# What's next after ISSUE 2 and ISSUE 3?

**M. Brignole**

*Arrhythmologic Centre and Syncope Unit – Lavagna, Italy*

ISSUE 3

SYNCOPE

# Study design

**ILR screening phase**

Pts affected by **severe, recurrent** reflex syncopes, **aged >40 yrs**

↓

**Tilt Table Testing (Passive + TNT)**

↓

**ILR implantation (Reveal DX/XT)**

↓

ILR follow-up (max 2 yrs)

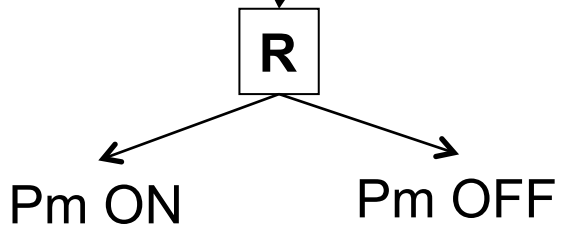
↓

**ISSUE 3 therapy phase**

ILR eligibility criteria:

- *Asystolic syncope ≥3 s, or*
- *Non-syncopal asystole ≥6 s*

↓

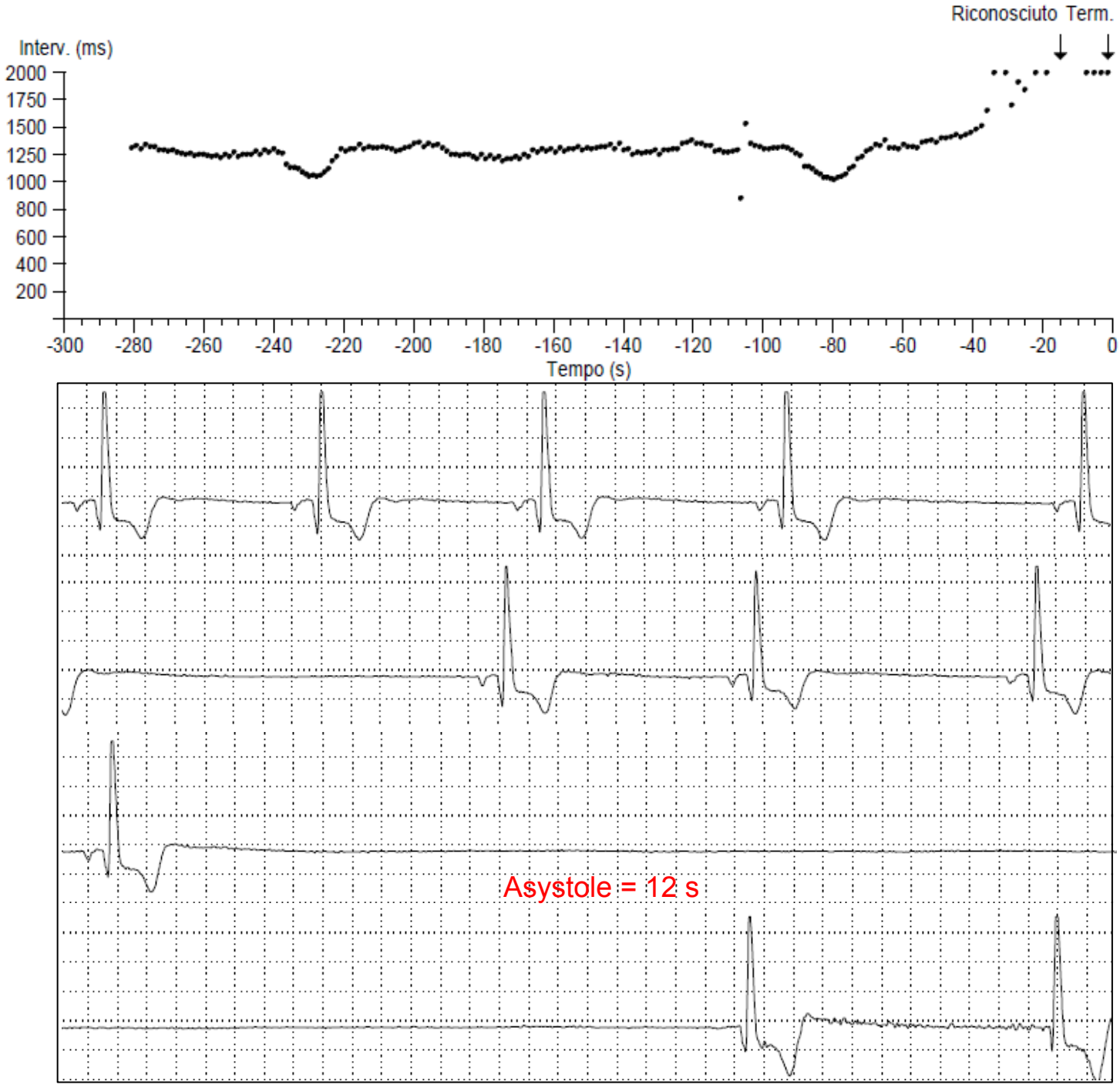



