Increase of Ventricular Interval during Atrial Fibrillation by AV Node Vagal Stimulation: Chronic Clinical AVNS Download Study

Running title: Bianchi et al.; Vagal stimulation to reduce inappropriate shocks

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Abstract:

Background - Patients with a high ventricular rate during atrial fibrillation (AF) are at increased risk of receiving inappropriate implantable cardioverter defibrillator (ICD) shocks. The objective was to demonstrate the feasibility of high frequency atrioventricular-nodal stimulation (AVNS) to reduce the ventricular rate during AF to prevent inappropriate ICD shocks.

Methods and Results - Patients with a new atrial lead placement as part of a CRT-D implant and a history of paroxysmal or persistent AF were eligible. If proper atrial lead position was confirmed, AVNS software was uploaded to the CRT device, tested and optimized. AVNS was delivered via a right atrial pacing lead positioned in the posterior right atrium. Software allowed initiation of high frequency bursts triggered on rapidly conducted AF. Importantly, the efficacy was evaluated during spontaneous AF episodes between 1 and 6 months after implant. Forty-four patients were enrolled in 4 centers. Successful atrial lead placement occurred in 74%. Median implant time of the AVNS lead was 37 minutes. In 26 (81%) patients, manual AVNS tests increased the ventricular interval by > 25%. Between 1 and 6 months, automatic AVNS activations occurred in 4 patients with rapidly conducted AF, and in 3 patients, AVNS slowed the ventricular rate out of the ICD shock zone. No adverse events were associated with the AVNS software.

Conclusions - The present study demonstrated the feasibility of implementation of AVNS in a CRT-D system. AVNS increased ventricular interval > 25% in 81% of patients. AVNS did not influence the safety profile of the CRT-D system.

Clinical Trial Registration - ClinicalTrials.gov; Unique Identifier: NCT01095952.

Key words: atrial fibrillation, vagal stimulation, shock, AV-node stimulation, dromotropic effect, parasympathetic nerve stimulation, shock reduction
Introduction

An implantable cardioverter defibrillator (ICD) has become an important treatment modality in patients at risk of sudden cardiac death. However, patients with an ICD are also at risk of receiving inappropriate shocks, possibly affecting mortality, quality of life and overall ICD longevity. About half of the inappropriate ICD shocks have been found to be due to atrial tachycardia (AT) and atrial fibrillation (AF).

Slowing the AV node conduction, i.e. high frequency atrioventricular nodal vagal stimulation (AVNS) can be achieved by selective stimulation of the parasympathetic nerve fibers arising from the inferior ganglionated plexus to the AV node using an endocardial atrial pacing lead. AVNS has recently emerged as a non-pharmacological treatment to reduce the ventricular rate during AF.

In this multicenter study, we tested the hypothesis that automated intermittent selective stimulation of parasympathetic nerves fibers, innervating the AV-node, increases the ventricular interval during rapidly conducted AF and may prevent inappropriate ICD shocks. This feasibility study reports on the implant procedure data and safety aspects of the AVNS software.

Methods

In this multi-center study, forty-four patients were included. The study took place at 4 sites, i.e. in Aachen, Germany; Rome, Italy; Uppsala, Sweden and Zwolle, the Netherlands. The protocol was approved by the Medical Ethics Committees of participating hospitals and the Competent Authorities of the relevant countries. All adverse events, technical observations and deaths were reviewed by an independent Adverse Event Advisory Committee.

In- and exclusion criteria

Patients with a documented history of paroxysmal or persistent AF were eligible for this study if
they had an indication for:

- Cardiac resynchronization therapy and defibrillator (CRT-D) implant;
- Upgrade to CRT-D from a single-chamber device;
- Upgrade or revision to CRT-D with an atrial lead positioned septally at the AVNS site or a dislodged atrial lead;

Exclusion criteria were: permanent atrial fibrillation; patients, who were not on anti-coagulant therapy; advanced AV block; patients who had previously undergone valvular surgery, which potentially resulted in damage of the AV-node or the parasympathetic nerve(s), patients who had previously undergone AV or AF ablative procedures, which potentially resulted in damage of the AV-node or the parasympathetic nerve(s); age < 18 years; pregnancy and participation in other studies, which could potentially conflict with this study.

