



# Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope

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## Aims

Opinions differ regarding the effectiveness of cardiac pacing in patients affected by reflex syncope. We assessed a standardized guideline-based algorithm in different forms of reflex syncope.

## Methods and results

In this prospective, multi-centre, observational study, patients aged >40 years, affected by severe unpredictable recurrent reflex syncope, underwent carotid sinus massage (CSM), followed by tilt testing (TT) if CSM was negative, followed by implantation of an implantable loop recorder (ILR) if TT was negative. Those who had an asystolic response to one of these tests received a dual-chamber pacemaker. Population: 253 patients, mean age  $70 \pm 12$  years, median 4 (3–6) syncope, 89% without or with short prodromes. Of these patients, 120 (47%) received a pacemaker and 106 were followed up for a mean of  $13 \pm 7$  months: syncope recurred in 10 (9%). The recurrence rate was similar in 61 CSM+ (11%), 30 TT+ (7%), and 15 ILR+ (7%) patients. The actuarial total syncope recurrence rate was 9% (95% confidence interval (CI), 6–12) at 1 year and 15% (95% CI, 10–20) at 2 years and was significantly lower than that observed in the group of 124 patients with non-diagnostic tests who had received an ILR: i.e. 22% (95% CI, 18–26) at 1 year and 37% (95% CI, 30–43) at 2 years ( $P = 0.004$ ).

## Conclusion

About half of older patients with severe recurrent syncope without prodromes have an asystolic reflex for which cardiac pacing goes along with a low recurrence rate. The study supports the clinical utility of the algorithm for the selection of candidates to cardiac pacing in everyday clinical practice.

## Clinical Trial Registration

<http://www.clinicaltrials.gov>. Unique identifier: NCT01509534.

## Keywords

Syncope • Cardiac pacing • Tilt table test • Carotid sinus massage • Implantable loop recorder

## Introduction

While cardiac pacing is commonly considered ineffective in the vasodepressor and mixed forms of reflex syncope, opinions differ regarding the effectiveness of cardiac pacing in patients affected by cardio-inhibitory reflex syncope.<sup>1–3</sup> This uncertainty is due to the

lack of large randomized trials. Moreover, the matter is complicated by the fact that the confidence interval (CI) reflex is usually diagnosed by means of different methods, i.e. carotid sinus massage (CSM), tilt table testing (TT), and prolonged ECG monitoring [mostly by implanted loop recorders (ILR)] and the few trials that have evaluated the efficacy of pacing have analysed each form of syncope separately.

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No comparative study has been performed yet. As a result, guidelines make separate recommendations for these different clinical situations. Clinical practice differs from the somewhat artificial world of trials, in that the above examinations are variously combined together in individual patients. Generally, pragmatic studies are designed to determine the effects of an intervention under the usual conditions in which it will be applied, whereas conventional explanatory biomedical trials are primarily designed to determine the effects of an intervention under ideal circumstances.<sup>4</sup>

In this pragmatic study, we assessed the effectiveness of a comprehensive guideline-based diagnostic algorithm and the syncopal recurrence rate after dual-chamber pacemaker therapy in patients affected by any form of CI reflex syncope diagnosed by means of CSM, TT or ILR.

## Methods

The multi-centre, prospective observational Syncope Unit Project (SUP) 2 study was conducted in 10 Italian structured syncope units selected among those of the network of syncope units certified by the Gruppo Italiano Multidisciplinare per lo studio della Sincope (GIMSI, [www.gimsi.it](http://www.gimsi.it)). Patient recruitment started in January 2012 and ended in December 2013. Follow-up ended in June 2014. The study protocol was approved by each Institutional Review Board.

### Patient selection

The study included consecutive patients aged  $\geq 40$  years affected by severe, unpredictable, recurrent, and reflex syncope. Syncopes were defined as 'severe' when they impaired the patient's quality of life (because of high frequency) and their occurrence was 'unpredictable', in that they occurred without, or with very short ( $< 10$  s) prodromes (thus exposing patients to risk of trauma). Syncopes were defined as 'recurrent' when the patient had had at least two episodes during the previous year (including the index episode) or three episodes during the

previous 2 years (including the index episode). In accordance with the guidelines of the European Society of Cardiology<sup>1</sup> reflex syncope was considered likely when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Specifically, we excluded patients with: (i) suspected cardiac arrhythmic syncope [inadequate sinus bradycardia ( $< 50$  bpm) or sinoatrial block, second-degree Mobitz I atrioventricular block, second-degree Mobitz II or third-degree atrioventricular block, paroxysmal tachyarrhythmia or ventricular tachycardia, and bundle branch block]; (ii) severe structural heart disease and/or significant ECG abnormalities, as defined in the Table 2 of those guidelines;<sup>1</sup> (iii) orthostatic hypotension; and (iv) non-syncopal causes of transient loss of consciousness. Moreover, we excluded patients with (v) reflex syncopes due to reversible causes, e.g. vasoactive drugs, concomitant diseases, etc.