Circulation 2012;125:2566-2571

ISSUE 3

SYNCOPE

# ISSUE 3 population



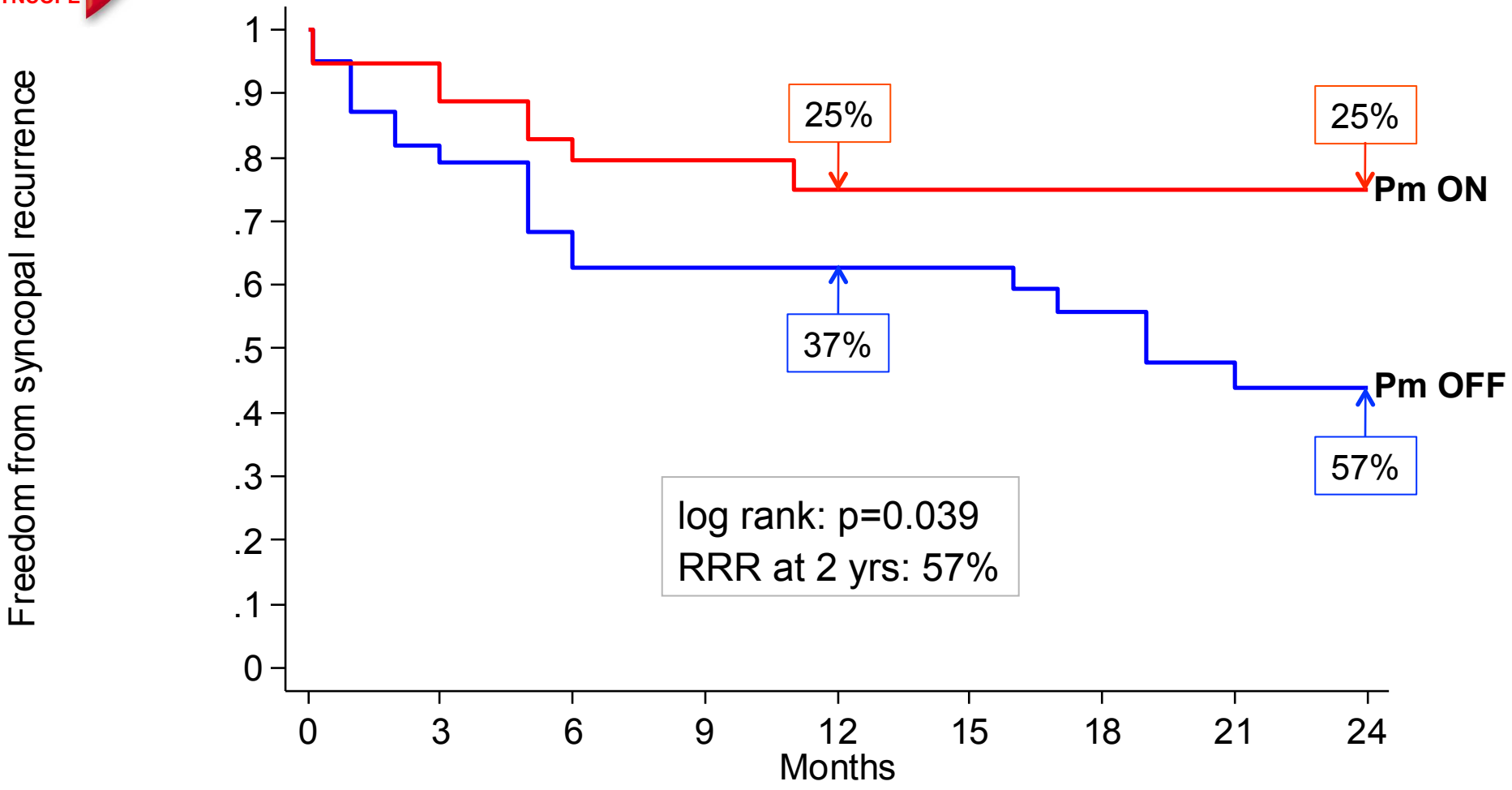

#8_4, 30/01/2009

ISSUE 3

SYNCOPE

# First syncope recurrence

*(intention-to-treat)*




Number at risk

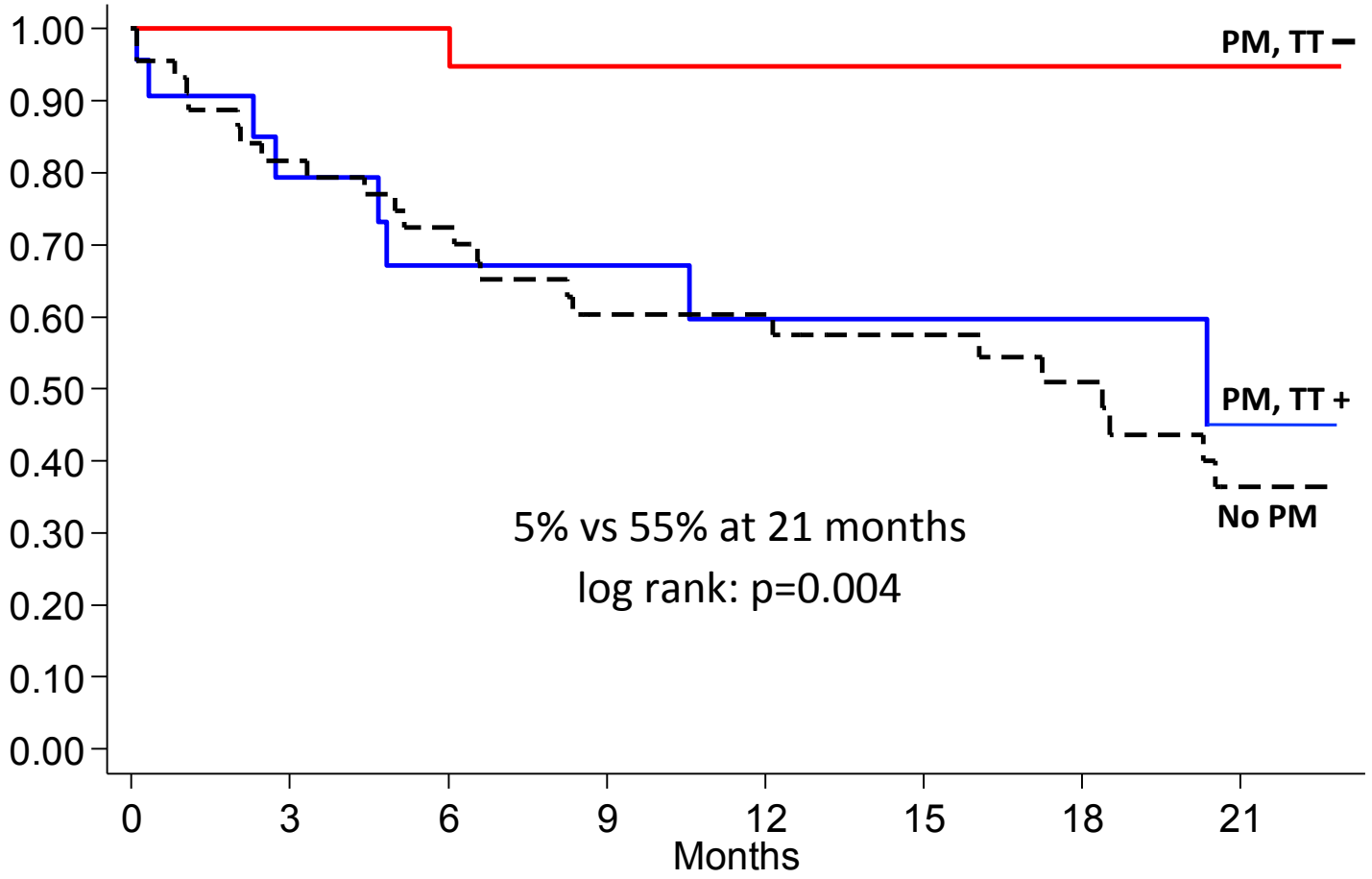
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pm OFF | 39 | 31 | 25 | 21 | 21 | 18 | 15 | 12 | 8 |
| Pm ON | 38 | 32 | 27 | 22 | 16 | 14 | 13 | 13 | 11 |

**Circulation 2012;125:2566-2571**

# Factors predicting recurrence of syncope after pacemaker therapy (II)

| *Characteristics* | **Recurrence** n=9 | **No recurrence** n=43 | **P value** |
|---|---|---|---|
| **Tilt testing: positive** | 89% | 42% | 0.0004 |
| - Asystolic (Vasis 2B) | 44% | 23% | ns |
| - Non-asystolic | 44% | 19% | ns |
| **ILR findings (asystole)** | | | |
| - Asystole duration, sec | 9 | 8 | ns |
| - Type 1A (sinus arrest) | 44% | 63% | ns |
| - Type 1B (sinus brady + AV block) | 33% | 14% | ns |
| - Type 1C (AV blocK) | 22% | 24% | ns |
| **Systolic blood pressure** | | | |
| - Supine, mmHg | 135 | 130 | ns |
| - Standing, mmHg | 127 | 118 | ns |

