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FASTTRACK CLINICAL RESEARCH
Arrhythmias

Cardiac pacing in severe recurrent reflex syncope and tilt-induced asystole

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Aim The benefit of cardiac pacing in patients with severe recurrent reflex syncope and asystole induced by tilt testing has not been established. The usefulness of tilt-table test to select candidates for cardiac pacing is controversial.

Methods and results We randomly assigned patients aged 40 years or older who had at least two episodes of unpredictable severe reflex syncope during the last year and a tilt-induced syncope with an asystolic pause longer than 3 s, to receive either an active (pacing ON; 63 patients) or an inactive (pacing OFF; 64 patients) dual-chamber pacemaker with closed loop stimulation (CLS). The primary endpoint was the time to first recurrence of syncope. Patients and independent outcome assessors were blinded to the assigned treatment. After a median follow-up of 11.2 months, syncope occurred in significantly fewer patients in the pacing group than in the control group [10 (16%) vs. 34 (53%); hazard ratio, 0.23; $P = 0.00005$]. The estimated syncope recurrence rate at 1 year was 19% (pacing) and 53% (control) and at 2 years, 22% (pacing) and 68% (control). A combined endpoint of syncope or presyncope occurred in significantly fewer patients in the pacing group [23 (37%) vs. 40 (63%); hazard ratio, 0.44; $P = 0.002$]. Minor device-related adverse events were reported in five patients (4%).

Conclusion In patients aged 40 years or older, affected by severe recurrent reflex syncope and tilt-induced asystole, dual-chamber pacemaker with CLS is highly effective in reducing the recurrences of syncope. Our findings support the inclusion of tilt testing as a useful method to select candidates for cardiac pacing.

Study registration ClinicalTrials.gov identifier NCT02324920, Eudamed number CIV-05-013546.

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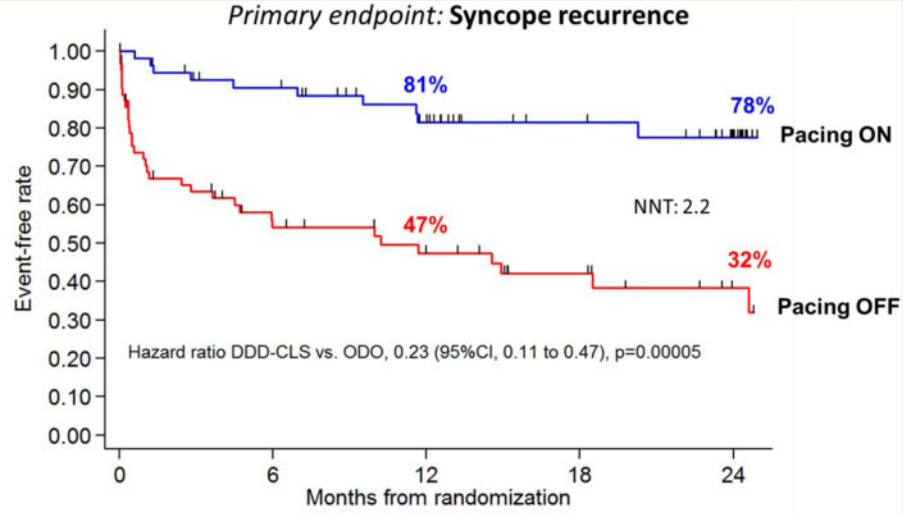
Graphical Abstract



Keywords Syncope • Reflex syncope • Tilt testing • Asystolic syncope • Pacemaker • Cardiac pacing • Closed loop • stimulation

An estimated 50% of the general population will have a syncopal event at some point of life, most frequently caused by vasovagal reflex.[1] Although the clinical course is benign in most cases, especially in the younger population, severe forms of reflex syncope account for ~14% of primarily older patients. Frequent unpredictable syncopal events in these patients may be severely disabling, justifying mechanism-specific treatments.[1]

Although there is a rationale for cardiac pacing in the dominant cardioinhibitory forms of reflex syncope (in contrast to the dominant vasodepressor forms), the benefit of pacing in patients with reflex syncope and tilt-induced asystole or bradycardia has not been established.[2] The usefulness of tilt-table testing to diagnose cardioinhibitory reflex has been questioned as tilt-induced syncope mostly identifies vasodepressor susceptibility.[1,3,4] Reproducibility and specificity of tilt responses have also been disputed.[4] In patients with asystolic vasovagal syncope diagnosed by implantable loop recorder, subsequent cardiac pacing was even more effective after a negative than after a positive baseline tilt test (syncope recurrence rates 2% vs. 33% at 3 years, respectively).[2] Therefore, the 2017 American guideline for syncope did not recommend pacing when asystolic syncope is diagnosed by tilt testing.[4] In contrast, the 2018 European guideline[1] recommended pacing as Class IIb indication based on the additional evidence from an observational study[5] and a small randomized crossover trial.[6] Further research is needed to improve current guidelines.[1,4]

