Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole : Third International Study on Syncope of Uncertain Etiology (ISSUE-3): A Randomized Trial

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Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole

Third International Study on Syncope of Uncertain Etiology (ISSUE-3) A Randomized Trial

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Background—The efficacy of cardiac pacing for prevention of syncopal recurrences in patients with neurally mediated syncope is controversial. We wanted to determine whether pacing therapy reduces syncopal recurrences in patients with severe asystolic neurally mediated syncope.

Methods and Results—Double-blind, randomized placebo-controlled study conducted in 29 centers in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial. Patients were ≥40 years, had experienced ≥3 syncopal episodes in the previous 2 years. Initially, 511 patients, received an implantable loop recorder; 89 of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope within 12±10 months and met criteria for pacemaker implantation; 77 of 89 patients were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. The data were analyzed on intention-to-treat principle. There was syncope recurrence during follow-up in 27 patients, 19 of whom had been assigned to pacemaker OFF and 8 to pacemaker ON. The 2-year estimated syncope recurrence rate was 57% (95% CI, 40–74) with pacemaker OFF and 25% (95% CI, 13–45) with pacemaker ON (log rank: $P=0.039$ at the threshold of statistical significance of 0.04). The risk of recurrence was reduced by 57% (95% CI, 4–81). Five patients had procedural complications: lead dislodgment in 4 requiring correction and subclavian vein thrombosis in 1 patient.

Conclusions—Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope. The observed 32% absolute and 57% relative reduction in syncope recurrence support this invasive treatment for the relatively benign neurally mediated syncope.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359203.

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Key Words: pacemakers ■ syncope ■ implantable loop recorder

The efficacy of pacemaker therapy for prevention of syncopal recurrences in patients affected by neurally mediated syncope (NMS) was questioned after 2 randomized, double-blind, controlled trials failed to prove superiority of cardiac pacing over placebo of unselected patients with positive tilt testing.[1,2] The prospective, observational Second International Study on Syncope of Uncertain Etiology (ISSUE-2)[3] showed that the mechanism of spontaneous NMS syncope, documented by implantable loop recorder (ILR), was heterogeneous with asystolic syncope accounting for

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The investigators in the ISSUE-3 study are listed in the online-only Data Supplement Appendix.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.082313/-/DC1.

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approximately one-half of the syncope events. Although pacing may be potentially effective when asystole is documented at the time of syncope, there is no rationale for the use of pacing in patients without asystole in whom the likely mechanism is a dominant hypotensive reflex. The mechanism of spontaneous NMS documented by ILR is reproducible within patients.[4] In ISSUE-2,[3] the patients with asystolic NMS treated with pacemaker showed a >80% relative risk reduction of syncopal recurrence in comparison with untreated groups. However, ISSUE-2 was not a formal controlled double-blind trial. Consequently, ISSUE-3 was designed to assess the apparent pacing benefit observed in ISSUE-2, but in a randomized controlled trial.

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Methods

The International Study on Syncope of Uncertain Etiology (ISSUE-3) was a multicenter, prospective, randomized, double-blind study evaluating the effectiveness of pacing therapy for preventing syncope recurrence in patients with documented spontaneous asystolic NMS.

Patients Selection

Patients included in this study were ≥40 years and had experienced, in the previous 2 years, ≥3 syncopal episodes of likely NMS etiology. In this study, NMS was defined as any form of reflex syncope, with the exception of carotid sinus syndrome, and a sufficiently severe enough clinical presentation to warrant specific treatment. These individuals received an ILR and were followed up (prestudy screening phase).