### Study protocol

Eligible patients underwent the following sequential algorithm, which was drawn up in accordance with the recommendations of the European Society of Cardiology's guidelines on syncope<sup>1,3</sup> (Figure 1).

- Initially, patients underwent CSM according to the 'method of symptoms';<sup>1,5,6</sup> if a diagnosis of CI carotid sinus syndrome (CSS) was made, a dual-chamber pacemaker was proposed and follow-up immediately started. In accordance with the 'method of symptoms', CI-CSS was established when spontaneous symptoms (syncope or pre-syncope) were reproduced in the presence of an asystolic pause  $> 3$  s. Thus, an asymptomatic CI reflex was not considered sufficient to establish a diagnosis, as this is a frequent finding in the general older population;<sup>7</sup> these patients proceeded to the next step.
- If CSM was negative or the response was vasodepressor, the patient underwent TT according to the Italian protocol,<sup>8</sup> if a diagnosis of CI form [i.e. Vasovagal Syncope International Study (VASIS) 2B form] was made, a dual-chamber pacemaker was proposed and follow-up immediately started. The Italian protocol<sup>8</sup> consists of  $60^\circ$ – $70^\circ$  passive tilting for 20 min or until syncope occurs. If the passive tilt phase did not induce syncope, 0.4 mg sublingual nitroglycerine was

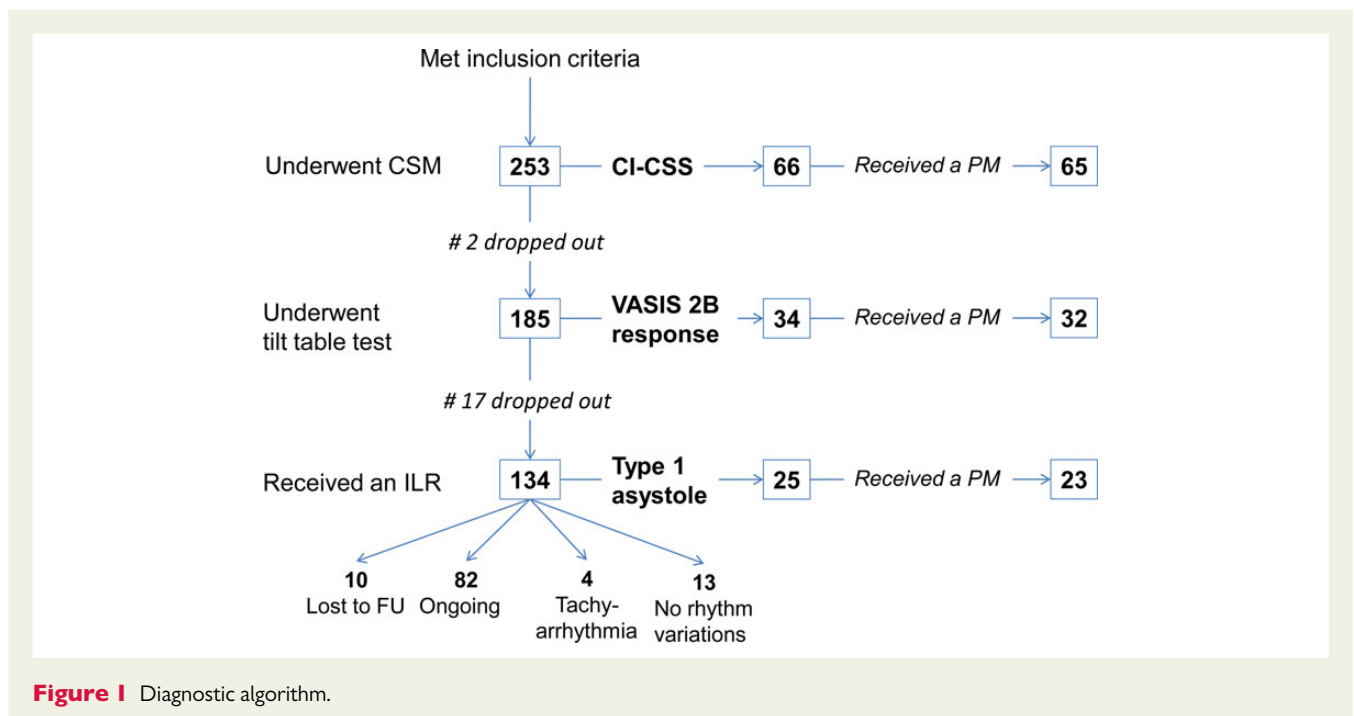


Figure 1 Diagnostic algorithm.