Pacemakers with rate-responsive closed loop stimulation (CLS) system continuously analyse trends of right ventricular intracardiac impedance during systolic phases to gather information about speed of myocardial contraction and adjust pacing rate accordingly.[7] Recently, in acute tilt testing studies, pacemakers with CLS have shown the ability to institute a rapid pacing rate at the time of impending tilt-induced syncope.[8,9] This early pacemaker response partly sustained cardiac output and blood pressure, preventing or delaying cardioinhibitory vasovagal syncope despite a concomitant vasodepressor component.[9]

We therefore initiated a formal randomized controlled trial to assess the efficacy of dual-chamber pacing with CLS in preventing syncopal recurrences as compared with inactive pacemaker implantation in tilt-induced cardioinhibitory reflex syncope.

Methods

The Benefit of Dual-Chamber Pacing with Closed Loop Stimulation in Tilt-Induced Cardioinhibitory Reflex Syncope (BIOSync CLS) study was a multicenter, randomized, placebo-controlled, patient- and outcome-assessor-blind trial conducted at 24 sites in Italy, France, Spain, Portugal, Netherlands, and Canada. Recruitment started in October 2015 and ended in March 2020. The trial was approved by the ethics committee at each participating site. All patients provided written informed consent. The trial rationale, design, and protocol have been described previously.[10]

Patient selection

Patients aged 40 years or older, affected by at least two episodes of unpredictable severe reflex syncope during the last year, who had syncope with an asystolic pause of >3 s induced by tilt testing, were eligible for

