

What is the Role of Pacemakers in Patients with Syncope

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Role of Pacing in Syncope

Potential Conflicts of Interest

Consultant to Medtronic

Research Grants from Medtronic

Paid Lecturer for St Jude Medical,
Transoma, Biotronik and Sorin

Share-holder in ACSI

Role of Pacing in Syncope

- When Syncope is due to Atrioventricular Block the Role of Pacing is well defined
- But the Role of Pacing is far less clear in Vasovagal Syncope

When to Pace in VVS?

First answer is 'NEVER'.

But this needs to be qualified by examining the literature.

Asystole on a tilt test in a young person (<40yrs) is not an indication for pacing.

The Role of Pacing as Therapy for VVS

- VVS with +HUT and cardioinhibitory response:
Class IIb indication for pacing
- Three randomized, prospective trials reported benefits of pacing in select VVS patients:
 - VPS I¹
 - VASIS²
 - SYDIT³
- Subsequent study results less clear
 - VPS II⁴
 - Synpace⁵
 - INVASY⁶

¹Connolly SJ. *J Am Coll Cardiol*. 1999;33:16-20.

²Sutton R. *Circulation*. 2000;102:294-299.

³Ammirati F. *Circ*. 2001;104:52-57.

⁴Connolly S. *JAMA*. 2003;289:2224-2229.

⁵Giada F. *PACE*. 2003;26:1016 (abstract).

⁶Occhetta E, et al. *Europace*. 2004;6:538-547.

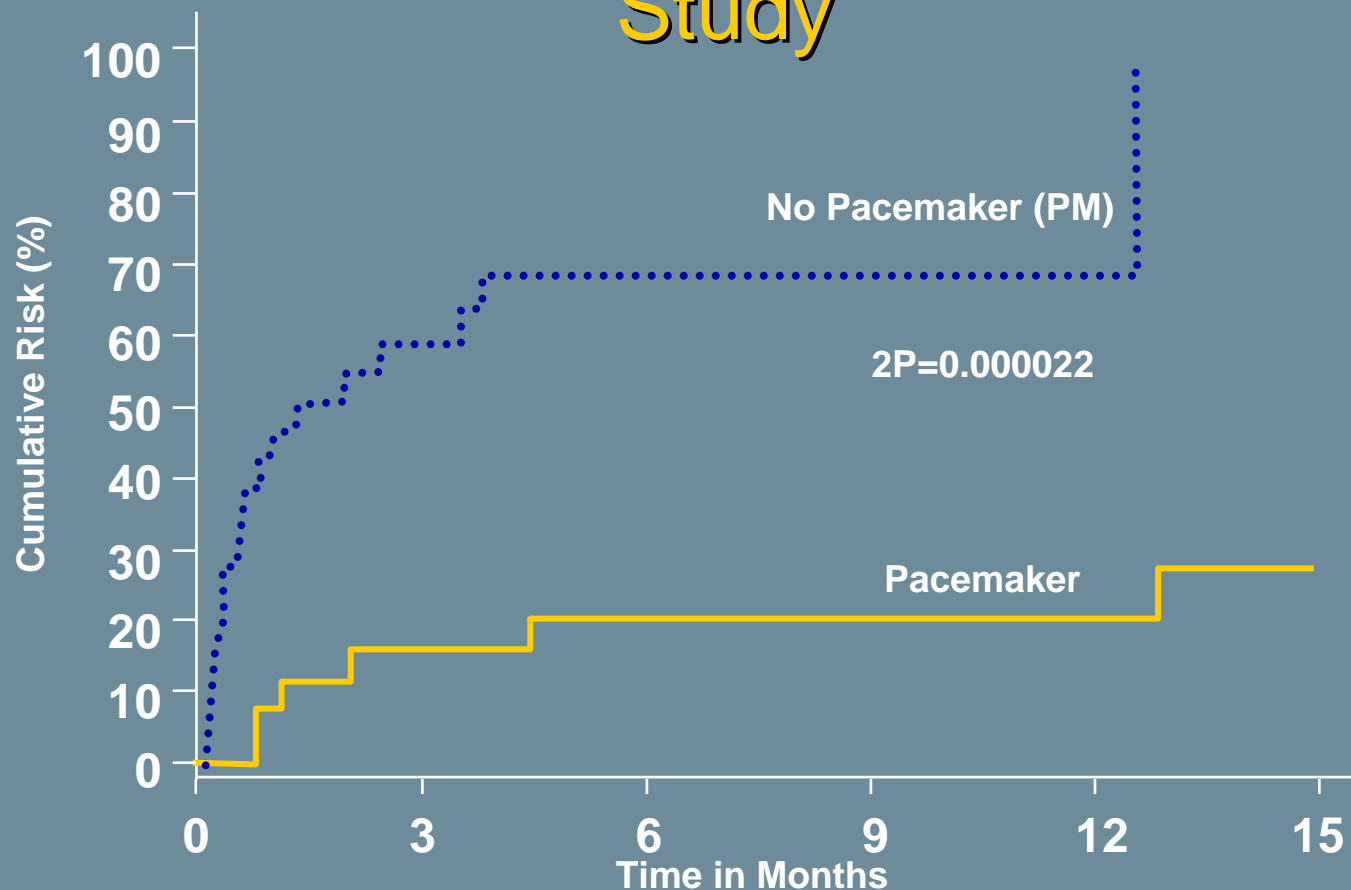
VPS I

North American Vasovagal Pacemaker Study

- Objective: To evaluate pacemaker therapy for severe recurrent vasovagal syncope
- Randomized, prospective, single centre
- N=54 patients
 - 27: DDD pacemaker with rate drop response
 - 27: No pacemaker
- Inclusion: Vasodepressor response
- Primary outcome: First recurrence of syncope

VPS I

North American Vasovagal Pacemaker Study



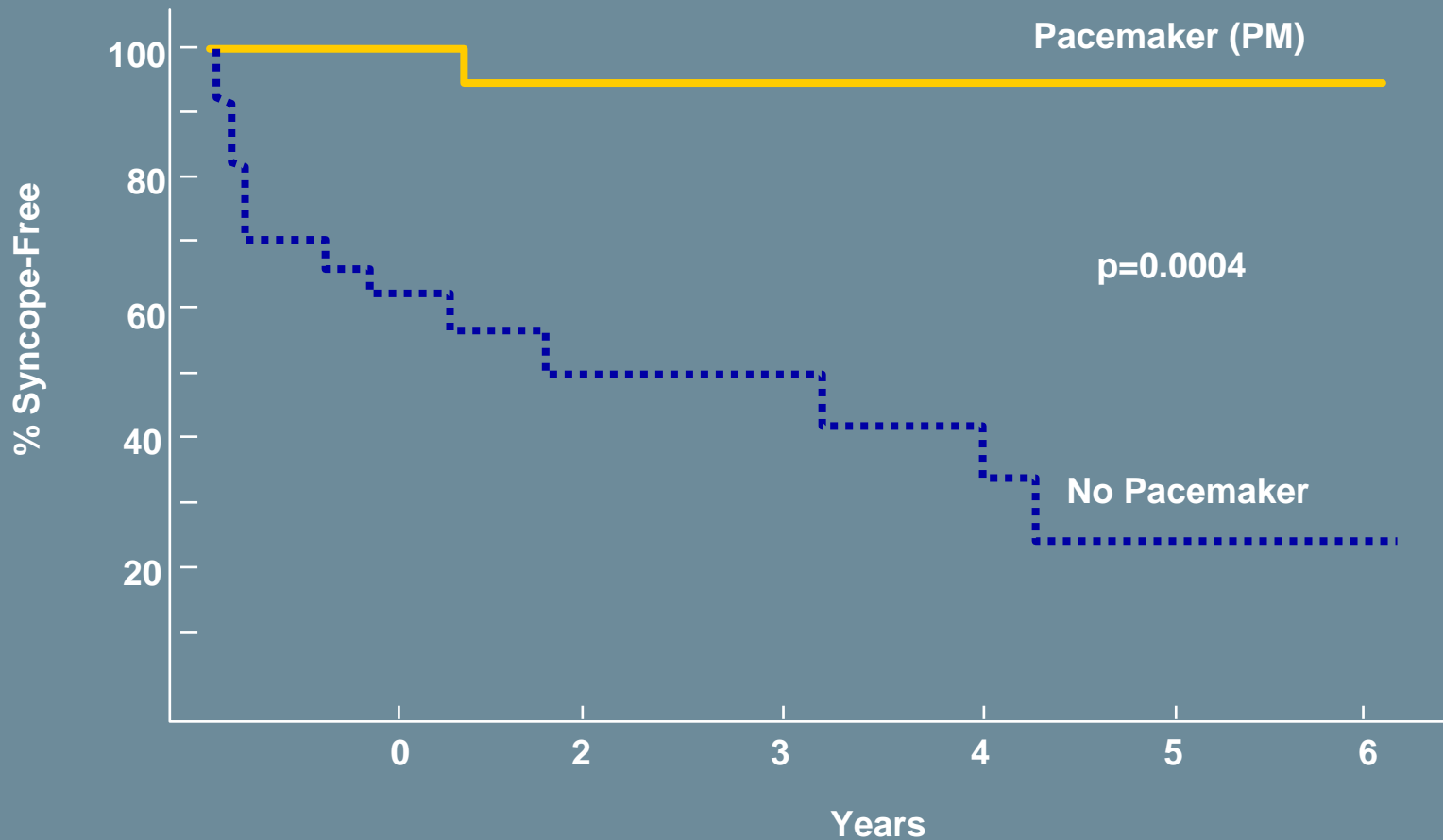
6 (22%) with PM had recurrence vs. 19 (70%) without PM
84% RRR (2p=0.000022)

