Sincope vasovagale: differenti manifestazioni cliniche e ruolo dell'elettrostimolazione

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ALFA – Alliance to Fight Atrial fibrillation, Mestre – Venice, Italy

Syncope / Definition

- ✓ Transient loss of consciousness of
  - rapid onset,
  - short duration,
  - spontaneous complete recovery

Eur Heart J 2009; 30: 2631-2671

Syncope

Underlying mechanism

Transient global cerebral hypoperfusion

Eur Heart J 2009; 30: 2631-2671

Classification of syncope

Reflex (neurally-mediated) syncope

Vasovagal:
- Mediated by emotional distress: fear, pain, instrumentation, blood phobia.
- Mediated by orthostatic stress.

Situational:
- Cough, sneeze.
- Gastrointestinal stimulation (swallow, defaecation, visceral pain).
- Micturition (post-micturition).
- Post-exercice.
- Post-prandial.
- Others (e.g., laught, brass instrument playing, weightlifting).

Carotid sinus syncope

Atypical forms (without apparent triggers and/or atypical presentation).

Syncope due to orthostatic hypotension

Primary autonomic failure:
- Pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia.

Secondary autonomic failure:
- Diabetes, amyloidosis, uraemia, spinal cord injuries.

Drug-induced orthostatic hypotension:
- Alcohol, vasodilators, diuretics, phenotiazines, antidepressants.

Volume depletion:
- Haemorrhage, diarrhoea, vomiting, etc.

Cardiac syncope (cardiovascular)

Arrhythmia as primary cause:

Bradycardia:
- Sinus node disfunction (including brady-cardia/ tachycardia syndrome).
- Atrioventricular conduction system disease.
- Implanted device malfunction.

Tachycardia:
- Supraventricular.
- Ventricular (idiopathic, secondary to structural heart disease or to channelopathies).

Drug induced bradycardia and tachyarrhythmias

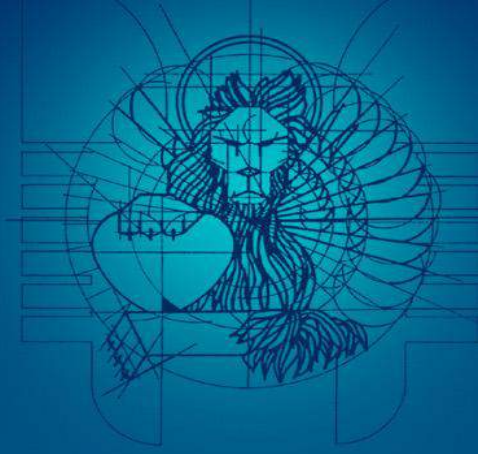
Structural disease:

Cardiac: *cardiac valvular disease, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, etc), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valves dysfunction.*

Others: *pulmonary embolus, acute aortic dissection, pulmonary hypertension.*

European Heart Journal 2009;30:2631-2671

Neurally-mediated Syncope



Neurally –mediated syncope refers to a reflex that, when triggered, gives rise to vasodilatation and bradycardia, although the contribution of both to systemic hypotension may differ considerbly

Eur Heart J 2004; 25: 2054-2072

Vasovagal Syncope

- Typical
- Atypical

Typical VVS

Is diagnosed when LOC is precipitated by triggers such as emotional distress or orthostatic stress and is associated to autonomic prodromes

2009 ESC Guidelines on Syncope. Eur Heart J 2009; 30: 2631-2671

VVS / Triggers

Emotional distress: intense excitement, fear, severe pain, disgust, blood phobia, instrumentation, medical setting.

Orthostatic stress: prolonged standing / sitting, particularly in crowded places and in hot enviroments.

Alboni P. et al. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

VVS / Diagnosis

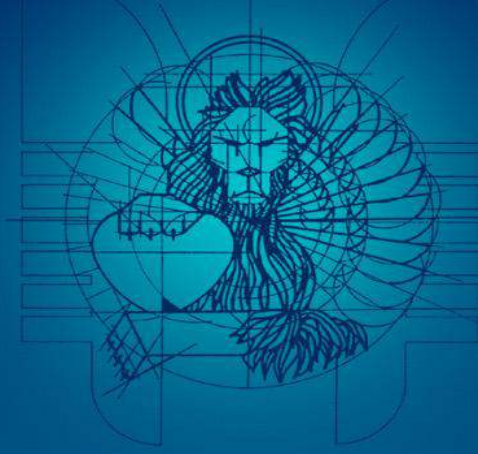
Prodromes due to activation of autonomic system.

Vagal activation: nausea, vomiting, abdominal discomfort, yawning, sighing, etc.

Sympathetic activation: pallor, sweating, palpitations, pupillary dilatation,.

Alboni P. et al. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

VVS / Diagnosis

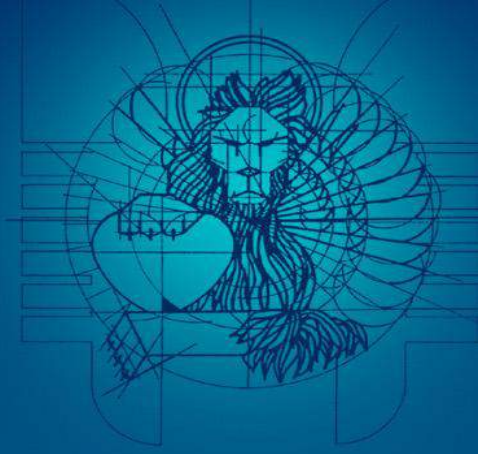


Besides autonomic symptoms, there may be also prodromal symptoms due to

cerebral hypoperfusion: blurred vision, dizziness, lightheadedness,.

Alboni P. et al. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

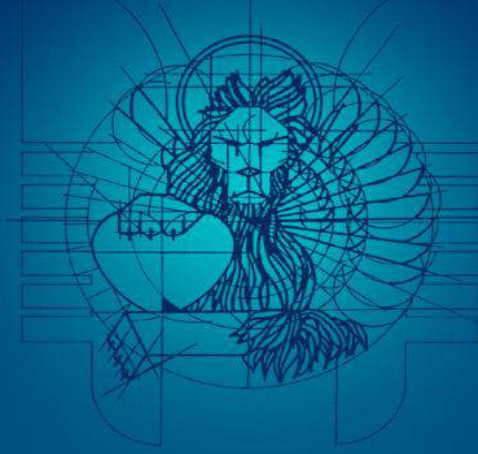
Atypical VVS



Is diagnosed when the episodes of LOC occur without any evident trigger and prodromes, the tilt test is positive, and other competing causes of syncope have been excluded

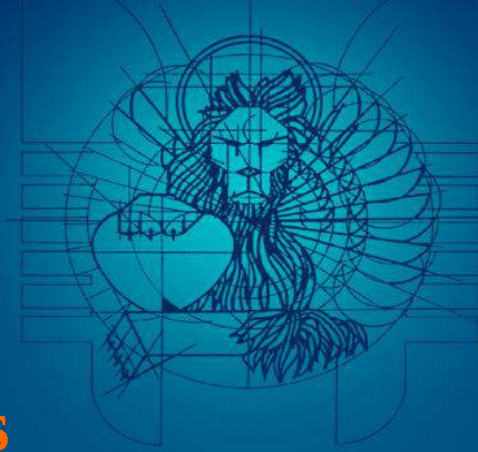
2009 ESC Guidelines on Syncope. Eur Heart J 2009; 30: 2631-2671