In accordance with the guidelines of the European Society of Cardiology,[5,6] NMS was considered likely when the clinical history was consistent with NMS and competing diagnoses were excluded. Patients with positive and negative tilt table testing were included. Patients were excluded if they had one or more of the following features[1]: cardiac abnormalities that suggested cardiac syncope (overt heart failure; ejection fraction ≤40%; old or recent myocardial infarction; hypertrophic or dilated cardiomyopathy; clinically significant valvular disease; sinus bradycardia <50 bpm or sinoatrial block; Mobitz I second-degree atrioventricular (AV) block; bundle-branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; preexcited QRS complexes; prolonged QT interval; Brugada syndrome; arrhythmogenic right ventricular cardiomyopathy)[2]; symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement[3]; nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy). Patients with carotid sinus syndrome and documented symptomatic bradycardia during carotid sinus massage were also excluded because this is an accepted indication for cardiac pacing.[5,6] The assessment of the severity of the clinical presentation was based on the definitions of high frequency or high risk provided by those guidelines.[5,6] In particular, syncope was defined as very frequent when it altered the quality of life of the patient and at high risk when syncope was unpredictable (absence of premonitory symptoms), thus not being amenable to prevention by standard measures (ie, physical maneuvers, sitting, squatting, etc) and exposing patients to risk of trauma or occurring during the performance of a high-risk activity (eg, driving, machine operation, etc).

Study Design

Eligible patients for the Pacemaker (Pm) trial (study phase) were those who, during the prestudy screening phase, had syncopal recurrence with documented asystolic pause (sinus arrest or AV block) ≥3 s at the time of syncope, or asymptomatic or presyncopal episodes with documentation asystolic pause (sinus arrest or AV block) ≥6 s (type 1 of the ISSUE classification[7]). Eligible patients underwent dual-chamber pacemaker implantation.

The protocol was approved by a research ethics board at each center, and each patient provided signed informed consent. The full study protocol has been previously published.[8]

Randomization and Programming

Immediately after implantation of a dual-chamber pacemaker, patients were randomly assigned 1:1 to dual-chamber pacing (DDD) with an AV delay sufficient to minimize unnecessary ventricular pacing or sensing without pacing with default diagnostic functions. Randomization was made centrally and was assigned automatically to each patient via Internet. The randomization list was blocked per center, with randomly varying block sizes of 2 and 4. The centers were not aware of the block sizes. The pacemaker was programmed by the implanting physician or technician, who were not blinded, whereas treatment allocation was kept blind to patient and clinical follow-up physician. In addition to randomized controlled trial, eligible patients who for any reason were not randomly assigned entered into a registry and were followed-up, and patients who had been randomly assigned, as well, to have a complete picture of the outcome of eligible patients.

Patients randomly assigned to DDD were programmed in rate drop response pacing mode, a feature of the pacemaker that instituted rapid DDD pacing if the device detected a rapid decrease in heart rate. Based on a post hoc analysis of spontaneous asystolic episodes documented by ILR in the ISSUE-2 study,[9] the protocol specified that the initial rate drop response parameters should be a lower rate of 40/min (for 2 beats) or a drop size of 20 beats with a drop rate of 50/min within a detection window of 1 minute and an intervention rate of 90/min for 1 minute.

Outcomes

After pacemaker implantation, all patients were followed up quarterly for 24 months or up to the first episode of recurrence of syncope by a physician who was blind to the pacemaker mode. The primary study outcome was the comparison of the number of patients with syncopal recurrence in the 2 study arms according to the intention-to-treat principle. Patients were requested to report syncope episodes as soon as possible after the event occurred. Evidence of syncope was collected from pacemaker and ILR interrogation.

Statistical Analysis

Based on the ISSUE-2 results,[3] this study was designed to have 80% power to detect a 1-year absolute reduction of 25% in the risk of recurrence of first syncope in the treatment arm applying a log-rank test with a 2-sided significance level of 0.05 ($\alpha<0.01$ at ad interim and $\alpha<0.04$ at final analysis). At inception, the study was designed with 1-sided significance in keeping with the Second Vasovagal Pacemaker Study (VPS II) trial.[1,8] At the implementation stage, the Steering Committee decided to use 2-sided testing to increase the rigor of the study design. With a sequential design, the study was planned to be stopped when a total of 27 primary end point events, irrespective of the study arms, would be reached. An ad interim analysis was predefined at the time of 20 primary end point events (75% of the total). No center was allowed to recruit >10% of the total number of the study population.

