Management of anticoagulation in patients undergoing leadless pacemaker implantation

Rodolfo San Antonio, MD, * † Fredy Chipa-Ccasani, MD, * † José Apolo, MD, * Markus Linhart, MD, ‡ Omar Trotta, MD, * Margarida Pujol-López, MD, * Mireia Niebla, RN, * Francisco Alarcón, MSc, * Emilce Trucco, MD, ‡ Elena Arbelo, MD, PhD, †§ Ivo Roca-Luque, MD, PhD, * Eduard Guasch, MD, PhD, †§ Josep Brugada, MD, PhD, †§ Lluís Mont, MD, PhD, †§ José María Tolosana, MD, PhD †§

From the *Arrhythmia Section, Cardiovascular Clinic Institute, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain, ‡Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain, §Arrhythmia Section, Cardiology, Hospital Universitari Doctor Josep Trueta, Girona, Catalonia, Spain, and †Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain.

BACKGROUND The Micra transcatheter pacing system (Micra TPS) is often implanted in patients with atrial fibrillation and thus with increased thromboembolic risk. It is unknown whether the use of anticoagulants, associated with the use of a large venous introducer, implies an increased risk of bleeding in this group of patients.

OBJECTIVE The purpose of this study was to assess the incidence of bleeding and thromboembolic complications after Micra TPS implantation with and without therapeutic anticoagulation.

METHODS This single-center observational study included 107 consecutive patients receiving the Micra TPS from 2014 to 2018. At procedure completion, a figure-of-eight suture was placed at the femoral puncture site after sheath withdrawal and was maintained for 24 hours. In patients receiving enoxaparin or new oral anticoagulants, treatment was discontinued 12 or 24 hours before the procedure, respectively, and was reinitiated 4–6 hours postprocedure. In those receiving vitamin K antagonists (VKAs), dosing was not discontinued and the procedure was performed if the international normalized ratio was less than 3.

RESULTS Sixty-four patients (60%) did not receive anticoagulants. Of the 43 (40%) who did, 29 (67%) received VKAs, 8 (19%) received new oral anticoagulants, and 6 (14%) received enoxaparin. Two patients presented hemorrhagic or thromboembolic complications during short-term follow-up: 1 woman receiving VKAs presented hemorrhagic pericardial effusion without tamponade and 1 woman not receiving anticoagulants presented thrombosis of the ipsilateral saphenous vein.

CONCLUSION Bleeding and thromboembolic complications after receiving Micra TPSs are infrequent. The use of anticoagulant therapy, regardless of the type, does not increase the complications associated with the procedure.

KEYWORDS Anticoagulation; Bleeding; Leadless pacemaker; Micra transcatheter pacing system; Thromboembolic event

Introduction

Leadless intracardiac pacemakers are an emergent technology designed to reduce lead and subcutaneous pocket-related complications of traditional cardiac implantable electronic devices.1,2 The Micra transcatheter pacing system (Micra TPS; Medtronic, Minneapolis, MN) has an excellent implant success rate and low rates of complications such as device dislodgment, infection requiring device removal, or bleeding and vascular events, up to 12 months postimplantation.3-5

As a single-chamber ventricular pacemaker (VVI), the Micra TPS is especially recommended for patients with permanent or persistent atrial arrhythmias and slow intrinsic heart rates6 and is thus frequently used in patients receiving chronic oral anticoagulant therapy for increased thromboembolic
risk. Current guidelines include the use of standard transvenous pacemakers without interrupting vitamin K antagonists (VKAs) if the international normalized ratio (INR) is less than 3. This recommendation is based on randomized studies. For patients treated with new oral anticoagulants (NOACs), heparin bridging is not indicated, and a recent randomized controlled trial, the BRUISE CONTROL-2, found that device procedures can be performed with or without interruption of NOACs with a similar low risk of significant wound hematoma. However, evidence-based guidelines are not yet available for periprocedural management of anticoagulant therapy in leadless intracardiac pacemaker implantation. In order to implant the Micra TPS, a large venous sheath (outer diameter 27 F) is required to place the device in the right ventricle through the femoral vein. It is unknown whether perioperative maintenance of anticoagulant therapy implies an increased risk of bleeding in this group of patients when a large-caliber (27-F) venous sheath is used, particularly at the vascular access site. Conversely, interrupting anticoagulation might promote thromboembolic events in these patients.

