ISSUE 3

International Study on Syncope of Uncertain Etiology 3

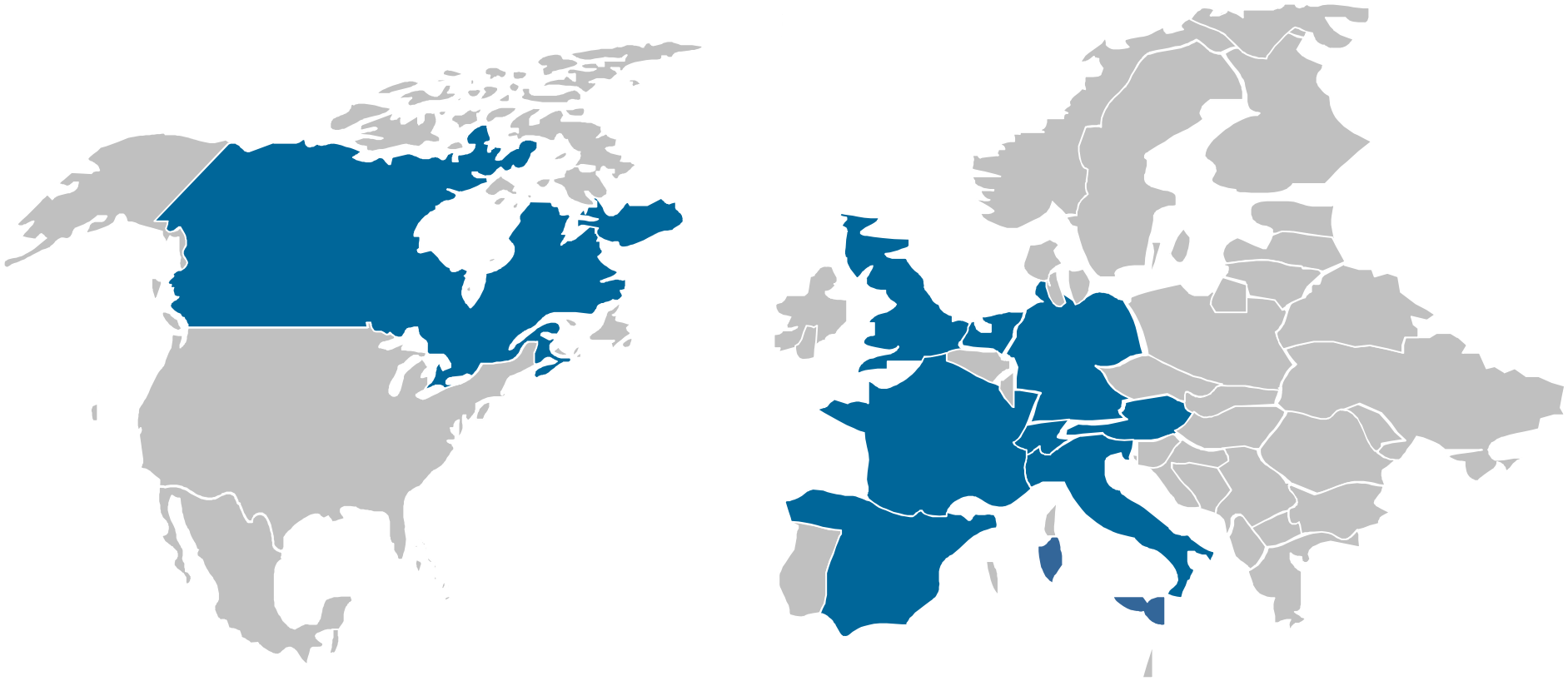
Pacemaker therapy for patients with neurally-mediated syncope and documented asystole

A randomized controlled double-blind trial

ISSUE 3

SYNCOPE

International Study on Syncope of Uncertain Etiology 3



Total 29 centers

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International Study on Syncope of Uncertain Etiology 3

Background:

Two RCTs* failed to prove superiority of cardiac pacing over placebo of unselected NMS patients with positive tilt testing

Study hypothesis:

Pacing therapy is effective for preventing syncope recurrence in patients with NMS and documented asystole

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* VPS II trial. JAMA 2003; 289: 2224-2229
  Synpace trial. Eur Heart J 2004: 25: 1741–1748

