Prevention of Syncope through Permanent Cardiac Pacing in Patients with Bifascicular Block and Syncope of Unexplained Origin: The PRESS Study

Running title: Santini et al.; Prevention of syncope using pacemaker

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Journal Subject Code: [120] Pacemaker
Abstract:

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

**Methods and Results** - PRESS is a multicenter, prospective, randomized, single blinded study designed to demonstrate a reduction in symptomatic events in patients with BFB and syncope of undetermined origin implanted with permanent pacemaker. Device programming at DDD with a lower rate of 60 ppm is compared to backup pacing at DDI with a lower rate of 30 ppm. The endpoint consisted of: 1) syncope; 2) symptomatic pre-syncopal episodes associated with a device intervention (ventricular pacing); 3) symptomatic episodes associated with intermittent or permanent atrio-ventricular block (any degree). 101 patients were enrolled and randomized. Primary endpoint events at two years were observed in 23 patients, with a significant lower incidence in the study group (HR: 0.32; 95% CI: 0.10 – 0.96; p=0.042). Reduction of any symptoms, associated or not with device intervention, was superior in DDD60 compared to DDI30 (HR: 0.4; 95% CI: 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 BFB 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 cardio-inhibitory origin, compared to 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.

**Key words**: pacemakers; syncope; Bifascicular Block; randomized controlled trial
Introduction

Bifascicular block (BFB) is a conduction disturbance with reported prevalence of 1–1.5%, with up to 25% of adult patients presenting with syncope\textsuperscript{1-6}. The cause of syncope in these patients is difficult to assess and may be due in part to transitory conduction disturbances at the pre-sinus, sinus, or atrio-ventricular node level\textsuperscript{6-8}. These patients may also present with ventricular tachycardia\textsuperscript{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\textsuperscript{6,11-14}.

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 useful in identifying specific causes often lack in specificity\textsuperscript{10,13,14,18}. Therefore, the current evidence led the ACC-AHA-HRS committee to consider permanent pacemaker implantation as a class IIA indication for BFB patients presenting with syncope of undetermined origin\textsuperscript{11,12,19}. However, the guidelines do not state which pacing modality should be chosen for these patients (single vs dual chamber). Limited information is available on the recurrences of syncopal episodes, hospitalizations and quality of life for these patients after pacemaker implantation. The PRESS study (PREvention of Syncope through permanent cardiac pacing in patients with bifascicular block) was designed to investigate the role of pacemaker in preventing symptom recurrences in patients with bifascicular block 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 symptoms recurrences in patients with bifascicular block 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 pre-syncopal episodes associated with a cardio-inhibitory origin (including symptomatic temporary or permanent atrio-ventricular block). 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 (Insignia™, Boston Scientific Corporation) and randomized to two parallel arms. The treatment arm included devices programmed to DDD pacing mode with a 60 ppm lower rate and AV interval ≥200 msec (DDD60). The control arm included those programmed with to 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 endpoint of the study was to demonstrate at two years after implant a reduction in the treatment group of the following composite: 1) syncopal episodes of any origin; 2) symptomatic pre-syncopal 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 atrio-ventricular block (any degree) or to sustained ventricular tachycardia. Pre-syncopal episodes with symptoms and without loss of consciousness were included as primary endpoints only if associated either with a documented bradycardia at ECG or with consistent ventricular pacing >1% detected by pacemaker diagnostics. Other symptoms were classified as primary endpoint only in the presence of documented evidence of AV block of any degree.

Secondary endpoint included: 1) comparison of each of the three separate components of
the primary endpoint in the two study groups; 2) comparison of symptomatic episodes of any origin between the two study groups; 3) rhythm disease progression in the entire cohort of patients (AV block, bradycardia, atrial fibrillation); 4) comparison of documented atrial fibrillation in the two study groups; 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, EP study, to rule out any possible preexisting 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 atrial fibrillation 3) sinus node dysfunction or Brady-Tachy syndrome; 4) 2nd or 3rd degree atrio-ventricular block (AVB), diagnosed at ECG or during EP study; 5) spontaneous or inducible sustained ventricular tachycardia; 6) minimal nocturnal heart rate inferior to 35 bpm documented at Holter monitoring. Patients with significant structural heart disease (EF <40%) were also excluded. Detailed description for the diagnostic examinations to assess these criteria are detailed in appendix.