The aim of this study was to evaluate the incidence of bleeding and thromboembolic complications during short-term follow-up by using periprocedural anticoagulation therapy in patients undergoing Micra TPS implantation.

Methods
All patients undergoing Micra TPS implantation from February 2014 to September 2018 were included in this single-center observational study. All met class I or II guideline–based indications for de novo permanent VVI pacing. No exclusion criteria were applied. The study was approved by the local institutional research ethics committee. Data reporting was consistent with the recommendations included in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Primary outcome measures included the incidence of bleeding, thromboembolic, and vascular events, which were evaluated at implantation, before hospital discharge, and 30 days postprocedure. On the basis of anticoagulation therapy at implantation, patients were divided into 2 groups: the anticoagulation group and the non-anticoagulation group.

Periprocedural anticoagulation strategies
Treatment was not discontinued in patients treated with VKAs (acenocoumarol), and implantation was performed if the INR did not exceed 3.0. In all cases, the INR was tested on the day of implantation. In nonurgent cases, it was additionally tested 24–48 hours before the procedure in order to adjust the acenocoumarol dose to achieve an INR between 2.0 and 3.0 on the day of implantation.

Dosing was suspended 12 hours before implantation in patients treated with low-molecular-weight heparin (enoxaparin). If bleeding complications did not occur, it was reinitiated 4–6 hours after implantation.

In patients treated with NOACs, dosing was suspended the morning before the day of implantation (24 hours before the procedure). As with enoxaparin, if bleeding complications did not occur, it was reinitiated 4–6 hours after the procedure.

Micra TPS implantation technique
All procedures were performed in our center by 2 experienced electrophysiologists (L.M. and J.M.T.) with long experience in femoral central venous access and who received specific training from the manufacturer.

The Micra TPS implantation procedure has been described elsewhere. The femoral vein was punctured using a modified Seldinger technique and an anatomical approach. The Micra introducer (outer diameter 27 F; inner diameter 23 F) with a silicone oil–coated dilator tip was advanced through a guidewire, reaching the right atrium. The device, within a deflectable catheter delivery system, was inserted through the Micra introducer. Both the introducer and the Micra delivery catheter were irrigated with unfractionated heparin (5000 IU/500 mL) diluted in 0.9% NaCl (flow rate 2–5 mL/min) to avoid air embolism or clotting. The delivery system was positioned in the right ventricle, and the Micra TPS was affixed to the myocardium by 4 flexible electrically inactive nitinol tines. After verifying that the device was adequately attached and provided proper electrical measures (pacing threshold, pacing impedance, and R-wave amplitude), the tether was cut and the delivery system was removed. Unlike procedures performed by other groups, the use of a bolus of intravenous heparin or the performance of angiography to ensure catheter position was left to the discretion of the implanting physician and was used in a minority of cases. Finally, the sheath was removed and a subcutaneous figure-of-eight suture was placed to achieve hemostasis (Figure 1) followed by application of a pressure dressing at the femoral puncture site. The suture and bandage were maintained overnight (16–24 hours), and a clinical groin examination was performed after removal.

Definitions of bleeding and thromboembolic and vascular complications
A hemorrhagic event was defined as 1 or more of the following: puncture site bleeding or groin hematoma requiring blood transfusion, prolonged hospital stay, delay of mobilization, and/or hospital readmission; retroperitoneal bleeding; and hemorrhagic pericardial effusion with or without symptoms of cardiac tamponade.

An arterial thromboembolic event was defined as either acute ischemic stroke, transient ischemic attack, or acute peripheral arterial ischemia. A venous thromboembolic event was defined as acute pulmonary embolism or acute deep vein thrombosis.

A vascular complication was defined as an iatrogenic pseudoaneurysm requiring ultrasound-guided compression, percutaneous thrombin injection, or surgical repair or iatrogenic arteriovenous or lymphatic fistula regardless of the need for treatment.
Statistical analysis

Categorical variables, represented as counts (percentages) were compared using the \( \chi^2 \) test. Continuous variables were expressed as means and standard deviations, and between-group comparisons were made using the Student \( t \) test. Nonparametric continuous variables were described as medians and interquartile ranges (IQRs). The Wilcoxon signed-rank test was used to compare nonparametric variables. Statistical significance was recognized when the 2-sided \( P \) value was less than .05. Statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Chicago, IL).