VVS / Mechanisms

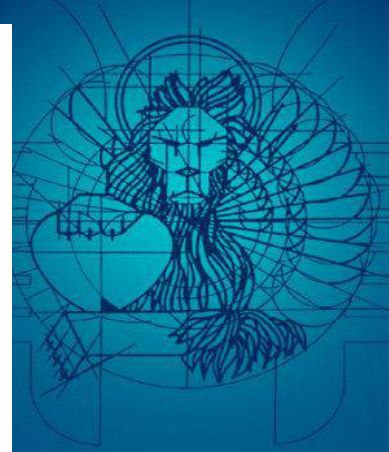


The pathophysiological mechanism underlying vasovagal syncope is still uncertain, is probably different in different patients and difficult to establish in the single case

VVS / Mechanisms



- **Activation of Ventricular Mechanoreceptors**
- **Activation of Atrial / Pulmonary Baroreceptors**
- **↓ Sensitivity of Aortic / Carotid Baroreceptors**
- **Paroxysmal Discharges from Higher CNS Centers**
- **Abnormality in Central Processing of Afferent Signals**
- **↑ Release of Endorphins, Serotonin, Vasopressin, NO**
- **↑ Responsiveness of Peripheral Cardiac/Vasc Receptors**



Decrease in venous return (reduced preload)

↓

Reduced ventricular filling

↓

Increased sympathetic tone

↓

Hypercontractility of ventricles with underfilled chamber

↓

Ventricular mechanoreceptor activation

↓

Feedback to medulla (CNS) via afferent vagus nerve

↓

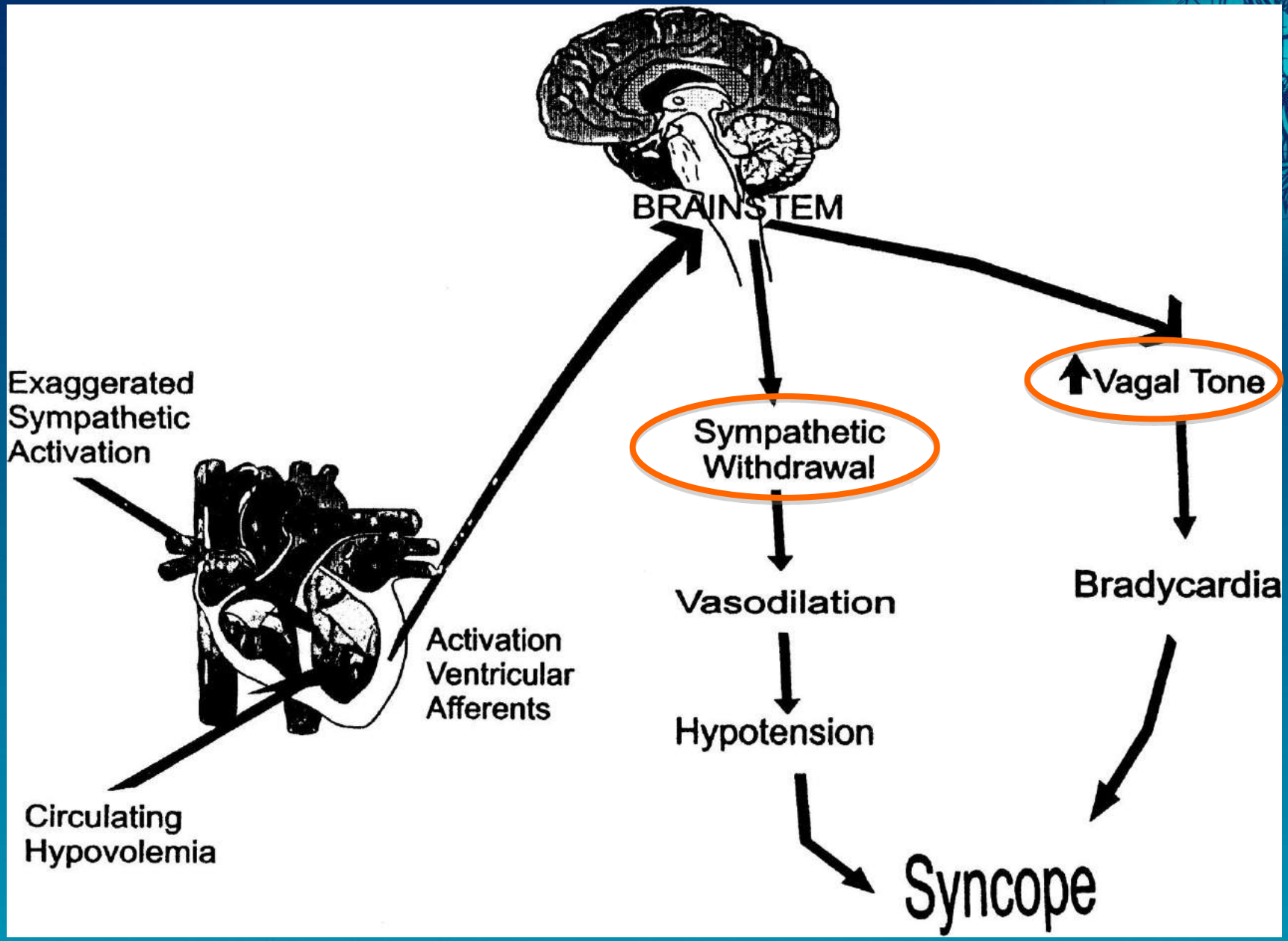
Sympathetic withdrawal, parasympathetic overdrive

↓

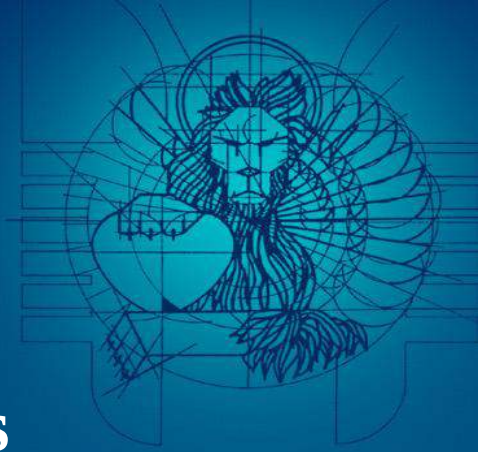
Bradycardia and hypotension

↓

SYNCOPE


BRAINSTEM
Exaggerated
Sympathetic
Activation
Activation
Ventricular
Afferents
Circulating
Hypovolemia
Sympathetic
Withdrawal
Vasodilation
Hypotension
Vagal Tone
Bradycardia
Syncope

