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Atrial Fibrillation Ablation in Patients With Therapeutic International Normalized Ratio

Comparison of Strategies of Anticoagulation Management in the Periprocedural Period

Oussama M. Wazni, MD; Salwa Beheiry, RN; Tamer Fahmy, MD; Conor Barrett, MD; Steven Hao, MD; Dimpi Patel, DO; Luigi Di Biase, MD; David O. Martin, MD, MPH; Mohamed Kanj, MD; Mauricio Arruda, MD; Jennifer Cummings, MD; Robert Schweikert, MD; Walid Saliba, MD; Andrea Natale, MD

Background—The best approach to management of anticoagulation before and after atrial fibrillation ablation is not known.

Methods and Results—We compared outcomes in consecutive patients undergoing pulmonary vein antrum isolation for persistent atrial fibrillation. Early in our practice, warfarin was stopped 3 days before ablation, and a transesophageal echocardiogram was performed to rule out clot. Enoxaparin, initially 1 mg/kg twice daily (group 1) and then 0.5 mg/kg twice daily (group 2), was used to “bridge” patients after ablation. Subsequently, warfarin was continued to maintain the international normalized ratio between 2 and 3.5 (group 3). Minor bleeding was defined as hematoma that did not require intervention. Major bleeding was defined as either cardiac tamponade, hematoma that required intervention, or bleeding that required blood transfusion. Pulmonary vein ablation was performed in 355 patients (group 1 = 105, group 2 = 100, and group 3 = 150). More patients had spontaneous echocardiographic contrast in groups 1 and 2. One patient in group 1 had an ischemic stroke compared with 2 patients in group 2 and no patients in group 3. In group 1, 23 patients had minor bleeding, 9 had major bleeding, and 1 had pericardial effusion but no tamponade. In group 2, 19 patients had minor bleeding, and 2 patients developed symptomatic pericardial effusion with need for pericardiocentesis 1 week after discharge. In group 3, 8 patients developed minor bleeding, and 1 patient developed pericardial effusion with no tamponade.

Conclusions—Continuation of warfarin throughout pulmonary vein ablation without administration of enoxaparin is safe and efficacious. This strategy can be an alternative to bridging with enoxaparin or heparin in the periprocedural period. (Circulation. 2007;116:000-000.)

Key Words: ablation ■ fibrillation ■ atrium ■ coagulation

Management of anticoagulation before and after atrial fibrillation (AF) ablation is necessary to prevent thromboembolism while avoiding bleeding complications. The best approach to the management of anticoagulation before and after the AF ablation procedure is not known. Although protocols differ, most centers discontinue warfarin before pulmonary vein isolation and use subcutaneous enoxaparin or intravenous heparin to “bridge” anticoagulation before and after ablation.1-3

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Correspondence to Andrea Natale, MD, Head, Section of Pacing and Electrophysiology, Co-Director, Center for Atrial Fibrillation, Department of Cardiovascular Medicine, Cleveland Clinic, 60 Stonewood Dr, Cleveland, OH 44195. E-mail nataleam@roadrunner.com

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ed to the electrophysiology laboratory in AF. They all had undergone a successful cardioversion of persistent AF but were experiencing persistent AF at the time of the procedure.

Minor bleeding was defined as hematoma that did not require intervention. Major bleeding was defined as either cardiac tamponade, hematoma that required intervention, or bleeding that required blood transfusion.

Early in our practice, warfarin was routinely stopped 2 to 3 days before ablation. Enoxaparin, initially 1 mg/kg twice daily (group 1) and then 0.5 mg/kg twice daily (group 2), was used to bridge patients after ablation. No enoxaparin was given 12 hours before ablation. Subsequently, warfarin was continued without interruption, with the international normalized ratio (INR) maintained between 2 and 3.5 (group 3). All patients in the present series had a transesophageal echocardiogram performed on the day of the procedure.

Ablation Procedure
Details of the AF ablation procedure used in the present study have been published elsewhere. In brief, all of the patients included in the present series were ablated with an 8-mm ablation catheter with intracardiac echocardiographic microbubble monitoring. In most patients in the present series, sinus rhythm was achieved with direct-current cardioversion at the end of the procedure.