During the follow-up, the cumulative number of patients with the primary end point, but not the relative distribution of these episodes between the 2 randomized arms, was made available to the End Point Committee. Statistical analysis was performed by an independent statistician who was not involved in the study. Neither the End Point Committee, nor the Steering Committee were informed of the results before study closure. The primary analysis of the study was planned as a comparison of the cumulative risk of syncope between the 2 treatment groups with the use of a log-rank test. The risk of syncope recurrence was based on hazard ratio obtained by means of the univarate Cox model, with the use of the Breslow method for ties. All randomly assigned patients were analyzed according to the intention-to-treat principle. Thus, all outcomes were attributed to the randomly assigned treatment groups regardless of compliance to assigned treatment.

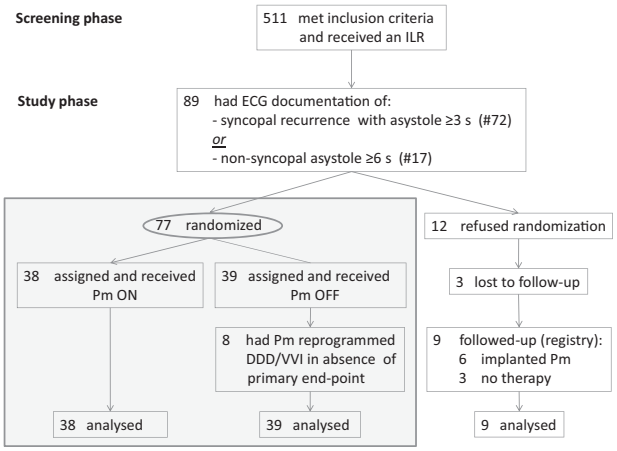

Figure 1. Patients' flow. ILR indicates implantable loop recorder; Pm, pacemaker.

Results

Screening Phase

Initially, 511 patients met the inclusion criteria for the prestudy screening phase and received an ILR implantation. During a mean observation of 12±10 months, syncope recurred in 185 (36%) patients and was documented by the ILR in 141 (28%) patients. Events were classified according to the ISSUE classification[7] as type 1 (asystole) in 72, type 2 (bradycardia) in 16, type 3 (slight or no rhythm variations) in 37, and type 4 (tachycardia) in 16. Moreover, ECG documentation of nonsyncopal (asymptomatic or presyncopal) asystolic events of ≥6 s was made in 17 patients. Thus, in total, 89 patients with asystolic events were eligible for the randomized Pm trial (Figure 1). They had a mean asystolic pause of 11±4 s (range, 3–44 s). The patients with syncope had an asystolic pause of 12±10 s and those without syncope had an asystolic pause of 10±6 s.

Patients

Study participants were enrolled from April 2007 to April 2011 and follow-up concluded in August 2011. A total of 77 patients of the 89 eligible patients were randomly assigned from 29 hospitals in Italy (12 hospitals), Spain (6 hospitals), Germany (3 hospitals), Canada (2 hospitals), United Kingdom (2 hospitals), Austria (1 hospital), France (1 hospital), The Netherland (1 hospital), and Switzerland (1 hospital). Of these patients, 38 were assigned to the Pm ON arm, and 39 were assigned to the Pm OFF arm. Reasons for nonrandomization in the remaining 12 patients were as follows: investigator's decision to implant a pacemaker because of severity of syncope in 6 cases, and patient's refusal to be randomly assigned in 6 cases. These patients were followed up in the ISSUE registry (Figure 1). The patients' characteristics were well matched in the randomized arms and in the registry group (Table). During follow-up, in the absence of occurrence of the primary end point, 8 patients assigned to the Pm OFF arm had their Pm reprogrammed to DDD (6 cases) or to VVI 40 bpm (2 cases) because of ILR documentation of prolonged nonsyncopal asystole in 2 patients and investigator/patient's decision (because of patient's high-risk activity) in the other cases. According to the intention-to-treat principle, these patients were analyzed in the Pm OFF arm.

