



# **IL PACEMAKER NELLE SINCOPI RIFLESSE ALLA LUCE DELLO STUDIO ISSUE-3**

**Tigullio Cardiologia 4.4.2014**

- 1. INQUADRAMENTO CLINICO DEL PAZIENTE**
- 2. SELEZIONE DEI PAZIENTI DA SOTTOPORRE A PM**
- 3. IMPATTO DEL PM SULLA QUALITA' DI VITA E RECIDIVE**
- 4. ALTRE POSSIBILI TERAPIE IN COMBINAZIONE**
- 5. LOOP RECORDER NELL'ITER DIAGNOSTICO**

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### Neuro-cardiogenic syncope: Treatment

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
• Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence are indicated in all patients	I	C
• Isometric PCMs are indicated in patients with prodrome	I	B
• Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS	IIa	B
• Cardiac pacing should be considered in patients with frequent recurrent reflex syncope, age >40 years, and documented spontaneous cardioinhibitory response during monitoring	IIa	B

Guidelines for the diagnosis and management of syncope (version 2009)

<sup>10</sup> The Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC)

# *Context and Background:*

## THE EFFICACY OF CARDIAC PACING FOR PREVENTION OF SYNCOPAL RECURRENCES IN PATIENTS WITH NEURALLY MEDIATED SYNCOPE

- SYDIT. *Circulation* 2001    VASIS. *JAMA* 2003  
*Multicenter, randomized studies with results in favour of pacing (open-label)*
- VPS II trial. *JAMA* 2003    Synpace trial. *Eur Heart J* 2004  
*Randomized double-blind controlled trials failed to prove superiority of cardiac pacing over placebo of unselected patients with positive tilt-testing*
- Issue-2 showed that the mechanism of spontaneous NMS, documented by Implantable Loop Recorder (ILR) could identify a group of patients who may benefit from PM

## *ISSUE-2* Eur Heart J 2006; 27, 1085–1092

- Pacing potentially effective in patients with documented asystole
- The mechanism of spontaneous NMS documented by ILR was reproducible
- Asystolic NMS treated with pacemaker showed a >80% relative risk reduction of syncopal recurrence
- ISSUE-2 was not a formal controlled double-blind trial



## ISSUE 3

International Study on Syncope of Uncertain Etiology 3

# ISSUE-3

- Multi-center, prospective, randomized, double-blind study
- Objective: to determine if *pacing therapy reduces recurrences* in patients with *severe documented spontaneous asystolic NMS*

## *Methods: patients selection*

- *NMS is defined as any form of reflex syncope (exception of carotid sinus syndrom)*
- *Patients had to have a sufficiently **severe clinical presentation** to warrant specific treatment: high frequency or risk provided by guidelines:*
  - *invalidated quality of life*
  - *unpredictable syncope*
  - *syncope exposing patients to risk of trauma*
  - *occurrence of syncope during “high risk activity”*
- *These individuals received an ILR and were followed-up (**PRE-STUDY SCREENING PHASE**)*

## *Methods: exclusion of patients*

- *Cardiac abnormalities which suggested cardiac syncope*
- *Symptomatic orthostatic hypotension*
- *Non-syncopal loss of consciousness*

# Results: patients

Screening phase

511 met inclusion criteria and received an ILR

Study phase

89 had ECG documentation of:  
- syncopal recurrence with asystole  $\geq 3$  s (#72)  
*or*  
- non-syncopal asystole  $\geq 6$  s (#17)