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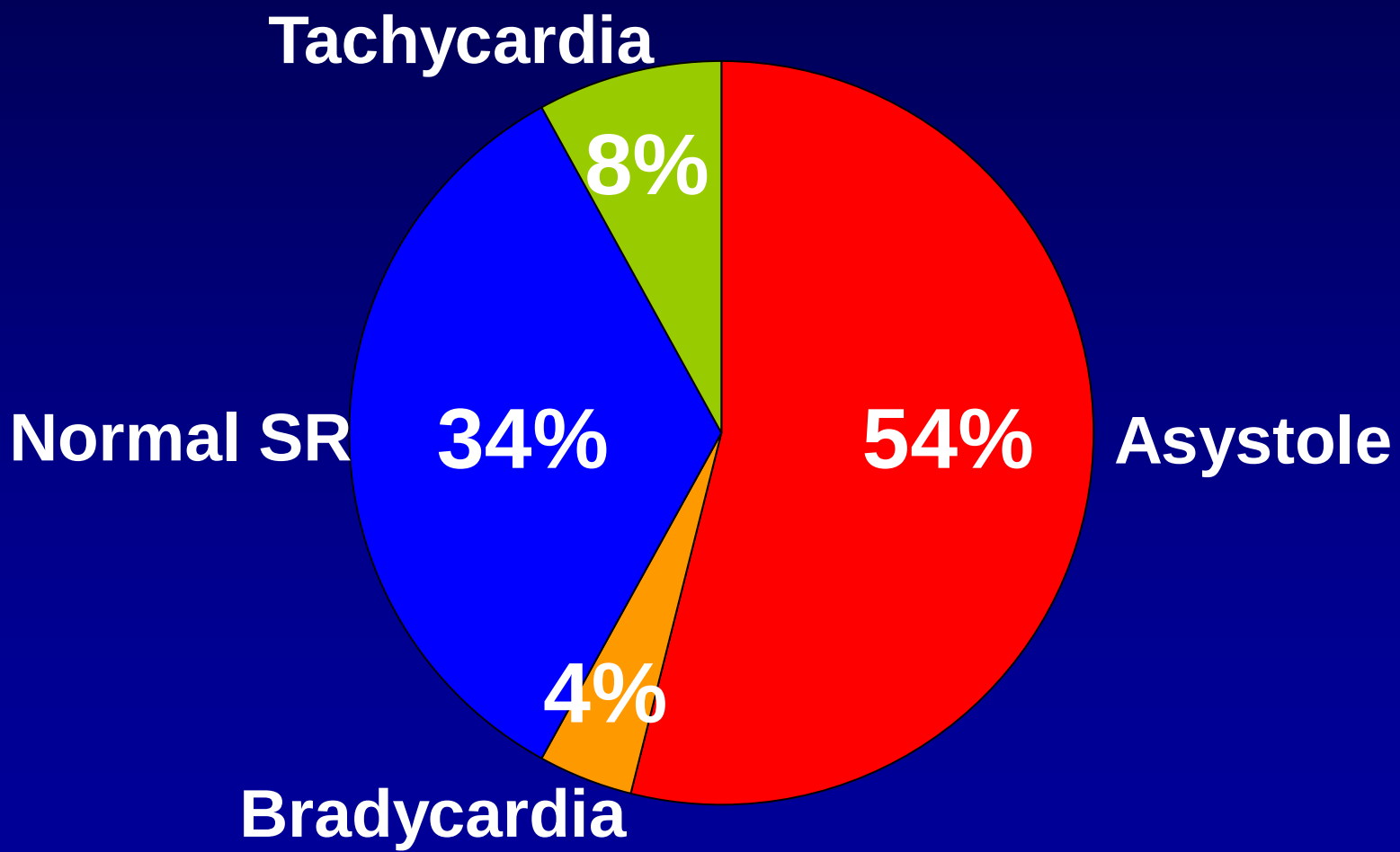
International Study on Syncope of Uncertain Etiology 2



Eur Heart J 2006; 27, 1085–1092

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SYNCOPE

ILR screening phase

• Clinical history consistent with NMS	If YES, continue
• Age ≥40 years	If YES, continue
• ≥3 syncope during last 2 years	If YES, continue
• So severe presentation (high risk or high frequency setting) to warrant specific treatment	If YES, continue
• Non-syncopal loss of consciousness	If NO, continue
• Symptomatic orthostatic hypotension	If NO, continue
• Cardiac abnormalities which suggested cardiac syncope	If NO, continue
• Carotid sinus syncope	If NO, continue
	ILR screening phase

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

Neurally-mediated syncope: therapy

Specific treatment (high risk or high frequency settings):

- **syncope is very frequent, i.e. alters the quality of life**
- **syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients to "high risk" of trauma**
- **syncope occurs during the prosecution of a 'high risk' activity (e.g., driving, machine operation, flying, competitive athletics, etc)**

ESC Guidelines on Management of Syncope – ***Update 2004***

ISSUE 3

SYNCOPE

Study design

ILR screening phase

Neurally-mediated syncopes

↓

ILR implantation (Reveal DX/XT)

↓

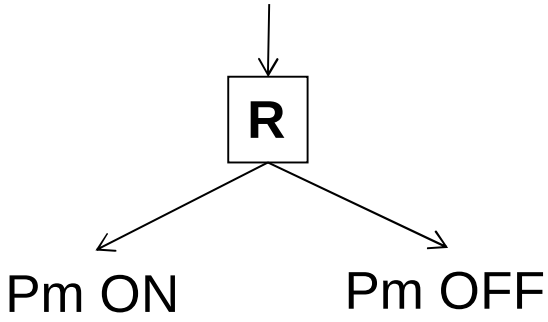
ILR follow-up (max 2 yrs)

↓

ISSUE 3 study phase

ILR eligibility criteria:

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

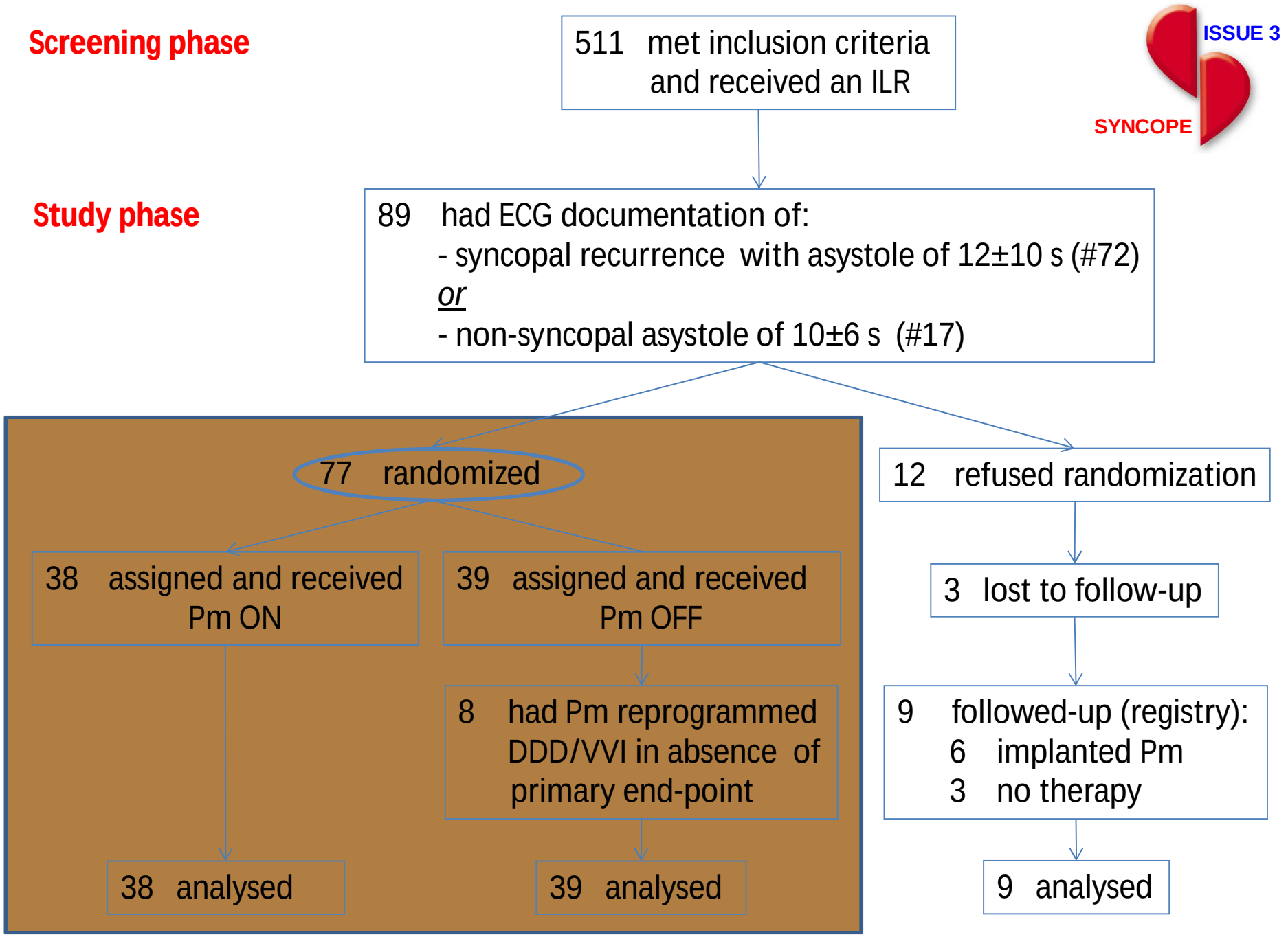


Primary end-point

Time to first syncope recurrence

Methods

- **Sequential design**: study planned to be stopped when a total of 27 primary end-point events, irrespective of study arm, would be reached (*80% power to detect a 1-year ARR of 25% in the Pm ON arm, with p=0.05*)
- **Primary analysis:** intention-to-treat
- **Blindness:** to patients and to follow-up physician
- **Randomization:** 1:1 centrally, blocked per center
- **Pm programming:** DDD-RDR vs ODO