Table. Patients' Characteristics

Characteristics	Pm ON n=38	Pm OFF n=39	Registry n=12
Age, mean (SD), y	63 (14)	63 (12)	63 (12)
Men, n (%)	20 (53)	16 (41)	7 (58)
Syncope events			
Total events, median (IQR)	7 (4–12)	8 (5–10)	7 (5–13)
Events in the last 2 y, median (IQR)	4 (3–5)	5 (3–6)	4 (3–5)
Events in the last 2 y without prodrome, median (IQR)	3 (1–4)	3 (0–5)	1 (0–2)
Age at first syncope, mean (SD), y	48 (25)	45 (23)	41 (23)
Interval between first and last episode, median (IQR), y	8 (3–29)	8 (3–24)	17 (7–43)
History of presyncope, n (%)	19 (50)	22 (56)	9 (75)
Hospitalization for syncope, n (%)	24 (63)	25 (64)	7 (58)
Injuries related to fainting, n (%)			
Major injuries (fractures, brain concussion)	2 (5)	4 (10)	2 (17)
Minor injuries (bruises, contusion, hematoma)	15 (39)	18 (46)	6 (50)
Typical vasovagal/situational presentation, n (%)	18 (47)	16 (41)	7 (58)
Atypical presentation (uncertain), n (%)	20 (53)	23 (59)	5 (42)
ILR documentation (eligibility criteria)			
Syncope and asystole ≥3 s, n (%)	30 (79)	32 (82)	10 (77)
Nonsyncopal pause ≥6 s, n (%)	8 (21)	7 (18)	2 (17)
Length of asystole, mean (SD)	10 (9)	12 (9)	12 (12)
Tilt testing: performed, n (%)	33 (87)	32 (82)	10 (83)
Positive of those performed, n (%)	14 (42)	23 (72)	6 (50)
Medical history, n (%)			
Structural heart disease	5 (13)	4 (10)	0 (0)
Hypertension	19 (50)	19 (49)	4 (33)
Diabetes	4 (11)	4 (10)	1 (8)
Concomitant medications, n (%)			
Antihypertensive	18 (47)	12 (31)	3 (25)
Psychiatric	4 (11)	2 (5)	0 (0)
Any other drugs	10 (26)	10 (25)	3 (25)

Pm indicates pacemaker; IQR, interquartile range; and ILR, implantable loop recorder.

Outcome

A total of 27 of 77 patients had syncope recurrence during follow-up: of these, 19 patients had been assigned to Pm OFF and 8 to Pm ON. The estimated product-limit syncope recurrence rate based on the intention-to-treat analysis was

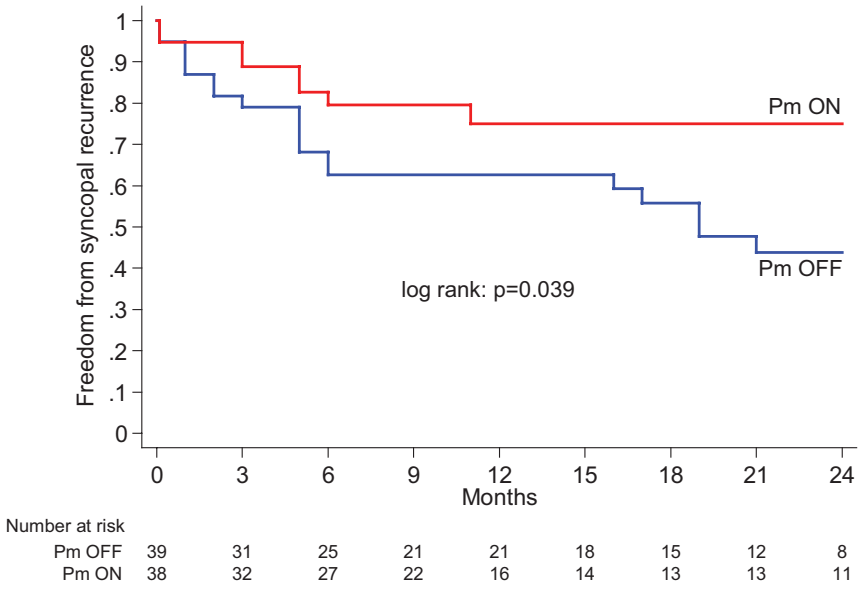

Figure 2. Time to first recurrence of syncope according to the intention-to-treat analysis. The probability value was calculated at the threshold of statistical significance of 0.04. Pm indicates pacemaker.

