



# Diagnosis, management, and outcomes of patients with syncope and bundle branch block

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## Aims

Although patients with syncope and bundle branch block (BBB) are at high risk of developing atrio-ventricular block, syncope may be due to other aetiologies. We performed a prospective, observational study of the clinical outcomes of patients with syncope and BBB following a systematic diagnostic approach.

## Methods and results

Patients with  $\geq 1$  syncope in the last 6 months, with QRS duration  $\geq 120$  ms, were prospectively studied following a three-phase diagnostic strategy: Phase I, initial evaluation; Phase II, electrophysiological study (EPS); and Phase III, insertion of an implantable loop recorder (ILR). Overall, 323 patients (left ventricular ejection fraction  $56 \pm 12\%$ ) were studied. The aetiological diagnosis was established in 267 (82.7%) patients (102 at initial evaluation, 113 upon EPS, and 52 upon ILR) with the following aetiologies: bradyarrhythmia (202), carotid sinus syndrome (20), ventricular tachycardia (18), neurally mediated (9), orthostatic hypotension (4), drug-induced (3), secondary to cardiopulmonary disease (2), supraventricular tachycardia (1), bradycardia–tachycardia (1), and non-arrhythmic (7). A pacemaker was implanted in 220 (68.1%), an implantable cardioverter defibrillator in 19 (5.8%), and radiofrequency catheter ablation was performed in 3 patients. Twenty patients (6%) had died at an average follow-up of  $19.2 \pm 8.2$  months.

## Conclusion

In patients with syncope, BBB, and mean left ventricular ejection fraction of  $56 \pm 12\%$ , a systematic diagnostic approach achieves a high rate of aetiological diagnosis and allows to select specific treatment.

## Keywords

Syncope • Bundle branch block • Electrocardiography • Pacemakers

## Introduction

The most common aetiology of syncope in patients with bundle branch block (BBB) is paroxysmal atrio-ventricular (A-V) block.<sup>1,2</sup> However, other mechanisms such as ventricular tachycardia (VT), supraventricular tachycardia (SVT), carotid sinus syndrome (CSS), neurally mediated, or orthostatic hypotension can

also cause syncope in this population.<sup>2</sup> In addition, some of these patients are at high risk of sudden death, primarily related to the presence and severity of structural heart disease.<sup>3–6</sup>

The first step in the diagnostic strategy is to identify patients who are at high risk of sudden death.<sup>7</sup> In these patients, an implantable cardioverter defibrillator (ICD)<sup>6,7</sup> is indicated. The diagnostic and therapeutic strategy in the remaining patients is

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controversial. Some authors suggest that because the most common cause of syncope in these patients is paroxysmal A-V block, a pacemaker should be indicated,<sup>8,9</sup> whereas others suggest following a comprehensive diagnostic approach that aims to document the cause of syncope before indicating any treatment.<sup>2,7</sup>

The Bradyarrhythmia detection in BBB (B4) Study is a multicentre, international, prospective, observational study that aims to analyse the clinical outcomes of patients with syncope and BBB following a systematic diagnostic approach, as recommended in guidelines for the diagnosis and management of syncope of European Society of Cardiology (ESC).<sup>7</sup>

## Methods

### Patients

Patients were included if they had at least one syncope in the last 6 months and BBB on ECG with a QRS duration of  $\geq 120$  ms. Patients with an indication for prophylactic ICD implantation due to low left ventricular ejection fraction (LVEF) were excluded from the study. Other exclusion criteria were pre-excitation, long QT syndrome, Brugada's syndrome, acute myocardial infarction, pregnancy, or life expectancy  $< 1$  year due to non-cardiac cause; patients who were geographically or otherwise inaccessible for follow-up or who were unwilling or unable to give informed consent were also excluded. The study was approved by the institutional review boards and signed informed consent was obtained from each patient at the time of enrolment.