Results

From February 2014 to September 2018, 107 patients underwent Micra TPS implantation in our unit. Fifty-four (50.4%) were previously included in the Micra Investigational Device Exemption study. No patients were lost to follow-up (30 days). The primary patient characteristics are listed in Table 1. The mean patient age at implantation was 78.1 ± 10.9 years, and 54 (50.4%) were men.

Overall, 64 patients (60%) did not receive anticoagulants and 43 (40%) were treated with perioperative anticoagulant therapy. Forty-nine patients (46%) had atrial fibrillation (AF) with a mean CHA2DS2-VASc risk score of 3.5 ± 1.0. The most frequent pacing indication was persistent or permanent AF with bradycardia (41 patients [38%]). Twenty-seven patients (25%) received atrioventricular block and sinus node dysfunction as opposed to AF with bradycardia in the anticoagulation group (Table 1).

Procedural characteristics

The Micra TPS was successfully implanted in 105 patients (98.1%). In 2 patients, the Micra TPS could not be implanted because of (1) the inability to obtain appropriate parameters after multiple (5) attempts to reposition the device, finally aborting the procedure because of the appearance of pericardial effusion; and (2) the inability to pass the tricuspid valve in a patient who previously underwent heart transplantation. The procedural characteristics are listed in Table 2. The median procedure time (from introducer in to introducer out) was 35 minutes (IQR 25–44 minutes). Most patients (82 [78%]) did not require device repositioning after initial deployment, and the majority of implants (104 [97%]) were successfully completed in 1 or 2 delivery attempts. Devices were predominantly placed in the mid-ventricular septum (78 [74%]) or the apical septum (26 [25%]). No devices were implanted in the inferior or lateral wall of the right ventricle.

Anticoagulation group

In the anticoagulation group, 42 of 43 patients (98%) had AF and 7 of 43 (17%) had mechanical heart valve prostheses (17%). Two-thirds (29 of 43 [67%]) were treated with uninterrupted VKA therapy. The median INR at implantation was 2.1 (IQR 1.6–2.3). Fourteen patients (33%) received non-VKA therapy: 8 (19%) received NOACs (apixaban in 5, dabigatran in 2, and rivaroxaban in 1) and 6 (14%) were treated with perioperative low-molecular-weight heparin (enoxaparin) as a bridge to oral anticoagulation (Figure 2). Of the 7 patients with mechanical heart valve prostheses, 4 had aortic valve replacements, 2 had mitral valve replacements, and 1 had both. In this subgroup, 1 patient received heparin and 6 patients received acenocoumarol (median INR 2.4; IQR 2.3–2.5). The reasons for enoxaparin bridging were as follows: (1) syncope associated with severe trauma requiring discontinuation of oral anticoagulation (4 patients) and (2) new diagnosis of AF during hospital admission (2 patients). At the same time, 5 patients (12%) were additionally treated with single antiplatelet therapy.

Non-anticoagulation group

In this group, 21 of 64 patients (33%) received single and 1 of 64 (1.5%) received dual antiplatelet therapy. The most common pacing indications were atroventricular block and sinus node dysfunction as opposed to AF with bradycardia in the anticoagulation group (Table 1).

Of note, 7 patients (11%) in this group had a history of AF and did not receive anticoagulation therapy. Because of the presence of multiple comorbidities that increased the risk of bleeding in these patients, anticoagulants were not administered.
Compared with the anticoagulation group, this group showed more frequent apical septum device placement (33% vs 12%; \(P = .01\)) and the final device position was less predominant at the mid-ventricular septum (67% vs 86%; \(P = .03\)). There were no differences between groups in the number of pacemaker implantation attempts or in procedure time.

Complications

The overall incidence of hemorrhagic, thromboembolic, and vascular complications during 30-day follow-up was 2 of 107 (1.9%): 1 of 64 (1.5%) in the non-anticoagulation group and 1 of 43 (2.3%) in the anticoagulation group.

One patient in the anticoagulation group (INR 2.0) presented mild pericardial effusion without tamponade during the procedure, not requiring pericardial drainage. This complication occurred in a thin elderly woman after 5 attempts to position the device. After analyzing the images, we confirmed that effusion occurred when the device was inadvertently placed at the apex. No other patient in either group presented bleeding. Another woman, from the non-anticoagulation group, presented symptomatic thrombosis of the ipsilateral saphenous vein (3 days postprocedure), requiring initiation of anticoagulant treatment and 3 additional days of hospitalization.