37% (95% CI, 24–55) at 1 year and 57% (95% CI, 40–74) at 2 years in the Pm OFF arm and 25% (95% CI, 13–45) at 1 year and 25% (95% CI, 13–45) at 2 years in the Pm ON arm (log rank; $P=0.039$ at the threshold of statistical significance of 0.04) (Figure 2). Based on this hazard ratio, the risk of syncope recurrence at 2 years was reduced by 57% (95% CI, 4–81). Asystolic pauses were documented during the study period in 8 patients assigned to the Pm OFF arm, and, in 2 of these patients, the documented pauses were responsible for syncope.

None of the 9 patients who refused randomization whose follow-up was available had syncope during 14±8 months of observation.

Adverse Events

One patient died of cancer. Five patients had procedure-related complications: right ventricle lead dislodgment in 2 patients, right atrial lead dislodgment in 2 patients, and subclavian vein thrombosis in 1 patient. No patient had severe adverse events as a consequence of recurrence of syncope.

Discussion

The main finding of this study is that dual-chamber permanent pacing is effective in reducing the recurrence of syncope in severe NMS patients ≥40 years in whom a long asystolic pause (mean, 11 s) has previously been documented by use of ILR. The observed 32% absolute and 57% relative reduction in syncope recurrence support the use of this invasive treatment for the relatively benign NMS in this circumstance. The overall strategy of using an ILR, with the consequent relatively certainty regarding mechanism, likely contributed to the positive findings.

In the ISSUE-2 study,[3] the estimated 2-year syncope recurrence rate was 12% in pacemaker patients and 41% in untreated patients with an absolute risk reduction of 29% and a relative risk reduction of 80% (95% CI, 45–93). The results of the present study are comparable in the magnitude of pacing benefit and are more convincing given the double-blind randomized controlled nature of the current study in comparison with the observational results in ISSUE2.

A comparison of this study with previous randomized double-blind trials is somewhat difficult because of important differences in study design, largely focused on patient selection. The Second Vasovagal Pacemaker Study (VPS II) trial[1] included 100 unselected patients with a typical history of vasovagal syncope and a positive tilt test; follow-up was shorter. The relative risk reduction in syncope recurrence with DDD pacing was 30% (95% CI, −33 to 63; $P=0.14$) in comparison with 57% in the present study. VPS II was designed and conducted at the beginning of the ILR era when the mechanism of spontaneous NMS was not completely understood. Because we know from ILR experience that about half of spontaneous neurally mediated episodes are asystolic in nature, we can expect that the relative risk reduction observed in VPS II would have been doubled up to 60% if only the patients with asystolic syncope were included, as was the case in ISSUE-3. The 60% figure is comparable to what we found in ISSUE-3. The vasovagal syncope and pacing trial (SyNPACE)[2] enrolled 29 unselected patients with positive tilt table testing. The trial was prematurely interrupted and greatly underpowered. Although SYNPACE was unable to show a benefit of pacemaker over placebo, the time to first syncope recurrence was longer with pacemaker therapy than with placebo in the 15 patients who had shown an asystolic (ventricular pause of 13±8 s) response during tilt table testing: 97 versus 11 days, $P=0.06$. No difference was found in the patients with a nonasystolic response. Therefore, in the light of the ISSUE trials results, our interpretation of the above findings is that the efficacy of pacemaker therapy has been hampered by the difficulty in identifying the relative contributions of vasodepression and bradycardia/asystole in patients with undocumented spontaneous syncope. ISSUE-2 and now ISSUE-3 demonstrate that when spontaneous syncope is documented to be associated with asystole, pacemaker therapy is beneficial. However, even in this situation, the importance of an associated hypotensive component is suspected

in those patients because 25% of Pm ON arm had syncopal recurrence despite pacemaker therapy.