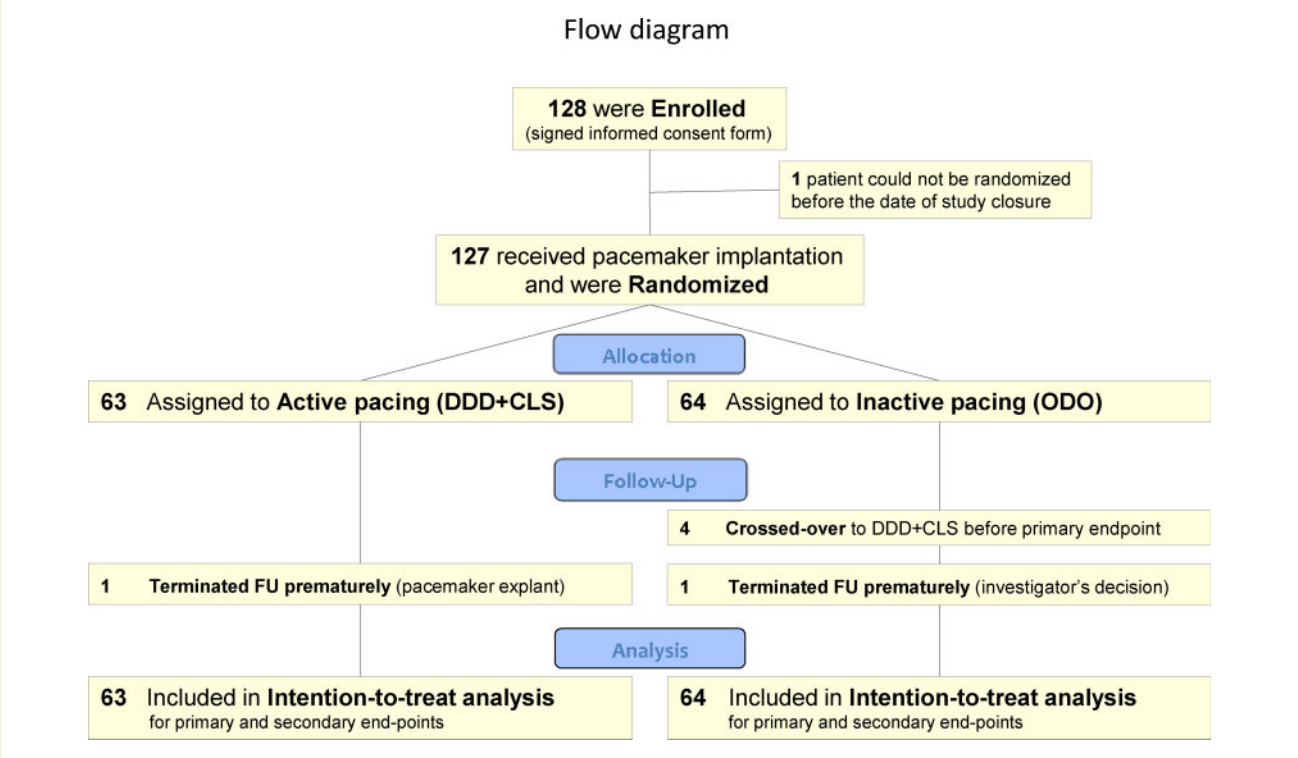


Figure 1 Study flow. FU, follow-up.

inclusion. Syncopes were defined as severe when they impaired the patient's quality of life (because of high frequency), or when they occurred unpredictably either without or with short prodromes.[1] Other competitive causes of syncope were excluded.[10]

The index tilt testing was performed according to the Italian protocol, which consists of a passive phase, followed by a sublingual nitroglycerin phase if syncope has not been induced during the passive phase.[11]

Implant, randomization, blinding, and follow-up

The enrolled patients underwent the implantation of a dual-chamber pacemaker with rate-responsive CLS feature (models Eluna 8 DR-T and Epyra 8 DR-T; Biotronik SE & Co. KG, Berlin, Germany). Prior to hospital discharge, patients were randomized 1:1 with a centralized non-stratified block procedure to the active group (pacing ON) or to the placebo (pacing OFF). In the active group, the pacemaker was programmed to the DDD-CLS mode with a basic rate of 50 bpm, a maximum CLS rate of 120 bpm, medium CLS rate-adaptive response, and resting rate control OFF. In the placebo group, the pacemaker was programmed to the ODO mode, allowing dual-chamber sensing without pacing. Full-device programming recommendations are reported in Supplementary material online, *Table S1*. After implantation, the patients were followed up quarterly for 24 months or until the occurrence of the first syncopal relapse.

Patients and outcome assessors were blinded to random assignments. Investigators could not be blinded and were therefore not allowed to communicate the pacing mode to the patient. The study endpoints were collected through a quarterly self-administered patient questionnaire and adjudicated by an independent, blinded clinical event committee. Investigators followed their patients in the pacemaker clinic, as usual, but were not involved in the collection and assessment of the study endpoints.

The 12-item self-administered patient questionnaire (Supplementary material online) was developed and validated for this trial to distinguish between syncope and presyncope or other symptoms and, in addition, to provide a standardized categorical description of the clinical presentation of syncope including duration, reproducibility with previous episodes, presence of prodromes, presence of witnesses, context, and consequences of the episode. A preliminary validation of the questionnaire[10] showed a patient-physician concordance in the diagnosis of syncope and presyncope of 96.1% [95% confidence interval (CI), 0.86–0.99]. The questionnaire is displayed in Supplementary material online, *Table S2*.

Endpoints

The primary endpoint was the time to the first post-randomization recurrence of a syncopal episode, defined as a transient complete loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery.[1] The secondary endpoint was the first recurrence of syncope or presyncope whichever came first. Presyncope was defined as signs and symptoms recognized by the patients as premonitory of imminent syncope but not followed by syncope.[1]

Statistical analysis

Based on the observed syncopal recurrence rate in the control arm of the ISSUE 3 trial,[12] the sequentially designed BIOSync CLS study was powered to detect a 40% relative reduction in the 2-year incidence of syncopal recurrences (from 57% to 34%) by a log-rank test, with statistical Type I and Type II errors of 0.05 (bilateral) and 0.20 (80% power), respectively.[10] With these assumptions, a sample size of 62 patients per