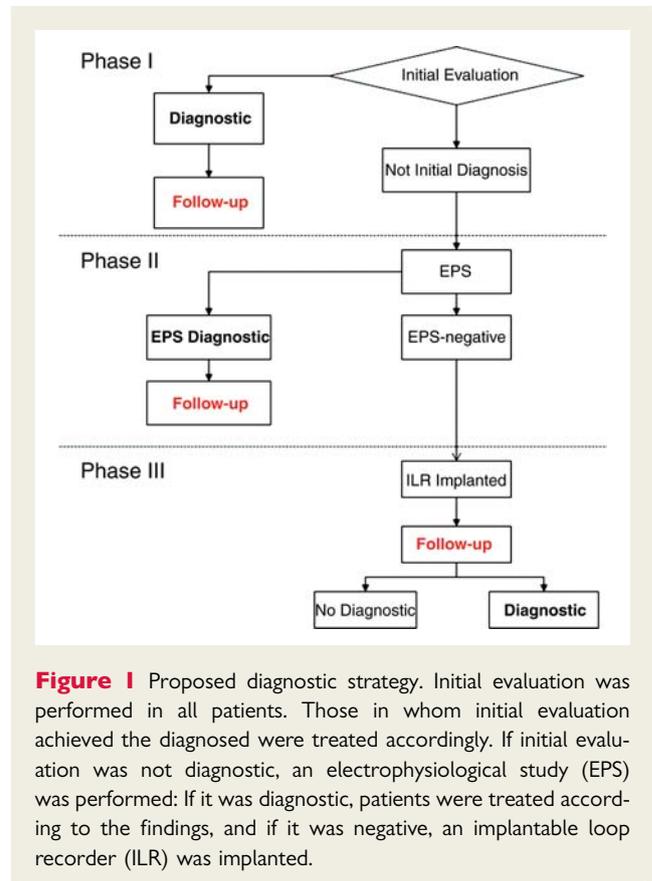
### Study protocol

A systematic diagnostic strategy was designed with three consecutive phases (Figure 1). Phase I consisted of initial evaluation including clinical history, physical examination, 12-lead electrocardiogram (ECG), measurement of blood pressure in supine and orthostatic positions, and an echocardiogram. Electrocardiographic monitoring (in hospital or Holter) was also recommended. Phase II consisted of an electrophysiological study (EPS). Carotid sinus massage was performed on all patients, but could be performed either at Phase I or at Phase II, during EPS. Phase III consisted of implantable loop recorder (ILR) implantation (Reveal Plus, Medtronic Inc.)

When the diagnosis was achieved at a given phase, specific measures or treatment were instituted and patients were followed. When the diagnosis was not achieved at a given phase, patients entered the following phase.

### Diagnostic criteria

According to the ESC guidelines,<sup>7</sup> the following aetiological diagnoses were established: neurally mediated, when syncope was precipitated by emotional triggers and was preceded by typical prodromal symptoms; orthostatic hypotension, when syncope occurred in relation to orthostatism and orthostatic hypotension was elicited<sup>10</sup>; drug induced, when there was a clear relationship between syncope and the introduction of a new hypotensive drug or a change in dosage; secondary to cardiopulmonary disease, when syncope was clearly related to an acute cardiopulmonary disorder; CSS, when syncope or near-syncope was reproduced during or immediately after carotid sinus massage in the presence of asystole  $> 3$  s and/or a fall in systolic blood pressure of  $> 50$  mmHg; and arrhythmic syncope, when complete or advanced A-V block, asystole  $> 3$  s, or the presence of sustained VT or rapid SVT was documented,<sup>11</sup> with or without syncope.<sup>12–14</sup> Non-



**Figure 1** Proposed diagnostic strategy. Initial evaluation was performed in all patients. Those in whom initial evaluation achieved the diagnosed were treated accordingly. If initial evaluation was not diagnostic, an electrophysiological study (EPS) was performed: If it was diagnostic, patients were treated according to the findings, and if it was negative, an implantable loop recorder (ILR) was implanted.

arrhythmic syncope was diagnosed when sinus rhythm was documented during a syncopal episode.

The EPS was considered diagnostic with the following findings<sup>7</sup>: sinus node recovery time  $> 1500$  ms; corrected sinus node recovery time  $> 525$  ms; baseline HV interval  $\geq 70$  ms; second- or third-degree His–Purkinje block during incremental atrial pacing or after intravenous class IC antiarrhythmic drugs or induction of sustained monomorphic VT or rapid SVT that provoked hypotension or reproduced spontaneous symptoms.

### Study endpoints

Clinical endpoints were recurrent syncope, documented spontaneous arrhythmias, or death due to any cause.

All patients were followed quarterly during the first 12 months. Those with longer follow-up had additional visits at 18 and 24 months or at study closure. Whenever there was a syncopal recurrence, an unscheduled control visit was performed.