In the randomized open-label Vasovagal Syncope International study (VASIS-PM)[10] and Syncope Diagnosis and Treatment Study (SYDIT)[11] trials, NMS patients were selected on the basis of a positive cardioinhibitory (mostly asystolic) response during tilt table testing. Apart from the use of tilt table–induced bradycardia to select subjects, the population of these 2 open trials had characteristics that were similar to those of the present study. In the VASIS-PM study, syncopal recurrence rate in the no treatment arm was 50% at 2 years, which is similar to the 57% observed in the present study. The control patients in the SYDIT trial were treated with β-blockers. Syncopal recurrence at 2 years in pacemaker arm was 6% in VASIS-PM and 7% in SYDIT, much lower than that observed in the present study. Any open-label trial has the potential for bias in reporting and assessment of outcomes. However, in light of the ISSUE-3 trial results, it seems that the induction of an asystolic NMS during tilt table testing can predict the efficacy of pacemaker therapy albeit to a lesser extent than that expected from VASIS-PM results. Overall, the value of bradycardia induced during tilt table testing in predicting pacing benefit must remain uncertain pending future studies.

Finally, in the randomized open-label pilot VPS I,[12] which included unselected patients with a typical history of vasovagal syncope and a positive tilt table test, syncope recurred in 22% of paced and 70% of nonpaced patients with most episodes occurring within the first 6 months. This speaks to a combination of physiological effects, as demonstrated in the blinded portion of the study, and the expectation effect that may be an aspect of open-label studies.[13]

The fact that pacing is effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be undertaken in the clinical context of a benign condition (in terms of mortality), which frequently affects young patients. Thus, cardiac pacing should be a last choice in highly selected patients affected by severe NMS. In this regard, the ISSUE studies focused on NMS subjects with a relatively high mean age, a history of recurrent syncope beginning in middle or older age, and frequent injuries probably due to lack of prodrome. The ISSUE-like patients match those defined by European Society of Cardiology guidelines as high risk or high frequency. Young patients, who usually have a more prolonged prodrome before loss of consciousness, were not included in the ISSUE population. Other therapies, eg, physical counterpressure maneuvers,[14] are more desirable in young patients. ISSUE patients were also quite different from the populations in VPS I and II.[1,12] For example, in these trials, the patients were younger (40–46 years in VPS I and 48–51 years in VPS II) and had a higher lifetime burden of syncope (a median of 14–35 in VPS I and a median of 15–20 in VPS II).

How many NMS patients will be candidates for pacemaker therapy based on findings in ISSUE-3? Although a screening log was not kept for the ISSUE 3 trial, we estimated that the patients who met the ISSUE 3 inclusion criteria were 9% of all patients affected by NMS referred for evaluation.[8] In the present study, 18% of these had an asystolic pause ≥3 s with syncope or ≥6 s without syncope after a mean observation of 12 months and therefore were eligible for pacing therapy. Based on the patient flow shown in Figure 1, 255 patients needed to have an ILR implanted, and 38 of them needed to have a pacemaker to prevent syncope recurrence in 11 patients. The critical role played by the ILR in screening, albeit in a large number of patients, was the ability to document the cardiac rhythm during spontaneous syncope, which would otherwise have been unavailable. Because ILR diagnostic yield is a function of the length of observation, this rate will probably increase by prolonging the ILR follow-up. Indeed, in a recent study,[15] the diagnostic yield of asystolic events on ILR rose to 40% when the observation period was prolonged to 4 years.