**AVNS software design**

An investigational AVNS algorithm (AVNSia) was developed to deliver AVNS (i.e. selective high frequency stimulation of parasympathetic nerves to the AV-node) in a “burst” pattern during the ventricular refractory period (50Hz, pulses 8, pulse width 1.5 ms, burst duration 160 ms) for 30 seconds via the posteroseptally positioned atrial lead. AVNS software could be uploaded to the Medtronic Consulta™ biventricular ICDs only. High frequency stimulation was performed during the refractory period of the ventricles to prevent induction of ventricular arrhythmia’s, in case of atrial lead dislodgement and movement of this lead into the right ventricle. AVNSia was designed to initiate when AT/AF is detected in combination with manual activation during the in-hospital tests or in combination with detection of 7 subsequent rapid ventricular intervals (< 360 ms) during the follow-up period. AVNSia was terminated if the therapy was ineffective (defined as < 150 ms reduction in median VV (ventricular) interval
checked at 5 ventricular intervals after AVNS was started), or if a single short VV interval (< 360 ms) was detected after this point, or if the programmed duration of AVNS therapy of 30 seconds had passed. Ventricular tachycardia (VT) and ventricular fibrillation (VF) limits were set to 360 and 300 ms respectively.

**Atrial lead implant procedure**

Atrioventricular (AV) nodal conduction is modulated by the parasympathetic nervous system through nerve fibers, residing in an epicardial plexus located in the posterior right atrium. These nerve fibers extend through the interatrial septum at the coronary sinus ostium and/or the posteroseptal right atrium. After right ventricular lead implantation, a standard atrial screw in lead (Medtronic type 5076 (2), 4076 (29) or St Jude’s 2088TC (1)) was directed and screwed into the posteroseptal region of the coronary sinus ostium. The septum is recognized as a feasible and safe site for chronic pacing to reduce paroxysmal AF recurrences, AF burden and progression to permanent AF, with the rationale of reducing the duration of atrial activation.

Pacing was delivered (10V, 1.5 ms, 30bpm above mean VR) through the atrial lead using an external pacemaker to exclude ventricular capture. In the event of ventricular capture, the atrial lead was repositioned. If the patient was in sinus rhythm (SR) during the implantation procedure, the following was verified: 1) Atrial lead impedance ≤ 1500 Ohm, 2) Pacing threshold ≤ 2V at 0.5 ms and 3) Far-field R-wave oversensing was not leading to atrial oversensing.

The atrial lead was considered implanted successfully during SR if significant AV conduction slowing (defined as a ≥25% increase of PR interval) could be induced using an external pulse generator by delivering high frequency burst stimulation (pulse amplitude 8V, pulse duration 1.5ms, frequency 50Hz, 8 pulses synchronized on P-wave to prevent AT/AF induction) and P-wave sensing was at least 0.5mV.
The atrial lead was considered implanted successfully during AF if significant AV conduction slowing, defined as a \( \geq 25\% \) increase of mean VV interval, could be induced using an external pulse generator by delivering 10 seconds of continuous high frequency stimulation (pulse amplitude 8V, pulse duration 1.5ms, frequency 50Hz). Patients in whom the atrial lead could not be successfully positioned were withdrawn from the study.

At the end of the surgical procedure, the AVNS software was uploaded to the CRT-D device through the telemetric system commonly used to program the device and tested. In patients with sinus rhythm, AF was induced by burst pacing. Pulse width was set at 1.5 ms and burst duration at 160 ms (to remain in ventricular refractory period). The threshold for a 25% increase in VV interval during AF was tested, with the voltage output titrated from 8, 6, 4 to 2 V. For the in-hospital tests, VV intervals obtained from continuous ECG recordings 30 seconds before the start of the AVNS\(_{\text{ia}}\) test were compared with those recorded 30 seconds after the start of the AVNS\(_{\text{ia}}\) test. The AVNS\(_{\text{ia}}\) was switched off at the end of the procedure.

**Follow-up**

Patients were required to be followed for six months, during which 1, 3 and 6 months visits were scheduled to obtain recordings of automatic AVNS\(_{\text{ia}}\) and arrhythmia, adverse events, medication, standard pacing tests and safety tests. The AVNS\(_{\text{ia}}\) was activated at the 1 month visit and deactivated at the 6 month visit, when the software function was removed from the device via the telemetric programmer. The AVNS\(_{\text{ia}}\) was programmed at 8V unless this gave symptoms during the in hospital tests, than the voltage was set at 6V for the follow-up period.

**Statistics**

**Sample size**

The primary objective was to assess the relative increase in VV interval during AT/AF by
AVNS<sub>ia</sub> programmed to maximal output during in-hospital tests. The primary end-point was the proportion of patients that achieved a VV interval increase of at least 25%. Assuming 70% of those with a successful atrial lead placement would fulfill this end-point, a confidence interval of 95% and a precision (i.e. half of the desired confidence interval width) of 15%, it was estimated that at least 37 patients would be needed to reach the primary end-point.