VVS / Mechanisms



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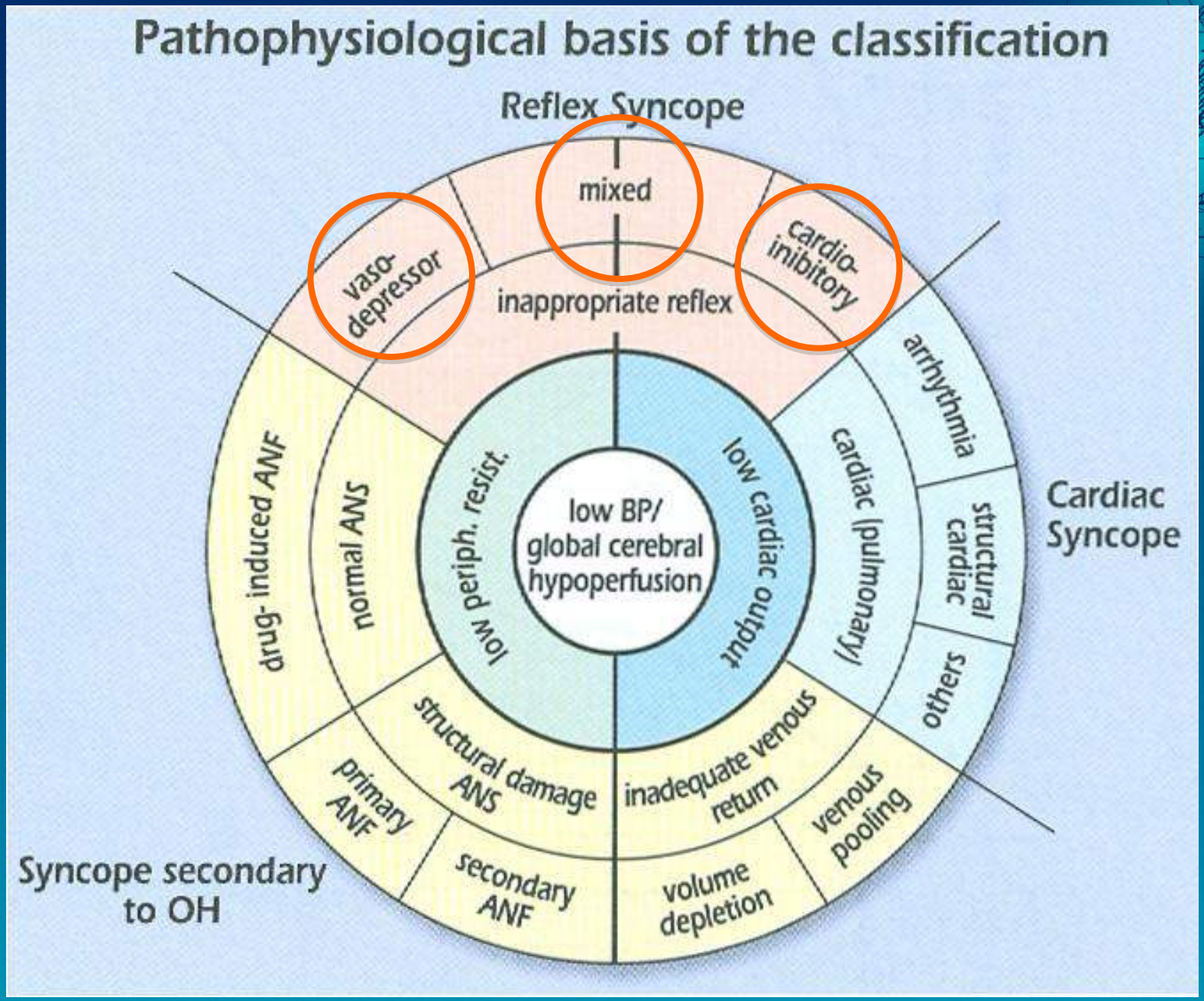


2009 ESC Guidelines on Syncope. Eur Heart J 2009; 30: 2631-2671

VVS / Epidemiology

- VVS is a common symptom, but its true incidence is difficult to estimate because only a small percentage of patients seek medical advice
- It is likely that up to 40% of people faint at least once in their life and prevalence is higher in the females.

Solbiati M, Sheldon RS. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

Frequency of the causes of syncope in general population, Emergency Department and specialized clinical settings from some recent studies

Setting	Source	Reflex, %	OH, %	Cardiac, %	Non-syncopal T-LOCs, %	Unexplained, %	Notes
General population	Framingham studies[3]	21	9.4	9.5	9	37	Mean age at entry of 51 ± 14 years, adolescents excluded. Other causes of syncope (medication, etc.) were found in 14.3% of the population. Furthermore, 44% of population did not seek a medical visit
ED	Ammirati[29]	35	6	21	20	17	
	Sarasin[35]	38*	24*	11	8	19	*Some differences in diagnostic definitions
	Blanc[30]	48	4	10	13	24	
	Disertori[34]	45	6	11	17	19	
	Olde Nordkamp[28]	39	5	5	17	33	
	Range	35–48	4–24	5–21	8–20	17–33	
Syncope Unit (dedicated facility)	Alboni[68]	56	2	23	1	18	In the Cardiology Department.
	Chen[36]	56	6	37	3	20	In the Cardiology Department. Total percentage is >100% because 18.4% of the patients had multiple diagnoses
	Shen[213]	65	10	6	2	18	In the ED
	Brignole[64]	65	10	13	6	5	Multicentre study of 19 syncope units with referral from Emergency Department and standardized diagnostic pathway (interactive decision-making software and central monitoring)
	Ammirati[62]	73	1	6	2	18	Out-patient referral
	Range	56–73	1–10	6–37	1–6	5–20	

ESC Guidelines on Syncope. Eur Heart J 2009; 30: 2631-2671

VVS / Epidemiology

- Syncope incidence shows a bimodal distribution, with two peaks: before 20 and after 65 years old.
- Vasovagal syncope is the most frequent type of syncope in young people; cardiovascular diseases, orthostatic hypotension and multiple causes are more prevalent in the elderly.

Solbiati M, Sheldon RS. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

Typical VVS / Diagnosis

Is easily diagnosed during the initial evaluation at the time of medical history taking, on the basis of its peculiar clinical features, in particular presence of the

1) characteristic triggers
2) prodromal symptoms

Alboni P. et al. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

Atypical VVS / Diagnosis

The diagnosis may be suspected at the initial examination if some clinical features are present, but should be confirmed by performing tilt testing and by excluding other competing diagnosis with further examinations.

Alboni P. et al. In Alboni P, Furlan R. (eds.) Vasovagal syncope, Springer 2015

Clinical features suggestive of VVS

- Absence of heart disease
- First episode at young age (<35 years)
- Long history of recurrent syncope (>4 years)
- During a meal or post-prandially (<2 hours)
- After exertion
- Concomitant use of vasodepressive drugs
- Migraine