administered while the table was maintained in the same position; the test was continued for 15 min after pharmacological challenge. Tilt testing was considered positive if syncope occurred in the presence of hypotension, with or without bradycardia. Positive responses were classified according to the New VASIS classification,<sup>9</sup> VASIS 2B form was defined when an asystole  $\geq 3$  s was induced.

- If TT was negative or the response was vasodepressor, the patient underwent ILR implantation and was followed up until a diagnosis was made or the study ended; if a diagnosis of CI form (i.e. type 1 of the International Study on Syncope of Uncertain Etiology (ISSUE) classification)<sup>10</sup> was made during the study period, a dual-chamber pacemaker was proposed and follow-up continued. A diagnosis of CI form was established when patients had syncopal recurrence with a documented asystolic pause  $> 3$  s at the time of syncope, or asymptomatic or pre-syncopal episodes with documentation of an asystolic pause  $> 6$  s.<sup>11,12</sup>

When a pacemaker was indicated, investigators were advised to use a dual-chamber pacemaker with rate hysteresis (allowing minimal ventricular pacing).

## Data management and follow-up

Baseline data and data from periodic follow-up examinations were recorded on electronic clinical report forms created by means of the SyncopeWeb platform, which was available to the GIMSI syncope units). SyncopeWeb (D.I.T., ASL 4, Chiavari, Italy), an upgrade of the EGSYS software utilized in previous studies,<sup>13</sup> is a web-based on-line interactive decision-making system developed to help the physician to follow the diagnostic pathway and the recommendations of the ESC guidelines.

## Objectives

This pragmatic study had two primary objectives: to assess the effectiveness of the above diagnostic algorithm and to assess the reduction in syncopal recurrences after dual-chamber pacemaker therapy in patients affected by any form of CI reflex syncope diagnosed by means of CSM, TT, or ILR. As a secondary objective, the rate of syncope recurrence after pacemaker implantation was compared with that observed in the group of patients with non-diagnostic tests who had received an ILR.

## Statistical analysis

Continuous data are shown as means  $\pm$  SDs or medians (25th–75th percentile), as appropriate, whereas absolute and relative frequencies were used to describe categorical data. The method of Kolmogorov and Smirnov was used to check the normality of distributions. Continuous variables were compared by one-way ANOVA or a non-parametric Kruskal–Wallis test with post-test, depending on data distribution. Heterogeneity between centres was tested by mean of a stratified Cox model and also a Cox model with random effect to modelling centre effects. The  $\chi^2$  test was used to compare multiple proportions. Differences with a two-sided  $P$ -value of  $< 0.05$  were indicated. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves, which were compared by means of the log-rank test. Analyses were performed by means of the MedCalc<sup>®</sup> software (Mariakerke, Belgium).

Assuming a 10% recurrence rate of syncope at 1 year after cardiac pacing as clinically reasonable, we estimated that 100 patients receiving a pacemaker would be enough to enable us to assess the primary objectives of the study, i.e. the effectiveness of the diagnostic algorithm, within 5% points (from 5 to 15%) of the true value with a 90% CI (based on Lwanga and Lemeshow one-sample size determination). This sample

size would also be sufficient in order to compare pacemaker and ILR groups (secondary objective). Indeed, with at least 90 patients each in the pacemaker and ILR groups, the study would have 90% power to detect a reduction from 30 to 10% in syncopal recurrence at 1 year, with a probability of 95% and an attrition of 10% (based on log-rank parametric method for exponential data).

## Results

The baseline clinical features of the population enrolled are summarized in *Table 1*. In brief, we enrolled 253 patients, mean age  $70 \pm 12$  years, median 4 (3–6) syncopes, 89% without or with short prodromes. No heterogeneity between centres was found.