VASIS

Vasovagal Syncope International Study

- **Objective: To evaluate pacemaker therapy for severe cardioinhibitory tilt-positive neurally mediated syncope**
- **Randomized, prospective, multi-centre**
- **N=42 patients**
 - **19: DDI pacemaker (80 bpm) with rate hysteresis (45 bpm)**
 - **23: No pacemaker**
- **Inclusion: Positive cardioinhibitory response**
- **Primary outcome: First recurrence of syncope**

VASIS VAsovagal Syncope International Study



Results:

1 (5%) with PM had recurrence vs. 14 (61%) without PM

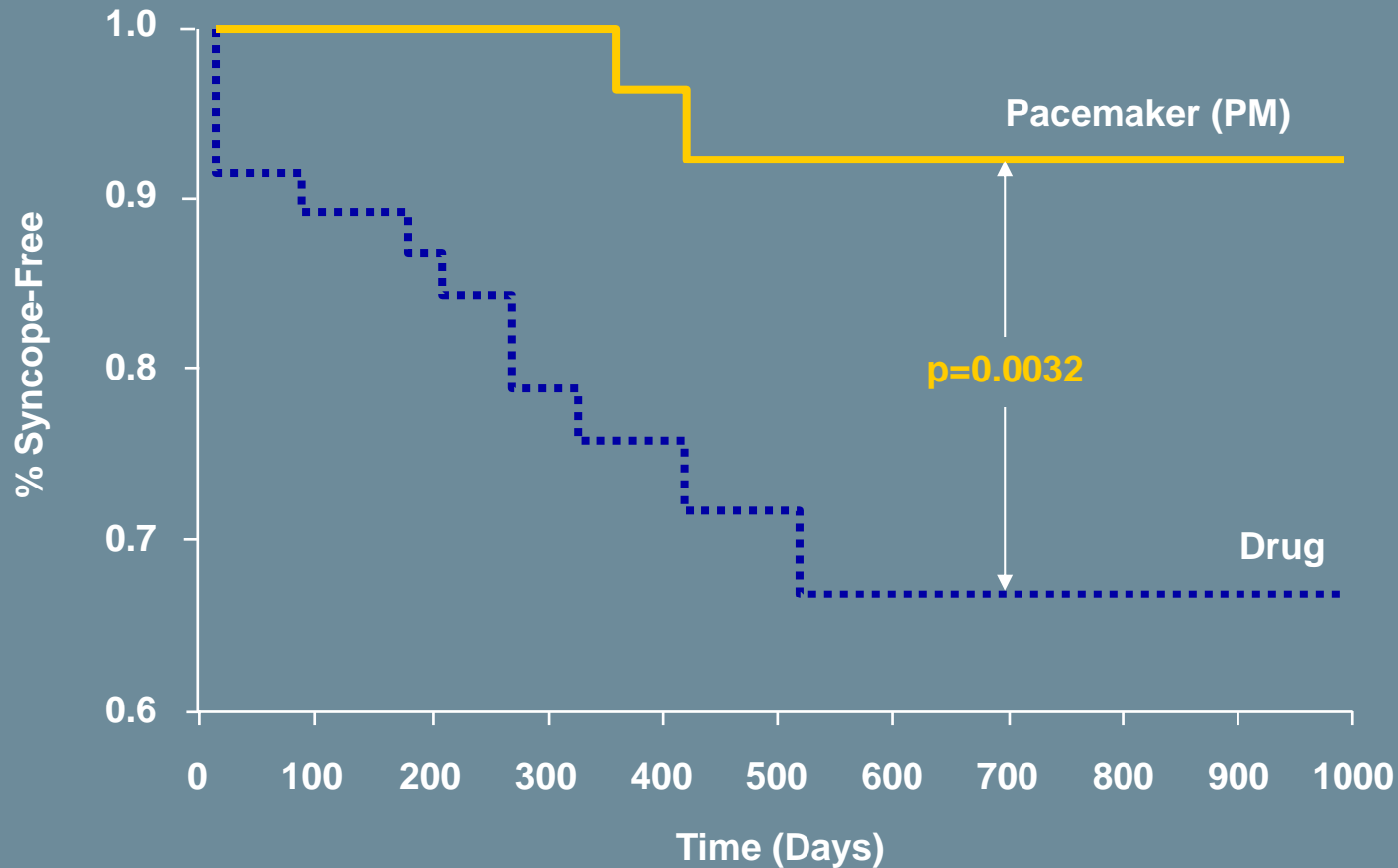
SYDIT

Syncope Diagnosis and Treatment

- **Objective:** To compare the effects of cardiac pacing with pharmacological therapy in patients with recurrent vasovagal syncope
- **Randomized, prospective, multi-centre**
- **N=93 patients**
 - 46: DDD pacemaker with rate drop response
 - 47: Atenolol 100 mg/d
- **Inclusion:** Positive HUT with relative bradycardia
- **Primary outcome:** First recurrence of syncope