### Statistical analysis

Data were sent by investigators via a dedicated Internet website that maintained the database and issued data-clarification forms.

The occurrence of clinical endpoints was compared between patients in whom diagnosis was achieved at Phase I or II, and who consequently were treated according to the diagnosis, and patients in whom an ILR was implanted after negative diagnostic work-up at Phases I and II. Comparison between groups was performed with Student's *t*-test or the Mann–Whitney non-parametric 'U' test, as appropriate, for continuous variables, and with Fisher's exact test or the  $\chi^2$  test for proportions. Time to the onset of events was analysed

by means of the Kaplan–Meier survival curves, which were compared using the log-rank test. Statistical significance was set at the standard value of  $P < 0.05$ . All reported  $P$ -values are two-tailed.

SPSS (SPSS Inc., Chicago, IL, USA) software version 12.0 statistical package was used for the statistical analyses.

## Results

### Patients

Between January 2003 and January 2006, 423 patients were eligible for the study (Figure 2). Overall, 100 patients were excluded from the analysis due to the following reasons: 7 patients had incomplete data at baseline, 19 had incomplete follow-up (6 after initial diagnosis, 6 after EPS, and 7 after ILR implantation), and 74 did not follow the proposed algorithm: EPS was not performed in 20 and ILR was not implanted in 54. There were not statistical differences in demographic data, the presence of structural heart disease, the type of BBB or previous history of syncope, between the 323 included and 100 excluded patients.

The study population consisted of 323 patients. The demographic and clinical characteristics are listed in Table 1. It can be observed that patients who were diagnosed at Phase II had their first syncope episode at older age, had higher incidence of ischaemic or dilated cardiomyopathy, and had lower LVEF, but keeping in normal values.

Patients were followed for  $19.2 \pm 8.2$  months (median 21.8; inter-quartile range 12.1).

### Aetiological diagnosis

At the end of follow-up, an aetiological diagnosis was established in 267 patients (82.7%; Table 2), with the following diagnoses: bradyarrhythmia in 202 (paroxysmal A-V block documented at initial evaluation or by ILR in 88, abnormal infrahisian findings at EPS in 70, sick sinus syndrome or severe sinus bradycardia in 15, alternating BBB documented at initial evaluation in 4, and not specified in 25), CSS in 20, VT in 18, neurally mediated syncope in 9, orthostatic hypotension in 4, drug-induced in 3, secondary to cardiopulmonary disease in 2 (1 with severe aortic stenosis and 1 with pulmonary thrombo-embolism), SVT in 1, bradycardia–tachycardia syndrome in 1, and non-arrhythmic syncope in 7.