Table 1 Characteristics of the patients at baseline

	All (n = 127)	Active group DDD-CLS (n = 63)	Control group ODO mode (n = 64)
Age (years)	62 ± 12	62 ± 11	63 ± 12
Male sex, *n* (%)	82 (65)	45 (71)	37 (58)
History of syncope			
Number of syncopes during lifetime	5 (3–10)	5 (3–10)	5 (3–11)
Number of syncopes during last year	3 (2–4)	3 (2–4)	2 (2–4)
Age at the time of first syncope (years)	53 (28–65)	53 (30–65)	54 (25–68)
History of presyncope, *n* (%)	66 (59)	32 (58)	34 (60)
Previous ineffective alternative therapies, *n* (%)			
Physical counterpressure manoeuvers	59 (46)	34 (54)	25 (39)
Vasoactive drugs	9 (7)	5 (8)	4 (6)
Heart rate (beats per minute)	68 ± 10	68 ± 8	68 ± 11
Resting systolic blood pressure (mmHg)	128 ± 13	128 ± 12	127 ± 14
Arrhythmias, *n* (%)			
First degree atrioventricular block	5 (4)	4 (6)	1 (2)
History of atrial fibrillation	15 (12)	7 (11)	8 (12)
Atrial fibrillation at enrolment	1 (1)	1 (2)	0 (0)
Medical history, *n* (%)			
Hypertension	57 (45)	23 (36)	34 (53)
Diabetes	12 (9)	6 (9)	6 (9)
Hypertensive cardiopathy	32 (25)	13 (21)	19 (30)
Coronary artery disease	8 (6)	3 (5)	5 (8)
Valvular disease	4 (3)	3 (5)	1 (2)
Neurological diseases	4 (3)	2 (5)	2 (5)
Ejection fraction (echo) (%)	60 (55–62)	60 (55–60)	60 (55–63)
Concomitant medications, *n* (%)			
Any hypotensive medication	60 (47)	27 (43)	33 (52)
ACE inhibitors	32 (25)	15 (24)	17 (27)
Angiotensin II receptor blockers	13 (10)	4 (6)	9 (14)
Alpha antagonists	11 (9)	5 (8)	6 (9)
Diuretics	10 (12)	6 (15)	4 (10)
Calcium antagonists	15 (12)	5 (8)	10 (16)
Beta-blockers	15 (12)	7 (11)	8 (12)
Psychiatric drugs	6 (5)	3 (5)	3 (5)
Antiplatelets	24 (19)	8 (13)	16 (25)
Anticoagulant	4 (3)	2 (3)	3 (3)
Tilt testing			
Syncope during passive phase, *n* (%)	25 (20)	16 (25)	9 (19)
Syncope during nitroglycerin phase, *n* (%)	102 (80)	47 (75)	55 (81)
Maximum asystolic pause (s)	8.6 (5–18)	7 (5–20)	10 (6–18)
Sinus arrest, *n* (%)	113 (89)	56 (89)	57 (89)
Atrioventricular block	14 (11)	7 (11)	7 (11)

Values are given as *n* (%) and continuous variables are given as mean ± SD or median (interquartile range), as appropriate.
ACE, angiotensin-converting enzyme.

study arm was needed, to be further increased by 2% due to a slight power loss caused by planned interim analyses. Overall, 128 subjects (64 per study arm) were deemed necessary to reach the study objective of 62 primary endpoint events with the required power.

The primary and secondary endpoints were analysed according to the intention-to-treat principle. Kaplan–Meier plots were generated, and the estimated survival functions of the study groups were tested with the two-sided log-rank test. Dependence of survival on major baseline predictors was studied with proportional hazard Cox models. Hazard ratio and relative 95% CI were calculated for each predictor. Proportional hazard assumption was tested with Schoenfeld's residual test. Distributions of continuous data are described as means (± standard deviation [SD]) or by median and interquartile range. Absolute and relative frequencies were used to compare categorical data.

Table 2 Primary and secondary clinical endpoints[a]

	Active group DDD-CLS ($n = 63$)	Control group ODO mode ($n = 64$)	Hazard ratio (95% CI)	*P*-value
Primary endpoint: syncope recurrence, *n* (%)	10 (16)	34 (53)	0.23 (0.11–0.47)	0.00005
Secondary endpoint: syncope or presyncope recurrence, *n* (%)	23 (37)	40 (63)	0.44 (0.26–0.73)	0.002

[a]Observed and estimated syncope and presyncope recurrences calculated with the product-limit method, according to the intention-to-treat analysis. The median follow-up was 11.2 months.

Two interim analyses at 40% and 70% of the required primary endpoint events and a final analysis were planned. Significance levels for testing the primary study hypothesis were based on the Lan-DeMets alpha spending function approach to group-sequential design with symmetric O'Brien-Fleming boundaries to control the overall probability of Type I error <0.05: $P < 0.0008$ for the first interim analysis and $P < 0.015$ for the second interim analysis were assumed as predefined early stopping rules and otherwise $P < 0.045$ for the final analysis for efficacy or harm. All other tests were considered significant with $P < 0.05$. Data were managed with the Stata/SE 11.1 (StataCorp LP, Texas, USA) and SAS 9.4 (SAS Institute, North Carolina, USA) statistical packages.

