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# Prevention of Syncope Through Permanent Cardiac Pacing in Patients With Bifascicular Block and Syncope of Unexplained Origin

## The PRESS Study

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***Background***—Syncope in patients with bifascicular block (BFB) is a common event whose causes might be difficult to assess.

***Methods and Results***—Prevention of syncope through permanent cardiac pacing in patients with bifascicular block (PRESS) is a multicenter, prospective, randomized, single-blinded study designed to demonstrate a reduction in symptomatic events in patients with bifascicular block and syncope of undetermined origin implanted with permanent pacemaker. Device programming mode (NASPE/BPEG code) at DDD with a lower rate of 60 ppm is compared with backup pacing at DDI with a lower rate of 30 ppm. The end point consisted of (1) syncope, (2) symptomatic presyncopal episodes associated with a device intervention (ventricular pacing), and (3) symptomatic episodes associated with intermittent or permanent atrioventricular block (any degree). One hundred one patients were enrolled and randomized. Primary end point events at 2 years were observed in 23 patients, with a significant lower incidence in the study group (hazard ratio, 0.32; 95% confidence interval [CI], 0.10–0.96; $P$=0.042). Reduction of any symptoms, associated or not with device intervention, was superior in DDD60 compared with DDI30 (hazard ratio, 0.4; 95% confidence interval, 0.25–0.78; $P$=0.0053). Fourteen patients developed other rhythm diseases and met class I indication for pacing. The annual incidence of rhythm disease development was 7.4%.

***Conclusions***—In patients with bifascicular block and syncope of undetermined origin, the use of a dual chamber pacemaker programmed to DDD60 led to a significant reduction of syncope or symptomatic events associated with a cardioinhibitory origin, compared with DDI30 programming. Symptoms associated with a new onset of rhythm disease were found in 15% of the population at 2 years.

***Clinical Trial Registration Information***—clinicaltrials.gov; Identifier: NCT01463358.

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**Key Words:** bifascicular block ■ pacemakers ■ randomized controlled trial ■ syncope

Bifascicular block (BFB) is a conduction disturbance with reported prevalence of 1% to 1.5%, with up to 25% of adult patients presenting with syncope.[1–6] The cause of syncope in these patients is difficult to assess and may be, in part, due to transitory conduction disturbances at the presinus, sinus, or atrioventricular (AV) node level.[6–8] These patients may also present with ventricular tachycardia.[9,10] Patients with BFB and syncope represent a heterogeneous population, which is difficult to stratify and where the selection of an appropriate therapy may be challenging.[6,11–14]

**Clinical Perspective on p 107**

Different techniques are used in clinical practice to investigate the cause underlying syncope, including either invasive (electrophysiological study) or noninvasive (ECG, Holter monitoring, tilt table test). These methods, despite being useful

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in identifying specific causes, often lack in specificity.[10,13–18] Therefore, the current evidence led the American College of Cardiology–American Heart Association–Heart Rhythm Society (ACC–AHA–HRS) committee to consider permanent pacemaker implantation as a class IIA indication for BFB patients presenting with syncope of undetermined origin.[11,12,19] However, the guidelines do not state which pacing modality should be chosen for these patients (single versus dual chamber). Limited information is available on the recurrences of syncopal episodes, hospitalizations, and quality of life for these patients after pacemaker implantation. The prevention of syncope through permanent cardiac pacing in patients with BFB (PRESS) study was designed to investigate the role of pacemaker in preventing symptom recurrences in patients with BFB and history of syncope of unknown origin.

## Methods

PRESS (study registration: NCT01463358) is a multicenter, prospective, randomized, single-blinded study designed to investigate the role of pacemakers in reducing symptom recurrences in patients with BFB who experienced syncope, whose origin was undetermined in nature after screening for causes with the currently indicated diagnostic techniques. The objective of the study was to demonstrate that permanent dual chamber (DDD) pacing is effective in reducing the recurrence of symptoms, including syncope or presyncopal episodes associated with a cardioinhibitory origin (including symptomatic temporary or permanent AV block [AVB]). The study was approved by the Institutional Ethics Committee of the participating centers.