VVS / Laboratory investigations

- Tilt testing
- ILR
- ATP test

THE LANCET, JUNE 14, 1986

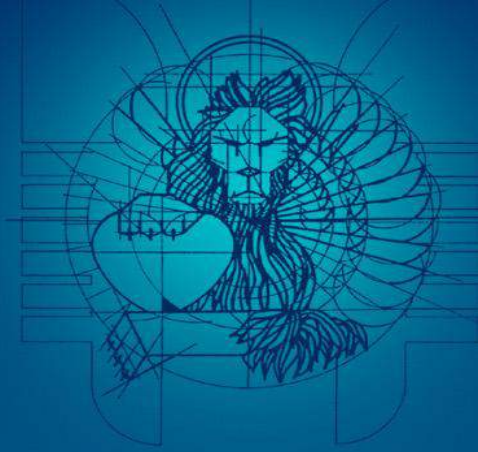
HEAD-UP TILT: A USEFUL TEST FOR INVESTIGATING UNEXPLAINED SYNCOPE

ROSE ANNE KENNY
JOHN BAYLISS
ANN INGRAM
RICHARD SUTTON

Westminster Hospital, London SW1

Head-up tilt test

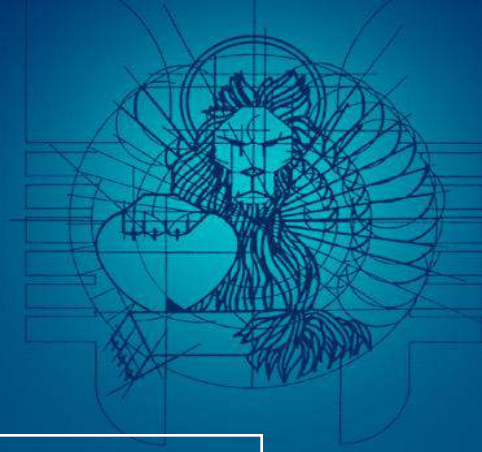
for the diagosis of Vasovagal Syncope



Very popular

& widely accepted method

Protocols / Head-up tilt test



Unmedicated

- Short-duration
- Long-duration

Pharmacologic

- Isoproterenol
- Nitroglycerin
- Edrophonium
- Adenosine
- Clomipramine

Head-up tilt testing for diagnosing vasovagal syncope: A meta-analysis

Cinzia Forleo *[,1], Pietro Guida [1], Massimo Iacoviello, Manuela Resta, Francesco Monitillo, Sandro Sorrentino, Stefano Favale

Int J Cardiol 2013; 168: 27-35

This was the first meta-analysis providing data in a systematic fashion on sensitivity and specificity of head-up tilt testing for assessing

Table 2
Sensitivity, specificity and diagnostic odds ratios of head-up tilt testing protocols according to tilt phases and pharmacological agents used.

	Sensitivity (%)	Specificity (%)	Diagnostic odds ratio
Passive phase alone	25 (21–30)	99 (97–99)	10.08 (7.59–13.40)
Isoproterenol phase alone	48 (37–59)	88 (81–92)	5.94 (4.33–8.16)
Nitroglycerine phase alone	60 (53–66)	90 (84–93)	11.44 (8.97–14.59)
→ Overall passive protocols	37 (29–46)	96 (92–98)	10.14 (6.70–15.34)
→ Overall isoproterenol protocols	61 (52–69)	86 (79–91)	8.33 (6.38–10.86)
→ Overall nitroglycerine protocols	66 (60–72)	89 (84–92)	14.40 (11.50–18.05)
→ Overall protocols	59 (53–64)	91 (87–93)	11.28 (9.63–13.22)

Estimates with 95% confidence intervals.

Forleo C, et al. Int J Cardiol 2013; 168: 27-35

HUTT / Diagnosis of VVS

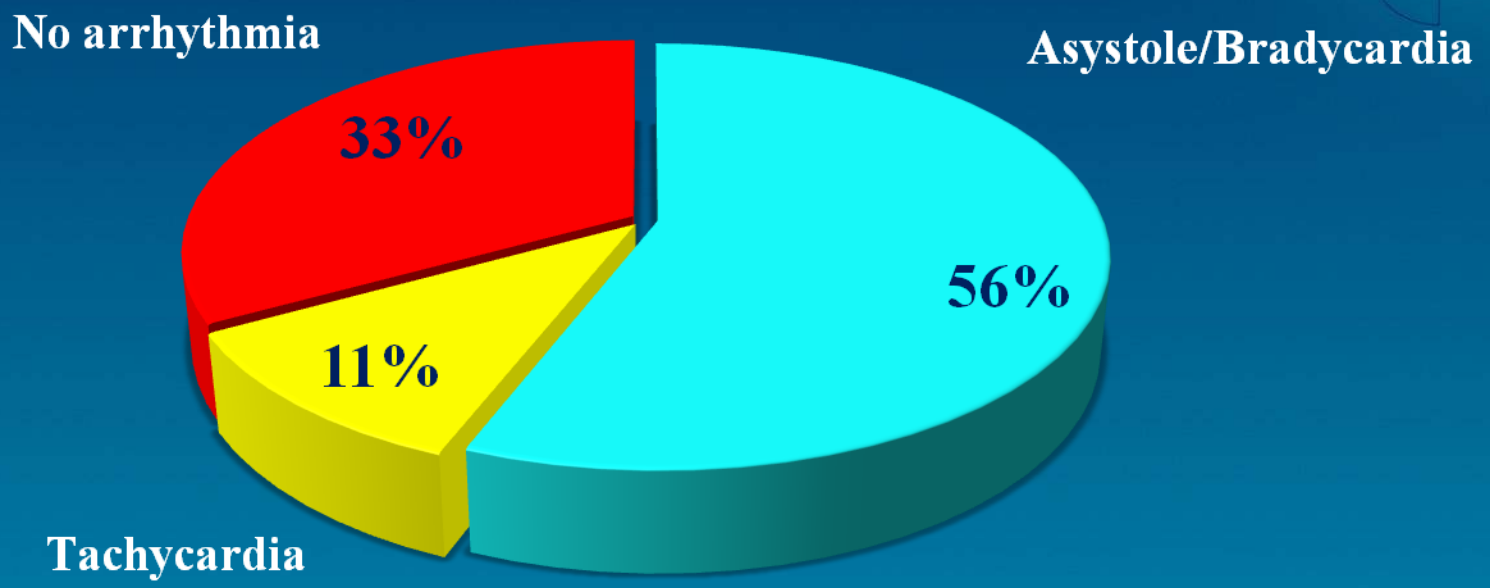
- Head-up tilt testing is characterized by high overall yield for diagnosing VVS, enabling to support the test as a first choice investigation in the assessment of individual susceptibility to neurally mediated syncope
- Tilt testing protocols potentiated with nitroglycerin have the highest diagnostic accuracy (greatest sensitivity with acceptable specificity) and should be preferred

VVS / Laboratory investigations

- Tilt testing
- ILR
- ATP test

Unexplained syncope / Late ILR

Pooled data from 11 studies



Diagnostic yield: 35% (176/506)

Moya Circulation 2001, Menozzi Circulation 2002, Brignole Circulation 2001, Krahn Circulation 1995, Khran Ciculation 1999, Nierop PACE 2000, Boersma Europace 2004, Lombardi Europace 2005, Pierre Europace 2008

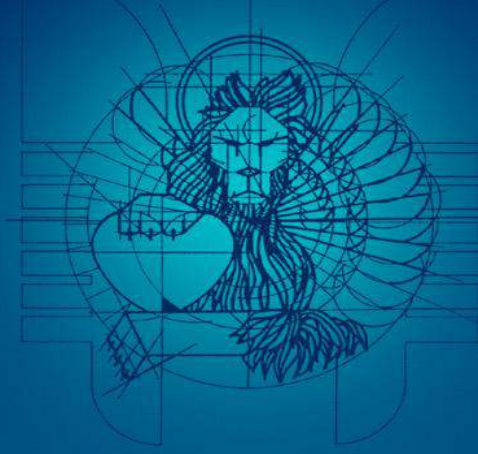
AP-HRS, October 28-30, 2010 - Jeju Island, Korea