After signing informed consent, patients underwent dual chamber pacemaker implantation; randomization occurred at patient discharge post implant (block randomization with block size = 4 allocation, ratio 1:1). Medical therapy was prescribed according to physician discretion. The use of Beta 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 two years after enrollment with standard in-clinic visit programmed at one 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 endpoint reached. Primary endpoint 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 endpoint, 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 of 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, standard deviation, median and quartiles for continuous data, according to distribution. Primary and secondary endpoints were analyzed with a survival analysis techniques and the Kaplan-Meier method. Log-rank test was also used to analyze the primary endpoint. Additionally, Cox model with robust standard errors was used to analyze both primary and secondary endpoints to account for intra site 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 two years-follow-up, two 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 COPD; 1 myocardial infarction), yielding to a total of 93 patients at the end of the follow up period.

The composite primary endpoint occurred in 23 patients (22.8%) at two 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 (HR: 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 NNT=5.23). The first event occurred in these 23 patients was syncope in 14 (13.9%), pre-syncope in 6 (5.9%) and AV block in 3 (3%) patients. Additionally, the proportion of patients presenting with syncope, pre-syncope and AV block alone, considered as independent events, were compared in the two study groups (table 2), indicating that a significant difference is still preserved between the DDD60 and DDI30 for pre-syncope and AV block 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 pre-syncopal episodes due to a documented cardio-inhibition was 34 in 22 patients (21.8%): 9 patients had recurrences after the first episode with 6 patients having one recurrence and 3 patients with two recurrences. All patients with pre-syncope recurrences were originally programmed in the DDI30 (control group). Reprogramming of pacing mode from DDI30 to DDD60 occurred in 15 patients following the first event of syncope or pre-syncope. In 13 of these cases the event has been adjudicated as primary endpoint. Among the 9 patients originally programmed at DDI30 and with recurrent pre-syncope, only 2 had the device reprogrammed to
DDD60 after the first episode.

Overall, a symptomatic episode (syncope or pre-syncope), 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 (HR: 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.

14 patients developed a Class I indication for permanent pacing during the course of the study (10 symptomatic AV block, 2 Brady-Tachy, 1 sinus bradycardia, 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 AV block, with 5.38%). With regard to the 10 patients who showed a complete AV block 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 one hospitalization for symptomatic Heart Failure, associated or not with AV block, yielding an annual incidence of 3.7%. In DDD60 group median pacing rate was: 26% for atrium (IQR: 1%-48%) and 23% for ventricle (IQR: 1%-35%). 10 patients (9.9%) had a history of paroxysmal AF before implant. During follow up, a total of 44 episodes of atrial fibrillation were retrieved in 26/101 patients. Episodes were retrieved either at ECG or from implanted device diagnostics.

Among the 26 patients with atrial fibrillation, 7 were patients with documented pre-implant atrial fibrillation history and 19 were patients with new onset, post-implant, atrial fibrillation episodes. The total annual incidence of atrial fibrillation in this sample was 13.1%. None of these patients presented with ventricular tachycardia during the course of the follow up.

**Discussion**

Bifascicular 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\textsuperscript{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 bifascicular block population are heterogeneous, the most frequent being neurally mediated syncope or intermittent high degree atrio-ventricular (AV) block\textsuperscript{7,20,23,24}. Additionally, several studies focusing on follow-up of BFB patients with previous syncope reported consistent rates of temporary or permanent AV block development over time\textsuperscript{8,11,25-28}. Despite the high incidence of electric disturbances of the conduction system, electro-physiological study (EPS) at the time of the hospital observation has limited positive predictive value\textsuperscript{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 in order to identify the nature of associated syncopal recurrences and consequently its most appropriate treatment\textsuperscript{5, 24, 27, 31, 32}. Current guidelines set in the last 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\textsuperscript{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, pre-syncope or AV block when compared to a substantially negligible electrical treatment. Indeed, the programming to DDI-30 bpm of the control group patients was chosen in order 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 bpm.
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 pre-selection of patients, symptoms associated with new onset of a rhythm disease including AV block, brady-tachy or bradycardias or chronic atrial fibrillation 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 endpoint, a significant difference between the study group and controls is shown only with respect to pre-syncope and to symptoms associated with AV block, 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 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 cardio-inhibitory episode, syncope events that occurred in this sample were likely due to vasodepressor syndrome, hypotension from non-cardiac etiology (e.g., excessive medications/postural orthostasis) or a neurological issue not detected with the pre-enrollment tilt test screening.