Screening phase
511 met inclusion criteria and received an ILR
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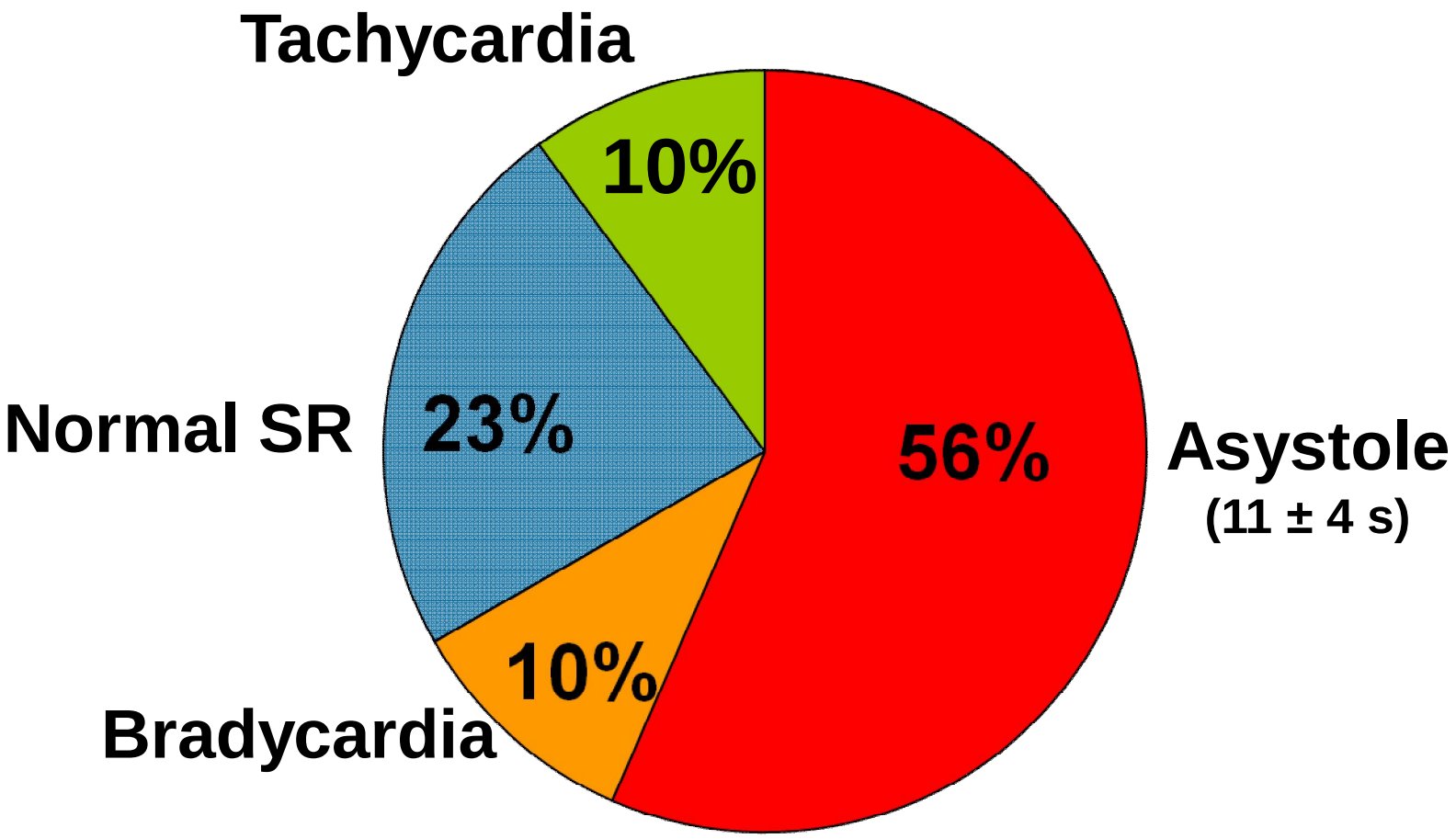
SYNCOPE
Study phase
89 had ECG documentation of:
- syncopal recurrence with asystole of 12±10 s (#72)
or
- non-syncopal asystole of 10±6 s (#17)
77 randomized
12 refused randomization
38 assigned and received Pm ON
39 assigned and received Pm OFF
3 lost to follow-up
8 had Pm reprogrammed DDD/VVI in absence of primary end-point
9 followed-up (registry):
6 implanted Pm
3 no therapy
38 analysed
39 analysed
9 analysed