All patients enrolled into the study were implanted with a dual chamber pacemaker (InsigniaTM, Boston Scientific Corporation, St Paul, MN) and randomized to 2 parallel arms. The treatment arm included devices programmed to DDD pacing mode with a 60 ppm lower rate and AV interval ≥200 ms (DDD60). The control arm included those programmed with DDI mode and 30 ppm lower rate (DDI30). Device programming in the control arm was aimed at minimizing pacing as much as possible, while providing a safety backup stimulation. The primary end point of the study was to demonstrate a reduction in the treatment group of the following composite at 2 years after implant: (1) syncopal episodes of any origin, (2) symptomatic presyncopal episodes (including dizziness and near-syncope without loss of consciousness) associated with a documented device intervention (ventricular pacing), and (3) symptomatic episodes associated with documented episodes of intermittent, or permanent AVB (any degree) or to sustained ventricular tachycardia. Presyncopal episodes with symptoms and without loss of consciousness were included as primary end points only if associated either with a documented bradycardia at ECG or with a consistent ventricular pacing >1% detected by pacemaker diagnostics. Other symptoms were classified as primary end point only in the presence of documented evidence of AVB of any degree.

Secondary end point included (1) comparison of each of the 3 separate components of the primary end point in the 2 study groups, (2) comparison of symptomatic episodes of any origin between the 2 study groups, (3) rhythm disease progression in the entire cohort of patients (AVB, bradycardia, and atrial fibrillation [AF]), (4) comparison of documented AF in the 2 study groups, and (5) recurrence of symptoms after device reprogramming from DDI30 to DDD60. This study included patients with BFB and a history of syncope of unknown origin, currently indicated to permanent pacing according to ACC-AHA-HRS guidelines (class IIA). Subjects were eligible to participate in the study if they met the following inclusion criteria: ECG documentation of BFB defined as complete left bundle-branch block or complete right bundle-branch block associated with left anterior hemiblock or left posterior hemiblock with at least 1 episode of syncope in a period of 6 months preceding enrollment. All eligible patients underwent complete laboratory screening, including ECG, Holter monitoring, tilt test, carotid sinus massage, electrophysiological study (EPS), to rule out any possible pre-existing cause of syncope. Patients were excluded if the cause of syncope was identified among the following: (1) vasovagal syncope, (2) carotid sinus syndrome, (3) persistent or permanent AF, (3) sinus node dysfunction or brady-tachy syndrome, (4) second or third degree AVB, diagnosed at ECG or during EPS, (5) spontaneous or inducible sustained ventricular tachycardia, and (6) minimal nocturnal heart rate inferior to 35 beats per minute documented at Holter monitoring. Patients with significant structural heart disease (ejection fraction < 40%) were also excluded. Detailed description for the diagnostic examinations to assess these criteria is detailed in the Appendix in the online-only Data Supplement.

After signing informed consent, patients underwent dual chamber pacemaker implantation; randomization occurred at patient discharge after implant (block randomization with block size = 4 allocation, ratio 1:1). Medical therapy was prescribed according to physician discretion. The use of β-blockers was not recommended during the course of the study unless needed for other reasons. Amiodarone or other antiarrhythmic drugs were not discontinued during the study.

Each enrolled patient was followed for 2 years after enrollment with standard in-clinic visits scheduled at 1 month and every 3 months after randomization.

Both pacing mode and lower rate stimulation were required to remain unchanged unless specific symptomatic episodes occurred and the end point reached. Primary end point analysis was completed according to an intention-to-treat protocol with respect to device programming. In the case of device reprogramming after the occurrence of the primary end point, recurrences of episodes in the remaining follow-up period were also collected. At the end of the follow-up period, for each patient, the pacing mode and rate could be programmed at physician's discretion.

### Sample Size and Statistical Analysis

The PRESS study was designed to demonstrate an absolute reduction of at least 20% of events between the study group and the control group, assuming 30% of events in the control group at 2 years. Aiming at $\alpha$=0.05, a 80% power, and a 10% attrition per year, the study required a sample size of 101 patients. Descriptive statistics are used to describe collected data: absolute numbers and proportions for discrete data; mean, SD, median, and quartiles for continuous data, according to distribution. Primary and secondary end points were analyzed with a survival analysis techniques and the Kaplan–Meier method. Log-rank test was also used to analyze the primary end point. In addition, Cox model with robust standard errors was used to analyze both primary and secondary end points to account for intrasite correlation.