SYDIT

Syncope Diagnosis and Treatment



2 (4%) with PM had syncope recurrence vs. 12 (26%) without PM

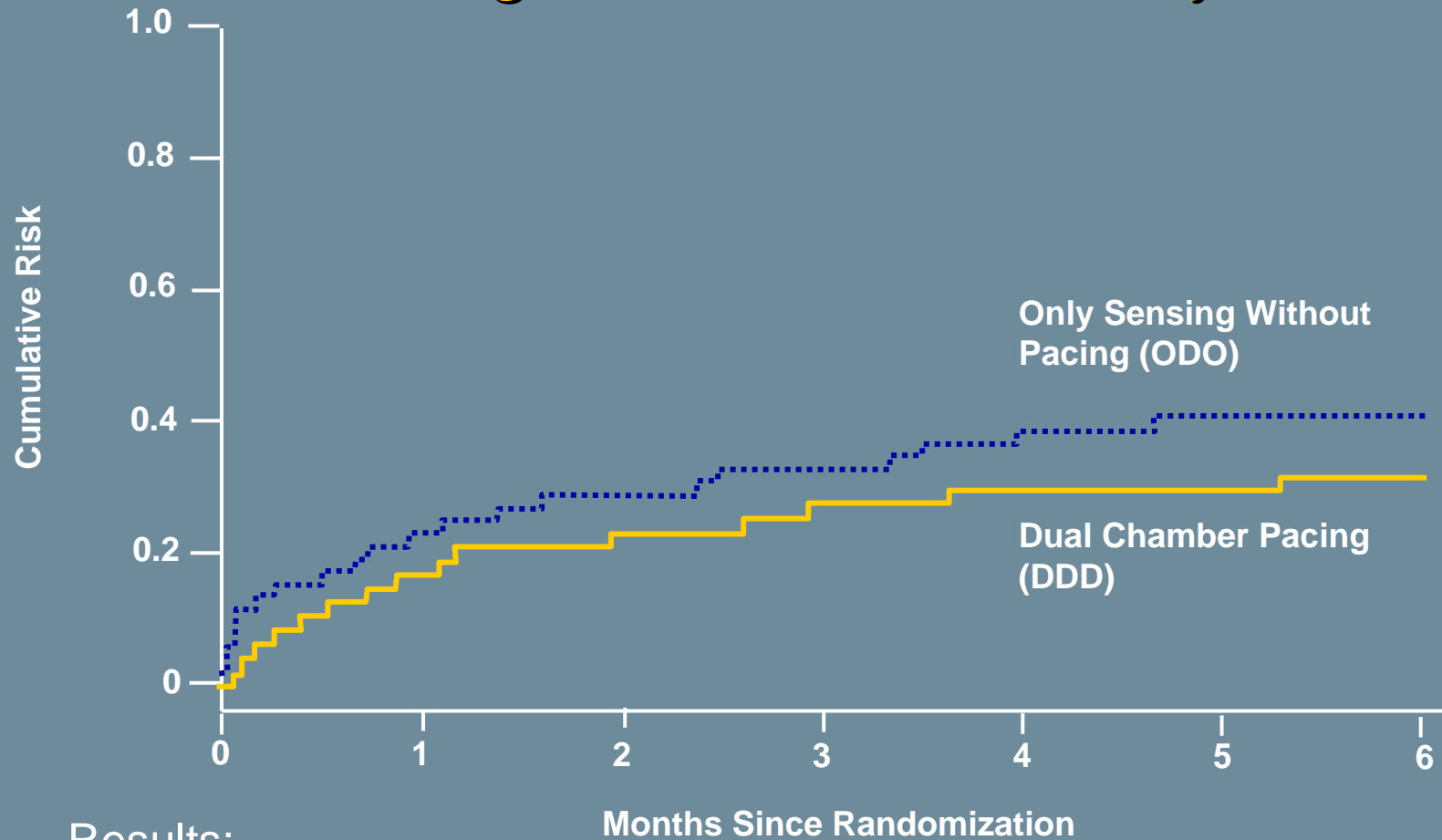
VPS II

Vasovagal Pacemaker Study II

- **Objective:** To determine if pacing therapy reduces the risk of syncope in patients with vasovagal syncope
- **Randomized, double-blind, prospective, multi-centre**
- **N=100 patients**
 - 52: Only sensing without pacing
 - 48: DDD pacemaker with rate drop response
- **Inclusion:** Positive HUT with (HRxBP) < 6000/min x mm Hg
- **Primary outcome:** First recurrence of syncope

VPS II

Vasovagal Pacemaker Study II



Results:

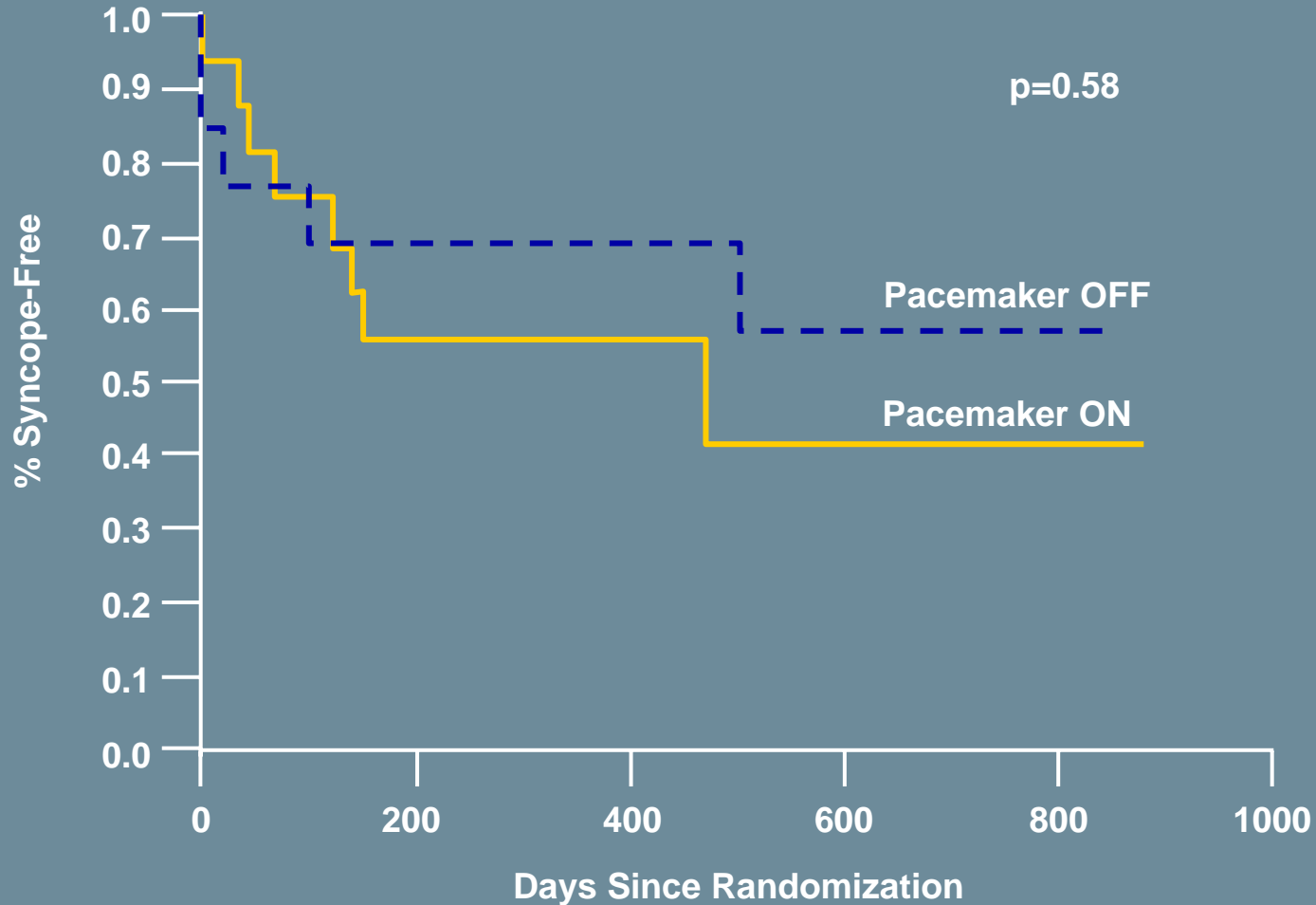
33% recurrence with pacing vs. 42% with only sensing (p=ns)

SYNPACE

Vasovagal Syncope and Pacing

- **Objective:** To determine if pacing therapy will reduce syncope relapses in patients with recurrent vasovagal syncope, compared with those having a pacemaker programmed OFF
- **Randomized, double-blind, prospective, multi-centre, placebo-controlled**
- **N=29 patients**
 - 16: DDD PM with rate drop response programmed ON
 - 13: PM programmed OFF (OOO mode)
- **Inclusion:** Recurrent VVS and +HUT with asystolic or mixed response
- **Primary outcome:** First recurrence of syncope