ILR screening phase: documented events



Total end-points: 158

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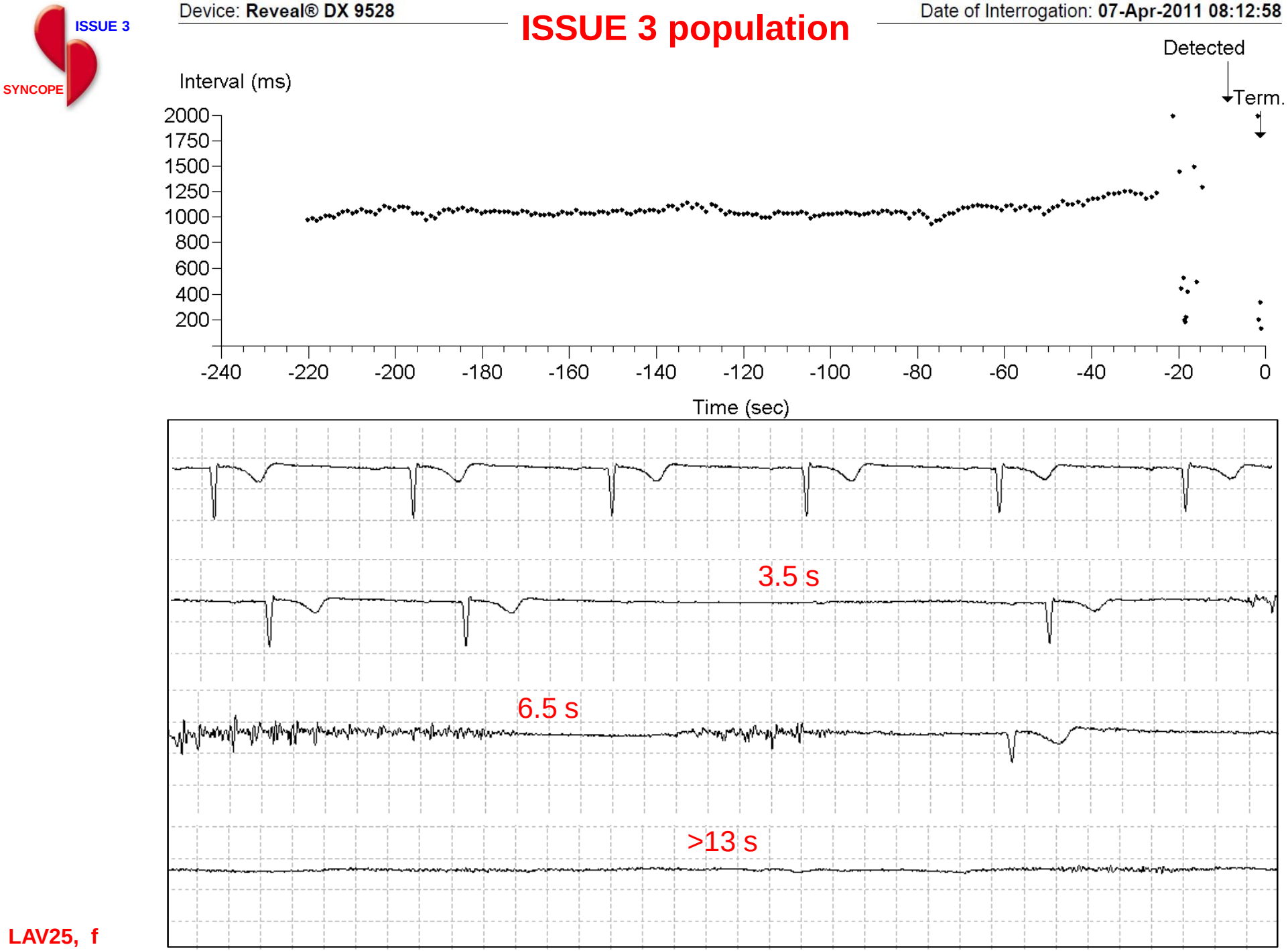
ISSUE 3 population



LAV25, f

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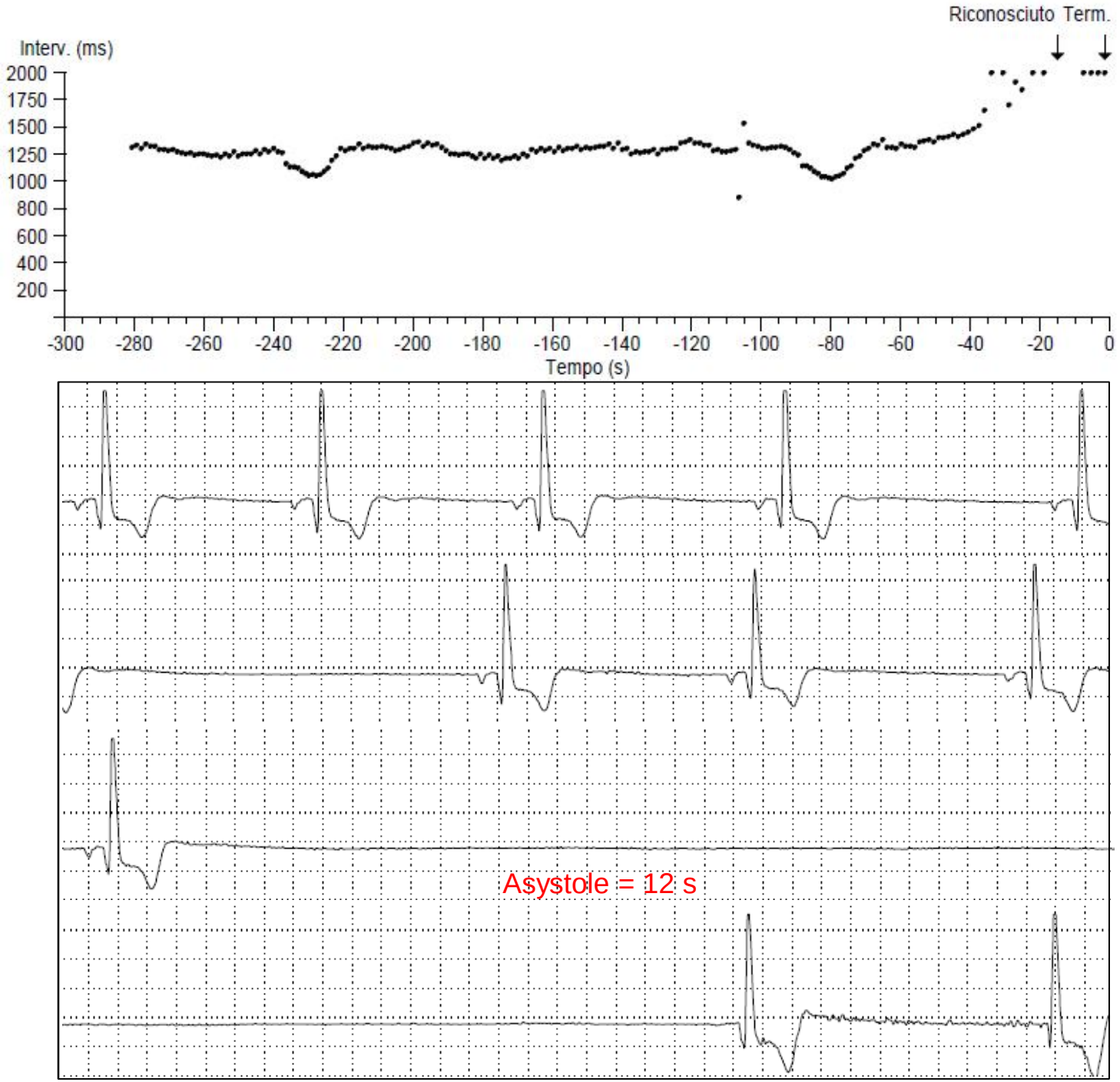
ISSUE 3 population