The right femoral vein, left femoral vein, and right internal jugular vein were accessed with 2 8F, 10.5F, and 8F sheaths, respectively. The right internal jugular vein was accessed under fluoroscopy with a wire in the internal jugular vein inserted through 1 of the right femoral vein sheaths or by use of ultrasound guidance.

The left atrium was accessed with double transseptal punctures for mapping (Lasso-Biosense/Webster, Diamond Bar, Calif) and ablation (Biosense/Webster, 8-mm tip) guided by intracardiac echocardiography (Acuson, Siemens, Malvern, Pa). During the procedure, continuous monitoring with intracardiac echocardiography allowed assessment for any pericardial effusion. Patients were sedated lightly with intracardiac echocardiographic microbubble monitoring.

Follow-Up
Patients were examined the next day, before discharge. Patients who were from other cities were informed beforehand that they were requested to spend an additional night in the local area. All patients were instructed to call weekly (for the first 3 months) with their ECG transmissions, at which time a dedicated electrophysiology nurse would discuss with the patients their progress of recovery, with specific questioning about chest pain, shortness of breath, and puncture sites. If any reason for concern existed, and depending on the situation, the patients were directed to seek attention either in their local emergency department or by follow-up with their local physician. If any physician/emergency department contact took place in relation to the procedure, all documentation was sent to our AF center. All patients, with no exceptions, were followed up in our AF center clinic 3 to 4 months after ablation with a CT scan to check for pulmonary vein stenosis and a clinic visit with the electrophysiology physician who performed the procedure. During this visit, all interval developments, including complications related to the procedure, were reviewed. All information collected was entered into our AF center registry.

Statistical Analysis
Statistical analysis was performed with SPSS for Windows (Microsoft, Redmond, Wash) version 13.0 (SPSS Inc, Chicago, Ill) for asymptotic tests and SAS version 8.0 (SAS Institute Inc, Cary, NC). Continuous variables are expressed as mean±SEM. Continuous variables of the 3 groups were compared with 1-way ANOVA. Categorical variables are expressed as percentages and were compared with the Fisher-Freeman-Halton exact test for 3x2 tables.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
One hundred five patients (Table 1) with persistent AF received enoxaparin 1 mg/kg twice daily for bridging after ablation (group 1), and 100 patients received enoxaparin 0.5 mg/kg twice daily (group 2). One hundred fifty patients were given their usual warfarin dose without interruption (group 3). Patient characteristics are presented in Table 1. The 3 groups were comparable with respect to age, gender, hypertension, and structural heart disease. The INR was approximately 1.1 in groups 1 and 2 and 2.7±0.5 in group 3 P<0.01. The left ventricular ejection fraction in the groups was comparable at 54.3±8% versus 52.4±9.3% versus 55.8±8%, respectively, as were the left atrial diameter and creatinine levels (Table 1). The maximum activated clotting time during the procedure was comparable in all groups: 468 seconds in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LMWH 1 mg/kg BID (n=105); Group 1</th>
<th>LMWH 0.5 mg/kg BID (n=100); Group 2</th>
<th>Warfarin (n=150); Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±9.6</td>
<td>55.5±12.0</td>
<td>55.1±10.6</td>
<td>0.652</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>21</td>
<td>20</td>
<td>25</td>
<td>0.477</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.3±8</td>
<td>52.4±9.3</td>
<td>55.8±8</td>
<td>0.312</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>4.4±0.9</td>
<td>4.5±0.8</td>
<td>4.4±0.7</td>
<td>0.481</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
<td>1.0±0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>INR</td>
<td>1.17±0.3</td>
<td>1.2±0.2</td>
<td>2.7±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximum ACT, s</td>
<td>468</td>
<td>475</td>
<td>500</td>
<td>0.6</td>
</tr>
<tr>
<td>SEC, %</td>
<td>25</td>
<td>26</td>
<td>2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; LA, left atrium; ACT, activated clotting time; and SEC, spontaneous echocardiographic contrast.
Table 2. Complications

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Exact P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke, n</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Pericardial effusion,n</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0.69</td>
</tr>
<tr>
<td>Minor bleeding, n</td>
<td>23</td>
<td>19</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding, n</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

group 1, 475 seconds in group 2, and 500 seconds in group 3. Spontaneous echocardiographic contrast was present in 25% of the patients in group 1 compared with 26% in group 2 and only 2% in group 3. All patients were in sinus rhythm at the end of the procedure.