Limitations

Similarly to all previous trials, we used DDD pacemakers with rate hysteresis algorithms. We are unable to evaluate whether the rate drop response algorithm used in this trial provided an additional benefit to that of a DDD pacemaker without this feature. In an ISSUE-2 substudy,[9] we estimated that the same rate drop response parameters would have been able to anticipate the onset of intervention pacing in 58% of patients by a median of 5.7 s.

Although first-event occurrence is optimal for single or rare serious outcomes, eg, death or hospitalization, it is not optimal for repetitive, relatively benign events such as NMS recurrence. Nevertheless, all randomized trials considered first syncope as the primary outcome of the study. In the case of syncope trials, syncope burden would likely give a better picture of the clinical benefit of pacemaker therapy. For example, in the ISSUE-2 trial,[3] paced patients had only 0.05±0.15 episodes of syncope per year with a relative risk reduction of 87% in comparison with pretreatment period. In the study of Sud et al,[16] syncope burden decreased from 2.17 per year to 0.45 per year in patients with likely reflex syncope and from 4.57 per year to 0 per year in the patients in whom intrinsic AV block was most likely the cause of symptoms.

Finally, owing to its sequential design, the study is underpowered to make any subgroup analysis. Future and ongoing studies will investigate whether subgroups of patients benefit more from a pacemaker.[17]

Sources of Funding

The study was funded by Medtronic Bakken Research Center. The sponsor had no access to the database until the primary analysis of the study was completed.

Disclosures

Dr Brignole reports receiving modest consultancy fee from Medtronic and being direct shareholding of F2 solutions; Dr Sutton is a Consultant to Medtronic receiving modest fees and a paid lecturer for St Jude Medical; Dr Moya reports receiving modest consultancy fee from Medtronic; Dr Blanc reports receiving limited consultant fee from Medtronic and St. Jude Medical; Dr Deharo reports receiving limited consultant fees from Medtronic; and Dr Beiras reports receiving limited consultant fee from Medtronic and St. Jude Medical.

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CLINICAL PERSPECTIVE

We evaluated a treatment strategy based on early application of the implantable loop recorder in patients ≥40 years with a certain or highly likely diagnosis of neurally mediated syncope based on clinical evaluation. In our patients, therapy was delayed until documentation of a spontaneous prolonged (mean, 11 s) asystolic event was obtained by implantable loop recorder. In this highly selected population, which we estimated to be 9% of neurally mediated syncope patients referred for evaluation, cardiac-pacing therapy is effective in reducing syncopal recurrences. We found that ≈1 of 3 pacemaker patients will benefit from pacing therapy within the subsequent 2 years.