SYNPACE Vasovagal Syncope and Pacing



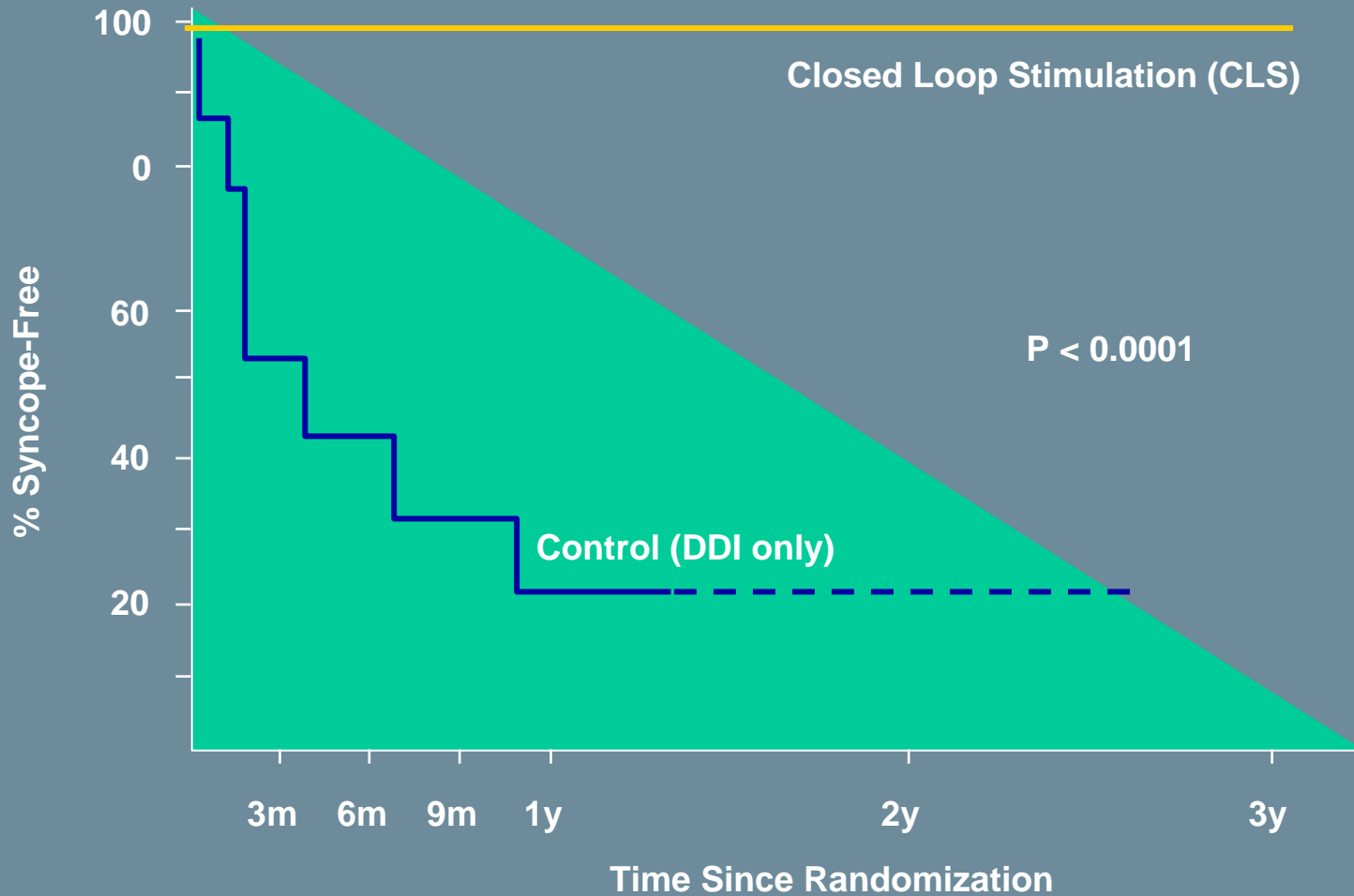
50% recurrence with pacing ON vs. 38% with pacing OFF (p=ns)

INVASY

Inotropy Controlled Pacing in Vasovagal Syncope

- **Objective:** To evaluate Closed Loop Stimulation (CLS), a form of rate-adaptive pacing using RV impedance, in preventing recurrence of VVS
- **Randomized, prospective, single-blind, multi-centre**
- **N=50 patients**
 - **41: CLS therapy**
 - **9: Control (pacemaker programmed in DDI)**
- **Inclusion:** Recurrent VVS and +HUT with cardioinhibition
- **Primary outcome:** Recurrence of two VVSs during a minimum of 1 year of follow-up

INVASY (Inotropy Controlled Pacing in Vasovagal Syncope)



Patients with CLS had no syncope recurrence and improved quality of life



ISSUE 2

International Study on Syncope of Uncertain Etiology 2

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 (or ATP test)
- therapy delayed until ILR documentation of the basis of syncope



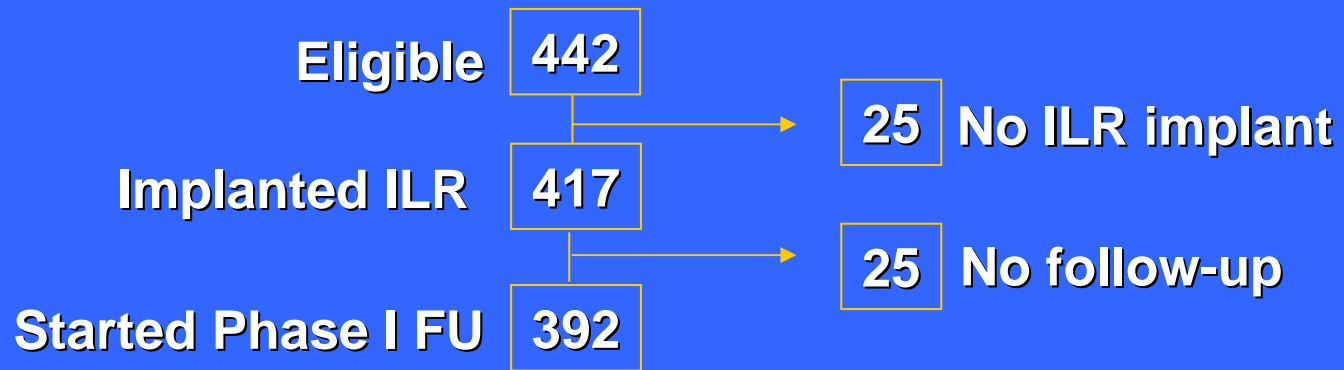
ISSUE 2

International Study on Syncope of Uncertain Etiology 2

Diagnostic work-up during the initial evaluation

• Age > 30 years	If YES, continue
• ≥ 3 syncope during last 2 years	If YES, continue
• So severe a presentation as to require treatment	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