Therapy of Vaso-Vagal Syncope

Antonio Raviele, MD, FESC, FHRS

Cardiovascular Department, Ospedale dell'Angelo, Mestre – Venice, Italy

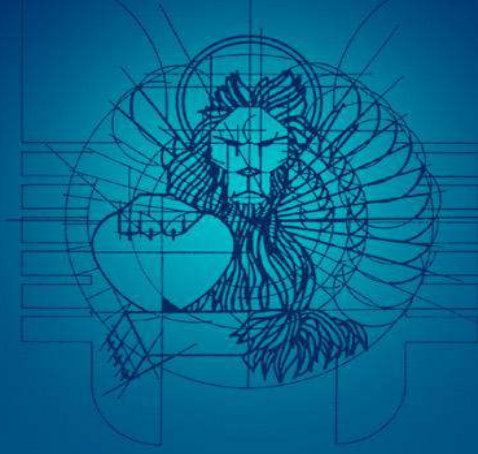
Treatment of VVS



Only rarely

necessary

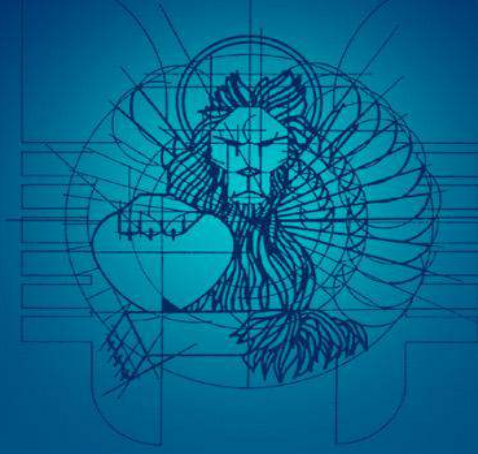
Vasovagal Syncope



- Is a begnin condition
- Is not a threat to life
- Does not impair quality of life

Majority of cases

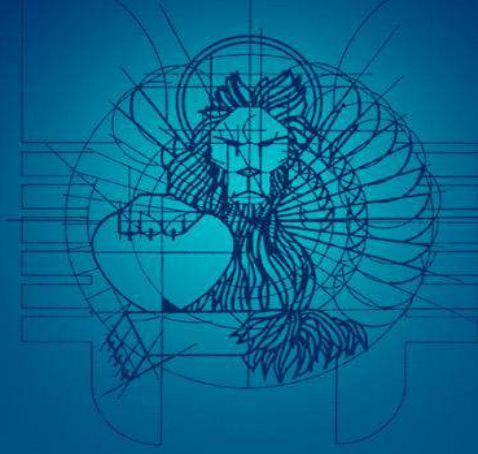
Treatment - VVS



- Frequent syncopal episodes
- No predictable circumst. / warning sympt.
- Important physical injury
- Potential occupational hazard

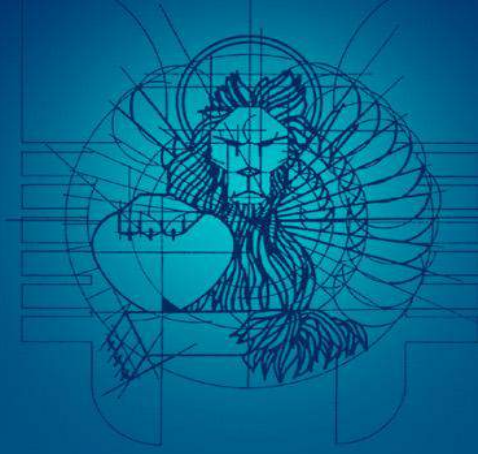
Indicated

Therapeutical Options



- Non-pharmacological
- Pharmacological
- Electrical

VVS / Rationale for pacing

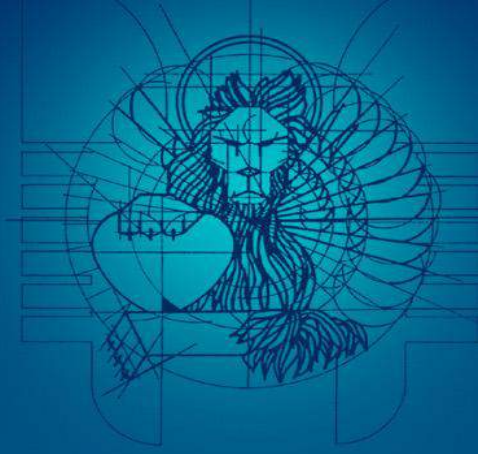


To counteract

the cardioinhibitory component

of the pathological reflex

Pacing for VVS / Studies



- Randomized open-label control
- Randomized double-blind placebo-control

Randomized open-label controlled studies

	VPS	VASIS	SYDIT
Pts no.	54	42	93
Mean age	43	60	58
Median no. of syncopes	14-35	5.5	7-8
Tilt test	+	+	+
Control arm	no pm	no pm	atenol
Recurrence (Pm arm)	22%	5%	4%
Recurrence (control arm)	70%	61%	25%
p value	0.000	0.000	0.004
Pacemaker	RDR	DDI 45-80	RDR

Risk ↓

83%

92%

Mean FU: few mo – 3.7 yrs

VPS. J Am Coll Cardiol 1999; 33: 16-20
VASIS. Circulation 2000; 102: 294-299 SYDIT. Circulation 2001;104:52-57

Randomized double-blind placebo-controlled trials

	VPS II	SYNPACE
Pts no.	100	29
Mean age	49	53
Median no. of syncopes	16	14-10
Tilt test	+ / -	+
Control arm	pm off	pm off
Recurrence (Pm arm)	33%	50%
Recurrence (control arm)	42%	38%
p value	ns	ns
Pacemaker	RDR	RDR

Risk ↓

-21%

+32%

VPS II. JAMA 2003; 289: 2224-2229

SYNPACE. Eur Heart J 2004; 25: 1741-8

Randomized double-blind placebo-controlled trials

a substancial placebo effect

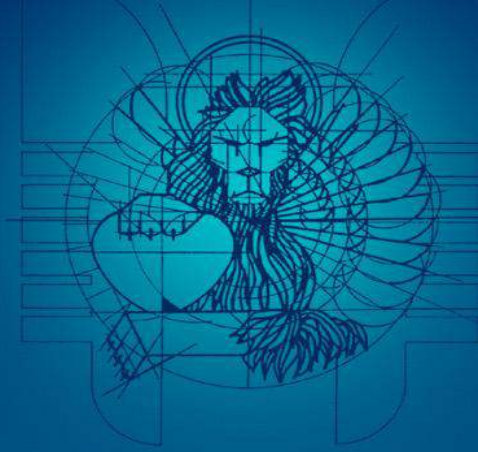
of pacemaker implantation

VVS / Limitation of pacing

The vasodepressor component

is not affected by pacing and may be responsible for the LoC at the time the pathological reflex develops