# Syncope recurrence after PM therapy according to tilt test results




Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PM TT+ | 26 | 14 | 10 | 9 | 8 | 6 | 4 | 3 |
| PM TT- | 26 | 19 | 19 | 15 | 11 | 10 | 9 | 9 |
| NO THER | 45 | 35 | 31 | 22 | 22 | 18 | 14 | 9 |

Circ Arrhythm Electrophysiol 2014;7:10-16

European Heart Journal (2014) **35**, 2211–2212
doi:10.1093/eurheartj/ehu255

CURRENT OPINION

# Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis

**Richard Sutton[1]* and Michele Brignole[2]**

A positive tilt test suggests the presence of a **hypotensive susceptibility**, which plays a role in causing syncope irrespective of the etiology and mechanism of syncope.

# 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope

Robert S. Sheldon, MD, PhD, FRCPC, FHRS (Chair),[1] Blair P. Grubb II, MD, FACC (Chair),[2]

| Recommendations - Pacemaker for VVS | Class | LoE |
|---|---|---|
| Dual-chamber pacing can be effective for patients 40 years of age or older with recurrent and unpredictable syncope who have a documented pause ≥3 seconds during clinical syncope or an asymptomatic pause ≥6 seconds. | IIa | B-R |
| Tilt-table testing may be considered to identify patients with a hypotensive response who would be less likely to respond to permanent cardiac pacing. | IIb | B-NR |