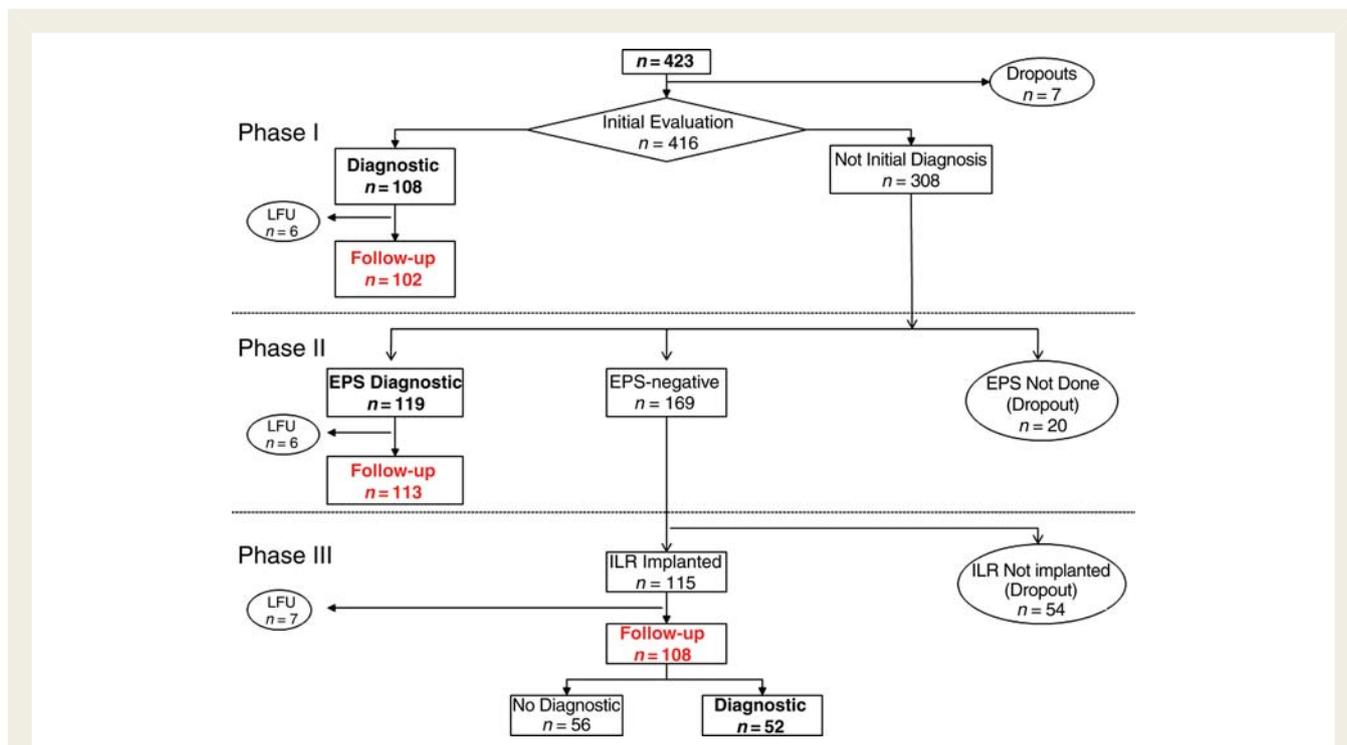
### Treatments

At the end of follow-up, a pacemaker was implanted in 220 (68.1%) patients, an ICD in 19 (5.8%), and radiofrequency catheter ablation was performed in 3 patients (Table 3). In the remaining patients who had other diagnoses, such as neurally mediated, orthostatic, or drug-related syncope, aetiology-specific measures were applied.

### Endpoints

Of the 215 patients in whom diagnosis was achieved at Phase I or II and who were treated according to the findings, a syncopal recurrence was observed in 15 (7%). In contrast, syncope recurred in 36 of 108 (33%) patients in whom an ILR was implanted ( $P < 0.001$ ; Figure 3).

At follow-up, 5 of 14 (36%) patients in whom an ICD was implanted due to inducible VT at EPS had appropriate discharges.



**Figure 2** Flowchart of included patients. From 423 patients initially eligible, only 323 (represented in red) entered in the study. The reasons for exclusion were incomplete data at baseline (7), lost of follow-up (LFU): 6 after initial diagnosis, 6 after electrophysiological study (EPS), and 7 after implantable loop recorder (ILR) or lack of adherence to protocol (20 without diagnosis at initial evaluation in whom an EPS was not performed and with negative EPS in whom ILR was not implanted).