Pacing for VVS

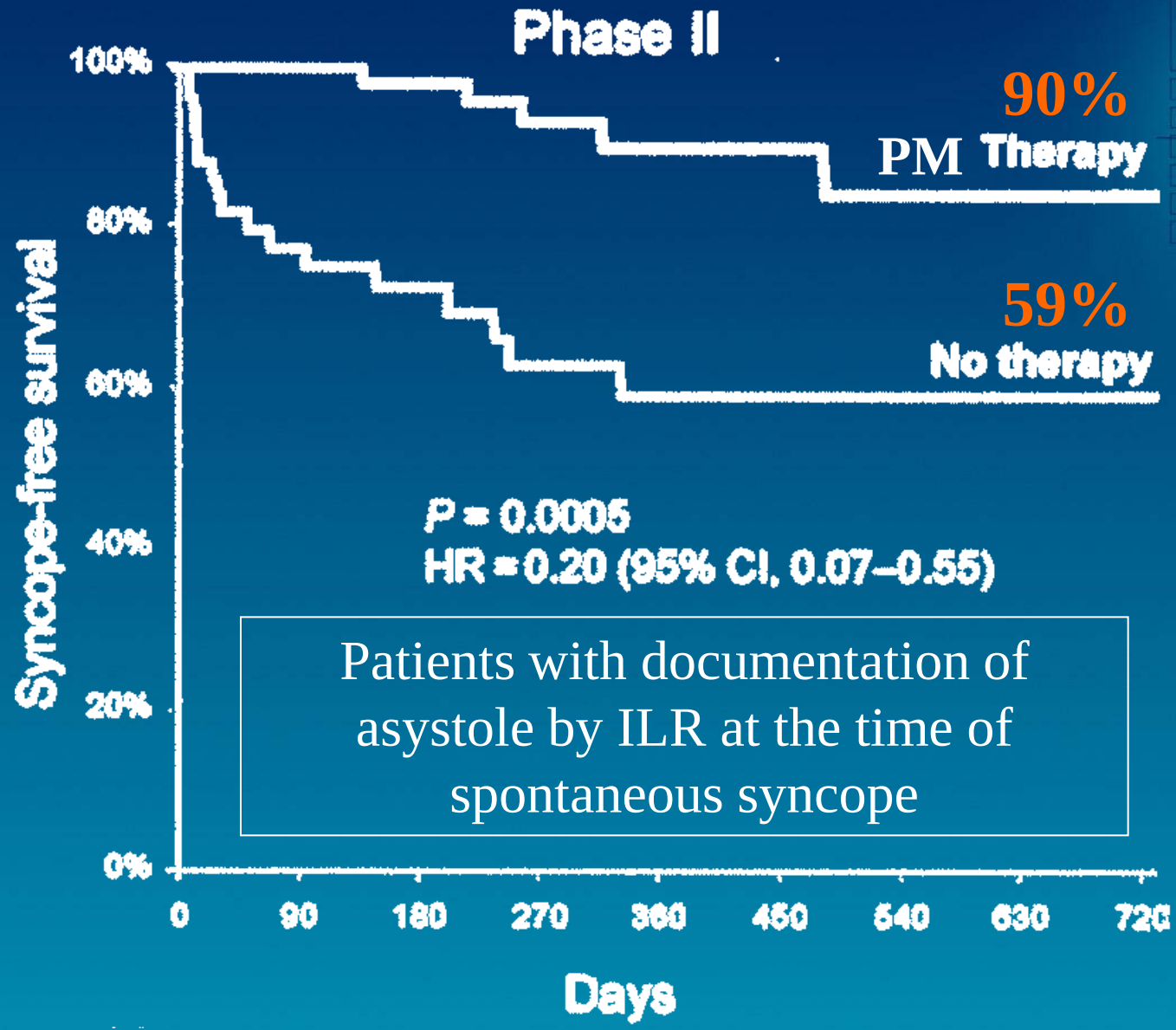


It has been suggested that selecting patients with vasovagal syncope for PM implantation on the basis of the results of implantable loop recorder may give better results

Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope

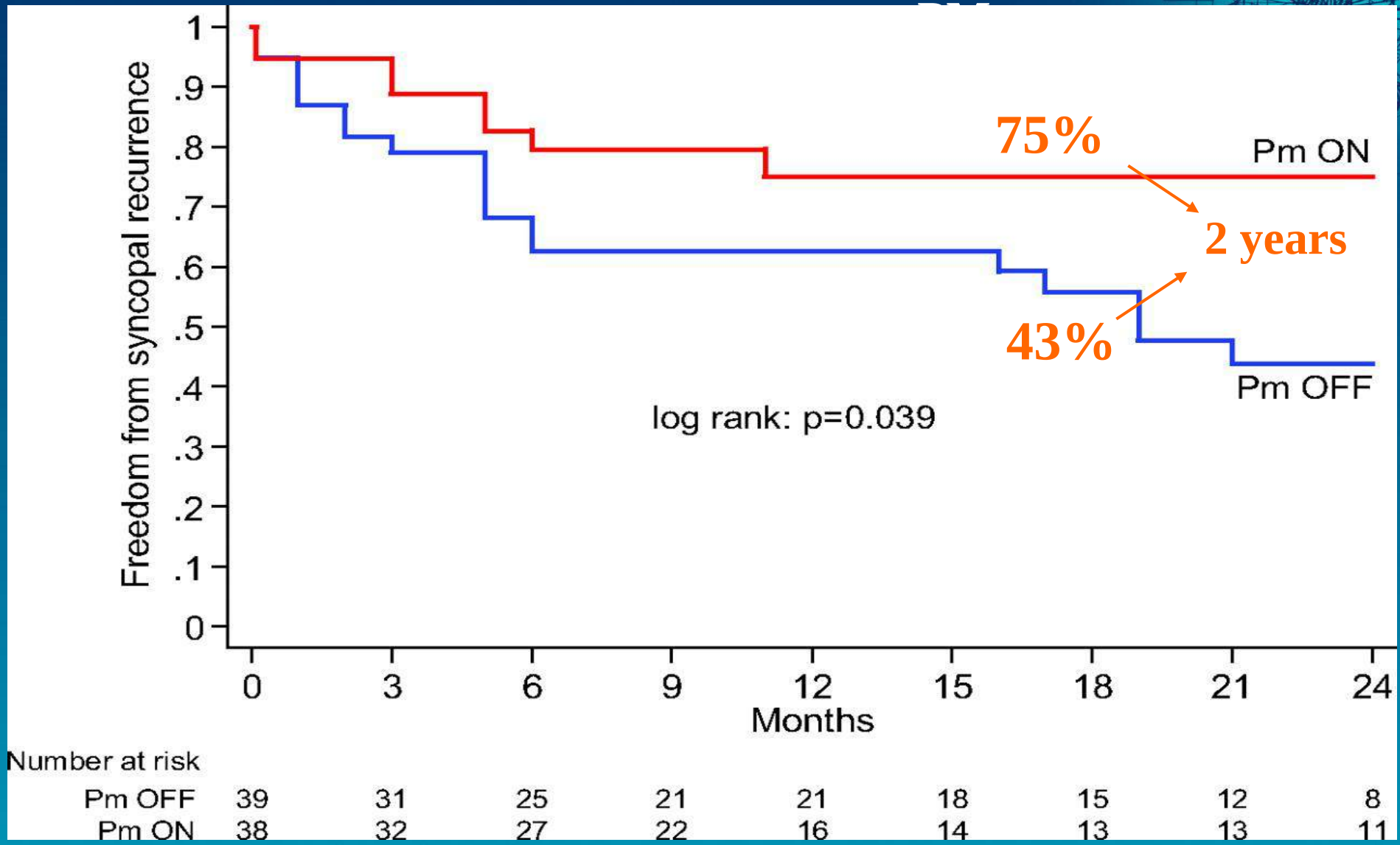
Michele Brignole[1*], Richard Sutton[2], Carlo Menozzi[3], Roberto Garcia-Civera[4], Angel Moya[5], Wouter Wieling[6], Dietrich Andresen[7], David G. Benditt[8], and Panos Vardas[9] for the International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group