# Vasovagal Syncope: Pacemaker Treatment in Adults

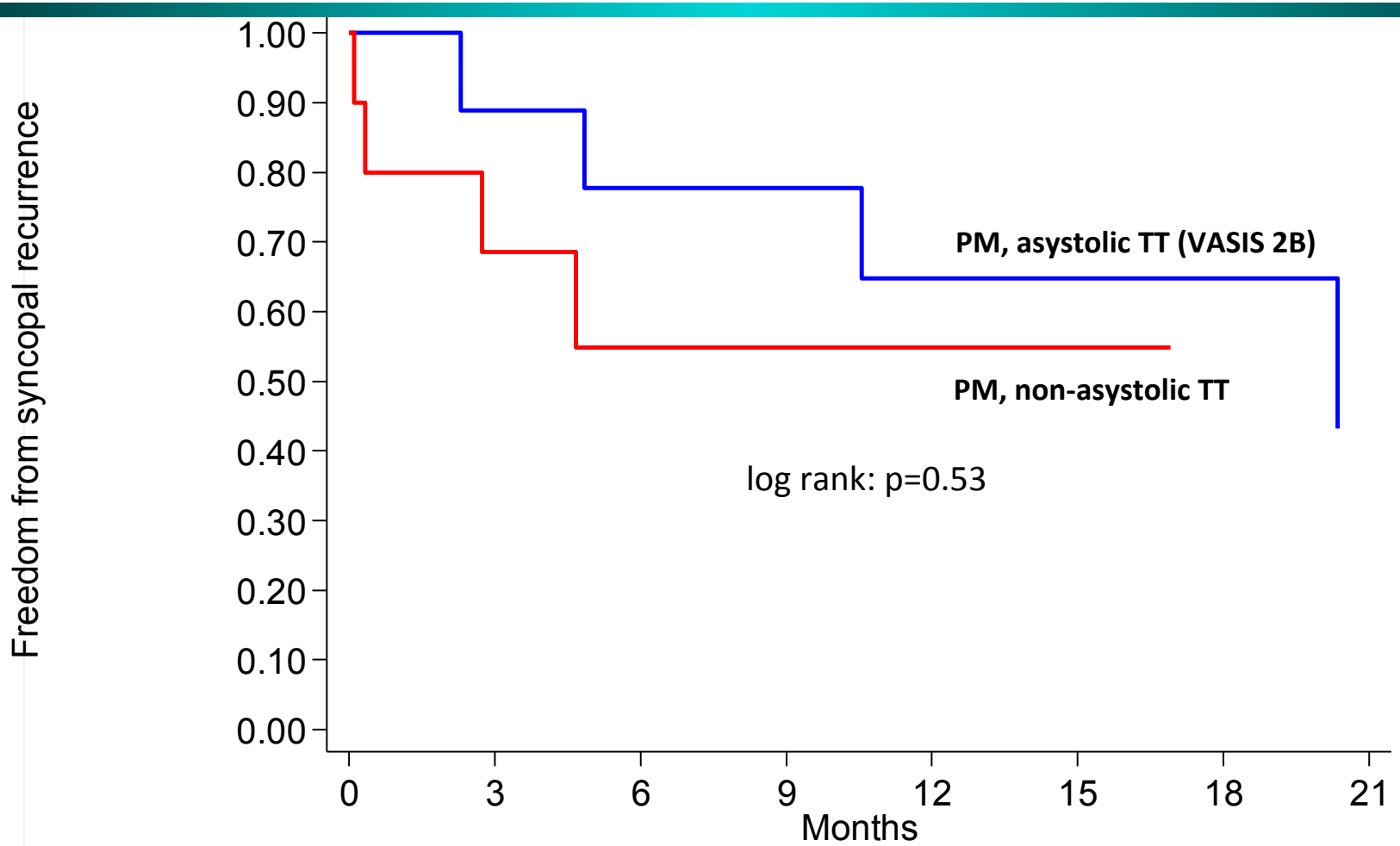
***Unresolved issue***

**Tilt-positive asystolic syncope (so called VASIS 2B form)**

ISSUE 3

SYNCOPE

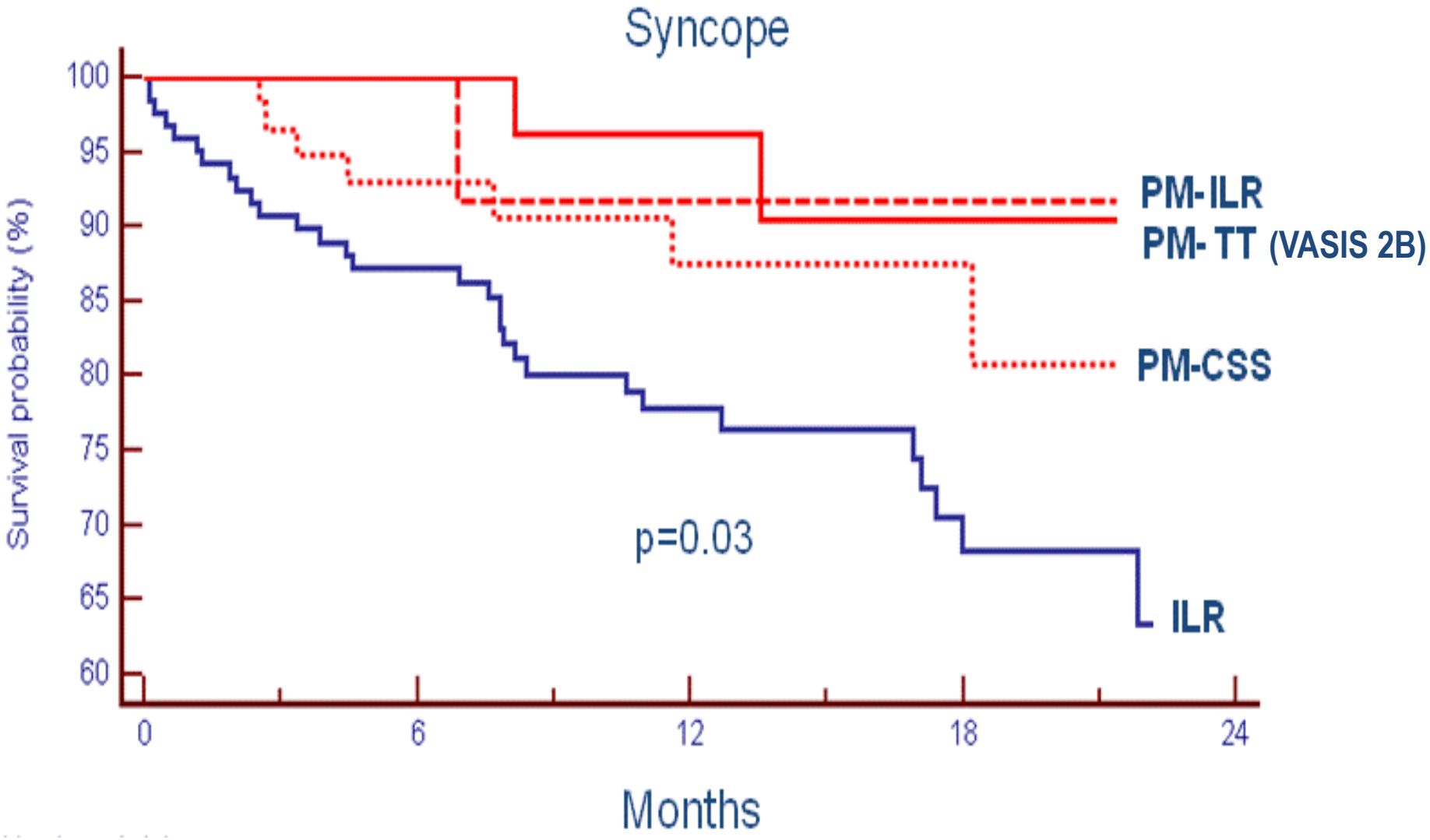
# Syncope recurrence after PM therapy according to tilt test response