In accordance with the study algorithm (*Figure 1*), CSM was performed in all 253 patients. CI-CSS was found in 66 (26%), while another 10 had a vasodepressor response  $\geq 50$  mmHg (with reproduction of syncope in 1). In CI-CSS, the mean pause was  $9.2 \pm 6.4$  s; this was obtained in the standing position in 67% of cases and supine in 33%. Tilt testing was performed in 185 patients and was positive in 103 (56%): 34 (18%) had a CI (VASIS 2B) response, 46 mixed, and 23 vasodepressor. In the CI (VASIS 2B) form, the longest pause was  $21 \pm 15$  s; this was obtained during the passive phase in 18 patients and during the nitroglycerine phase in 16. Finally, an ILR was implanted in 134 patients (53%). A diagnosis was made in 38 patients (28%) during a mean follow-up of  $11 \pm 8$  months: a CI (type 1) response was found in 25 (19%), no rhythm variations in 12 (9%), and tachycardia in 2 (1.5%). A total of 37 episodes of syncope were documented by ILR in 31 patients and a non-syncopal pause  $> 6$  s established a diagnosis in another seven patients. The longest pause was  $13 \pm 11$  s. No patient died during the observation period, seven suffered mild traumas related to syncope recurrence, and one patient underwent ILR explantation owing to pocket infection. Finally, 120 (47%) patients received a pacemaker.

## Outcome

Follow-up data were obtained in 106 (88%) patients who had received a dual-chamber pacemaker: 61 (51%) in the CSS group, 30 (25%) in the TT group, and 15 (12%) who received a pacemaker later, once an ILR diagnosis of asystolic syncope had been obtained (*Table 2*); no follow-up was available in the other 14 (12%) pacemaker patients in whom the study ended before their first visit or who were lost to follow-up. A rate-drop response feature (consisting of rate hysteresis at 40 bpm and rapid pacing at 90 bpm in the event of a rapid fall in spontaneous heart rate) was programmed in 72 patients. During a mean follow-up of  $13 \pm 7$  months, syncope recurred in 10 (9%) of patients. The recurrence rate was similar in CSM+ patients (11%), TT+ patients (7%), and ILR+ patients (7%). Overall, pacemaker patients had 200 syncopal episodes in the year before pacemaker implantation, excluding the index episode, and 11 episodes in the year following implantation. A total of 29 episodes of pre-syncope occurred in 11 patients; in 8 of these, the pacemaker memory stored episodes of activation of the rate-drop response feature. The actuarial total syncope recurrence rate was 9% (95% CI, 6–12) at 1 year and 15% (95% CI, 10–20) at 2 years. This was not different among the three subgroups of pacemaker patients, but was significantly lower than that observed in the group of 124