Interim analyses

On 16 April 2020, following the second interim analysis, the Data Safety Monitoring Board (Supplementary material online) informed the sponsor that the difference observed between the two arms fulfilled the stopping rule criterion. In agreement with the Coordinating Clinical Investigator, the sponsor accepted the Board's recommendation to terminate the trial prematurely on account of the evident superiority of the results in one study arm, to minimize risks in the subjects randomized to the control group. Investigators were asked to terminate study procedures with the recommendation to activate pacing functions (DDD-CLS preferably) in all inactive devices.

Results

Patients

A total of 128 patients were enrolled at 24 sites (listed in the Supplementary material online). The last enrolled patient was not randomized because of premature study closure. The remaining 127 patients were randomly assigned to the active pacing arm ($n = 63$) or to the control arm ($n = 64$) and were included in the final analysis (*Figure 1*). The mean age was 63 ± 12 years and 65% were male. Patients' characteristics at baseline were similar in the two groups, with a median of five syncopal events during the lifetime and three during the last year (*Table 1*). At the tilt testing at enrolment, the median duration of the asystolic pause was 8.6 s (interquartile range, 5–18), caused by sinus arrest in 89% of cases. Additional details on the history of syncopal episodes are provided in Supplementary material online, *Tables S3* and *S4*.

Four patients initially assigned to the control arm had presyncope and had their pacemakers activated before the primary endpoint. These patients were analysed in the original arm, according to the intention-to-treat principle. No study patient had a syncope or presyncope in the period between pacemaker implantation and randomization [median 0 days (interquartile range, 0–2)]. After enrolment, patients continued ongoing therapies, except for 17 patients (4 in the active group and 13 in the control group) who withdrew antihypertensive drug therapy.

Outcome

The median follow-up duration after randomization was 11.2 months (interquartile range, 2.5–22.1), with no significant difference between groups. At the time of study closure, syncope had occurred in 10 of 63 patients (16%) in the active pacing group and in 34 of 64 patients (53%) in the control group [hazard ratio, 0.23 (95% CI: 0.11–0.47), $P = 0.00005$] (*Table 2* and *Figure 2*). The product-limit estimate of syncope recurrence rate was 19% (95% CI: 10–33) vs. 53% (40–56) at 1 year and 22% (12-39) vs. 68% (52-84) at 2 years, for pacing vs. control group, respectively. The number needed to treat was 2.2. The clinical features of the 44 syncopal episodes are shown in Supplementary material online, *Table S5*. Potential effects of imbalances in gender, by-country, and by-site recruiting rates were explored in the sensitivity analyses of the primary endpoint and in on-treatment and per-protocol analyses. All analyses were consistent with the results of the primary analysis (Supplementary material online, *Table S6* and Supplementary material online, *Figures S1* and *S2*).

The combined endpoint of syncope or presyncope recurred in 23 patients (37%) in the active group and in 40 patients (63%) in the control group [hazard ratio, 0.44 (95% CI: 0.26–0.73)] (*Table 2* and *Figure 2*). A subgroup analysis of the primary outcome, as shown in *Figure 3*, indicates a consistency of a treatment effect across subgroups of factors of interest. The length of asystolic pause at the index tilt testing was not predictive of the primary endpoint [hazard ratio, 0.99 (95% CI: 0.96–1.01), $P = 0.37$].

Adverse events

No patient died during the study or had a severe adverse event because of syncope recurrence. Five (4%) patients had device-related complications: self-resolved pericarditis due to pacemaker lead perforation, atrial lead pin insertion problem requiring implant revision, inappropriate detection of atrial arrhythmic episodes caused by oversensing, palpitations due to frequent CLS activations resolved by pacemaker reprogramming, and device explantation as a consequence of lead dislodgment.

Discussion

In patients aged 40 years or older, affected by severe recurrent reflex syncope and tilt-induced asystole, dual-chamber pacemaker with CLS reduced syncope recurrences highly significantly compared to