Additionally, it is reasonable to hypothesize that patients with cardio-inhibitory episodes have turned into most of the pre-syncope symptoms, especially in the control group. Additionally, the fact that these syncopal recurrences occurred in patients implanted with pacemaker regardless of device programming, rule out the possible placebo effect of pacing, as hypothesized in previous studies. However, it should be noted that the study was not powered to separately evaluate individual endpoint events.

PRESS is the first randomized study for a BFB population involving a very strict
selection and screening process. Specifically, diagnostic criteria used for the patients selection (including ECG, Holter, TTT, and EPS) were used to exclude other possible causes for syncopal episodes. The fact that 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 one group to no therapy or to a loop recorder implant. Additionally, 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 AV block in patients with BFB, as well as those BFB with negative EPS. Despite a thorough assessment of AV block development (especially those of transient nature) was not possible in our study, a conservative estimate for development of a class IA indication for pacemaker, mainly due to AV block, 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 two 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 empiric pacing therapy could be appropriate. This could be also supported by the consideration that, the mean age of this population (75 yrs), together with prevalence of AF (25% in this group), would lead to requiring the use of AA 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 which 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 endpoint was driven by patient symptoms, with no possibility to accurately assess cardiac rhythm disease development, especially when related to transient episodes of atrio-ventricular block. Accordingly, using only pacemaker diagnostics to detect occurrence of a block allowed us to detect only a conservative estimate for assessing the AV block development in this population. Additionally, the study was single blinded and a registry of patients excluded (i.e. positive to any of the screening test) was not kept.

Conclusion
The present study demonstrated that the use of dual chamber permanent pacing (DDD 60) in
BFB patients with syncope of undiagnosed origins after diagnostic screening, results in a significant reduction of the combination of syncope/pre-syncopal episodes or other symptomatic episode of cardio-inhibitory 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.