#8_4, 30/01/2009

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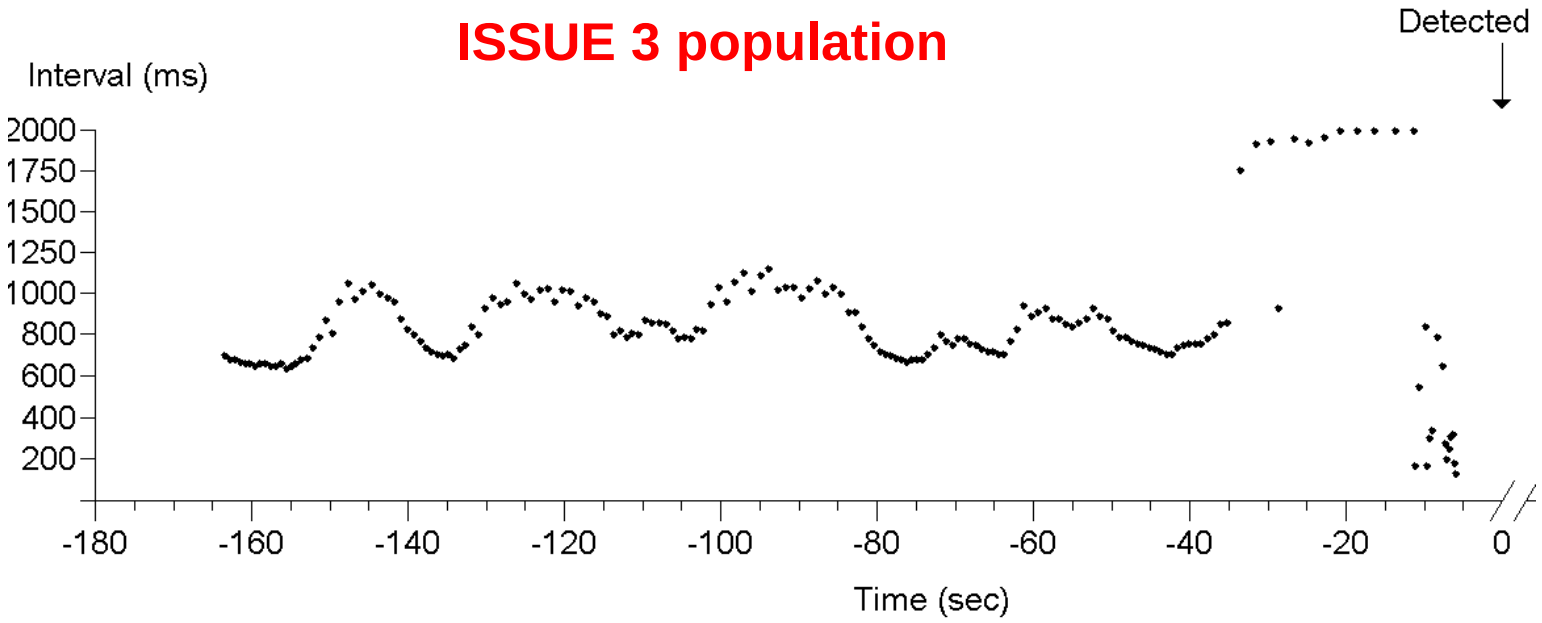
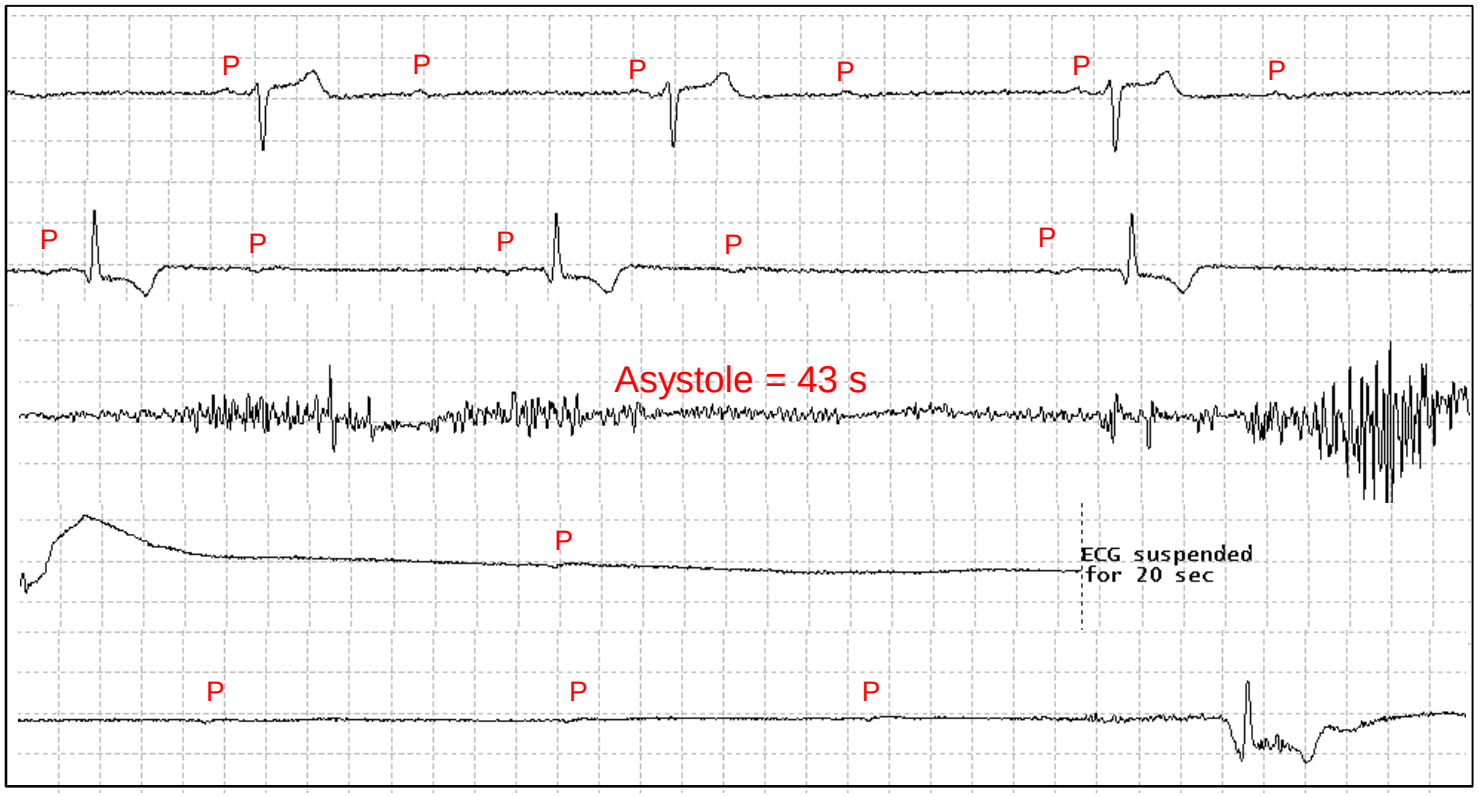
ISSUE 3 population