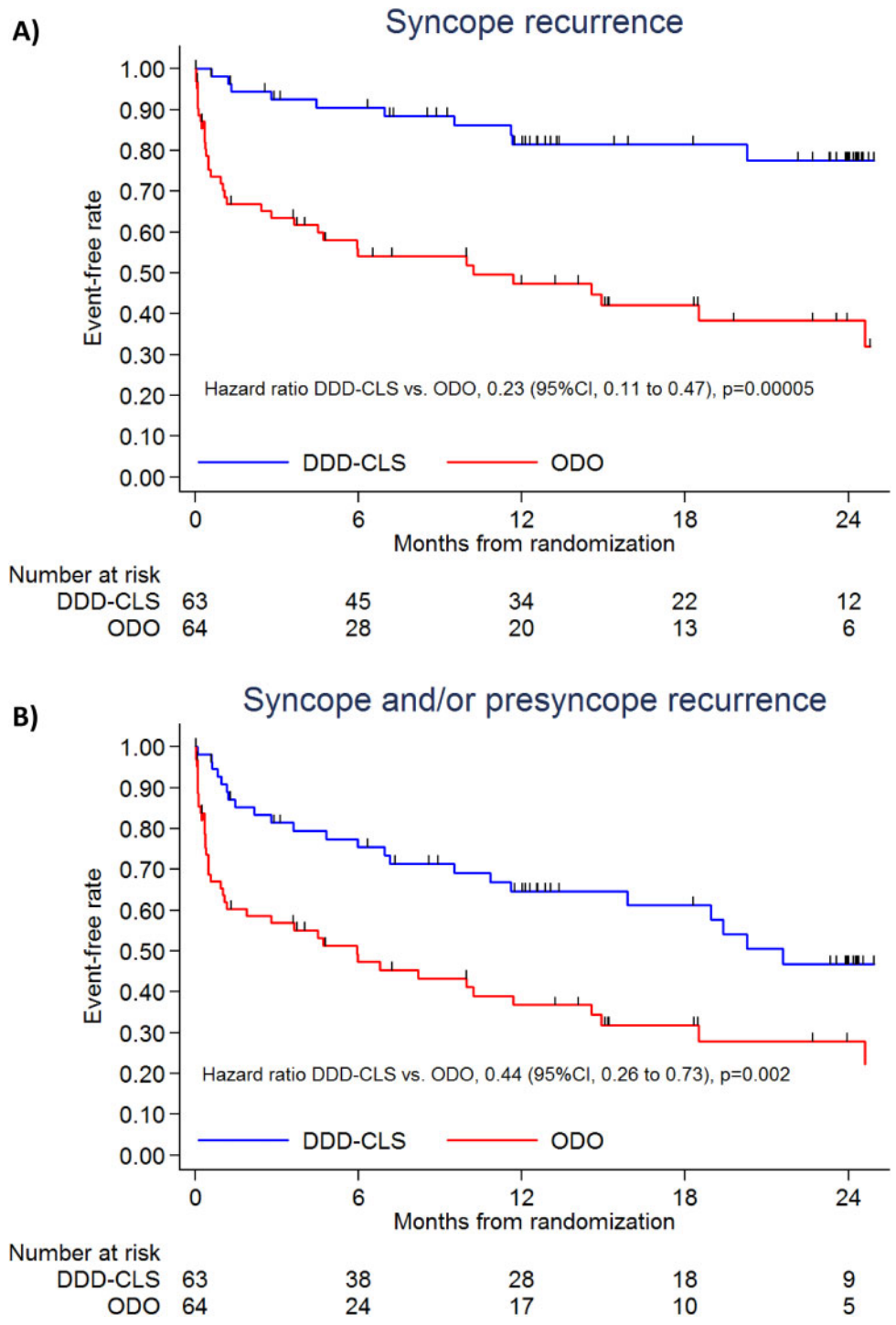


Figure 2 Kaplan–Meier curves comparing survival free of symptoms. (*A*) Primary endpoint and (*B*) combined endpoint of syncope or presyncope.

no active pacing treatment. The relative and absolute risk reduction at 2 years was 77% and 46%, respectively. The number needed to treat was 2.2, about half of the maximum 4.3 assumed during study design. Although a screening log was not generated within the present study, available data from a large cohort[13] allow estimation that eight out of every 100 patients (aged >40 years) affected by reflex syncope will have an asystolic pause longer than 3 s (average duration, 8 s) during tilt testing performed according to the Italian protocol.[11] This number will increase up to 18 in selected patients with clinical characteristics meeting the inclusion criteria for the BIOSync