**Table 1** Baseline characteristics

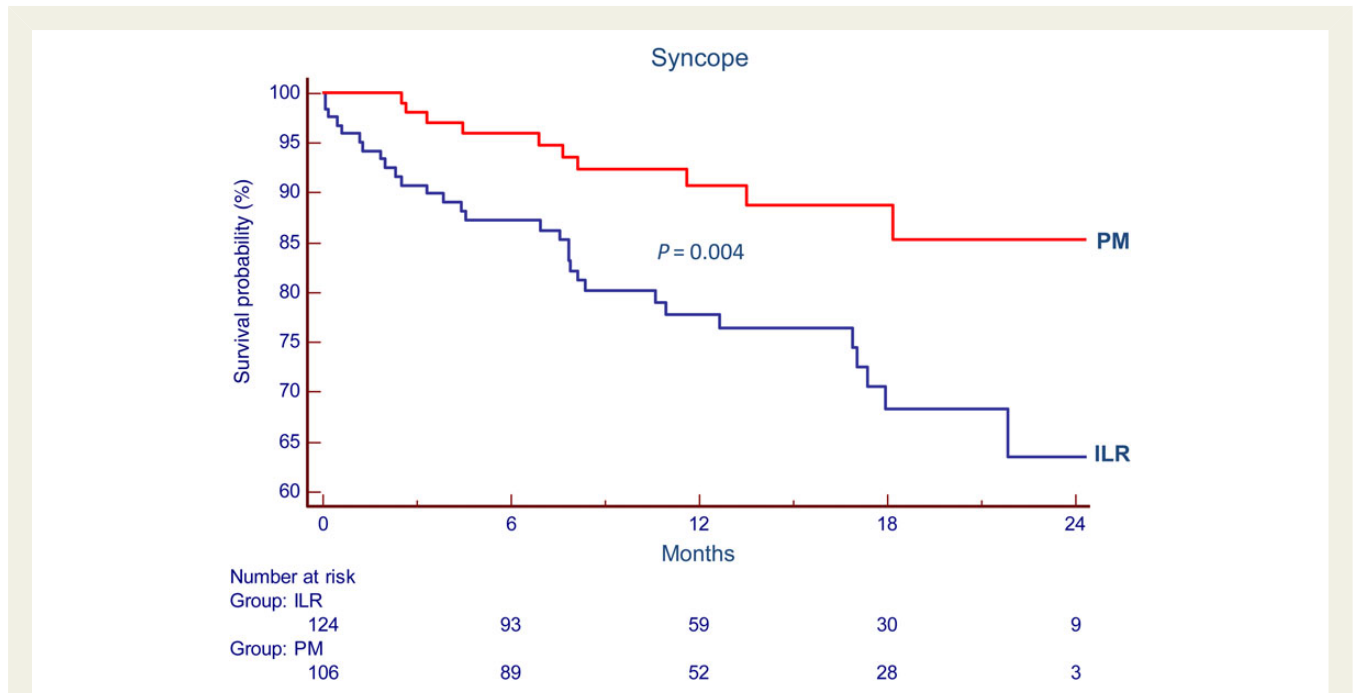
Characteristics	Total population n = 253	CSS group n = 66	Asystolic TT group (VASIS 2B) n = 34	ILR group n = 134
Age, mean (SD) (years)	70 ± 12	77 ± 9 <sup>a</sup>	65 ± 11 <sup>a</sup>	68 ± 13 <sup>a</sup>
Men, no. (%)	128 (51)	45 (68) <sup>a</sup>	14 (41) <sup>a</sup>	62 (46) <sup>a</sup>
Syncope events				
Total syncopes, median (IQR)	4 (3–6)	4 (3–6)	4 (3–7)	4 (3–6)
Syncopes in the previous year, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
Syncopes in the previous 2 years, median (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	3 (2–4)
Age on first syncope, mean (SD) (years)	61 ± 20	70 ± 16*	48 ± 25*	59 ± 20*
Syncopes without or with prodromes <10 s, no. (%)	211/237 (89)	56/64 (88)	22/27 (81)	120/132 (91)
History of pre-syncope, no (%)	88/228 (39)	21/62 (34)*	15/27 (56)*	45/124 (36)*
Hospitalization for syncope, no (%)	127/238 (53)	34/62 (55)	11/29 (38)	72/131 (55)
Injuries related to fainting, no (%)				
Major injuries (fractures, brain concussion)	50/234 (21)	7/63 (11)	6/27 (22)	32/129 (25)
Minor injuries (bruises, contusion, and haematoma)	152/237 (64)	44/64 (69)	16/27 (59)	84/131 (64)
Medical history, no (%)				
Structural cardiac abnormalities	54/247 (22)	15/65 (23)	9 (26)	28/131 (21)
ECG abnormalities	40/242 (17)	16/64 (25)	7 (21)	16/129 (12)
Hypertension	145/240 (60)	37/64 (58)	15/29 (52)	87/131 (66)
Diabetes	38/233 (16)	12/63 (19)	5/29 (17)	21/126 (17)
Neurological/psychiatric disorders	27/234 (12)	10/63 (16)	2/29 (7)	13/127 (10)
Concomitant vasoactive medications, no. (%)	148/242 (61)	37/63 (59)	14/29 (48)	80/132 (61)
Angiotensin-converting enzyme inhibitors	84 (35)	25 (40)	8 (28)	49 (37)
Angiotensin-receptor blocker	32 (13)	6 (10)	5 (17)	20 (15)
β-Blockers	35 (14)	8 (13)	6 (21)	16 (12)
Calcium antagonists	39 (16)	8 (13)	4 (14)	25 (19)
α-Antagonists	12 (5)	4 (6)	0 (0)	8 (6)
Diuretics	34 (14)	8 (13)	2 (7)	23 (17)
Nitrates	5 (2)	3 (5)	1 (3)	1 (1)
Psychiatric	21 (10)	2 (3)	0 (0)	15 (11)

The column 'Total Population' includes 19 patients who dropped out (see Figure 1).