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Supplemental Material

Appendix

The following centers and investigators participated in the ISSUE-3 trial:
Italy: Ospedale di Bolzano, Bolzano - *M. Tomaino and F. Pescoller*; Ospedali del Tigullio, Lavagna - *P. Donateo and D. Oddone*; Ospedale di Manduria, Taranto - *V. Russo, Dr. F. Pierri and M.G. Matino*; Ospedale SS. Antonio e Biagio e Cesare Arrigo, Alessandria – *E. Vitale and R. Massa*; Presidio Ospedaliero di Casarano, Lecce - *G. Piccinni and D. Melissano*; Arcispedale S.Maria Nuova, Reggio Emilia - *C. Menozzi and G. Lolli*; AO di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania - *M. Gulizia and M. Francese*; Ospedale S.Giovanni Battista Le Molinette, Torino - *M. Iorfida and P. Golzio*; Azienda Ospedaliera Villa Scassi, Genova - *G. Gaggioli and M. Laffi*; Ospedale Santa Croce, Moncalieri - *F. Rabjoli and C. Cecchinato*; Azienda Ospedaliera Universitaria Careggi, Firenze - *A. Ungar, M. Rafanelli, V. Chisciotti and A. Morrione*; Ospedale S. Pietro Igneo, Fucecchio - *A. Del Rosso and V. Guernaccia*; Ospedale di Venere, Bari - *M. Palella and C. D'Agostino*; Ospedale San Giovanni di Dio e Ruggi D'Aragona, Salerno - *A. Campana and M. Brigante*; Ospedale della Misericordia, Grosseto - *G. Miracapillo and L. Addonisio*; Ospedale S. Maria della Misericordia, Udine – *A. Proclemer and D. Facchin*; Ospedale Santa Croce e Carle, Cuneo - *A. Vado and A. Menard*i; Ospedale S. Gerardo - Monza, *A. Vincenti and S. De Ceglia*; Ospedale San Giovanni di Dio, Firenze - *A. Bartoletti and Domenico Rossi;* Ospedale Franz Tappeiner, Merano - *R. Paulmichl*; Ospedale Maria Vittoria, Torino - *M. Giammaria and F. Orlando*; Ospedale S.Anna, Como - *G. Botto and G. Russo*. **Spain**: Complejo Hospitalario Universitario de Vigo, Vigo - *X. Beiras Torrado and E.G. Campo*; Hospital Universitario Vall d'Hebron, Barcelona - *Á. Moya, I. Roca, N. Rivas, J. Perez, G. Senador and C. Alonso*; Consorcio Hospitalario Provincial de Castellón, Castellón - *L. Fácila Rubio, F. Perez Alcalá, V. Montagud Balaguer, A. Peset and T. Mut*; Hospital Universitario Puerta de Hierro, Madrid - *J.Toquero Ramos*, *I. F. Lozano and V. Castro;* Complejo Hospitalario Universitario de Albacete, Albacete - *J.F. García Sacristán, R. Ceres and J. Enero*; Hospital General Universitario Gregorio Marañón, Madrid - *F. Atienza, Á. Arenal and E. Gonzalez Torrecilla*; Hospital General de Granollers, Granollers - *E. Chueca and J. Mercader*; Hospital Clínico Universitario de Valencia, Valencia - *R. Garcia Civera, R. Ruiz Granell and S. Morell Cabedo*. **Germany:** Kardiologiske Gemeinschaftspraxis, Riesa – *H.H. Ebert and G. Stenzel*; Vivantes Klinikum Am Urban, Berlin - *D. Andresen, G. Wedegärtner and I. Atmowihardjo*; Vivantes Humboldt, Berlin – *U. Bach and J. Ohler*; Charité - Campus Benjamin Franklin, Berlin – *S. Spencker and A. Schirdewahn*; Klinikum der Universität München - Großhadern und Innenstadt, München – *S. Kääb and M.F. Sinner*; Kreiskrankenhaus Hameln, Hameln-Pyrmont – *H. Topp.* **United Kingdom**: St Mary's Hospital, London - *R. Sutton and D. Francis*; William Harvey Hospital, Kent - *K. Kamalvand and M. Asgari.* **Canada**: Hopital du Sacre-Coeur de Montreal , Montreal – *T. Kus and M. Strurmer*; University of Western Ontario, London - *A. Krahn, R. Yee and G.J. Klein*; University of Calgary, Calgary – *R. Sheldon and G. Sumner*; Vernon Jubilee Hospital, Vernon – *P. Smylie and C. Polasek*; Hamilton Health Sciences Center, Hamilton – *C. Morillo, J. Healey and S. Connolly*. **The Netherland**: Atrium Medisch Centrum, Heerlen - *A.J.J. Aerst*; Academisch Medisch Centrum, Amsterdam - *W. Wieling and R.E. Knops*; Catharina Ziekenhuis, Eindhoven - *L.R.C Dekker and P.H. van der Voort*; Medisch Centrum Alkmaar, Alkmaar - *J.H. Ruiter and J.J.C.M. Romme*. **France**: Hôpital de la Timone, Marseille - *J.C. Deharo and E. Peyrouse*; Hôpital de la Cavale Blanche, Brest - *J.J. Blanc and M. Fatemi*. **Switzerland**: Centre Hospitalier Universitarie Vaudois – Lausanne – *E. Pruvot and D. Graf.* **Austria**: A.ö. Bezirkskrankenhaus Hall, Hall in Tirol – *W. Grander and P. Eller.*

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