Neither arterial thromboembolic nor vascular complications were observed in either group during follow-up.

Discussion

The primary findings of this study were as follows: (1) Forty percent of patients who received a Micra TPS were treated with perioperative anticoagulation therapy; (2) the incidence of bleeding or thromboembolic complications was low, independent of whether patients received anticoagulant therapy; and (3) Micra TPSs allowed various perioperative anticoagulation strategies to be used safely.

About 60%–70% of all patients included in the 2 largest studies assessing the safety and efficacy of the Micra TPS were in AF. Therefore, although not described, the percentage of patients treated with oral anticoagulation was high. In both studies, perioperative anticoagulation management was left to the discretion of the implanting

### Table 1 Baseline clinical characteristics of the patients included in the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 107)</th>
<th>No anticoagulant therapy (n = 64)</th>
<th>Anticoagulant therapy (n = 43)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>78.1 ± 10.9</td>
<td>78.5 ± 13.0</td>
<td>77.6 ± 7.0</td>
<td>.64</td>
</tr>
<tr>
<td>Sex: male</td>
<td>54 (50.4)</td>
<td>36 (56)</td>
<td>18 (42)</td>
<td>.14</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 ± 6</td>
<td>58 ± 6</td>
<td>58 ± 7</td>
<td>.99</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>49 (46)</td>
<td>7 (11)</td>
<td>42 (98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>16 (15)</td>
<td>11 (17)</td>
<td>5 (12)</td>
<td>.43</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>25 (24)</td>
<td>13 (20)</td>
<td>12 (29)</td>
<td>.36</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (60)</td>
<td>39 (61)</td>
<td>25 (58)</td>
<td>.77</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (17)</td>
<td>8 (12)</td>
<td>10 (23)</td>
<td>.14</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>7 (6)</td>
<td>0</td>
<td>7 (17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>7 (6)</td>
<td>2 (3)</td>
<td>5 (12)</td>
<td>.08</td>
</tr>
<tr>
<td>Pacing indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia associated with AF</td>
<td>41 (38)</td>
<td>5 (8)</td>
<td>36 (83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>20 (19)</td>
<td>17 (27)</td>
<td>3 (7)</td>
<td>.01</td>
</tr>
<tr>
<td>AV block</td>
<td>24 (22)</td>
<td>22 (34)</td>
<td>2 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other reasons</td>
<td>22 (21)</td>
<td>20 (31)</td>
<td>2 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single antiplatelet therapy</td>
<td>26 (24)</td>
<td>21 (33)</td>
<td>5 (12)</td>
<td>.01</td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>.42</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or as n (%).

AF = atrial fibrillation; AV = atrioventricular; LVEF = left ventricular ejection fraction.

### Table 2 Characteristics of the procedure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 107)</th>
<th>No anticoagulant therapy (n = 64)</th>
<th>Anticoagulant therapy (n = 43)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time (min)</td>
<td>35 (28–44)</td>
<td>35.5 (28–44)</td>
<td>32.5 (25–45)</td>
<td>.33</td>
</tr>
<tr>
<td>Successful implantation on the first attempt</td>
<td>82 (78)</td>
<td>50 (79)</td>
<td>32 (76)</td>
<td>.66</td>
</tr>
<tr>
<td>Final device position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical septum</td>
<td>26 (25)</td>
<td>21 (33)</td>
<td>5 (12)</td>
<td>.01</td>
</tr>
<tr>
<td>Mid-septum</td>
<td>78 (74)</td>
<td>42 (67)</td>
<td>36 (86)</td>
<td>.03</td>
</tr>
<tr>
<td>Outflow tract</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (2)</td>
<td>.22</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or as n (%).
physician. Despite the high prevalence of these patients, data on perioperative anticoagulation strategies are lacking. Contrary to these studies, we compared the incidence of complications by using perioperative anticoagulation therapy. Furthermore, we describe various anticoagulant strategies used in Micra TPS recipients who required anticoagulation therapy.

At 30 days, the incidence of complications after Micra TPS implantation reported in the Micra Investigational Device Exemption study and the Micra Transcatheter Pacing System Post-Approval Registry ranged between 2.89% and 1.98%. The events observed primarily involved the groin puncture site and cardiac effusion/perforation.\(^\text{4,5}\) The low incidence of complications observed in our study is in agreement with most of the data published elsewhere,\(^\text{2,13}\) demonstrating the safety of Micra TPS implantation independent of periprocedural anticoagulant treatment. However, contrary to these data, Valiton et al\(^\text{15}\) described a high incidence (6.6%) of complications in a cohort of 92 patients. The difference could be explained by operator experience.