**Table 1** Patient characteristics

	Total	Phase I	Phase II	Phase III	P-value
Patients, <i>n</i>	323	102	113	108	
Age in years, mean ± SD	73 ± 10	74 ± 11	75 ± 8	73 ± 10	0.396
Male gender, <i>n</i> (%)	206 (63.8)	60 (58.8)	82 (72.6)	64 (59.3)	0.055
Total syncope episodes during lifetime, median (25°–75° percentile)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	0.076
Syncope episodes lasting 6 months, median (25°–75° percentile)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.114
Age at first syncope, mean ± SD	72 ± 11	72 ± 13	74 ± 9	70 ± 12	0.034
History of pre-syncope, <i>n</i> (%)	125 (38.7)	46 (45.1)	34 (30.1)	45 (41.7)	0.058
Hospitalization for syncope, <i>n</i> (%)	230 (71.2)	74 (72.5)	86 (76.1)	70 (64.8)	0.168
Syncope without prodromes, <i>n</i> (%)	183 (56.7)	49 (48.0)	65 (57.5)	69 (63.9)	0.067
Syncope preceded by palpitations, <i>n</i> (%)	18 (5.6)	9 (8.8)	6 (5.3)	3 (2.8)	0.160
Trauma related to syncope (total), <i>n</i> (%)	96 (29.7)	24 (23.5)	34 (30.1)	38 (35.2)	0.181
Severe trauma related to syncope, <i>n</i> (%)	44 (13.6)	15 (14.7)	15 (13.3)	14 (13.0)	0.926
Baseline ECG, <i>n</i> (%)					
LBBB	131 (40.6)	35 (34.3)	49 (43.4)	47 (43.5)	0.094
RBBB	67 (20.7)	26 (25.5)	24 (21.2)	17 (15.7)	
RBBB with left anterior hemi-block	111 (34.4)	34 (33.3)	34 (30.1)	43 (39.8)	
RBBB with left posterior hemi-block	8 (2.5)	2 (2.0)	5 (4.4)	1 (0.9)	
Alternating LBBB and RBBB	5 (1.5)	4 (3.9)	1 (1.0)	0 (0.0)	
RBBB with left anterior and posterior hemi-block	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	
PR interval (ms), mean ± SD	187 ± 45	192.2 ± 54	198.9 ± 44.4	170 ± 33.4	<0.001
Structural heart disease, <i>n</i> (%)	161 (49.8)	48 (47.1)	71 (62.8)	42 (38.9)	0.005
Ischaemic heart disease	59 (18.3)	14 (13.7)	31 (27.4)	14 (13.0)	0.007
Valvular heart disease	38 (11.8)	13 (12.7)	17 (15.0)	8 (7.4)	0.198
Dilated cardiomyopathy	23 (7.1)	7 (6.9)	14 (12.5)	2 (1.9)	0.009
Hypertrophic cardiomyopathy	13 (4.0)	1 (1.0)	8 (7.1)	4 (3.7)	0.071
Hypertensive heart disease	49 (15.2)	19 (18.2)	18 (15.9)	12 (11.1)	0.304
Other	7 (2.2)	1 (1.0)	3 (2.7)	3 (2.8)	0.608
LVEF (%), mean ± SD	56 ± 12	56 ± 12	52 ± 14	60 ± 10	<0.001
LVEF < 40%, <i>n</i> (%)	26 (8.0)	8 (7.8)	16 (14.2)	2 (1.9)	0.004
Atrial fibrillation, <i>n</i> (%)	34 (10.5)	16 (15.7)	12 (10.8)	6 (5.6)	0.057
Diabetes, <i>n</i> (%)	72 (22.3)	27 (26.5)	28 (24.8)	17 (15.7)	0.128
Hypertension, <i>n</i> (%)	221 (68.4)	71 (69.6)	76 (67.3)	74 (68.5)	0.933
Neurological disease, <i>n</i> (%)	42 (13.0)	15 (14.7)	11 (9.7)	16 (14.8)	0.440

Demographic and clinical characteristics of the study population. The second column (total) represents all population; in the following columns, there are the data of patients who were diagnosed at Phase I, Phase II, or who entered at Phase III. LBBB, left bundle branch block; RBBB, right bundle branch block; LVEF, left ventricular ejection fraction.

The following arrhythmias were recorded with ILR (Table 2): A-V block (36 patients: 20 during a syncopal episode and 16 asymptomatic); asystole (5 patients); VT or ventricular fibrillation (3 patients), and an episode of rapid atrial fibrillation followed by sudden asystole in 1 patient.

Twenty patients (6%) died at follow-up: 6 due to no cardiac causes; 7 due to cardiac non-arrhythmic causes (5 due to heart failure and 1 due to acute aortic dissection); 3, all with implanted pacemakers, due to unknown causes; 1 had a sudden, undocumented syncope with a subdural hematoma, and 3 had sudden death (all 3 with ILR; in 2, the device was not interrogated, and in 1, a ventricular fibrillation was documented). There was no difference in mortality rate between patients diagnosed at Phase I or II,

who received appropriate treatment, compared with those who had implanted ILR (6.0 vs. 6.5%,  $P = 0.878$ ).

No differences were found in mortality or syncope recurrence with respect to the presence or absence of structural heart disease, or the type of BBB.

## Discussion

The main finding in this study is that in patients with syncope, BBB, and preserved LVEF, the application of a systematic diagnostic strategy in accordance with ESC guidelines achieves a high rate of diagnosis (82.6%) with a low rate of mortality (6%), allowing clinicians to institute aetiology-specific treatment.