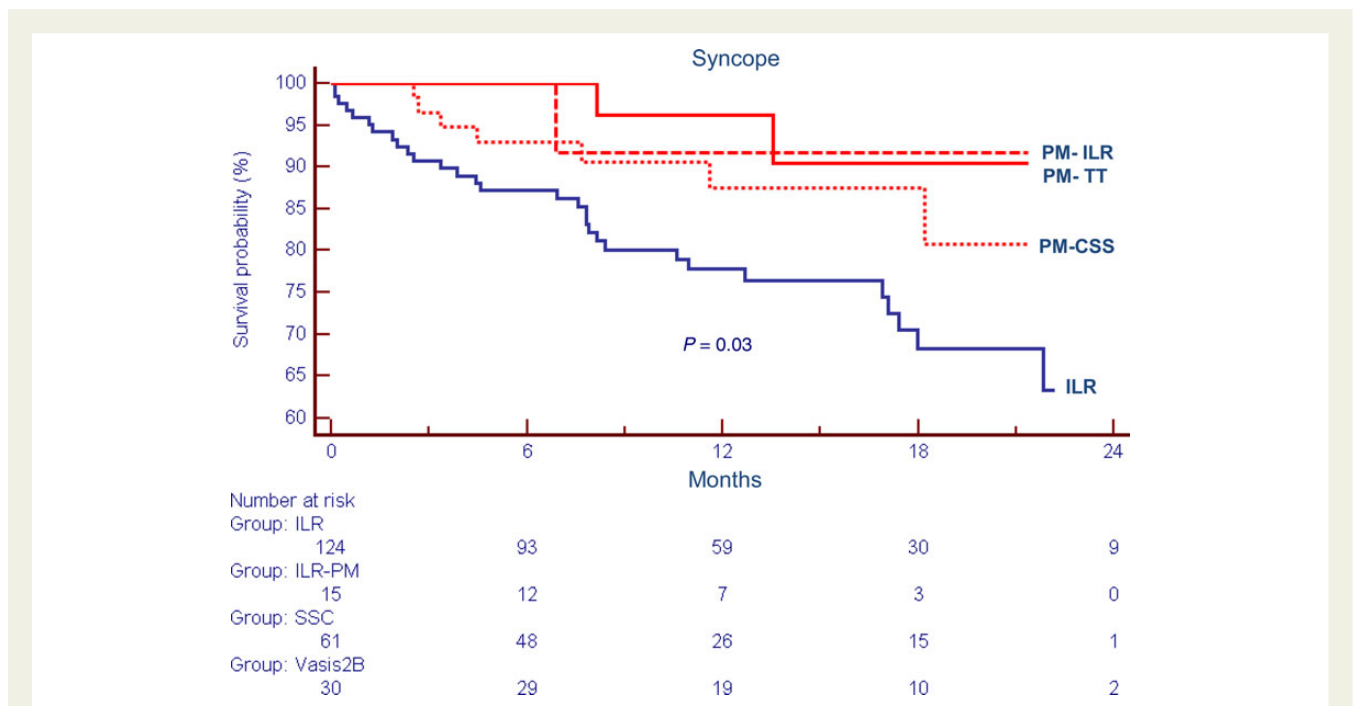
\*Field with significant differences between subgroups ( $P < 0.05$ ).

**Table 2** Outcome after cardiac pacing

Characteristics	Total population with Pm n = 106	CSS group n = 61	Asystolic TT group (VASIS 2B) n = 30	ILR group n = 15
Total number of syncopes in the year before implantation, excluding the index episode	200	118	51	28
Total number of syncopes in the year after implantation (%)	11 (5)	6 (5)	1 (2)	2 (7)
Follow-up duration, months	13 ± 7	12 ± 7	16 ± 4	12 ± 7
Number of patients with syncope recurrence (%)	10 (9)	7 (11)	2 (7)	1 (7)
Number of patients with syncope and/or pre-syncope recurrence (%)	19 (18)	10 (16)	6 (20)	3 (20)
1-year estimated product-limit syncope recurrence rate (95% CI)	9 (6–12)	12 (7–17)	4 (0–8)	8 (0–16)
2-year estimated product-limit syncope recurrence rate (95% CI)	15 (10–20)	19 (11–27)	10 (3–17)	8 (0–16)



**Figure 2** Time to first recurrence of syncope. PM = pacemaker, ILR = implantable loop recorder.



**Figure 3** Time to first recurrence of syncope in the 3 pacemaker subgroups and in the implantable loop recorder group. PM = pacemaker, ILR = implantable loop recorder.

patients with non-diagnostic test who had received an ILR: i.e. 22% (95% CI, 18–26) at 1 year and 37% (95% CI, 30–43) at 2 years ( $P = 0.004$ ) (Figures 2 and 3). No patient died during the observation

period nor suffered trauma related to syncope recurrence. Five patients had documentation of transient atrial tachyarrhythmias unrelated to syncope recurrence.