## Results

A total of 101 patients were enrolled in the study and randomized (52 to DDD60 group; 49 to DDI30) from March 2005 to February 2009. Patient characteristics are shown in Table 1. During the 2-year follow-up, 2 patients withdrew from the study, 3 were lost to follow-up, and 4 died before the end of follow-up (causes of death: 1 undetermined during sleep, 1 cerebral hemorrhage, 1 respiratory failure in patient with chronic obstructive pulmonary disease, and 1 myocardial infarction), yielding to a total of 93 patients at the end of the follow-up period.

The composite primary end point occurred in 23 patients (22.8%) at 2 years with median time to event of 5.4 months, of which 16 (32.6%) in the DDI30 group and 7 (13.5%) in DDD60 group (hazard ratio, 0.32 [0.10–0.96]; $P$=0.042). Kaplan–Meier curves (Figure 1) showed a significant reduction of events in the treatment group (with a number-needed-to-treat [NNT]=5.23). The first event occurred in these 23 patients was syncope in 14 (13.9%), presyncope in 6 (5.9%), and AVB in 3 (3%) patients. In addition, the proportion of patients presenting with syncope, presyncope, and AVB alone, considered as independent events, was compared in the 2 study groups (Table 2), indicating that a

**Table 1. Baseline Demographic and Clinical Characteristics**

| Parameter | Overall* (N=101) | Control* (N=49) | Treatment* (N=52) |
|---|---|---|---|
| Age, y | 77±8 | 78±8 | 76±7 |
| Left ventricular ejection fraction, % | 57±10 | 59±10 | 55±10 |
| QRS duration, ms | 128±36 | 127±40 | 128±39 |
| PR duration, ms | 175±60 | 171±62 | 179±60 |
| Months from first episode | 6 [1–12] | 6 [1–12] | 12 [1–12] |
| No. of syncope in last 6 mo | 1 [1–2] | 1 [1–3] | 1 [1–2] |
| No. of presyncope in last 6 mo | 0 [0–1] | 0 [0–1] | 0 [0–1.5] |
| Patients with previous sudden syncope with physical trauma | 42/101 (42%) | 20/49 (41%) | 22/52 (42%) |
| Minimum heart rate at Holter | 47±9 | 50±10 | 49±8 |
| Male | 61/101 (60%) | 26/49 (53%) | 35/52 (67.3%) |
| Etiology: none | 33/101 (33%) | 16/49 (33%) | 17/52 (33%) |
| Etiology: ischemic | 19/101 (19%) | 9/49 (18%) | 10/52 (19%) |
| Etiology: valvular | 2/101 (2%) | 1/49 (2%) | 1/52 (2%) |
| Etiology: dilated | 2/101 (2%) | 0/49 (0%) | 2/52 (4%) |
| Etiology: hypertensive | 47/101 (47%) | 27/49 (55%) | 20/52 (38%) |
| Etiology: other | 13/101 (13%) | 4/49 (8%) | 9/52 (17%) |
| Atrial fibrillation history | 10/101 (10%) | 6/49 (12%) | 4/52 (8%) |
| Previous hospitalizations (all-cause) | 41/101 (41%) | 19/49 (39%) | 22/52 (42%) |
| Previous hospitalizations (heart failure) | 2/101 (2%) | 2/49 (4%) | 0/52 (0%) |
| Diabetes mellitus | 26/101 (26%) | 14/47 (29%) | 12/49 (23%) |
| NYHA class I | 58/96 (60.4%) | 30/47 (64%) | 28/49 (57%) |
| NYHA class II | 29/96 (30.2%) | 14/47 (30%) | 15/49 (31%) |
| NYHA class III | 8/96 (8.3%) | 3/47 (6%) | 5/49 (10%) |
| NYHA class IV | 1/96 (1%) | 0/47 (0%) | 1/49 (2%) |
| ACE inhibitors | 27/101 (27%) | 10/49 (20%) | 17/52 (33%) |
| Antiarrhythmic | 12/101 (12%) | 8/49 (16%) | 4/52 (8%) |
| Anticoagulants/antiaggregants | 33/101 (33%) | 14/49 (28%) | 19/53 (37%) |
| β-Blockers | 19/101 (19%) | 9/49 (18%) | 10/52(19%) |
| $Ca^{2+}$ antagonists | 20/101 (20%) | 11/49 (22%) | 9/52 (17%) |
| Digitalis | 2/101 (2%) | 1/49 (2%) | 1/52 (2%) |
| Diuretics | 26/101 (26%) | 12/49 (24%) | 14/52 (27%) |
| Antihypertensive | 21/101 (21%) | 12/49 (24%) | 9/52 (17%) |
| Statins | 8/101 (8%) | 6/49 (12%) | 2/52 (4%) |