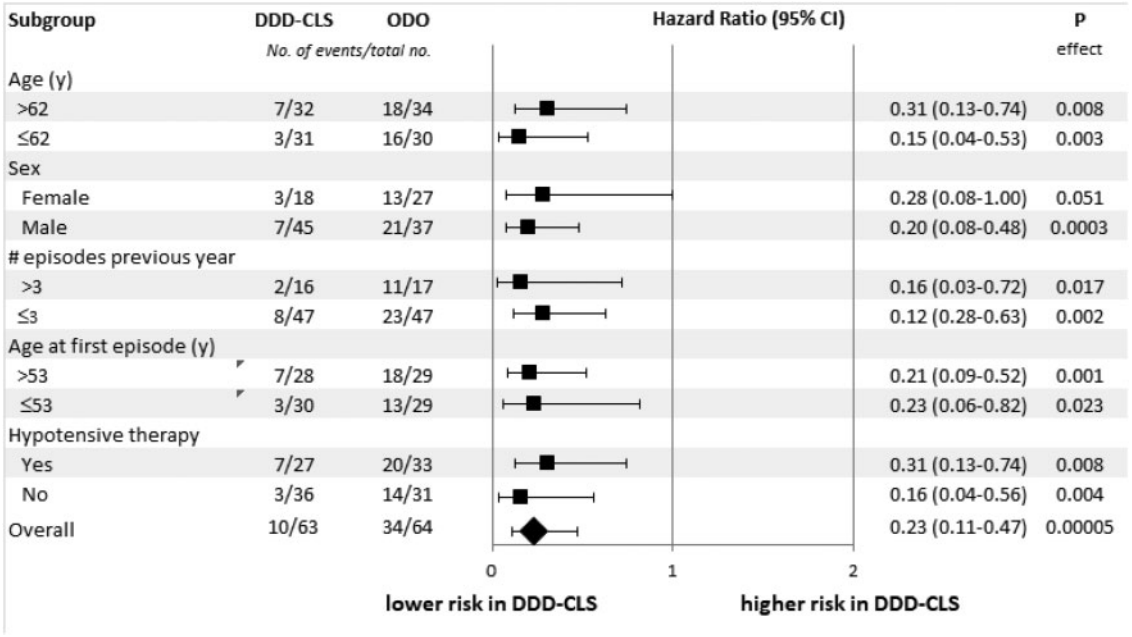
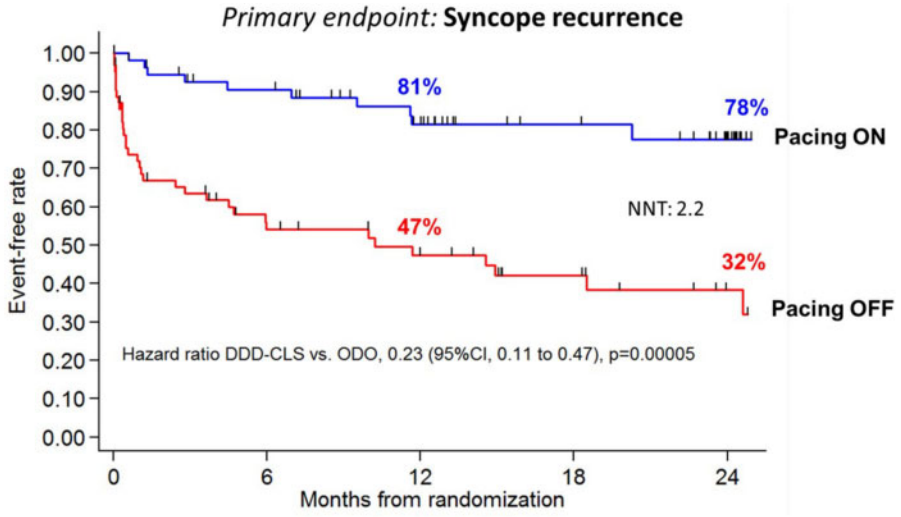


Figure 3 Subgroup analyses of the primary endpoint (forest plot). Hazard ratios are based on Cox proportional hazard model analyses.



Take home figure Kaplan–Meier curves comparing survival free of syncope.

CLS study[5] (Supplementary material online: Perspective: How Many Patients Are Potentially Eligible for Cardiac Pacing?) Overall, these findings support the inclusion of tilt testing as a useful method for the selection of candidates for cardiac pacing.