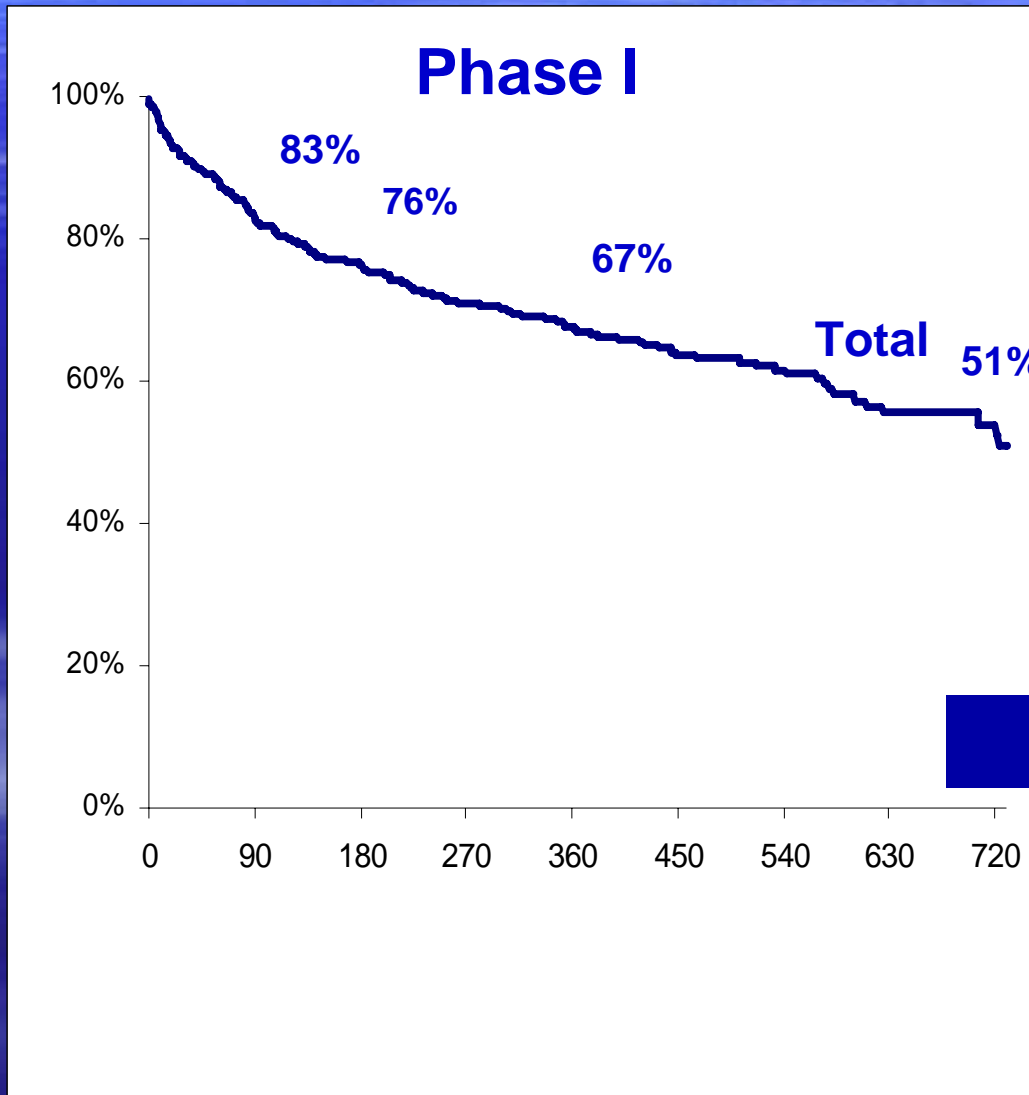


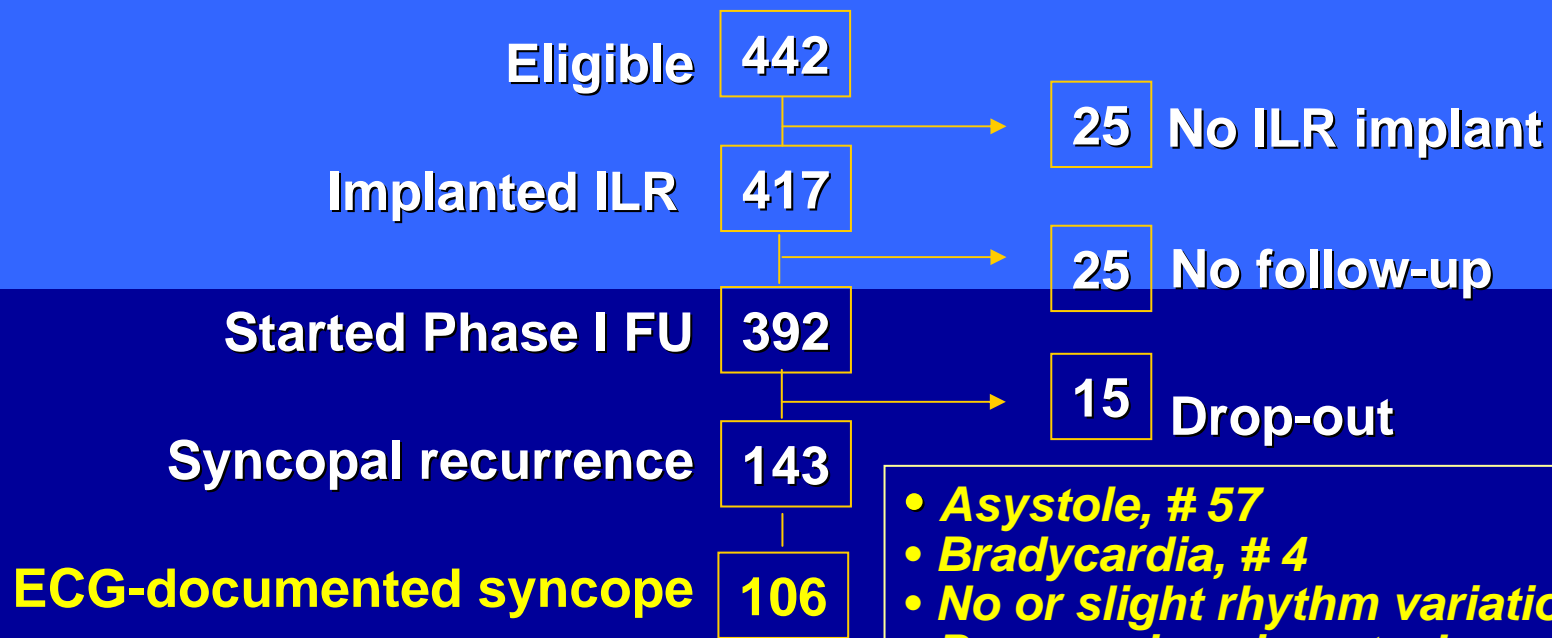
ISSUE-2 population

Features:

- Mean age 66 years
- History of recurrent syncope beginning in middle or older age
- Severe clinical presentation requiring treatment (high risk and/or high frequency)
- Atypical presentation without warning
- Frequent injury (?due to lack of warning)