ACE indicates angiotensin-converting enzyme; NYHA, New York Heart Association; PR, PR interval; and QRS, QRS interval. *Numbers are % (counts) or mean±SD.

significant difference is still preserved between the DDD60 and DDI30 for presyncope and AVB events separately but not for syncope alone.

A total of 19 syncopal episodes occurred in 14 patients, with 5 patients having a second episode (3 randomized in the control and 2 in the treatment arm). The total number of presyncopal episodes due to a documented cardioinhibition was 34 in 22 patients (21.8%): 9 patients had recurrences after the first episode with 6 patients having 1 recurrence and 3 patients with 2 recurrences. All patients with presyncope recurrences were originally programmed in the DDI30 (control group). Reprogramming of pacing mode from DDI30 to DDD60 occurred in 15 patients after the first event of syncope or presyncope. In 13 of these cases the event has been adjudicated as primary end point. Among the 9 patients originally programmed at DDI30 and with recurrent presyncope, only 2 had the device reprogrammed to DDD60 after the first episode.

Overall, a symptomatic episode (syncope or presyncope), regardless of its origin, occurred in 35 patients (34.6%) of which 22 (44.9%) in the control (DDI30) group and 13 (25%) in the treatment (DDD60) group (hazards ratio, 0.43 [0.25–0.78]; $P$=0.0053). Kaplan–Meier curve (Figure 2) showed a significant reduction in the event rates in the treatment group.

Fourteen patients developed a class I indication for permanent pacing during the course of the study (10 symptomatic AVB, 2 brady-tachy, 1 sinus bradycardia, and 1 permanent AF with slow ventricular response), accounting for an overall incidence of 7.4% per year of new class I indication for permanent pacing (the most prevalent being AVB, with 5.38%). Regarding the 10 patients who showed a complete AVB during the follow-up, 8 of them were in the control group (16.3%) and 2 (3.8%) in the treatment group. Fourteen patients had at least 1 hospitalization for symptomatic heart failure, associated or not with AVB, yielding an annual incidence