Considering early experiences in selective His bundle pacing without appropriate implant tools, an implant success rate of 67% was reported. We assumed that a similar result would be acceptable as first implant experiences in the AVNS study. It was estimated that approximately 55 patients needed to be enrolled to obtain the required 37 patients for the primary end-point. Slower than expected enrollments due to reimbursement difficulties resulted in an evaluation of the initial sample size calculations during the study. The proportion of patients meeting the primary end-point was found to be higher than expected. Therefore a new sample size calculation was performed, assuming 78% of those with a successful lead placed would fulfill the end-point and using a confidence interval of 95% and a precision (i.e. half of the desired confidence interval width) of 15%. The 32 successfully implanted patients appeared to be acceptable to meet the precision requirement of the primary objective.

Secondary objectives were to evaluate 1) the performance of AVNS<sub>ia</sub> in shock reduction during the follow-up period, 2) safety of AVNS<sub>ia</sub>, 3) to assess symptoms related to interventions of AVNS<sub>ia</sub>, both during acute tests and follow-up.

**Statistical Analyses**

The statistical analysis for this feasibility study was based on a “per-protocol” approach to assess the effect in those patients, who were able to receive the therapy. Continuous variables were expressed as mean with standard deviation in case of normal distribution or median with
interquartile ranges of the 25th and 75th percentile (IQR) when variables were not normally distributed. Chi-square tests were used to compare categorical data. Continuous data were compared with a paired t-test or Repeated Measures Analysis of Variance for more than two group comparisons. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS software version 9.3 (SAS Institute).

Results

Patient population

Forty-four patients were enrolled between January 2011 and June 2013. Baseline characteristics are displayed in Table 1. In one patient, the atrial lead placement was not attempted. 37 patients had a new device implantation, 5 underwent an upgrade to CRT-D with a new atrial lead placement and one patient already had a septally positioned right atrial lead. Atrial lead placement was successful in 32 (74%) patients. In 6 cases, a site with a negative dromotropic effect could not be found, and in 3 cases, the ventricular R wave influenced accurate atrial sensing. In one case, the atrial lead dislodged and could not be replaced due to a VT storm and in one case, the atrial pacing threshold was too high. Median implant time for the atrial lead was 37 minutes (IQR: 17-84), with a median number of (re)positioning of 3 (IQR: 1-7).

Directly after the implant procedure, the median atrial pacing threshold determined at 1 ms was 0.9 V (IQR 1-2), and median P wave amplitude was 1.6 mV (IQR 1-3), median Far Field R wave was 0 mV (IQR 0-1) and median pacing impedance was 494 Ω (IQR 456-627).

AVNSia test directly after implant

Directly after the implant procedure, AVNSia efficacy tests were performed manually in 11 patients, who were already in AF, and in 21 patients in whom AF was induced by burst pacing.
A typical example of the effects of AVNS_{ia} on the ventricular interval during AF is illustrated in Figure 1.

Manual AVNS_{ia} was always effective (> 150 ms increase in median VV interval at 5 VV intervals after it started) and was therefore never terminated due to inefficacy. In 26 patients (81%), AVNS_{ia} performed at 8V increased the ventricular interval by more than 25%. Baseline ventricular interval was 670 ± 220 ms, which was significantly increased during AVNS at 8V to 930 ± 310 ms (p < 0.001), corresponding to an average increase in ventricular interval of 40 ± 29%. In 12 patients, AVNS was tested at 2V, 4V and 8V, with a significant dose-dependent difference in terms of ventricular interval increase (% increase at 8V: 57 ± 34, 4V: 31 ± 21 and 2V: 27 ± 20, p < 0.001).

No patients experienced palpitations, shortness of breath, dizziness or phrenic nerve stimulation during the AVNS_{ia} test at maximal output. 5 out of 32 patients reported chest, arm or jaw discomfort during the AVNS_{ia} test, but only at 8V output.

**Follow-up**

Automatic AVNS activations occurred in 4 patients due to AT/AF with a ventricular interval less than 360 ms. In 5 AVNS activations in 3 patients, AVNS was associated with an increase in ventricular interval out of the ventricular tachycardia/ventricular fibrillation (VT/VF) zone, as displayed in figure 2. These patients did not receive an inappropriate ICD shock during the AF episode. The patient in whom automatic AVNS at 8V was not effective had an increase of VV interval of 7% during the in hospital test at 8V and did not receive an inappropriate ICD shock during the AF episode.