Brignole M et al. Circ Arrhythm Electrophysiol 2013

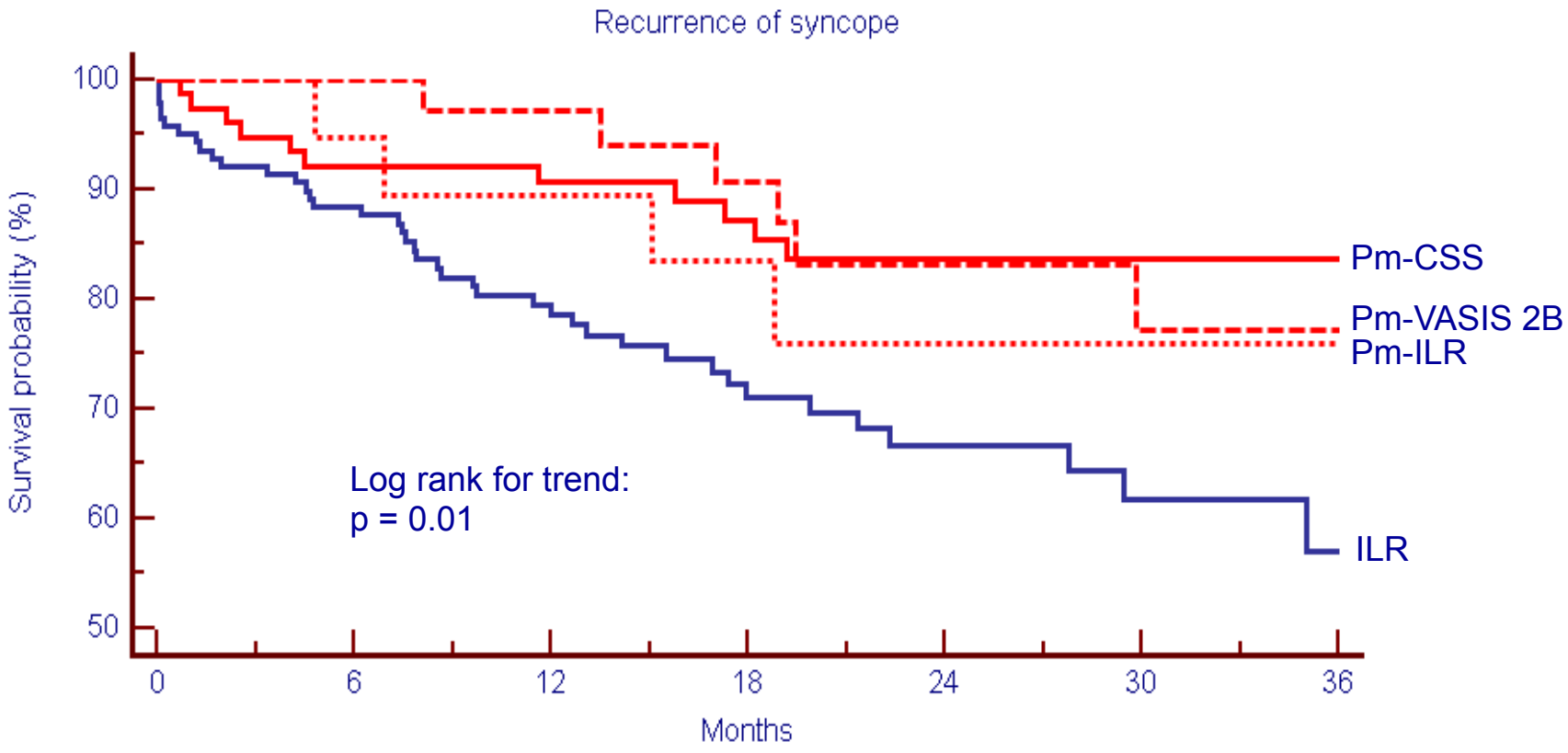
Syncope Unit Project 2 (SUP 2)

# Results




European Heart Journal 2015; 36: 1529–1535

# *SUP 2 study:* 3-years extended follow-up

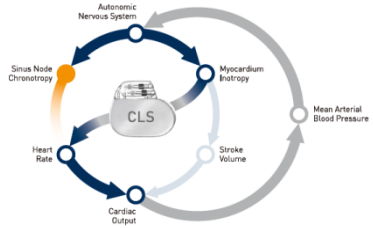



Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Group: ILR | | | | | | |
| 142 | 115 | 90 | 58 | 37 | 22 | 10 |
| Group: PM-CSS | | | | | | |
| 78 | 69 | 61 | 51 | 40 | 26 | 17 |
| Group: PM-ILR | | | | | | |
| 21 | 18 | 17 | 11 | 8 | 6 | 1 |
| Group: PM-VASIS 2B | | | | | | |
| 38 | 37 | 32 | 26 | 21 | 13 | 6 |