77 randomized

38 assigned and received Pm ON

39 assigned and received Pm OFF

12 refused randomization

3 lost to follow-up

8 had Pm reprogrammed DDD/VVI in absence of primary end-point

9 followed-up (registry):  
6 implanted Pm  
3 no therapy

38 analysed

39 analysed

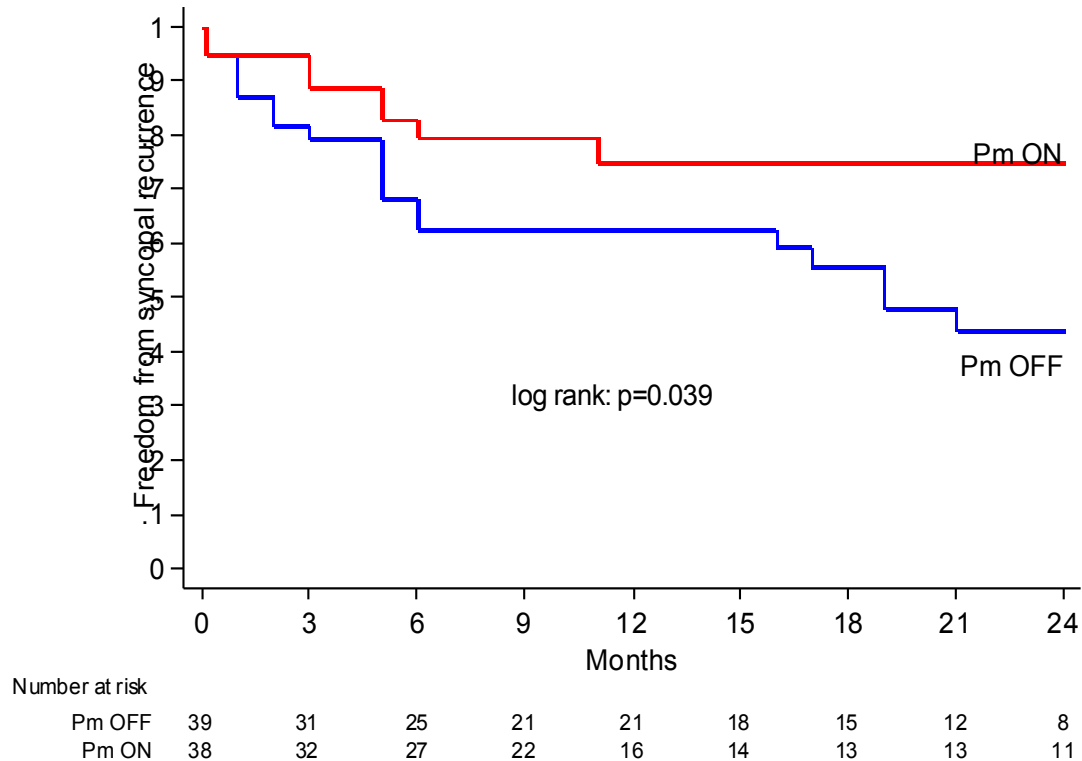
9 analysed



*Main Outcome Measure*

First recurrence of  
syncope

# Results: outcome



Time to first recurrence of syncope according to the intention-to-treat analysis

**CARDIAC PACING IN PATIENTS WITH NEURALLY-MEDIATED SYNCOPE AND DOCUMENTED ASYSTOLE. EFFECTIVENESS ANALYSIS FROM THE THIRD INTERNATIONAL STUDY ON SYNCOPE OF UNCERTAIN ETIOLOGY (ISSUE-3) REGISTRY**

R.Sutton, A.Ungar, M.Tomaino, V.Russo, R.Massa, D.Melissano, X.Beiras, N.Bottoni H.H.Ebert, M.Francesse, M.Jorfida, S.Giuli, A.Moya, D.Andresen, M.Brignole *on behalf of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators*

**ON-TREATMENT ANALYSIS**

**The recurrence of syncope occurred in 10 paced patients (17%) and in 40 non-paced patients (46%).**

**At 21 months, the estimated product-limit syncope recurrence rates were 27% and 54% respectively.**

**Risk of recurrence with cardiac pacing was reduced by 57%**

## *Adverse events*

- 1 patient died due to cancer
- **5 patients had procedure-related complications: right ventricle lead dislodgement (2), right atrial dislodgement (2), subclavian vein thrombosis (1)**
- Syncope recurrence resulted in injuries with mild bruising in 5 patients (4 in PM OFF arm)

## Conclusions ISSUE-3

- *Pacing is effective in reducing recurrence of syncope in patients  $\geq 40$  years with severe asystolic NMS (ILR). There was 32% absolute risk reduction and 57% relative risk reduction*
- *Pacing is effective (ISSUE 2 and 3) when spontaneous syncope is associated with asystole. The importance of an associated hypotensive component is suspected in 25% of “PM ON arm” patients who had syncopal recurrence despite PM*
- *The fact that pacing is effective does not mean that it is always necessary*