Ten patients developed 30 VF episodes, which were terminated by an ICD shock in 22 cases. AVNS was activated in one of these episodes, because the VF episode coincided with an
AT/AF episode (Fig. 3). After 5 ventricular beats the AVNS was automatically de-activated and did not delay the treatment with an appropriate ICD shock.

There were no differences found in the atrial pacing threshold \( p = 0.89 \), P-wave amplitude (when in sinus rhythm) \( p = 0.54 \), Far-field R-wave amplitude \( p = 0.63 \) and pacing impedance \( p = 0.24 \) at 1, 3 or 6 months when compared with implant. During follow-up, we did not observe ventricular capture due to AVNS_{ia}. Seven patients were lost to follow-up.

Safety

All safety issues related to the atrial lead placement or its procedure are displayed in Table 2. Of note, there were no adverse events related to the AVNS_{ia} software.

In two patients, an atrial lead dislodgement was diagnosed, 1 day and 24 days after implant, respectively. These leads were repositioned in the right atrial appendage. In the same patients, 2 left ventricular lead dislodgements were reported.

Discussion

In this feasibility study, high frequency stimulation of the right inferior ganglionated plexus with AVNS was successfully implemented using a conventional CRT-D system in 32 patients. Directly after the implant procedure, AVNS increased ventricular intervals by \( \geq 25\% \) in 81\% of these patients. AVNS did not influence the safety profile of the CRT-D implant and was not associated with adverse events. AVNS activations during follow-up increased the ventricular interval during AF. AVNS may be an important tool in reducing inappropriate shocks in patients with paroxysmal AF and an ICD.

Shock prevention

Significant improvements have been made to reduce inappropriate shocks in the last few years, ranging from 21\% during a 3 year German registry to 3-6\% in 1.4 years in a recent study. \(^{2, 3, 7, 34}\)
Furthermore, a reduction of ICD shocks was achieved by using higher VT/VF detection thresholds, longer VT/VF detection durations, use of supra ventricular tachycardia discriminators and use of anti-tachycardiac pacing.\(^{35}\) By using data from previous studies\(^{36-38}\) combining wavelet, T-wave discrimination, lead noise discrimination, lead integrity alert, and improved recognition of rhythm termination during charging, it appears to be possible to reduce the occurrence of inappropriate shocks within 1 year to 1.8 \%.\(^6\) The majority (55\%) of the inappropriate shocks were due to rapidly conducted AT/AF.\(^6\) The present study shows that AVNS is effective in increasing the ventricular interval during paroxysmal AF and may possibly reduce the inappropriate shock rate even more.

Safety

Implantation of the atrial lead was unsuccessful in 11 patients. Potentially, the angle of the atrial lead was too steep in relation to the myocardial wall compromising lead implant time and success rate. Furthermore, implant time of the atrial lead appears to be increased compared to normal atrial lead placement. A supportive sheath with an improved curve and stiffness can be designed, allowing easier navigation of the atrial lead and increasing implant success rate, while reducing procedure time. In addition, atrial lead dislodgement rate in the present study (6\%) appears to be in line with the 5\% dislodgement rate reported in a previous study on septally positioned atrial leads,\(^{39}\) compared to a 2\% dislodgement rate for atrial leads positioned in the right atrial appendage.\(^{40,41}\) Of note, atrial lead impedance, pacing threshold, impedance and far-field R-wave oversensing were within normal ranges and remained stable during follow-up.

The AVNS software was not associated with adverse events, neither during the implant procedure nor during the follow-up period. During the implant procedure, the ICD system was tested extensively to exclude ventricular capture, since this may induce VT/VF episodes due to
rapid pacing. We did not observe any VT/VF episodes related to AVNS. Importantly, AVNS does not prolong time to ICD shock in case of VT/VF, as is demonstrated in Figure 3. However, future studies with larger patient populations are necessary to provide sufficient statistical power for the safety aspects of AVNS.

Future studies.

AVNSia may be useful to prevent inappropriate shocks in patients with rapidly conducted paroxysmal AT/AF, as illustrated by the 3 patients, who did not receive an inappropriate ICD shock due to the application of AVNS. However, studies with a larger population size are necessary to provide more extensive clinical evidence. It should be noted though that chronic AF patients will be more readily treated by AV node ablation. Furthermore, lead placement and the AVNS software appeared to be safe in this feasibility study, but more studies are necessary to confirm these observations, potentially using leads with adapted stiffness, curvature, screws and implant tools.