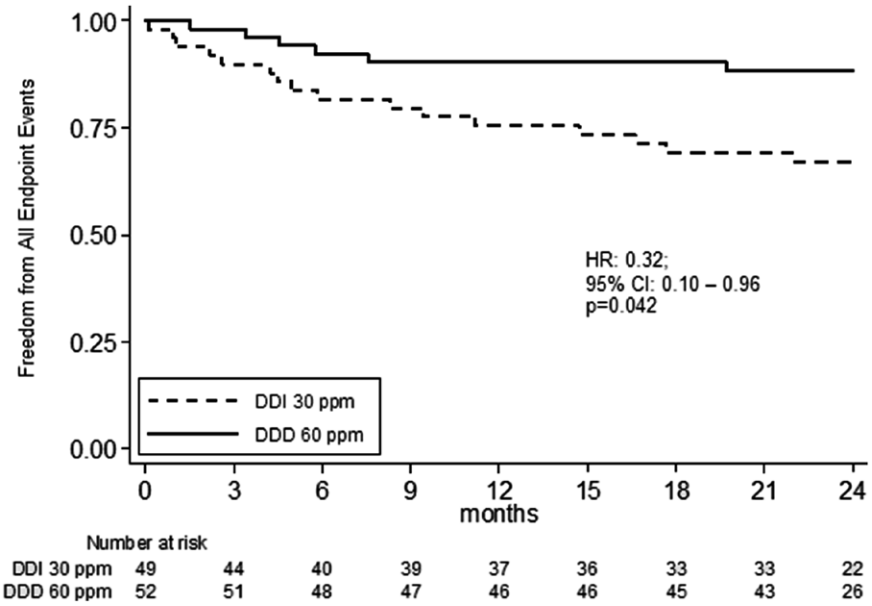


**Figure 1.** Kaplan–Meier curves: primary end point. CI indicates confidence interval; and HR, hazard ratio.

of 3.7%. In DDD60 group, median pacing rate was 26% for atrium (interquartile range, 1%–48%) and 23% for ventricle (interquartile range, 1%–35%). Ten patients (9.9%) had a history of paroxysmal AF before implant. During follow-up, a total of 44 episodes of AF were retrieved in 26 of 101 patients. Episodes were retrieved either at ECG or from implanted device diagnostics. Among the 26 patients with AF, 7 were patients with documented preimplant AF history and 19 were patients with new onset, postimplant, and AF episodes. The total annual incidence of AF in this sample was 13.1%. None of these patients presented with ventricular tachycardia during the course of the follow-up.

## Discussion

Bifasicular block, defined as complete left bundle-branch block or complete right bundle-branch block associated with left anterior hemiblock or left posterior hemiblock, is a condition associated with increased mortality, whose mechanisms are not well understood.[6–8,20–22] Syncope, associated or not with severe trauma or injuries, can be a frequent event in this population. The underlying causes explaining loss of consciousness in BFB population are heterogeneous, the most frequent being neurally mediated syncope or intermittent high degree AVB.[7,20,23,24] In addition, several studies focusing on follow-up of BFB patients with previous syncope reported consistent rates of temporary or permanent AVB development over time.[8,11,25–28] Despite the high incidence of electric disturbances of the conduction system, EPS at the time of the hospital observation has limited positive predictive value.[10,14,29,30] Accordingly, BFB patients with both history of previous syncope and a negative EPS have been the subject of several investigations involving pacemakers or loop recorders to identify the nature of associated syncopal recurrences and consequently its most appropriate treatment.[5,24,27,31,32] Current guidelines set, in the past 10 years, a class IIA recommendation for a pacemaker implantation in patients with BFB and experiencing syncope of apparently unexplained origin, to avoid the risk of syncopal recurrences and potential physical trauma.[19] The PRESS study was designed to assess the role of dual chamber pacing in preventing symptom recurrences in these patients and demonstrated that the use of a pacemaker programmed with a lower rate of 60 ppm (DDD60) resulted in a significant reduction of the combination of symptomatic events, including syncope, presyncope, or AVB when compared with a substantially negligible electric treatment. Indeed, the programming to DDI30 beats per minute of the control group patients was chosen to avoid as much as possible any paced beat, considering that the Holter screening criteria before implant included only patients with a spontaneous heart rate always higher than 30 beats per minute during the 24 hours. The beneficial effect of permanent pacing is more striking if we consider the rigid selection process that patients had undergone to be considered eligible for the study, ruling out any evident rhythm disease at the time of enrollment. Despite this precise preselection of patients, symptoms associated with new onset of a rhythm disease, including AVB, brady-tachy or bradycardias, or chronic AF with slow ventricular response, with class I indications for pacemaker implant, emerged in up to 15% of the study population.

Notably, by analyzing the components of the primary end point, a significant difference between the study group and controls is shown only with respect to presyncope and to symptoms associated with AVB, but not to syncope alone, which did not show any significant difference between DDD60 and DDI30. This result may be explained by the mechanisms of syncope occurring in this selected BFB population when

**Table 2. Two-Year Development of Syncope, Presyncope, and AV Block Alone**

| | Total | DDI30 | DDD60 | *P* |
|---|---|---|---|---|
| Syncope | 14 (13.9%) | 7 (14.3%) | 7 (13.5%) | 0.89 |
| Presyncope | 22 (21.8%) | 16 (32.6%) | 6 (11.5%) | *P*<001 |
| Symptomatic AV block | 10 (9.9%) | 8 (16.3%) | 2 (3.8%) | *P*<001 |

AV indicates atrioventricular.