The incidence of pericardial effusion found in our anticoagulation group was 1 of 43 (2.3%). Martínez-Sande et al\(^\text{14}\) described an incidence of 1 of 27 (3.7%) in patients treated with anticoagulant therapy. In our cohort, this low incidence of pericardial effusion, despite the use of anticoagulation therapy, could be explained by the final device position: device placement was at the mid-septum for most patients (74%), particularly in the anticoagulation group (86%). This has been associated with a lower incidence of cardiac perforation/pericardial effusion.\(^\text{3,16}\) Therefore, a recommendation to place the device at the mid-septum whenever possible, particularly in anticoagulated patients, is prudent. Other factors to consider are advanced age, low body mass index, female sex, prior myocardial infarction, and chronic lung disease, each of which has been associated with a high incidence of cardiac perforation.\(^\text{17}\) At the same time, it should be highlighted that additional device repositioning is associated with a 1.35-fold higher probability of effusion\(^\text{18}\) and the severe consequences of perforation with a Micra TPS owing to its size.\(^\text{15}\) The fact that most implants in our series did not need device repositioning could also explain the low incidence of pericardial effusion.

In our cohort, the groin puncture site did not present complications such as hematoma, retroperitoneal bleeding, arteriovenous fistula, or pseudoaneurysm. Three factors could explain our results: no intravenous bolus of heparin, surgeon skill, and hemostasis with a figure-of-eight suture.

The need for intraprocedural anticoagulation is not well-defined in previous studies.\(^\text{3,19}\) Although the manufacturer suggests the use of a bolus of intravenous heparin to prevent clot formation, in our series the bolus of heparin was only administered in 3 patients. This fact could explain the low rate of bleeding complications.\(^\text{2}\)

In our cohort, all implantation procedures were performed by 2 expert physicians with broad experience in femoral puncture and skills in catheter management. As usual in our center, a femoral vein access by a modified Seldinger technique and an anatomical approach was used. The use of vascular ultrasound to guide venous access has been strongly recommended and could reduce vascular complications.\(^\text{3}\)

A temporary subcutaneous figure-of-eight suture is a simple, inexpensive technique associated with a low complication rate after removal of a large-caliber venous introducer.\(^\text{20}\) This technique provides several advantages over other techniques such as manual compression, which might be necessary for as long as 15–20 minutes, and the use of a vascular closure device, which is a more complex and expensive technique.\(^\text{3}\) Therefore, the use of this type of suture followed by application of a pressure dressing at the femoral puncture site could help avoid groin complications, as seen in our study.

Pocket hematoma is a frequent complication associated with implanting traditional cardiac implantable electronic devices. The incidence is increased 2- to 3-fold in patients in whom VKAs are not discontinued and 10-fold in those in whom heparin is used to bridge oral anticoagulation.\(^\text{21}\) The Micra TPS eliminates the need to perform a wound incision and generate the pocket. This markedly reduces hemorrhagic complications associated with the procedure and thus allows the use of various types of anticoagulation without increasing the risk of bleeding complications.

**Limitations**

We acknowledge that this study has limitations. These results were obtained in a single center, and the Micra TPS was implanted by only 2 experienced operators. It is not clear whether similarly low complication rates can be achieved by less experienced operators.

The diagnosis of transient ischemic attack based solely on medical history is imprecise. Consequently, its incidence might be underestimated.

In this observational study, we did not strictly compare the various management strategies of perioperative anticoagulation and a low number of adverse events were observed. In addition, the proportion of patients with AF was lower than that in other studies as a result of our patient selection criteria. Therefore, large randomized studies are needed to determine the most adequate management of peri procedural...
anticoagulation in these patients. However, our study is the first to describe the safety of various anticoagulation strategies used during implantation of the Micra TPS.

Conclusion

The frequency of hemorrhagic, thromboembolic, and vascular complications after Micra TPS implantation is low. Differences between anticoagulation and non-anticoagulation groups in bleeding and thromboembolic complications were not found. Various perioperative anticoagulation strategies can be safely used in the implantation of the Micra TPS.

Acknowledgments

We are indebted to Neus Portella, BSc for secretarial assistance and Donna Pringle, BSc for English language editing.

References