Results: Syncopal-free survival



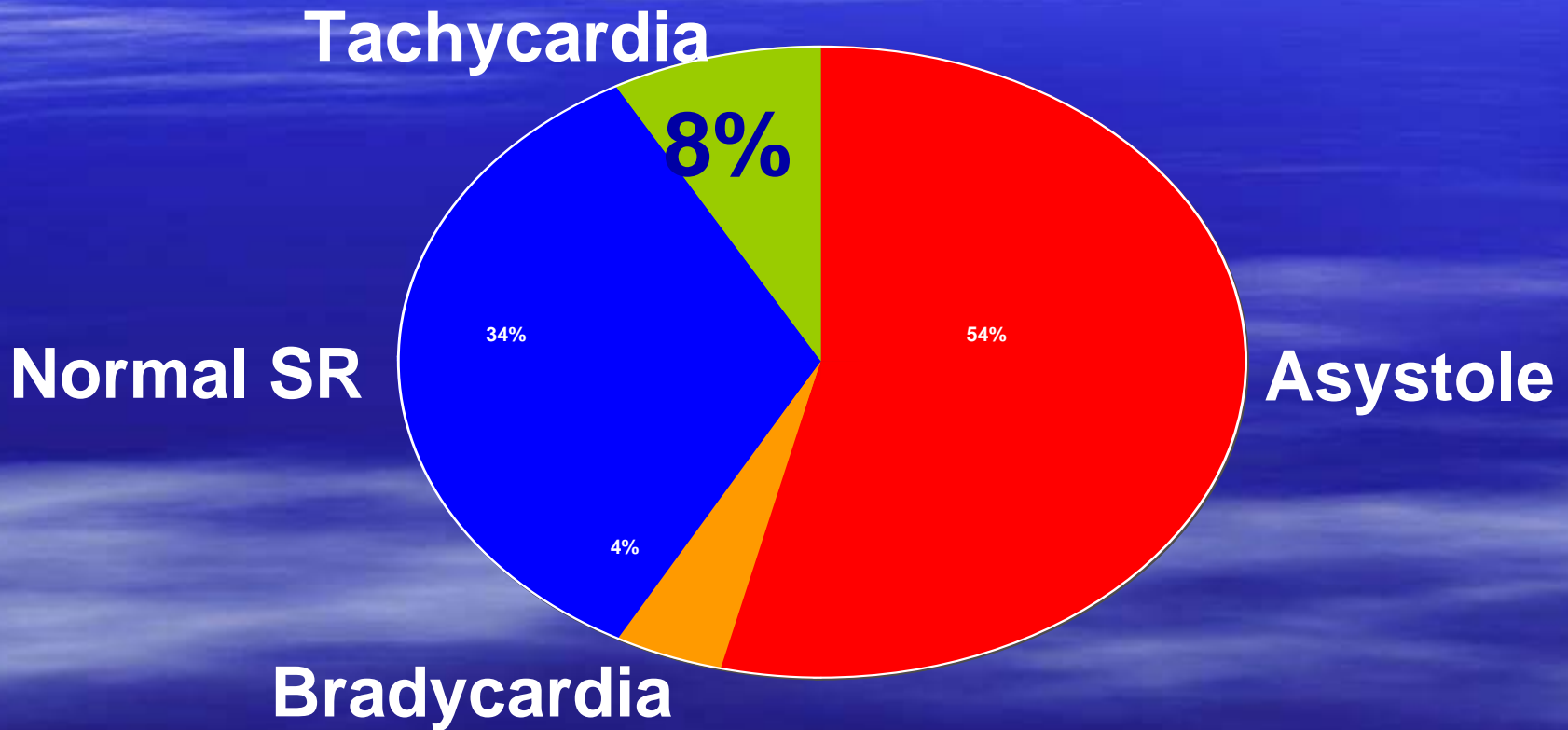


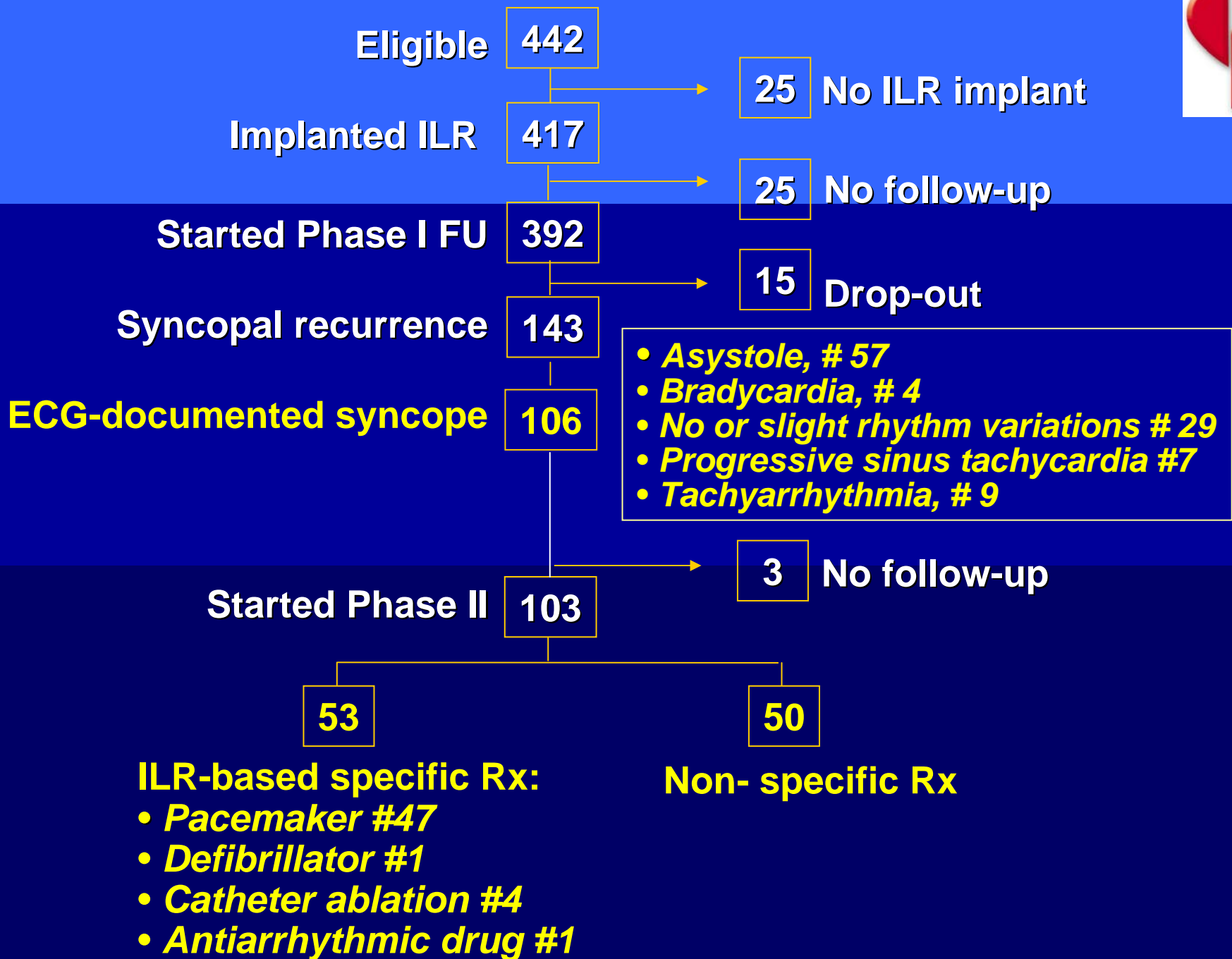
- *Asystole, # 57*
- *Bradycardia, # 4*
- *No or slight rhythm variations # 29*
- *Progressive sinus tachycardia #7*
- *Tachyarrhythmia, # 9*