## Discussion

The main result of this study is that, among older patients with severe recurrent syncope with no or minimal prodromes, utilization of this guideline-based diagnostic algorithm is able to identify those patients (about half) who have an asystolic reflex for which cardiac pacing goes along with a low recurrence rate. Although the study was not designed as a formal randomized trial, the low recurrence rate, which was irrespective of the index diagnostic test and significantly lower than in patients with non-diagnostic tests and ILR implantation, supports the clinical utility of the algorithm for the selection of candidates to cardiac pacing in everyday clinical practice.

The results of this pragmatic study (Table 2) are similar (within the confidence intervals) to those of most conventional explanatory biomedical trials. In a meta-analysis<sup>14</sup> of three studies of CSS patients, syncope recurred in 9% of patients who received a pacemaker (similar to the 11% rate in this study) and in 38% of controls during a mean observation period of 1–3 years. In the ISSUE-3 trial,<sup>12</sup> the 2-year estimated syncope recurrence rate in patients with ILR-documented asystole was 25% (95% CI, 13–45) on pacemaker therapy when both TT+ and TT– patients were included, but decreased to 5% (95% CI, 1–32) when only TT– patients were analysed; this latter rate is very similar to the 8% (95% CI, 0–16) rate observed in the present study in the ILR group. The effect of cardiac pacing in patients with CI (VASIS 2B) TT is more controversial, as most trials did not analyse TT responses separately. However, in the VASIS trial,<sup>15</sup> in which a prolonged asystolic pause—mean  $14 \pm 10$  s—was present in 86% of patients, the estimated 2-year recurrence rate was 6%, which is similar to the 8% (95% CI, 0–16) of the present study. In the Syncope Diagnosis and Treatment Study (SYDIT),<sup>16</sup> the 2-year estimated syncope recurrence rate was 7.2%. In contrast, the 1-year recurrence rate was 29% in the 8 asystolic patients of the Vasovagal Syncope and Pacing Trial,<sup>17</sup> and 35% (95% CI, 13–75) in the 14 asystolic patients of the ISSUE-3 sub-study.<sup>18</sup> Different entry criteria might have influenced these results; for example, in the latter two studies, patients were 10–20 years younger and about half had a history of typical vasovagal syncope.

For a correct interpretation of the present results, it is important to point out that the study population was not representative of the general population of patients affected by reflex syncope. Although the patients were consecutive, they were selected on the basis of strict inclusion criteria: age, frequency of episodes, and absence of prodromes. Virtually, no patients had a history of typical vasovagal syncope. In this regard, an analysis of the SUP<sup>19</sup> database showed that patients with these features constituted ~14% of the total population of the already selected population of patients referred for evaluation to specialized syncope units. In the present study, the prevalence of CI-CSS was 26%, i.e. 2- to 5-fold higher than in the general syncope populations of multi-centre studies,<sup>13,19</sup> and the incidence of a CI VASIS 2B response was 18%, i.e. 2-fold higher than in the general syncope population.<sup>9</sup> Consequently, a pacemaker was indicated in 47% of patients, whereas in the SUP study<sup>19</sup> only 10% received a pacemaker. We believe that the clinical inclusion criteria—i.e. advanced age, frequency of episodes, and absence of prodromes—were useful predictive factors for CI reflex syncope. Apart from some differences in age and gender in the CCS group, the three study groups had similar clinical

characteristics. The magnitude and ECG pattern of the asystolic reflex were also similar, as were the results of pacing therapy. All these findings suggest that the initial presentation (i.e. older age and no/short prodromes), rather than the type of index diagnostic investigation, characterized our population. Therefore, the results of the study cannot be extended to the general population of patients affected by reflex syncope, and any inference regarding indication for cardiac pacing in different patients should be avoided. The typical patient who is expected to benefit from cardiac pacing seems to be around the age of 70 years, to have a history of unpredictable syncope (i.e. without or with very short prodromes) starting in advanced age (mostly after the age of 40). It is likely that younger patients who have syncope preceded by prodromes would not benefit from pacemaker therapy to the same extent.