Because of the study design, we were unable to determine the incremental benefit of CLS over standard dual-chamber pacing. The CLS system measures intracardiac impedance curves of the right ventricle during systolic phases by injecting high-frequency subthreshold current pulses.[7] In an acute crossover tilt study comparing DDD-CLS and DDD modes,[9] DDD-CLS increased the pacing rate, starting from 8 min before syncope, to around 90 bpm and maintained the rate constant, precluding the subsequent vagally induced heart rate drop. Consequently, the onset of syncope was delayed by 4 min and the fall in blood pressure was reduced by 22 mmHg, on average. Overall, syncope was induced in 30% (DDD-CLS) vs. 77% of patients (DDD). It is not clear why CLS is activated in impending vasovagal

syncope. CLS has been shown to react to elevated intrinsic heart rate[14] and to other conditions that increase the velocity of myocardial contraction (active standing, handgrip, cold pressor test, mental stress, dobutamine infusion).[15–18] In brief, since at the time of impending syncope stroke volume and heart rate contribute similarly to blood pressure, an early heart rate increase driven by CLS may partly prevent blood pressure fall due to the vasodepressor reflex.[19]

Almost all studies in published literature, including patients with asystolic tilt response and applying some form of untreated control group, utilized an algorithm for rapid dual-chamber pacing, such as CLS or 'rate-drop response' in which an intrinsic heart rate drop of below ≈40 bpm triggers pacing at ≈80 bpm.[20,21] The recurrence of syncope during follow-up in these previous studies was lower in the active arm, for CLS: 9% vs. 46% at 1 year[6] and 19% vs. 47% at 5 years,[22] and for rate-drop response: 6% vs. 50%[20] and 23% vs. 43%[21] at 3 years, in subsets of patients with asystolic tilt response. Although all these studies showed a superiority of cardiac pacing over no pacing, they included a small number of randomized patients (<50)[6,20] or were not randomized.[21,22]

The positive results of the present study suggest the utility of tilt testing as a method for selecting pacemaker candidates. The efficacy of cardiac pacing in our study is similar to that for patients with spontaneous asystolic vasovagal syncope documented by implantable loop recorder in the ISSUE 3 trial (25% recurrence rate at 2 years).[12] There are two reasons in support of a good predictive value of an asystolic tilt response. First, asystolic response seems to be specific of vasovagal syncope and is unlikely to be induced in subjects without syncope or with other types of syncope.[23] Second, in the ISSUE 3 trial,[24] asystolic tilt response predicted asystolic events during prolonged ECG monitoring with a positive predictive value of 86% (95% CI, 70–95%). This point has important implications because, based on BIOSync CLS results, patients could undergo pacemaker implantation after a positive tilt test that induced asystolic response, without a need to wait on the confirmation of the diagnosis by an implantable loop recorder. Whether dual-chamber CLS pacing could be expanded to other patients with reflex syncope irrespective of asystolic tilt response may be the objective of future investigations.

Similar to most studies in the literature, a considerable number of patients in our study had syncope in the active pacing group, likely due to the vasodepressor component of the vasovagal reflex. Adding video recording to tilt testing, Saal *et al.*[25] recently showed that one-third of patients with asystolic tilt response lost consciousness before or within 3 s from the onset of asystole. With such a late cardioinhibitory manifestation before syncope, cardiac pacing possibly has no time to react effectively. Conversely, in the other two-thirds of patients, asystole preceded syncope by >3 s, a time probably sufficient for pacing to prevent the loss of consciousness. These different temporal patterns might be responsible for some recurrences in the present study. A new method for a more accurate selection of candidates for cardiac pacing by tilt testing could include the examination of these temporal patterns.

The pacemakers used in this study did not provide intracardiac electrogram recordings at the time of syncope in the control group nor of CLS mode activations in the active group. It was therefore not possible to establish a temporal relationship between symptoms and the onset of pacing. To overcome this limitation, implementation of CLS diagnostic functions, including a simultaneous recording of intracardiac electrogram and CLS impedance signals during symptoms, is desirable in the future generation of pacemakers.

The study was terminated early during the follow-up phase, which might have induced biases in effect estimations. However, early stopping rules were among the set of protective measures included in the risk analysis document provided to Competent Authorities to mitigate risks related to the special off-label ODO mode used in the control group.

In conclusion, in patients aged 40 years or older affected by severe recurrent vasovagal syncope and tilt-induced asystole, dual-chamber pacemaker with CLS is highly effective in reducing the recurrences of syncope.

Data availability

Data are available upon reasonable request to Alessio Gargaro, BIOTRONIK Italy S.p.a., Via delle Industrie 11, 20090, Vimodrone (MI).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The trial was funded by Biotronik SE & Co. KG, Berlin, Germany. The funder was assisted in study design, data analysis, and preparing this report. They had no role in data collection and interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest: A.G. and D.G. are employees of BIOTRONIK Italia, an affiliate of Biotronik SE & Co. KG, sponsor of the study. The other authors have no conflict of interest to declare.

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