ISSUE 2

International Study on Syncope of Uncertain Etiology 2





Patient characteristics

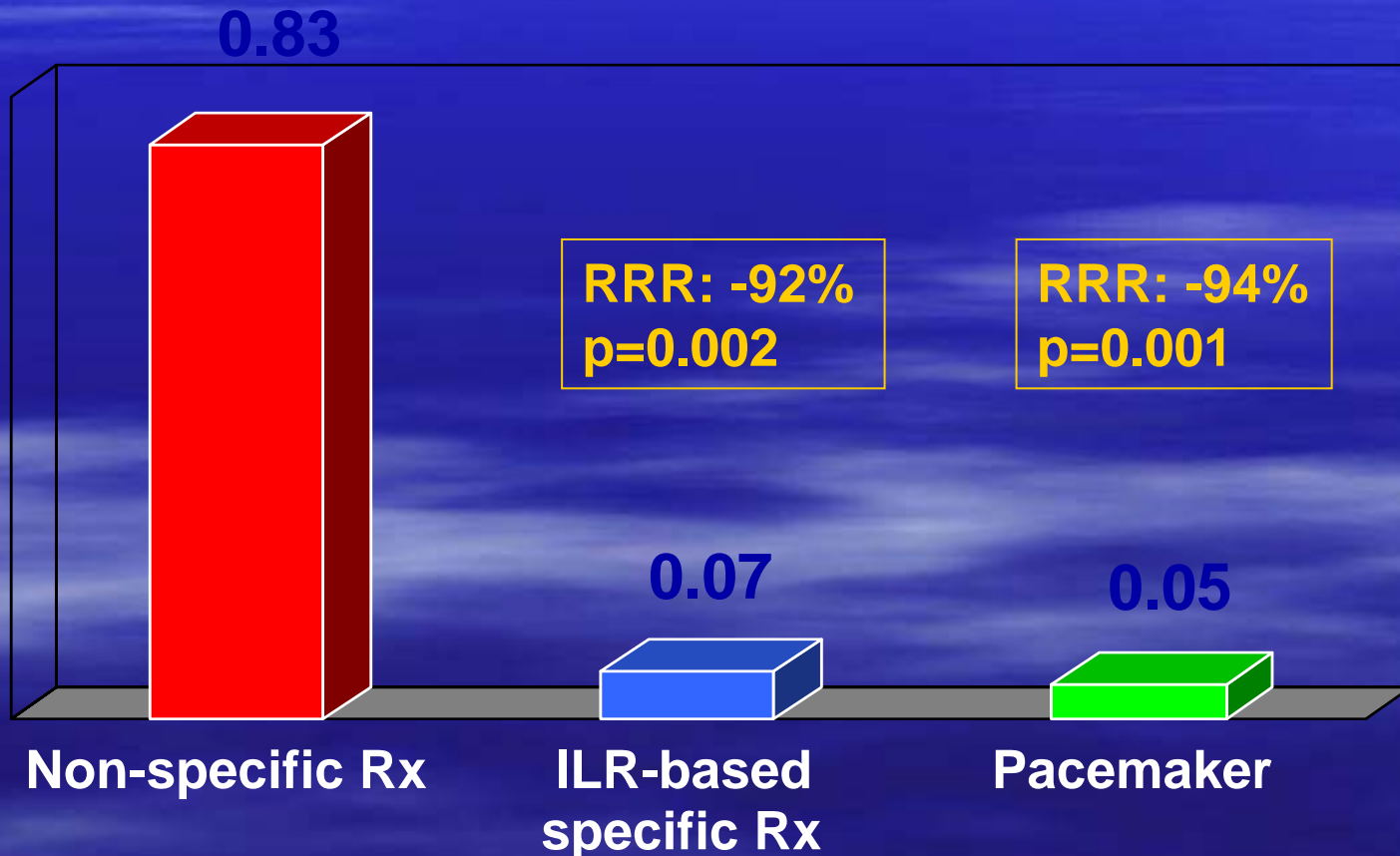
	Therapy	No therapy	
Mean age – yr	69 ±13	64±15	ns
Male gender	38%	50%	ns
Syncope – total number	5 (4-8)	6 (4-14)	ns
Syncope - last 2 years	4 (3-5)	4 (3-7)	ns
Syncope duration - yr	6 (4-14)	6 (4-12)	ns
Age at first syncope -yr	59 ±18	54±19	ns
History of presyncope	38%	46%	ns
Major injuries	25%	16%	ns
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

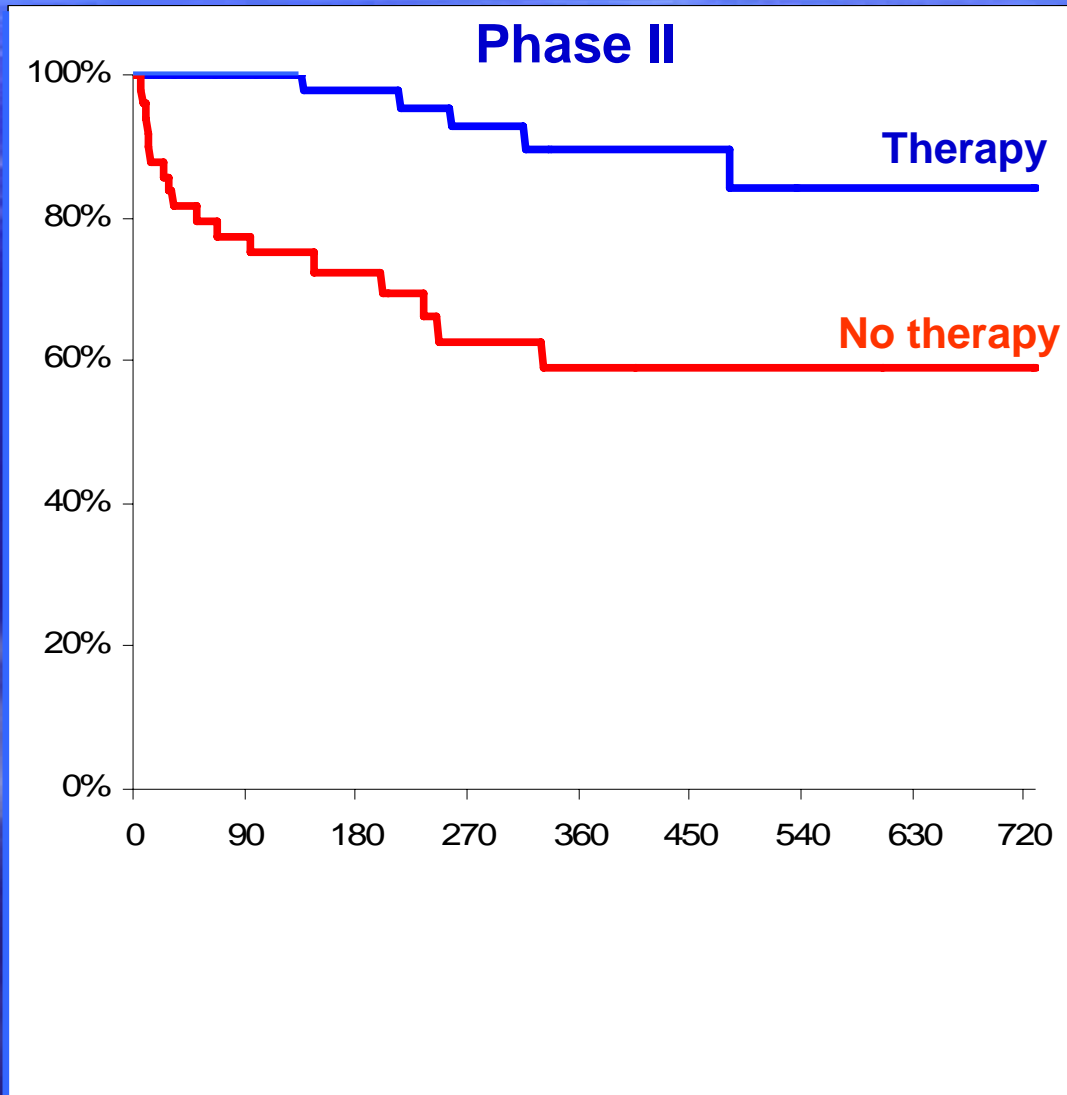
	Therapy	No therapy	
ECG: normal	87%	90%	ns
No SHD	91%	86%	ns
Hypertension	45%	48%	ns
Any neurological disease	38%	12%	ns
Diabetes	13%	4%	ns
Any therapy	38%	52%	ns
Antihypertensive drugs	28%	34%	ns
Tilt testing: performed	77%	98%	ns
Tilt testing: positive	37%	45%	ns
ATP test: performed	42%	58%	ns
ATP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