## Limitations

The total syncope burden fell dramatically from 200 episodes in the year before cardiac pacing to only 11 episodes in the year following cardiac pacing (95% relative reduction). It is likely that other mechanisms, in addition to cardiac pacing, contributed to this reduction. Indeed, a regression-to-the-mean effect was probably involved. It is known that syncopal recurrence is not constant, but rather fluctuates over time, peaking at the time of evaluation. Indeed, the number of syncopes also decreased in the ILR group. Moreover, we cannot exclude some placebo effect of device implantation. Finally, the possibility of an expectation effect has been raised by some.<sup>20</sup> However, whatever the causes of the reduced syncopal burden, the study showed the effectiveness of the proposed strategy, which is in accordance with the concept of pragmatic trials.<sup>4</sup>

In the light of some recent studies,<sup>21,22</sup> which were not available when this protocol was written, a positive vasodepressor response during TT seem to be useful to predict syncope recurrence in CSS paced patients. A positive response to TT should lead to additional measures for vasodilatation, e.g. reduction in hypotensive drugs, with potentially better outcomes.

## Conclusion/perspectives

In conclusion, this study validates a practical diagnostic algorithm which can be used in clinical practice in order to select patients affected by reflex syncope in whom cardiac pacing is a reasonable solution. The expected benefit in CI reflex syncope is not too different from that observed in paced patients affected by sick sinus syndrome and syncope in the DANPACE trial,<sup>23</sup> who had ~9 and 14% syncope recurrence rates 1 and 2 years, respectively, after pacemaker implantation.

## Funding

The SUP 2 trial was an investigator-initiated clinical registry sponsored by Gruppo Italiano Multidisciplinare per lo studio della Sincope (GIMSI) (see [www.gimsi.it](http://www.gimsi.it)).

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## Appendix

The following persons participated in the SUP 2 study.

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*Electronic database management:* Andrea Ponte, Department of Information Technology, Ospedali del Tigullio, Lavagna.

*Statistical analysis:* Michele Brignole, Lavagna.

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## References

- Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, vanDijk JG, Walma EP, Wieling W. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;**30**:2631–2671.
- Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;**11**:671–687.
- Brignole M, Auricchio A, Baron-Esquivas G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2013;**34**:2281–2329.
- Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furlong CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;**180**:E47–E57.
- Thomas JE. Hyperactive carotid sinus reflex and carotid sinus syncope. *Mayo Clin Proc* 1969;**44**:127–139.
- Puggioni E, Guiducci V, Brignole M, Menozzi C, Oddone D, Donateo P, Croci F, Solano A, Lolli G, Tomasi C, Bottoni N. Results and complications of the carotid sinus massage performed according to the "Method of Symptoms". *Am J Cardiol* 2002;**89**:599–601.
- Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern Med* 2006;**166**:515–520.
- Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, Menozzi C, Raviele A, Sutton R. The Italian protocol: a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;**2**:339–342.
- Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncope phase of the tilt test without and with nitroglycerin challenge. *Europace* 2000;**2**:66–76.
- Brignole M, Moya A, Menozzi C, Garcia-Civera R, Sutton R. Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. *Europace* 2005;**7**:14–18.
- Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;**27**:1085–1092.
- Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: third international study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;**125**:2566–2571.
- Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, Ponassi I, Mussi C, Maggi R, Re G, Furlan R, Rovelli G, Ponzi P, Scivales A. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. *Eur Heart J* 2006;**27**:76–82.
- Brignole M, Menozzi C. The natural history of carotid sinus syncope and the effect of cardiac pacing. *Europace* 2011;**13**:462–464.
- Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Gianini P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. *Circulation* 2000;**102**:294–299.
- Ammirati F, Colvicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52–57.
- Raviele A, Giada F, Menozzi C, Specca G, Orazi S, Gasparini G, Sutton R, Brignole M. The vasovagal syncope and pacing trial (Synpace). A randomized placebo-controlled study of permanent pacing for treatment of recurrent vasovagal syncope. *Eur Heart J* 2004;**25**:1741–1748.
- Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X, Moya A, Kus T, Deharo JC, Giuli S, Gentili A, Sutton R. Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative. *Circ Arrhythm Electrophysiol* 2014;**7**:10–16.
- Brignole M, Ungar A, Casagrande I, Gulizia M, Lunati M, Ammirati F, Del Rosso A, Sasdelli M, Santini M, Maggi R, Vitale E, Morrione A, Francese GM, Vecchi MR, Giada F. Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospital. *Europace* 2010;**12**:109–118.
- Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med* 2007;**120**:54–62.
- Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Brignole M. Clinical context and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'. *Europace* 2014;**16**:928–934.
- Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. *Eur Heart J* 2014;**35**:2211–2212.
- Ng Kam Chuen MJ, Kirkfeldt RE, Andersen HR, Nielsen JC. Syncope in paced patients with sick sinus syndrome from the DANPACE trial: incidence, predictors and prognostic implication. *Heart* 2014;**100**:842–947.