*Europace 2015*

# BioSync




## Benefit of dual-chamber pacing with Closed Loop Stimulation (CLS) in tilt-induced cardio-inhibitory reflex syncope.

## A randomized double-blind parallel trial

**M. Brignole (PI) - M. Tomaino (Co-PI)**

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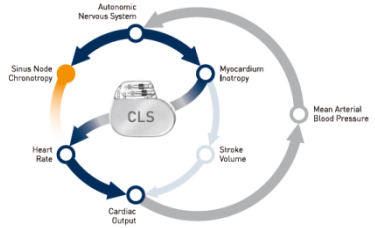
# Inclusion criteria




- **age >40 years**
- **significant limitation of social and working life due to unpredictable or frequent syncope recurrences, ≥2 within the last year.**
- **type 2B cardio-inhibitory response to TT (according to the VASIS classification)**
- **alternative therapies have failed or were not feasible**
- **exclusion of other possible competitive causes of syncope.**

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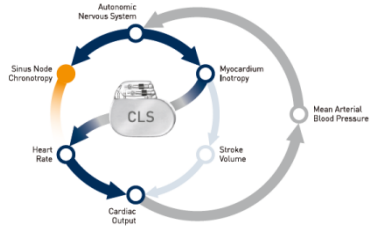
# Primary end-point




- **Time to first syncopal recurrence**
  1. **active group: treated with the Closed Loop Stimulation (CLS) in addition to the DDD pacing**
  2. **control group: ODO mode (sensing only)**

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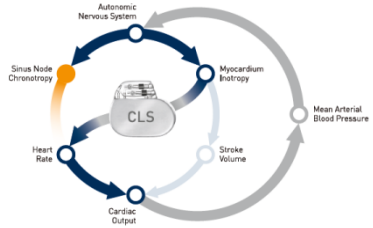
# Secondary end-points




1. **Clinical outcome:**

   **time to the first recurrence of pre-syncope or syncope, whichever comes first, as compared between the study groups during follow-up**

2. **One month TT tilt test study:**

   **parallel comparison of TT response 1-month after implantation between DDD-CLS and ODO mode**

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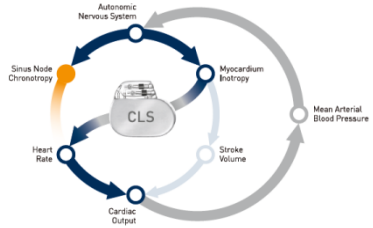


# Critical issues in obtaining reliable follow-up data in syncope trials

- Low recurrence of syncope (regression-to-the-mean effect)
- Real double-blindness impossible to achieve with devices
- Investigator's "expectation effect"
- Difficulty of obtaining a reliable history by non-experts

**Self-assessed patient questionnaire**

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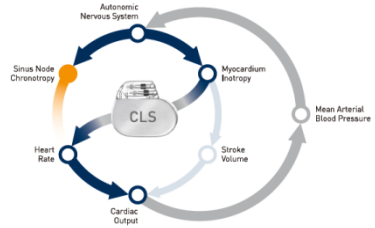


# Self-assessed patient questionnaire for clinical research in syncope

| Question items | Inter-rater agreement Kappa statistic |
|---|---|
| 1. Did you lose completely consciousness ? Y/N | 0.90 |
| 2. Was the episode similar to those you had had before? Y/N | 0.67 |
| 3. Was the episode of short duration ? Y/N | 0.21 |
| 4. Have you had time to stop and lie/sit down? Y/N | 0.67 |
| 5. Was the event witnessed by other people? Y/N | 0.70 |
| 6. Did the episode occur at home? Y/N | 0.69 |
| 7. What were you doing immediately before the event ?<br>- I was standing<br>- I was sitting<br>- I was lying<br>- I had just stood up | 0.58 |
| 8. Have you got injured due to the event? Y/N | 0.88 |
| 9. Did you go to the emergency room ? Y/N | 1.00 |
| 10. Were you hospitalized ? Y/N | 0.68 |

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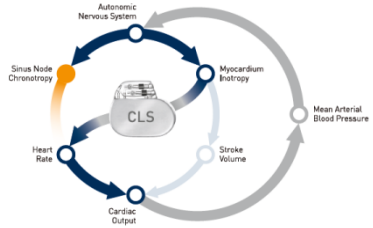


## Self-assessed patient questionnaire for clinical research in syncope

*Item #1*

Did you lose completely consciousness ?