Eur Heart J 2006; 27: 1085-92



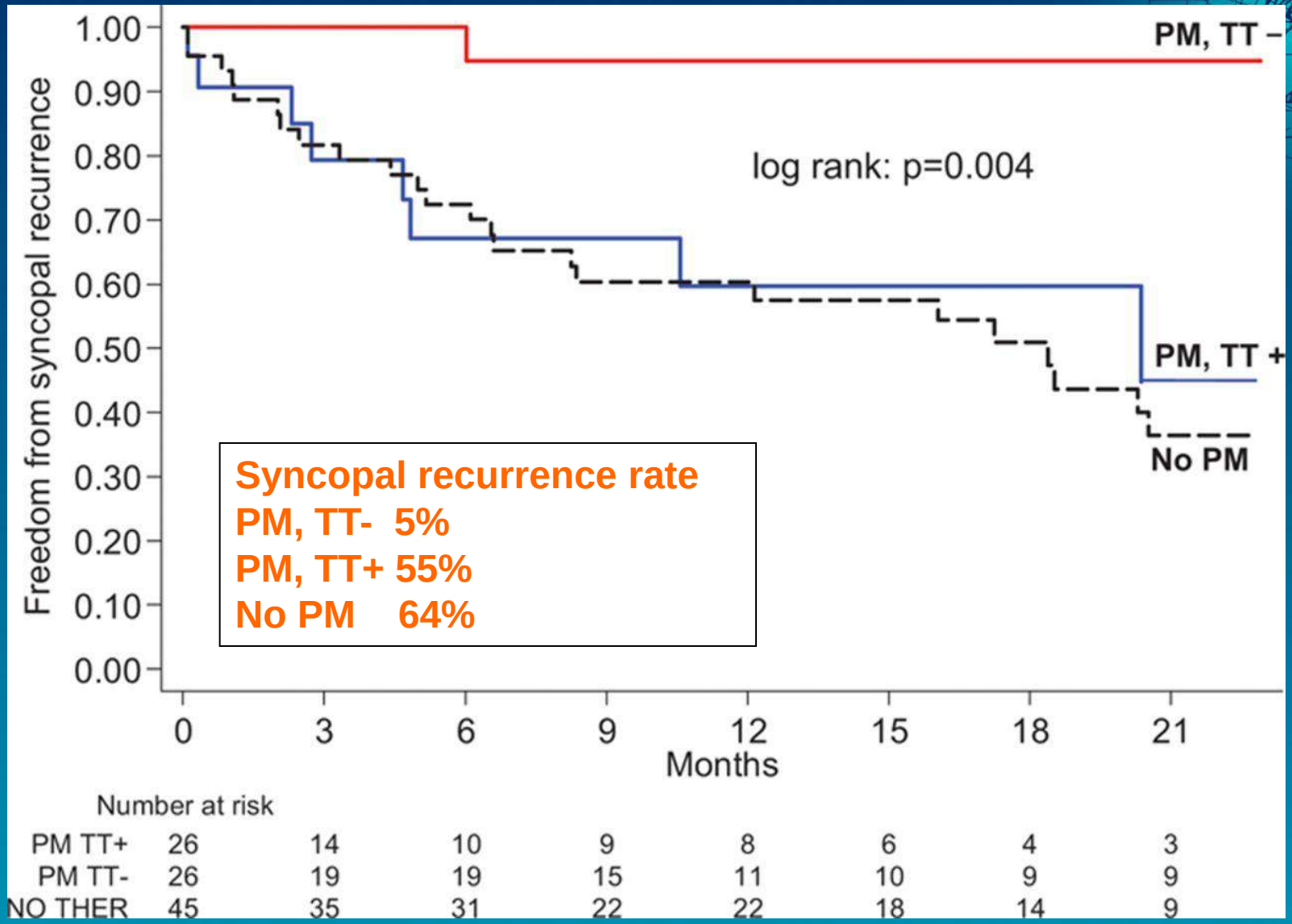
Brignole M et al. Eur Heart J 2006; 27: 1085-92

Time to first recurrence of syncope according to the intention-to-treat analysis (ISSUE III)



Brignole M et al. Circulation. 2012;125:2566-2571

Kaplan–Meier freedom from syncope recurrence after pacemaker therapy in tilt-negative asystolic neurally mediated syncope (NMS) and in tilt-positive asystolic NMS patients.