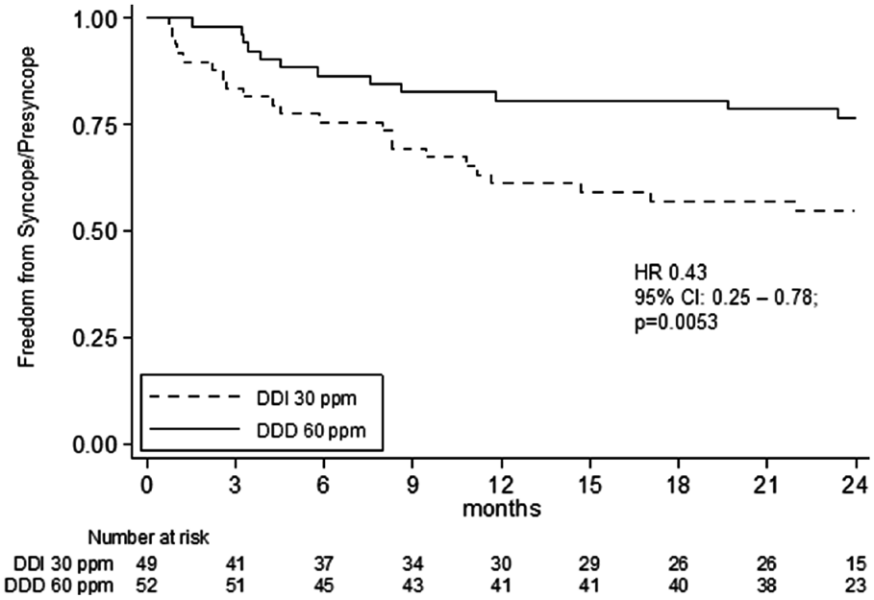


**Figure 2.** Kaplan–Meier curves: patient symptoms (syncope or presyncope of any origin). CI indicates confidence interval; and HR, hazard ratio.

implanted with a permanent pacemaker. Having device diagnostics that excluded ventricular arrhythmias and a pacemaker that warranted the presence of adequate pacing in both groups to prevent a cardioinhibitory episode, syncope events that occurred in this sample were likely due to vasodepressor syndrome, hypotension from noncardiac etiology (eg, excessive medications/postural orthostasis) or a neurological issue not detected with the pre-enrollment tilt test screening. In addition, it is reasonable to hypothesize that patients with cardioinhibitory episodes have turned into most of the presyncope symptoms, especially in the control group. In addition, these syncopal recurrences that occurred in patients implanted with pacemaker, regardless of device programming, rule out the possible placebo effect of pacing, as hypothesized in previous studies.[33] However, it should be noted that the study was not powered to evaluate individual end point events separately.

PRESS is the first randomized study for a BFB population involving a strict selection and screening process. Specifically, diagnostic criteria used for the patients selection (including ECG, Holter, tilt table testing, and EPS) were used to exclude other possible causes for syncopal episodes. A subgroup of these patients still presented with syncopal recurrences within a short time after implant (median of 5 months) supports the prevailing belief that these tests have limited predictive value. One of the most notable aspects of this study was the choice to implant a permanent pacemaker in both arms of the study. This was done for several reasons. The existence of class IIA indications in this population led to the choice to implant a pacemaker rather than to randomize 1 group to no therapy or to a loop recorder implant. In addition, as this study was mainly focused on patient symptoms, a more uniform therapy to all patients was a means to maintain patient blinding and thus to rule out a placebo effect on patient perceived symptoms that could have biased the results.

Previous studies have documented the incidence and new onset of either cardiac events or AVB in patients with BFB, as well as those BFB with negative EPS.[20–27] Although a thorough assessment of AVB development (especially those of transient nature) was not possible in our study, a conservative estimate for the development of a class IA indication for pacemaker, mainly due to AVB, was found in 13% of patients, with the event occurring most likely within a year from their enrollment. Differences in symptomatic AVB occurrence between the 2 groups showed that AVB was mainly recognized in the DDD30 group; this is explained by the fact that in the DDD60 group all blocks of transitory origin were not detected.

This study also demonstrated the potential value of pacemaker to prevent symptoms in a population where the diagnostic chain to exclude current class IA pacemaker indication (including EPS, tilt testing, Holter monitoring, and Echo) is often burdensome to perform in current practice. As noted in this study, despite the reliable determination of a bradyarrhythmia and its origin can be difficult in these patients, an annual incidence of 7.4% of indications for pacing together with a clinically significant reduction of symptomatic episode with a dual chamber pacemaker suggests that in a patient with a compelling history of sudden syncope, empirical pacing therapy could be appropriate. This could be also supported by the consideration that the mean age of this population (75 years), together with prevalence of AF (25% in this group), would lead to requiring the use of anti-arrhythmic drugs that contribute to the deterioration of intraventricular conduction in BFB patients.