| | Syncope expert | Patient |
|---|---|---|
| YES | **56** | **0** |
| NO | **3** | **18** |

*Inter-rater agreement, Kappa statistic: 0.90*
*p value: <0.0001*

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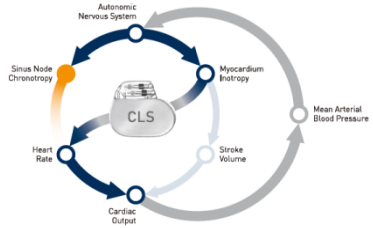
# Blinding




- Primary and secondary endpoint will be assessed through quarterly phone interviews performed by an external agency, blinded to the patient's randomization assignment
  - Patient: **BLIND**
  - External agency personnell: **BLIND**
  - Investigator: **NOT BLIND**
  - Primary/secondary endpoint Adjudication Board: **BLIND**

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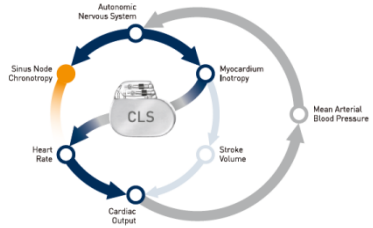
# Study flow-chart




Monitoring of primary endpoint event occurrence

IPG implant hospitalization

Enrollment

IPG implant

DDD+CLS

R

1:1

ODO

In-hospital visit 30 ± 14 days after discharge TT exam

Self-assessed patient questionnaire

In-hospital visits @ 12±1 months after discharge

In-hospital visits @ 24±1 months after discharge

In-hospital visit 30 ± 14 days after discharge TT exam

Self-assessed patient questionnaire

In-hospital visits @ 12±1 months after discharge

In-hospital visits @ 24±1 months after discharge

Every 3 months

Enrollment before implant

Randomization

Discharge

In-hospital visits

Closeout

Scheduled follow-up

Unscheduled follow-up

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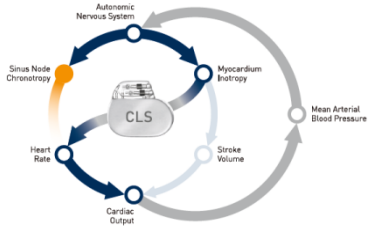
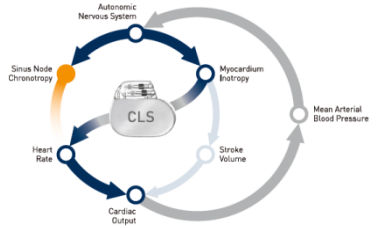
# Sample size calculation and statistical power




- **The BIOSync study is designed to detect a 40% relative reduction of the 2-years incidence of syncopal recurrences (from 57% (*) to 34%, NTT=4.3) with a statistical Type I and II errors of 0.05 (bilateral) and 0.20, respectively**
- **A sample size of 62 patients per study arm (124) is required + 2% (power loss induced by the interim analyses)**
- **With a sequential study design the study will stop when a total of 62 primary endpoint events will be collected.**
- **Interim analyses after 25 and 43 endpoint events**

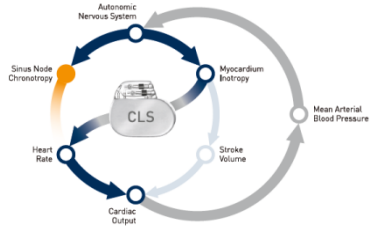
(*) derived from the control arm of the ISSUE 3 trial

# BioSync

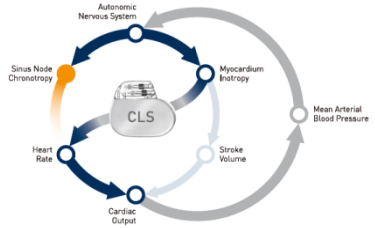

Autonomic
Nervous System
Sinus Node
Chronotropy
Myocardium
Inotropy
CLS
Mean Arterial
Blood Pressure
Heart
Rate
Stroke
Volume
Cardiac
Output

BioSync

# Inclusion criteria



# Publication policy




- **The first author of the primary publication will be Dr. Brignole**
- **The authors of the primary publication will be 10 investigators (or more, depending on the journal requirements) with the highest scores.**
- **A minimum of 3 members of the Steering Committee is warranted.**
- **Each Investigator will receive:**
  - ✓ 1 point for each enrolled subject
  - ✓ 1 point for each enrolled subject with complete and compliant data set
  - ✓ +0.25 points for each compliant and fully reported scheduled in-hospital follow-up
  - ✓ -0.25 points for each unreported or incompliant (e.g., out of window) scheduled follow-up visit
  - ✓ -1 point for each underreported or delayed reported Serious Adverse Event, and (Serious) Adverse Device Effect.