# ISSUE 3 International Study on Syncope of Uncertain Etiology 3

## *Limitations ISSUE-3*

- We are unable to evaluate if the RDR- algorithm used in this trial provided an additional benefit to that of a DDD pacemaker without RDR

# Two-year diagnostic yield of implantable loop recorder in patients with neurally-mediated syncope enrolled in the ISSUE-3 trial

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## PURPOSE

Since the diagnostic yield of implantable loop recorders (ILRs) is a function of the length of observation, this rate increases by prolonging the observation period. We assessed the diagnostic yield among the 284 patients enrolled in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial who completed the planned 2-year follow-up period.

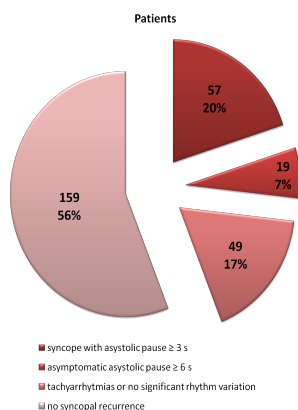
## METHODS

Eligible patients were  $\geq 40$  years, had suffered  $\geq 3$  severe syncopal episodes of suspected or certain neurally-mediated syncope (NMS) in the prior 2 years without significant electrocardiographic and cardiac abnormalities and irrespective of the Tilt Table Testing results.

Patients suffering orthostatic hypotension and carotid sinus syncope were excluded.

## RESULTS

284 pts out of 511 enrolled in the study from September 2006 to November 2010 have reached the 24 month follow-up. As reported by investigators, 76 patients (27%) had syncopal recurrence with asystolic pause  $\geq 3$  s (#57) or asystolic pause  $\geq 6$  s without syncope (#19) after a mean of  $7 \pm 8$  months (median 3 IQ 1,11). 49 patients (17%) after a mean of  $9 \pm 8$  months (median 6 IQ 2,14) had a diagnosis of tachyarrhythmia or syncope due to non-arrhythmic cause and 159 patients (56%) had no diagnosis at 24 month follow-up. **No baseline clinical variables** (age, gender, number of previous syncopes, typical vasovagal features, absence of prodrome, injuries related to syncope, associated medical diseases) **was able to predict the outcome with the exception of a positive tilt table test response** which was present in 60% of patients with asystolic syncope, 51% of those with non-asystolic syncope and in 36% of those without diagnosis ( $p=0.003$ ).



Clinical characteristics	Issue	Issue	No diagnosis	p-value
	type 1	other type	n=159	
	n=76	n=49		
Age, mean (SD), y	66 (11)	66 (13)	67 (11)	0.816
Men, No. (%)	37 (49)	22 (45)	66 (42)	0.578
<b>Syncope events:</b>				
- Total events, median (IQR)	6 (5-12)	6 (4-15)	6 (4-10)	0.660
- Events in the last 2 years, median (IQR)	4 (3-6)	4 (3-7)	4 (3-5)	0.058
- Events in the last 2 years without prodrome,	2 (0-4)	2 (0-4)	3 (1-4)	0.721
<b>median (IQR)</b>				
- Age at first syncope, mean (SD), y	49 (24)	49 (20)	5 (19)	0.743
- History of presyncope, n (%)	43 (57)	25 (51)	67 (43)	0.112
- Hospitalization for syncope, n (%)	45 (59)	30 (61)	78 (50)	0.219
- Injuries related to fainting, n (%)				
- Major injuries (fractures, brain concussion)	6 (8)	2 (4)	23 (15)	0.071
- Minor injuries (bruises, contusion, hematoma)	30 (40)	16 (33)	64 (41)	0.588
- Typical vasovagal/situational presentation, n (%)	28 (37)	16 (33)	51 (32)	0.788
- Atypical presentation (uncertain), n (%)	48 (63)	33 (67)	107 (68)	0.788
<b>Tilt testing: performed, No (%)</b>				
- Positive of those performed, No. (%)	39 (60)	23 (51)	51 (36)	<b>0.003</b>
<b>Medical history, n (%)</b>				
- Structural heart disease	11 (14)	4 (8)	24 (15)	0.450
- Hypertension	37 (49)	25 (51)	88 (56)	0.575
- Diabetes	10 (13)	4 (8)	19 (12)	0.681