Although sustained high-rate ventricular tachyarrhythmias can also be the cause of syncope in patients with BFB, in none of our cases a repetitive ventricular tachycardia has been detected by the device that is provided by a special algorithm for arrhythmia detection and storage. This result may be explained by careful selection of the patient population with exclusion of patients with significant structural heart disease and a consequent mean left ventricular ejection fraction of 57±10.

## Limitations

The main limitations of the present study are related to specific choices made in the design. The end point was driven by patient symptoms, with no possibility to accurately assess

cardiac rhythm disease development, especially when related to transient episodes of AVB. Accordingly, using only pacemaker diagnostics to detect occurrence of a block allowed us to detect only a conservative estimate for assessing the AVB development in this population. In addition, the study was single blinded and a registry of patients excluded (ie, positive to any of the screening test) was not kept.

## Conclusion

The present study demonstrated that the use of dual chamber permanent pacing (DDD60) in BFB patients with syncope of undiagnosed origins after diagnostic screening results in a significant reduction of the combination of syncope/presyncopal episodes or other symptomatic episode of cardioinhibitory origin. Although further randomized studies would be necessary to address some of the remaining questions on the nature of event recurrences in this population, this study suggests that the use of a dual chamber pacemaker in this patient population might be considered as a means for prevention of symptomatic event recurrences.

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## Disclosures

F. Accardi and G. Raciti are Boston Scientific employees. The other authors report no conflict of interest.

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## CLINICAL PERSPECTIVE

Bifascicular block is a rhythm disturbance linked with increased mortality, with an uneven occurrence of syncopal episodes, often associated with severe patient trauma or injuries. Although different techniques are indicated to investigate the cause underlying syncope (electrophysiological study, ECG, Holter monitoring, and tilt table testing), they have been reported to lack specificity and they are not commonly used in clinical practice. The prevention of syncope through permanent cardiac pacing in patients with bifascicular block study investigated the hypothesis that permanent pacing may play a role in bifascicular block patients with syncope that remains undiagnosed even after extensive diagnostic screening for an underlying rhythm disorder. This study demonstrates that the use of dual chamber pacemakers in these patients results in a significant reduction in the combination of syncopal/presyncopal episodes or other symptomatic episodes of cardioinhibitory origin. Albeit indirectly, this study also postulates the value of pacemakers to prevent symptoms in a population where diagnostic testing to exclude current class IA pacemaker indications is often burdensome to perform. Therefore, it is reasonable to consider that patients with bifascicular block and syncope could directly benefit from pacemakers without the need to undergo additional testing.

# SUPPLEMENTAL MATERIAL

## Appendix

The required diagnostic examination, that has been performed to verify the exclusion criteria listed above are the following: Electrocardiogram (ECG): to exclude any ongoing rhythm disturbance. Tilt Table Test (TTT): A 30 minutes TTT 60°/70° had to be performed to look for occurrence of syncope. If no syncope occurred in that timeframe Natispry was administered (0.30mg) and the test was prolonged for other 15 minutes. TTT was judged positive in case of syncope occurrence associated with bradycardia, hypotension, or both. Carotid sinus massage testing: the test was done for at least 10 seconds or until episode occurrence, both in supine and standing positon. ECG and pressure were monitored during the test. The test was judged positive if a syncope occurred during or immediately after the test together with asystole (≥3 sec.) and/or hypotension (≤50 mmhg). Electrophysiologic study (EPS): EPS was be done to exclude ventricular, supraventricular arrhythmias and AV conduction disturbances. The test was judged be positive if: 1) basal HV interval was ≥100ms or 2) an AV Block superior to 1st degree was induced with atrial incremental stimulation; or 3) monomorphic sustained VT was induced; or 4) sustained and symptomatic SVT were induced or 5) recovery time was ≥525 msec. 24 hour Holter monitoring: a minimum of 20 hour recoding was required with recording available during nighttime. Patients were excluded if heart rate averaged hour trend during sleep felt below 35 bpm, or if non-sustained VT were recorded. Echocardiography: four chamber view was performed to measure the LVEF. Only patients with a LVEF >40% were enrolled in the study.