Conclusion

The present study demonstrated the feasibility of implementation of AVNS in a CRT-D system. During the implant procedure, AVNS increased ventricular interval > 25% in 81% of patients. AVNS did not influence the safety profile of the CRT-D system. AVNS may be an important tool in reducing inappropriate ICD shocks in patients with a short ventricular interval during AF.

Conflict of Interests Disclosures: This study has been sponsored by Medtronic. S. Bianchi and P. Rossi have licence patent with Medtronic. P. Schauerte have received funding from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical for consulting and lectures. A. Elvan and P. Gal none. C. Blomström-Lundqvist Research support and/or consultancies for Medtronic, Boston, Bayer, BMS, Pfizer, Cardiomed, St. Jude Medical, Biotronik. L. Kornet and G. Wouters are employers of Medtronic. D. Mörtsell, C. Gemein Travel payment by Medtronic and lecture fees by Zoll EMS.
References:


Table 1: Patient demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Total (N = 44)</th>
<th>Successful Patients (N = 32)</th>
<th>Unsuccessful Patients (N = 12)</th>
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<tr>
<td><strong>Gender (N, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (86.4%)</td>
<td>27 (84.4%)</td>
<td>11 (91.7%)</td>
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<tr>
<td>Female</td>
<td>6 (13.6%)</td>
<td>5 (15.6%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>69 ± 8</td>
<td>68 ± 8</td>
<td>71 ± 7</td>
</tr>
<tr>
<td><strong>Height (cms)</strong></td>
<td>172 ± 10</td>
<td>171 ± 9</td>
<td>174 ± 10</td>
</tr>
<tr>
<td><strong>Weight (kgs)</strong></td>
<td>81 ± 14</td>
<td>79 ± 15</td>
<td>86 ± 12</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>27.1 ± 3.7</td>
<td>26.9 ± 3.8</td>
<td>27.8 ± 3.3</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>28.5 ± 5.5</td>
<td>28.6 ± 5.4</td>
<td>28.0 ± 6.1</td>
</tr>
<tr>
<td><strong>Valvular regurgitation, mitral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (31.8%)</td>
<td>11 (34.4%)</td>
<td>3 (25.0%)</td>
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<tr>
<td>Mild</td>
<td>16 (36.4%)</td>
<td>12 (37.5%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (18.2%)</td>
<td>6 (18.8%)</td>
<td>2 (16.7%)</td>
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<tr>
<td>Severe</td>
<td>5 (11.4%)</td>
<td>3 (9.4%)</td>
<td>2 (16.7%)</td>
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<tr>
<td><strong>NYHA</strong></td>
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<td>Class I</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Class II</td>
<td>3 (6.8%)</td>
<td>1 (3.1%)</td>
<td>2 (16.7%)</td>
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<tr>
<td>Class III</td>
<td>39 (88.6%)</td>
<td>30 (93.8%)</td>
<td>9 (75.0%)</td>
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<td>Class IV</td>
<td>1 (2.3%)</td>
<td>1 (3.1%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Not available</td>
<td>1 (2.3%)</td>
<td>0 (0.0%)</td>
<td>1 (8.3%)</td>
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<tr>
<td><strong>Primary Heart Failure</strong></td>
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<tr>
<td>Ischemic cardiomyopathy</td>
<td>23 (52.3%)</td>
<td>16 (50.0%)</td>
<td>7 (58.3%)</td>
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<tr>
<td>Idiopathic dilated</td>
<td>16 (36.4%)</td>
<td>12 (37.5%)</td>
<td>4 (33.3%)</td>
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<tr>
<td>Hypertensive</td>
<td>1 (2.3%)</td>
<td>1 (3.1%)</td>
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<td>Valvular</td>
<td>1 (2.3%)</td>
<td>1 (3.1%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Other</td>
<td>3 (6.8%)</td>
<td>2 (6.3%)</td>
<td>1 (8.3%)</td>
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<tr>
<td><strong>Symptoms Experienced in the Last Year</strong></td>
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<tr>
<td>Chest pain</td>
<td>6 (13.6%)</td>
<td>5 (15.6%)</td>
<td>1 (8.3%)</td>
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<td>Dizziness</td>
<td>9 (20.5%)</td>
<td>7 (21.9%)</td>
<td>2 (16.7%)</td>
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<tr>
<td>Dyspnea</td>
<td>36 (81.8%)</td>
<td>25 (78.1%)</td>
<td>11 (91.7%)</td>
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<td>Edema</td>
<td>10 (22.7%)</td>
<td>10 (31.3%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Exercise</td>
<td>11 (25.0%)</td>
<td>10 (31.3%)</td>
<td>1 (8.3%)</td>
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<tr>
<td>Fatigue</td>
<td>7 (15.9%)</td>
<td>5 (15.6%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (4.5%)</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Palpitations</td>
<td>9 (20.5%)</td>
<td>5 (15.6%)</td>
<td>4 (33.3%)</td>
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<tr>
<td>Orthopnea</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
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<tr>
<td><strong>Cardiovascular history</strong></td>
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<td></td>
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<tr>
<td>Coronary artery disease</td>
<td>20 (45.5%)</td>
<td>13 (40.6%)</td>
<td>7 (58.3%)</td>
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<tr>
<td>Prior Myocardial infarction</td>
<td>17 (38.6%)</td>
<td>12 (37.5%)</td>
<td>5 (41.7%)</td>
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</tbody>
</table>