**pacemaker therapy due to a documented long asystolic pause. The patients with a positive response to tilt table test are more likely to benefit from an ILR strategy.**

## DECLARATION OF INTEREST

M. Brignole reports receiving modest consultancy fee from Medtronic and being direct shareholding of F2 solutions; R. Sutton is a Consultant to Medtronic receiving modest fees and a paid lecturer for St Jude Medical; the other authors have no financial disclosures to make

**MISDIAGNOSIS OF NEURALLY-MEDIATED  
SYNCOPE AT INITIAL EVALUATION AND WITH  
TILT TABLE TESTING REVEALED BY  
PROLONGED ECG MONITORING**

**AN ANALYSIS FROM THE THIRD INTERNATIONAL STUDY ON  
SYNCOPE OF UNCERTAIN ETIOLOGY (ISSUE-3)**

A.Ungar, P.Sgobino, V.Russo, E.Vitale, R.Sutton, D.Melissano,  
X.Beiras, N.Bottoni, H.H.Ebert, M.Gulizia, M.Jorfida, A.Moya,  
D.Andresen, N.Grovale, M.Brignole *on behalf of the International  
Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators*

**According to the ILR findings, the accuracy of the  
diagnosis of NMS made on initial evaluation was 87%.  
The diagnostic accuracy of tilt table test was low: TT was  
positive in 56% NMS, 43% non-NMS; an asystolic  
response was present in 21% NMS and 0% non-NMS**



# Issue-3 subanalysis

CIRCAE/2013/001103-T1

The 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)

M.Brignole, P.Donateo, M.Tomaino, R.Massa, M.Iori, X.Beiras, A.Moya, T.Kus, J.C. Deharo, S.Giuli, A.Gentili and R.Sutton

***-Positive TTT is more likely correlated with a higher frequency of recurrences of syncope in the group treated using a PM, while a negative response seems to predict the success of the pacing therapy.***

-This result inverts the previous knowledges concerning the TT

***-The results of our study show the capacity of TTT to identify patients, who were treated with PM after evidence of a CI activity by ILR, with a possible concomitant vasodepressive form.***

***Consequently PM could not to be enough in a group of patients with positive TTT response.***

**LIMITED UTILITY OF PHYSICAL COUNTERPRESSURE  
MANOEUVRES IN PREVENTING SYNCOPAL RECURRENCE  
IN PATIENTS OLDER THAN 40 YEARS WITH RECURRENT  
NEURALLY-MEDIATED SYNCOPES.**

**AN ANALYSIS FROM THE THIRD INTERNATIONAL STUDY ON  
SYNCOPE OF UNCERTAIN ETIOLOGY (ISSUE-3)**

M.Tomaino, C.Romeo, E.Vitale, T.Kus, A.Moya, N.van Dijk, S.Giuli,  
A.Gentili, R.Sutton *on behalf of the International Study on Syncope  
of Uncertain Etiology 3 (ISSUE-3) Investigators*

**The benefit of PC maneuvers was limited in ISSUE-3  
patients affected by hypotensive NMS. The likely  
factors that hampered effectiveness of PC therapy  
were older age and absence of sufficiently long  
recognizable prodromal symptoms in the ISSUE-3  
population.**

## Considerations

- *from both therapeutic solutions there is an improvement on the patients' quality of life.*
- *“ICPM” is effective and the only treatment in class 1 of the Guidelines.*
- *PM in class 1 ???*

# ISSUE 3

## International Study on Syncope of Uncertain Etiology 3

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### • Neuro-cardiogenic syncope: Treatment

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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• Isometric PCMs are indicated in patients with prodrome	I	B
• Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS	IIa	B
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## ISSUE 3

# International Study on Syncope of Uncertain Etiology 3

### ***Principal investigators:***

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