**Table 2** Diagnosis

Diagnosis		n	
Analysed patients, n = 323			
Initial evaluation (Phase I), n = 102	Bradyarrhythmia	A-VB	52
		Alt BBB	4
		SSS	6
		NS	13
	CSS	6	
	Neurally mediated	9	
	Orthostatic hypotension	4	
	Drug-induced	3	
	VT	3	
	Cardiopulmonary	2	
EPS (Phase II), n = 113	Bradyarrhythmia	Infrahisian abnormalities	70
		SSS	4
		NS	12
	CSS	14	
	VT	12	
	SVT	1	
	ILR implantation (Phase III), n = 52	Bradyarrhythmia	A-VB
SA			5
Non-arrhythmic		7	
VT/VF		3	
Brady/tachy		1	
No diagnosis		56	

EPS, electrophysiological study; ILR, implantable loop recorder; A-VB, documentation of transient or advanced atrio-ventricular block, including type 2 second-degree atrio-ventricular block, with ECG, in hospital monitoring, Holter recording (Phase I), or ILR (Phase III); Alt BBB, alternating bundle branch block; SSS, sick sinus syndrome; NS, non-specified; CSS, carotid sinus syndrome; VT, ventricular tachycardia; SVT, supraventricular tachycardia; VF, ventricular fibrillation; SA, sinus arrest. Infrahisian abnormalities includes HV interval  $\geq 70$  ms or the presence of infrahisian block with atrial pacing or drug challenge.

As expected, the most common cause of syncope in these patients was bradyarrhythmia, mostly due to paroxysmal A-V block. However, following this diagnostic strategy, other aetiologies of syncope were recognized in 17.6% of this population, such as CSS, neurally mediated, or drug-related syncope, or syncope secondary to VT, SVT, or cardiopulmonary disease. In addition, an arrhythmic cause could be ruled out in several patients who had a syncopal event documented by ILR.

The initial evaluation achieved a diagnosis in 25% of the studied population. Although the most frequent diagnosis at EPS was a bradyarrhythmia (76%), VT or SVT was induced in 14%. The role of EPS in patients with BBB and preserved LVEF has been discussed. The documentation of prolonged HV interval<sup>15</sup> or infrahisian block with progressive atrial pacing<sup>16</sup> or after drug challenge with class IC antiarrhythmic drugs<sup>17</sup> has been identified as a marker for progression to A-V block, with an acceptable specificity, but with low

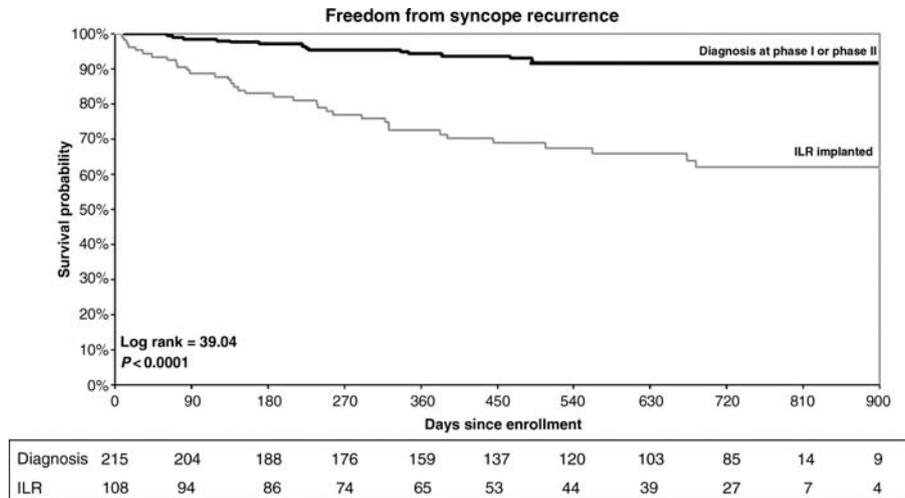
**Table 3** Treatments according to different phases

Treatment	n	
Analysed patients, n = 323		
Initial evaluation (Phase I)	PMK	82
	General measures/drug modification/PCM/other	16
	ICD	2
	RFA	1
	AVR	1
EPS (Phase II)	PMK	97
	ICD	14
	RFA	1
	No active treatment	1
ILR implantation (Phase III)	PMK	41
	ICD	3
	RFA	1
	No active treatment	51

EPS, electrophysiological study; ILR, implantable loop recorder; PMK, pacemaker implantation; ICD, implantable cardioverter defibrillator; RFA, radiofrequency catheter ablation; AVR, aortic valve replacement; PCM, physical counterpressure manoeuvres.