BMI: body mass index, LVEF: left ventricular ejection fraction.
### Table 2: SAE’s related to the procedure and/or system (AEAC classification).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term (MedDra)</th>
<th>Number of events</th>
<th>Events/Enrolled subjects [%] (N=44)</th>
<th>Relatedness</th>
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</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Device connection issue</td>
<td>1</td>
<td>2.3%</td>
<td>RA Lead, Implant procedure</td>
</tr>
<tr>
<td></td>
<td>Device dislocation</td>
<td>4</td>
<td>9.1%</td>
<td>LV Lead, RA Lead Implant procedure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachyarrhythmia</td>
<td>1</td>
<td>2.3%</td>
<td>Device (external pulse generator)</td>
</tr>
<tr>
<td>Infections</td>
<td>Implant site infection</td>
<td>1</td>
<td>2.3%</td>
<td>RA Lead, RV Lead, LV Lead, Implant procedure</td>
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Figure Legends:

**Figure 1:** Typical example of the effect of AVNS during in hospital test on ventricular rate during atrial fibrillation (AF). The atrial electrogram displays an episode of AF. Note the rapid and irregular ventricular rate at the left part of the tracing. At the black triangles, AVNS is activated. Note that immediately after the QRS complex, AVNS (8V, 8 pulses, 1.5 ms, synchronized on QRS) is applied and the ventricular rate instantly becomes slower and even necessitates ventricular pacing.

**Figure 2:** This graph shows the effect of AVNS on ventricular rate during AF in a typical patient during follow-up. On the left part of the graph irregular ventricular intervals are depicted. In the middle of the graph, ventricular rate during AF accelerates, reaching the VT/VF zone of the ICD. At a VT/VF count of 7 (red line in the middle of the graph) AVNS\textsubscript{ia} elicits an increase in VV intervals to approximately 600 ms, which is in between the sensor rate of 120 bpm (ventricular interval of 500 ms) and the lower rate of 80 bpm (ventricular interval of 750 ms), due to rate adaptive pacing. At the second red line the AVNS\textsubscript{ia} therapy is terminated after the programmed duration of 30 seconds. After this period the patient remained in AT/AF and it took 10 days until the ventricular interval reached the VT/VF zone again.

**Figure 3:** This figure displays activation of AVNS during a VT/VF episode, which occurred during follow-up. The top is the atrial electrogram, the middle is the ventricular EGM and the bottom EGM is the interpretation channel of the CRT-D. In the first part of the electrogram, before the first arrow, the patient is in AF with an irregular ventricular interval. At the first
arrow, the ventricular interval is < 360ms, activating AVNS after 7 ventricular beats (red arrow). After 5 ventricular intervals, the ventricular rate is not reduced, and AVNS is automatically ceased (purple arrow). After 21 ventricular intervals, the ICD correctly identifies the VT/VF episode, starts charging (blue arrow) and appropriately applies the ICD shock (green arrow), terminating the ventricular tachyarrhythmia (grey arrow). Note that the AVNS software does not influence the time to the appropriate ICD shock. VT/VF: ventricular tachycardia/ventricular fibrillation, AVNS: AV-node stimulation, FD: Fibrillation detection, CE: Electrical charging starts, CD shock: Cardio defibrillation by a shock.
Increase of Ventricular Interval during Atrial Fibrillation by AV Node Vagal Stimulation: Chronic Clinical AVNS Download Study
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