KM, m, 01/31/2010

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SYNCOPE

Patient characteristics (I)

Characteristics	**Pm ON** n=38	**Pm OFF** n=39	**Registry** n=12
Age, mean	63	63	63
Men	53%	41%	58%
Syncope events:			
- Total events, median	7	8	7
- Events last 2 years, median	4	5	4
- Events last 2 years without prodrome, median	3	3	1
- Age at first syncope, mean	48	45	41
- Interval between first and last episode, median	8	8	17
- History of presyncope	50%	56%	75%
- Hospitalization for syncope	63%	64%	58%
- Injuries related to fainting:			
- Major (fractures, concussion)	5%	10%	17%
- Minor (bruises, contusion, hematoma)	39%	46%	50%
- Typical vasovagal/situational presentation	47%	41%	58%
- Atypical presentation (uncertain)	53%	59%	42%

Patient characteristics (II)

Characteristics	**Pm ON** n=38	**Pm OFF** n=39	**Registry** n=12.
ILR documentation (eligibility criteria):			
- Syncope and asystole ≥3 s	79%	82%	77%
- Non-syncopal pause ≥6 s	21%	18%	17%
- Mean length of asystole, s	10	12	12
Tilt testing: performed	87%	82%	83%
- Positive of those performed	42%	72%	50%
Medical history			
- Structural heart disease	13%	10%	0%
- Hypertension	50%	49%	33%
- Diabetes	11%	10%	8%
Concomitant medications			
- Anti-hypertensive	47%	31%	25%
- Psychiatric	11%	5%	0%
- Any other drugs	26%	25%	25%

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SYNCOPE

ISSUE 3 population

Features:

- Mean age at presentation: >60 years
- History of recurrent syncopes beginning in middle or older age
- Severe clinical presentation requiring treatment (high risk and/or high frequency)
- Atypical presentation without warning
- Frequent injuries related to presentation without warning
- ILR documentation of long pauses (mean 11 seconds)

Estimated prevalence:

9% of patients affected by NMS referred to Syncope Clinic

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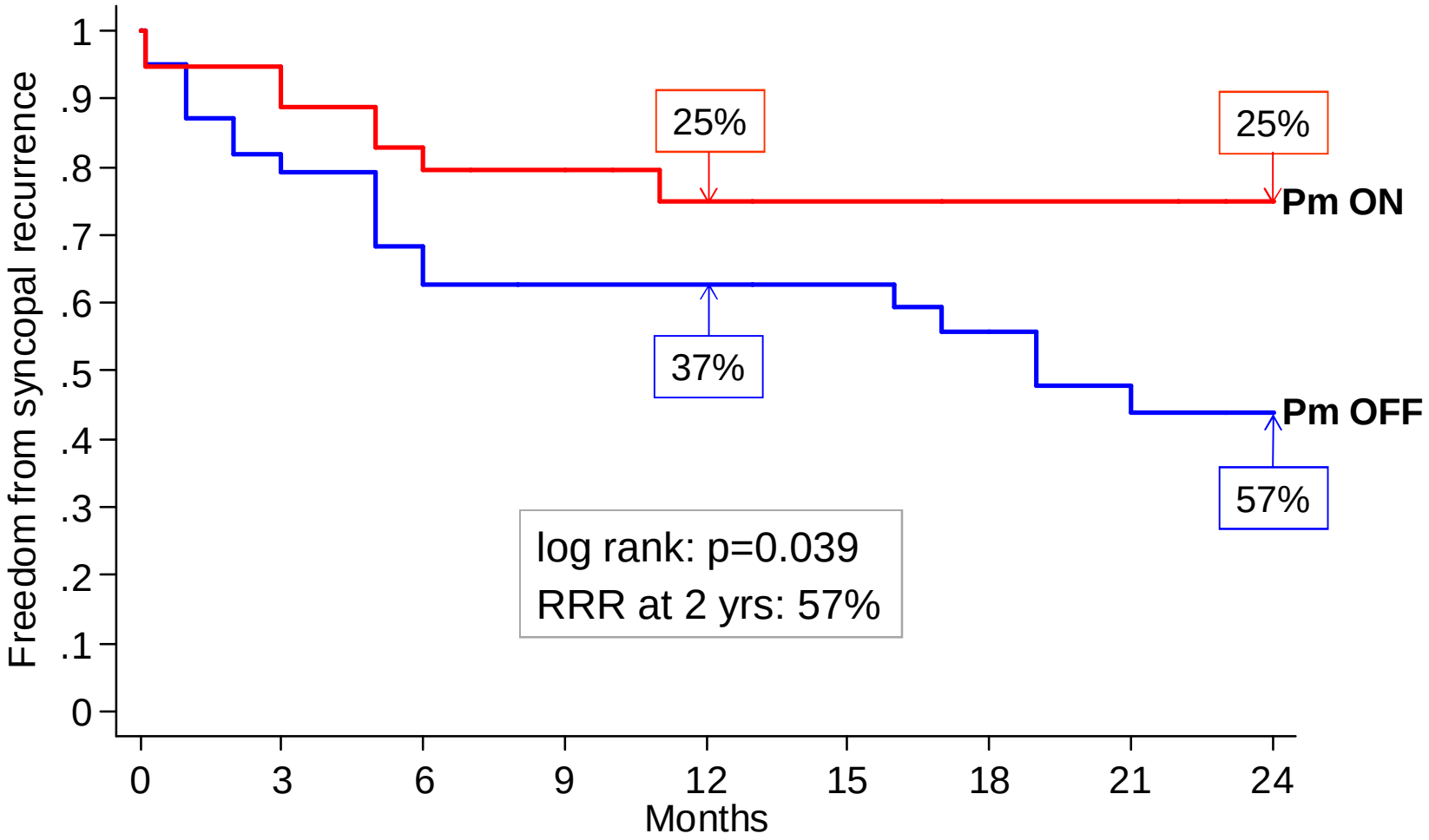
First syncope recurrence
(intention-to-treat)



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

Procedure-related complications

- RA lead dislodgment: 2 pts
- RV lead dislodgment: 2 pts
- Subclavian vein thrombosis: 1 pt

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Conclusions

- Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic NMS.
- The observed 32% absolute and 57% relative syncope reduction rate support the use of this invasive treatment for the relatively benign NMS.
- The overall strategy of using an ILR in order to determine indication for pacing likely contributed to the positive findings and explains the discrepancy with the negative results of some previous report.

ISSUE 3 in perspective

Who gets an ILR and (eventually) a PM ?

- 9% of patients affected by NMS referred to Syncope Clinic will receive a ILR
- 18% of pts receiving an ILR will be candidates for pacemaker therapy within 1 year and approximately 40% within 4 years
- 1 out of 3 pacemaker patients will benefit from pacing therapy within the subsequent 2 years (NNT=3)

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International Study on Syncope of Uncertain Etiology 3

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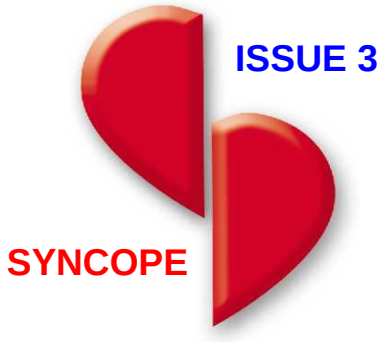

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Randomized controlled double-blind trial