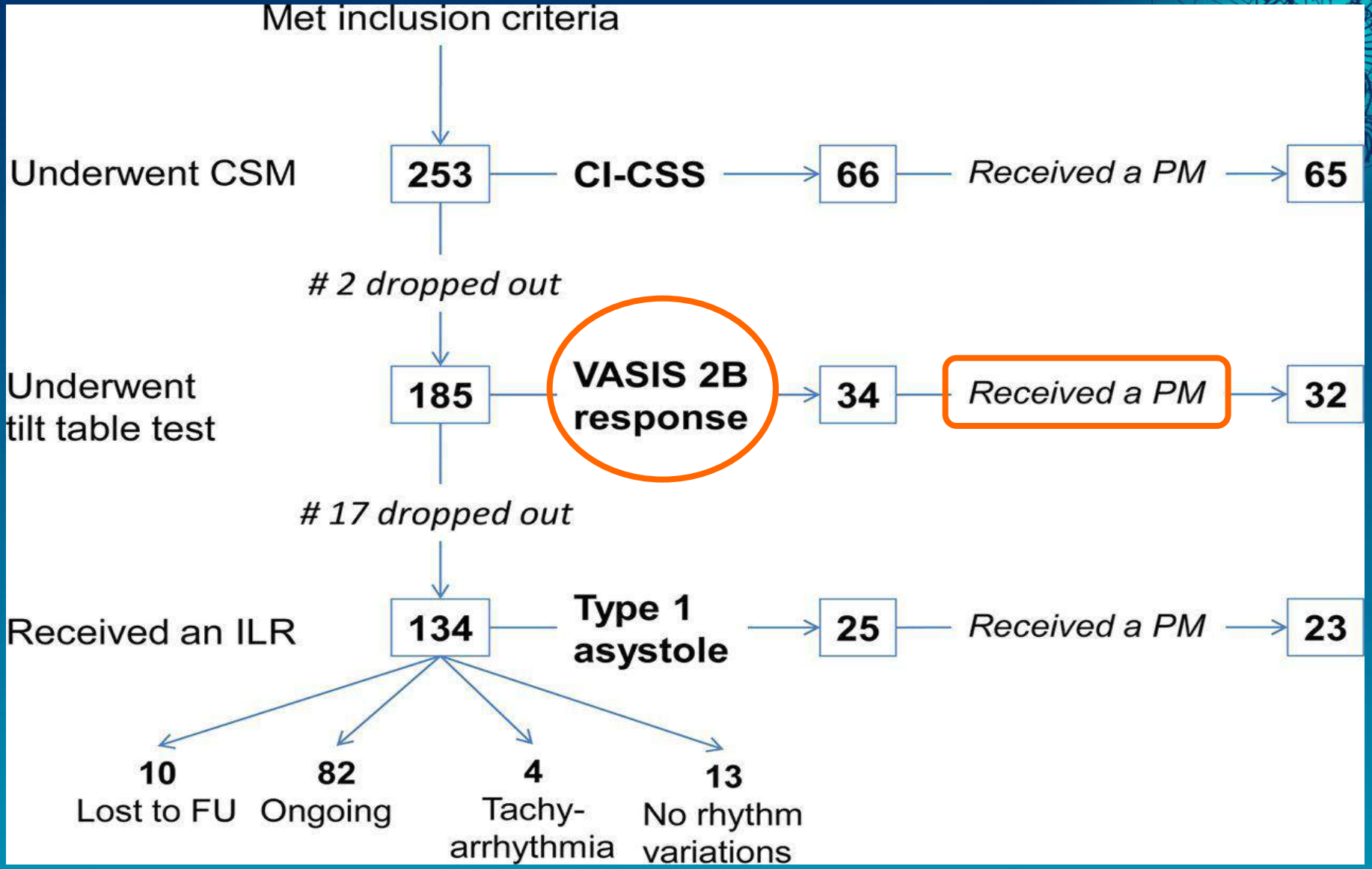


Brignole M et al. Circ Arrhythm Electrophysiol. 2014;7:10-16

HUTT / PM implantation

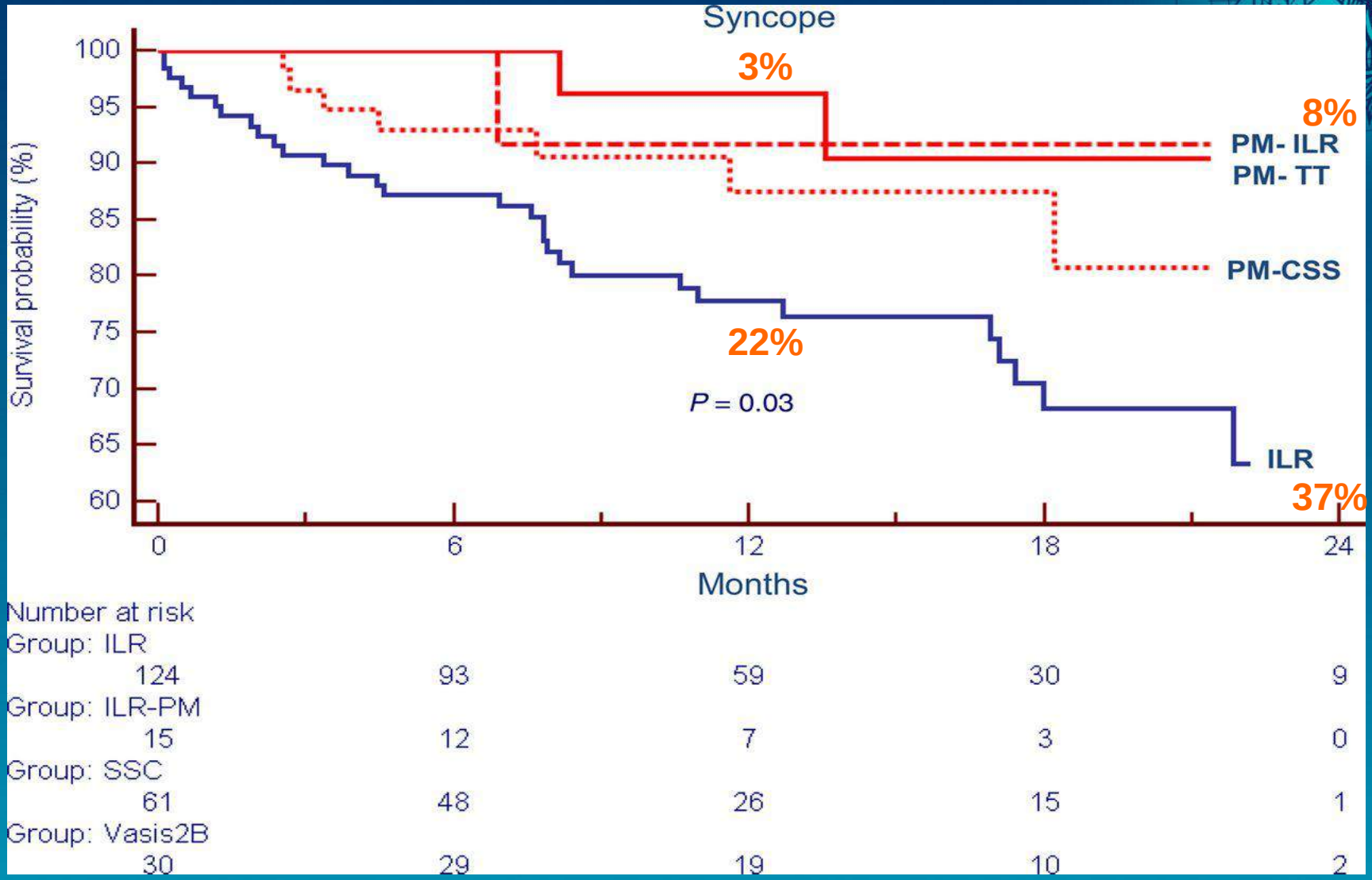
- These results suggest that HUTT may be utilized as a tool to decide pacemaker implantation in patients with presumed VVS but, paradoxally and differently from what believed in the past, only for patients with negative response to HUTT and with documented asystole during spontaneous syncopal recurrences in the follow-up.
- On the contrary, caution should be recommended over pacemaker implantation in patients showing asystole during HUTT.

Diagnostic algorithm



Michele Brignole et al. Eur Heart J 2015;36:1529-1535

Time to first recurrence of syncope in the 3 pacemaker subgroups and in the implantable loop recorder group.



Michele Brignole et al. Eur Heart J 2015;36:1529-1535

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

The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC)

Developed in collaboration with, European Heart Rhythm Association (EHRA)[1], Heart Failure Association (HFA)[2], and Heart Rhythm Society (HRS)[3]

Endorsed by the following societies, European Society of Emergency Medicine (EuSEM)[4], European Federation of Internal Medicine (EFIM)[5], European Union Geriatric Medicine Society (EUGMS)[6], American Geriatrics Society (AGS), European Neurological Society (ENS)[7], European Federation of Autonomic Societies (EFAS)[8], American Autonomic Society (AAS)[9]

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Eur Heart J 2009; 30: 2631-2671

VVS / Pacing indication

Class IIa recommendation

Cardiac pacing is recommended in patients 40 years of age or older, with frequently recurrent and unpredictable syncope, and with documented spontaneous pauses during electrocardiographic monitoring (≥3 sec if symptomatic and ≥6 sec if asymptomatic).

Moya A et al. Eur Heart J 2009; 30: 2631-2671

VVS / Pacing indication

However, owing to the risk of complications following pacemaker implantation and the fact that electrical therapy may be ineffective in a significant percentage of patients considered to be appropriate candidate (25% at 2 years in ISSUE III trial), pacing should be considered only in highly selected patients, especially those with repeated injury and limited or absent prodromes.

Sheldon RS et al. Heart Rhythm 2015; 12(6): e41-e63