**Funding Sources:** The PRESS study has been sponsored by Boston Scientific Corporation.

**Conflict of Interest Disclosures:** F. Accardi and G. Raciti are Boston Scientific employee.

**References:**


8. De Pasquale NP, Bruno ME. Natural history of combined right bundle branch block and left


Table 1: Baseline Demographic and Clinical Characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall* (N=101)</th>
<th>Control* (N=49)</th>
<th>Treatment* (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>77±8</td>
<td>78±8</td>
<td>76±7</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>57±10</td>
<td>59±10</td>
<td>55±10</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>128±36</td>
<td>127±40</td>
<td>128±39</td>
</tr>
<tr>
<td>PR duration (ms)</td>
<td>175±60</td>
<td>171±62</td>
<td>179±60</td>
</tr>
<tr>
<td>Months from 1st episode (mo)</td>
<td>6 [1-12]</td>
<td>6 [1-12]</td>
<td>12 [1-12]</td>
</tr>
<tr>
<td># syncope in last 6 mo</td>
<td>1 [1-2]</td>
<td>1 [1-3]</td>
<td>1 [1-2]</td>
</tr>
<tr>
<td># pre-syncope in last 6 mo</td>
<td>0 [0-1]</td>
<td>0 [0-1]</td>
<td>0 [0-1.5]</td>
</tr>
<tr>
<td>Pts with previous sudden syncope with physical trauma.</td>
<td>42/101 (42%)</td>
<td>20/49 (41%)</td>
<td>22/52 (42%)</td>
</tr>
<tr>
<td>Minimum heart rate at Holter</td>
<td>47±9</td>
<td>50±10</td>
<td>49±8</td>
</tr>
<tr>
<td>Male gender</td>
<td>61/101 (60%)</td>
<td>26/49 (53%)</td>
<td>35/52 (67.3%)</td>
</tr>
<tr>
<td>Aethiology - none</td>
<td>33/101 (33%)</td>
<td>16/49 (33%)</td>
<td>17/52 (33%)</td>
</tr>
<tr>
<td>Aethiology - ischemic</td>
<td>19/101 (19%)</td>
<td>9/49 (18%)</td>
<td>10/52 (19%)</td>
</tr>
<tr>
<td>Aethiology - valvular</td>
<td>2/101 (2%)</td>
<td>1/49 (2%)</td>
<td>1/52 (2%)</td>
</tr>
<tr>
<td>Aethiology - dilated</td>
<td>2/101 (2%)</td>
<td>0/49 (0%)</td>
<td>2/52 (4%)</td>
</tr>
<tr>
<td>Aethiology – hypertensive</td>
<td>47/101 (47%)</td>
<td>27/49 (55%)</td>
<td>20/52 (38%)</td>
</tr>
<tr>
<td>Aethiology – other</td>
<td>13/101 (13%)</td>
<td>4/49 (8%)</td>
<td>9/52 (17%)</td>
</tr>
<tr>
<td>Atrial Fibrillation history</td>
<td>10/101 (10%)</td>
<td>6/49 (12%)</td>
<td>4/52 (8%)</td>
</tr>
<tr>
<td>Previous hospitalizations (all-cause)</td>
<td>41/101 (41%)</td>
<td>19/49 (39%)</td>
<td>22/52 (42%)</td>
</tr>
<tr>
<td>Previous hospitalizations (heart failure)</td>
<td>2/101 (2%)</td>
<td>2/49 (4%)</td>
<td>0/52 (0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26/101 (26%)</td>
<td>14/47 (29%)</td>
<td>12/49 (23%)</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>58/96 (60.4%)</td>
<td>30/47 (64%)</td>
<td>28/49 (57%)</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>29/96 (30.2%)</td>
<td>14/47 (30%)</td>
<td>15/49 (31%)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>8/96 (8.3%)</td>
<td>3/47 (6%)</td>
<td>5/49 (10%)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>1/96 (1%)</td>
<td>0/47 (0%)</td>
<td>1/49 (2%)</td>
</tr>
<tr>
<td>Ace- inhibitors</td>
<td>27/101 (27%)</td>
<td>10/49 (20%)</td>
<td>17/52 (33%)</td>
</tr>
<tr>
<td>Anti arrhytmic</td>
<td>12/101 (12%)</td>
<td>8/49 (16%)</td>
<td>4/52 (8%)</td>
</tr>
<tr>
<td>Anticoagulants/ antiaggregants</td>
<td>33/101 (33%)</td>
<td>14/49 (28%)</td>
<td>19/53 (37%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>19/101 (19%)</td>
<td>9/49 (18%)</td>
<td>10/52 (19%)</td>
</tr>
<tr>
<td>Ca++ antagonists</td>
<td>20/101 (20%)</td>
<td>11/49 (22%)</td>
<td>9/52 (17%)</td>
</tr>
<tr>
<td>digitalis</td>
<td>2/101 (2%)</td>
<td>1/49 (2%)</td>
<td>1/52 (2%)</td>
</tr>
<tr>
<td>diuretics</td>
<td>26/101 (26%)</td>
<td>12/49 (24%)</td>
<td>14/52 (27%)</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>21/101 (21%)</td>
<td>12/49 (24%)</td>
<td>9/52 (17%)</td>
</tr>
<tr>
<td>Statins</td>
<td>8/101 (8%)</td>
<td>6/49 (12%)</td>
<td>2/52 (4%)</td>
</tr>
</tbody>
</table>

*Numbers are % (counts) or mean ± standard deviation.
Table 2: Two-years development of syncope, pre-syncope and AV block alone

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>DDI30</th>
<th>DDD60</th>
<th>P value</th>
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<tr>
<td>Syncope</td>
<td>14 (13.9%)</td>
<td>7 (14.3%)</td>
<td>7 (13.5%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Presyncope</td>
<td>22 (21.8%)</td>
<td>16 (32.6%)</td>
<td>6 (11.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic AV block</td>
<td>10 (9.9%)</td>
<td>8 (16.3%)</td>
<td>2 (3.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Kaplan Meier curves - Primary endpoint. HR: Hazard Ratio

Figure 2. Kaplan Meier curves – patient symptoms (Syncope or pre-syncope of any origin) HR: Hazard Ratio
Circulation
Arrhythmia and Electrophysiology

HR: 0.32;
95% CI: 0.10 – 0.96
p=0.042

Freedom from All Endpoint Events

0.00  0.25  0.50  0.75  1.00

0  3  6  9  12  15  18  21  24

months

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>DDI 30 ppm</th>
<th>DDI 30 ppm</th>
<th>DDI 30 ppm</th>
<th>DDI 30 ppm</th>
<th>DDI 30 ppm</th>
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<tr>
<td>DDI 60 ppm</td>
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<td>51</td>
<td>48</td>
<td>47</td>
<td>46</td>
<td>46</td>
<td>45</td>
<td>43</td>
</tr>
</tbody>
</table>

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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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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 position. 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.