Results: Syncope burden

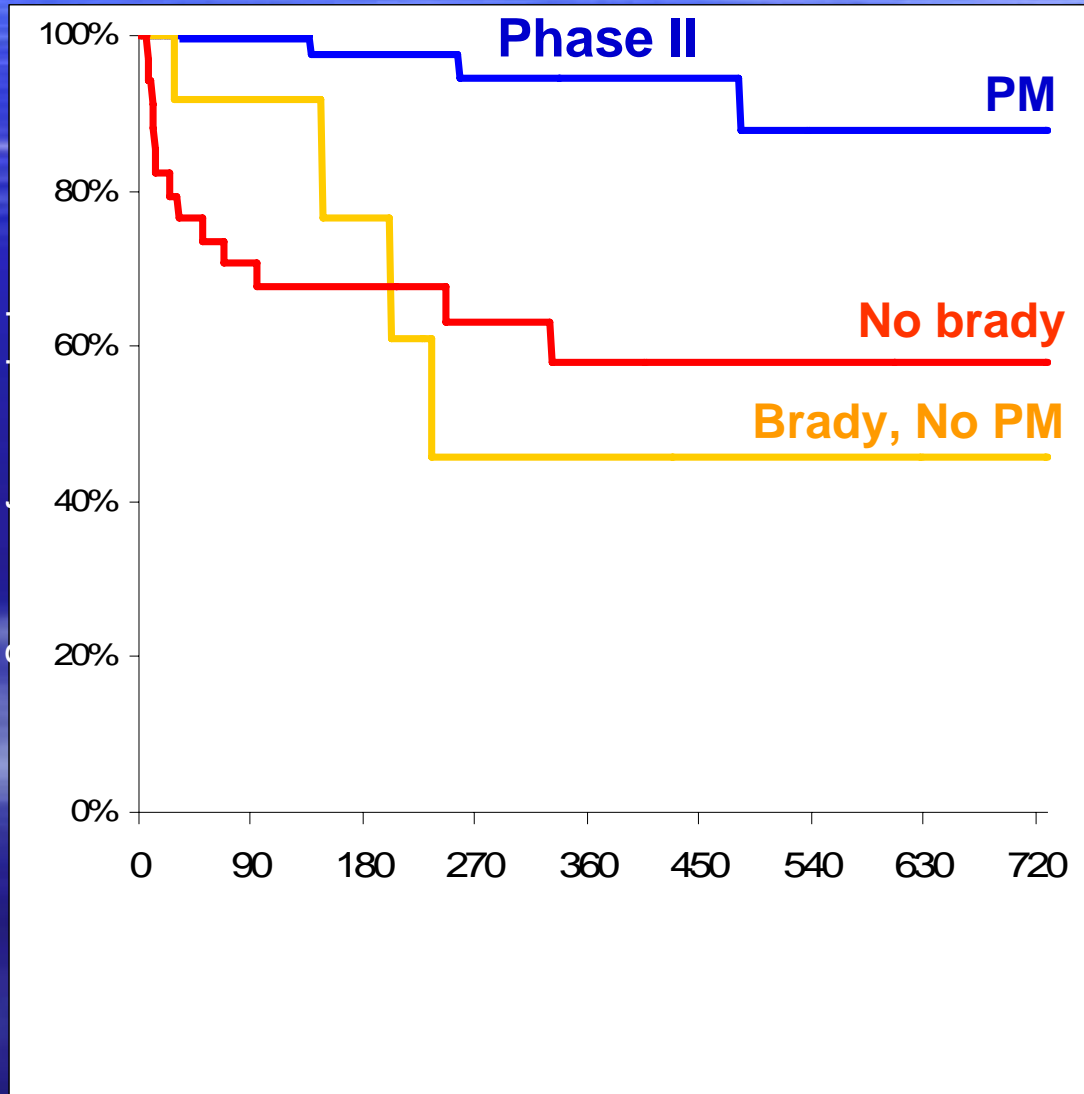
Episodes per patient/year



Results: Syncopal-free survival



Results: Pacemaker therapy





ISSUE 2

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

Conclusions

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

- safe and
- allows specific therapy

Expectation Effect

In a meta-analysis, preliminary trials have overestimated the treatment effect of pacemakers for vasovagal syncope

Data do not support use of pacemakers as first treatment

Longer adequately powered double-blind trials are required to examine whether a sustained benefit exists



ISSUE 3

**Randomized controlled
double-blind trial**

ISSUE 3 Study

Suspected VVS (screening phase)

Eligible patients

ILR implantation

Phase I FU

Phase I end-points

Suspected hypotensive NMS
(type 2,3,4A):brady, slight or no rhythm variations

PC manoeuvres trial

Suspected asystolic NMS (type 1):
•Asystolic syncope or
•Non-syncopal asystole 3"+3" or 6"

R

PM ON arm

Phase 2 FU

PM OFF arm

Phase 2 FU

Tachycardia (type 4B-D)

Indications for Pacing in VVS in 2009

Older patients with recurrent syncope who have documented asystole either on tilt or on long-term monitoring (ILR).

Failed medical therapy and severity of syncope will enhance the indication e.g., occurrence of incontinence of urine or abnormal movements.

Young patients can only be considered if pacing therapy becomes more effective than it is today. This may imply better triggering of pacing than by fall in heart rate e.g., RV function.

The results of ISSUE 3 are awaited

Thank you for your attention

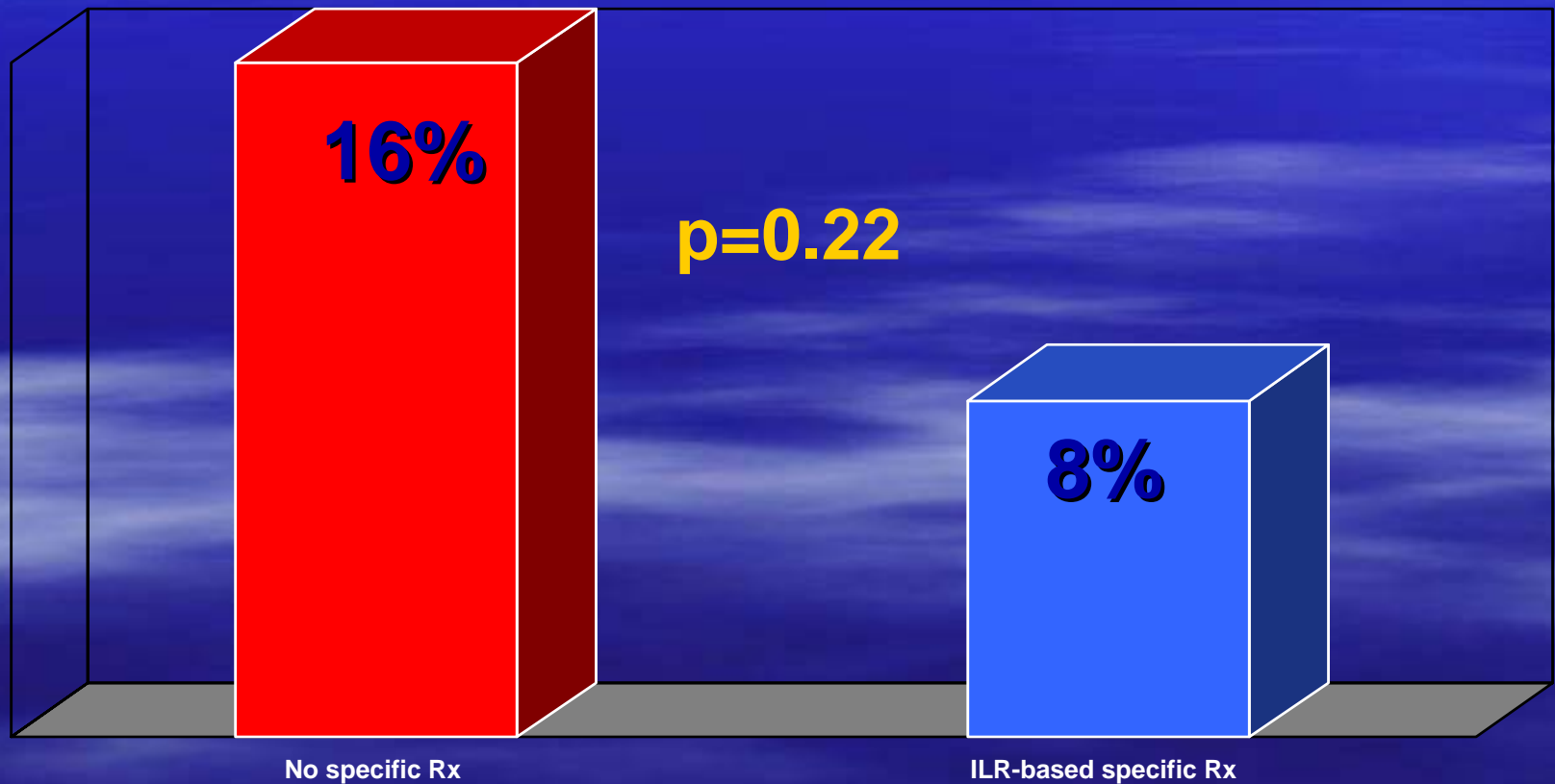
Patient characteristics (n=392)

Mean age – yr	66±14
Male gender	45%
Syncope – total number	6 (4-10)
Syncope - 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: 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