sensitivity. In addition, the role of programmed ventricular stimulation in these patients is controversial. Although Englund *et al.*<sup>18</sup> found that the induction of VT did not predict the occurrence of a ventricular arrhythmia at follow-up, Olshansky *et al.*<sup>19</sup> found that inducibility of VT increased the risk of sudden death at follow-up and Link *et al.*<sup>20</sup> found that the absence of inducibility, especially in patients with preserved LVEF, identified a group of patients with low risk of sudden death at follow-up. In our study population, the recurrence rate of syncope in patients treated according to the diagnoses achieved at Phases I and II was low, suggesting that those findings were specific. In addition, the rate of appropriate discharges in patients who received an ICD due to VT inducibility at EPS was similar to the discharge rate described in different published series in patients with ICD.<sup>21,22</sup> This similarity suggests that in our study, inducibility identified the patients who were at risk of developing VT at follow-up. However, the suggestion that the sensitivity of EPS is relatively low was confirmed, in our study, by the fact that in 45% of the patients with a negative EPS, an arrhythmia was still documented by ILR. Again, ILR showed that bradyarrhythmia was the most common cause of syncope in these patients, but it allowed us to recognize some patients with VT, and also identified a non-arrhythmic cause of syncope in some patients who otherwise may never had been identified.

The potential risk of sudden death or severe cardiovascular events may be a concern associated following this strategy. In fact, several series suggested that the presence of abnormal ECG or severe structural heart disease and specifically depressed LVEF are risk factors for death or severe cardiovascular events in short-term follow-up,<sup>1,3-5,23</sup> The relatively low mortality rate in this older population can be attributed to the fact that patients with depressed LVEF were probably not included and received



**Figure 3** The Kaplan–Meier survival curve of syncopal recurrences in patients in which the diagnosis was achieved at Phase I or II and were treated according to the diagnosis (black line) and those in which an ILR was implanted after a negative work-up in Phase I or II. Patients diagnosed and treated had a significant reduction or syncopal recurrence when compared with those with an ILR implanted.

an ICD. This explains why the mean LVEF is  $56 \pm 12$ , with very few patients with LVEF lower than 40%. In addition, most deaths were due to non-cardiac or non-arrhythmic causes. Some patients who received an implanted pacemaker died of unexplained causes, suggesting that bradyarrhythmia was not the cause of death in these patients. Admittedly, three patients died with an ILR implanted: in at least one of them, a ventricular fibrillation was documented that would not have been prevented by a pacemaker; in the other two, the cause of death remains unknown.

It can be argued that with a longer follow-up, some more patients would have syncopal recurrence or asymptomatic arrhythmias recorded by ILR, allowing clinicians to increase the number of patients with a final diagnosis.<sup>24–27</sup> This is true, but in any case reinforces the value of this diagnostic strategy, encouraging clinicians to monitor these patients and not to initiate any treatment until a definite diagnosis is achieved.

The study was not designed to determine whether this diagnostic strategy was better than implanting a pacemaker in the majority of patients, and consequently, we cannot declare which option might be better. Owing to the low mortality and low syncopal recurrence rate observed when following this strategy in this specific population, only a controlled trial including a great number of patients would be able to answer this question.

Admittedly, some patients were excluded from the study because in those patients the suggested algorithm was not followed. As this was an observational study, investigators could not be forced to follow the protocol in all patients, and a selection bias cannot be excluded. However, demographic and clinical characteristics of excluded patients were similar to those included patients, decreasing the probability of a selection bias.

In conclusion, in patients with syncope, BBB, and relatively preserved LVEF, a diagnostic strategy consisting of initial clinical evaluation, followed by EPS and, if negative, implantation of an

ILR, achieves a high rate of aetiological diagnosis. The high diagnosis rate in turn allows clinicians to select a specific treatment and to avoid unnecessary pacemaker implantation without a high rate of cardiovascular events or mortality. Whether this strategy is better than the strategy of implanting pacemakers into all patients with this clinical profile cannot be determined with current data.

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**Conflict of interest:** X.N. is an employee of Medtronic Iberica.

## Appendix

The following persons participated in the B4 study.

Coordinating Committee: R.G.-C. (Chair), A.M., F.A., M. Brignole, J.B., C.M., and X.N. Database electronic management: Remote Data Entry System, SL, Barcelona, Spain. Clinical monitors: M.P. López, G. Monzón, and N. Grovale; Statistical analysis: M. Martín, T. de Santo.

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