
- Atypical presentation without warning
- Frequent injuries probably due to presentation without warning

Weakness	Strenght
Non-randomized	Strong arrhythmic background
Open design (unblind)	Similar characteristics among study groups
	Pacemaker strongest independent predictor of benefit
	Active arm recurrence rate lower than that of previous studies

Recurrences with placebo in some RCT

VASIS	Placebo Etilefrine	24%
Madrid et al	Placebo Atenolol	46%
VPS II	Pacemaker OFF	40%
SYNPACE	Pacemaker OFF	38%

Supply



ISSUE 2

International Study on Syncope of Uncertain Etiology 2

The management of patients with suspected neurally-mediated syncope after the initial evaluation



Endorsed by European Heart Rhythm Association (formerly Working Group of Pacing of the European Society of Cardiology)

With the organizational support of Medtronic Inc.





ISSUE 2

International **S**tudy on **S**yncope of **U**ncertain **E**tiology **2**

**Early Application of an Implantable Loop Recorder
allows Effective Specific Therapy in Patients with
Recurrent Suspected Neurally-mediated Syncope**

Outcome measures

Phase 1:

- first syncope recurrence
- first ECG-documented syncope

Phase 2:

- first syncope recurrence
- total syncope burden

Recommended ILR-guided therapy:

- Cardiac pacing in asystolic and bradycardic patients;
- Counseling and non-specific therapy, in patients with normal sinus rhythm, including those with mild sinus tachycardia;
- Antiarrhythmic therapy in tachyarrhythmic patients.

Study flow

- Phase 1: ILR-based diagnosis
- Phase 2: ILR-guided therapy

Diagnostic work-up during the initial evaluation

• Age > 30 years	If YES, continue
• ≥ 3 syncope during last 2 years	If YES, continue
• So severe presentation to require treatment, if any	If YES, continue
• Non-syncopal loss of consciousness	If NO, continue
• Symptomatic orthostatic hypotension	If NO, continue
• Suspected or certain heart disease and high likelihood of cardiac syncope	If NO, continue
• Carotid sinus syncope	If NO, continue
	Patient eligible

Based on ESC Guidelines on Syncope, Eur Heart J, 2004