Complications

Thromboembolic Complications

One patient in group 1 developed an ischemic stroke 2 days after ablation. In group 2, 2 patients developed stroke. One patient developed dense left-sided hemiplegia during the procedure due to occlusion of the right middle cerebral artery, which was reopened with tissue plasminogen activator, with subsequent recovery. Another patient in group 2 developed an ischemic stroke 1 week after ablation. No thromboembolic events occurred in group 3 patients (Table 2).

Pericardial Effusion

Two patients in group 2 developed a symptomatic, large pericardial effusion that required pericardiocentesis = 1 week after discharge (Table 2). One patient in each of groups 1 and 3 developed mild pericardial effusion that required no intervention. These events were noted on intracardiac echocardiographic images during the procedure and verified later with transthoracic echocardiography.

Hematoma

Twenty-three patients in group 1 and 19 patients in group 2 developed groin hematomas (Table 2). Ten patients in each of groups 1 and 2 required additional hospitalization for observation. Nine of the patients from group 1 required blood transfusion. In group 3, 8 patients had hematomas; 2 of these required additional hospitalization for observation owing to the large size of the hematomas. Three pseudoaneurysms occurred in the groups that received enoxaparin (groups 1 and 2) and 2 in the warfarin group. These were all treated successfully with thrombin injection.

Discussion

The present study shows that continuation of warfarin throughout pulmonary vein antrum isolation without administration of enoxaparin before and after the procedure is safe and efficacious. This strategy can be used as an alternative to bridging strategies that utilize enoxaparin or heparin in the periprocedural period. This protocol can eliminate the need for enoxaparin, which is costly and inconvenient. We found that continuation of warfarin does not increase the risk of bleeding. In fact, such a strategy may confer more protection against thromboembolic events, especially in the postablation period, when patients are most vulnerable while waiting to achieve therapeutic INRs as they are bridged with enoxaparin. Although the numbers in the present series are small, a strategy that interrupts anticoagulation with warfarin clearly puts patients at risk for stroke.

In the present series, we found that the presence of spontaneous echocardiographic contrast was more common in the group in which warfarin was stopped. Spontaneous echocardiographic contrast has been shown to be a precursor of thrombus formation. Although treatment with antithrombotic medications has not been shown to resolve spontaneous echocardiographic contrast, it is not known whether taking such medications with therapeutic anticoagulation may prevent this. The present series suggests that if anticoagulation is continued at a therapeutic level, the formation of spontaneous echocardiographic contrast may be prevented, and thus, the risk of thromboembolism may be decreased. The use of enoxaparin, even at a reduced dose, not only afforded no protection but was associated with more bleeding complications.

No unified approach exists to the management of anticoagulation after ablation. Ablation in the left atrium clearly creates a very hypercoagulable milieu with potential risk of thrombus formation and stroke, especially after ablation, when anticoagulation is suboptimal.

Some centers advocate stopping warfarin in all patients before ablation. After ablation, heparin is given for the overnight stay, and then enoxaparin 0.5 mg/kg BID is given for bridging. The full dose is not usually given because of previous experience with large hematomas, consistent with the present findings.

In their recent report, Oral et al describe a strategy in which warfarin was stopped for 5 days and low–molecular-weight heparin (LMWH) was given instead. During the procedure, heparin was given to maintain an activated clotting time of 300 to 350 seconds, and after the procedure, heparin was given at a rate of 1000 U/h. Then, patients were discharged with LMWH at a dose of 0.5 mg/kg BID until the INR was >2. This lower dose was used because of their earlier experience with full-dose LMWH, which resulted in a large number of large groin hematomas. With such a strategy in a group of 755 patients, 7 embolic events occurred, of which 4 occurred in the first week after ablation and 3 in the second week. Only 2 patients had a thromboembolic event beyond 30 days after ablation. Oral et al attribute this concentration of early thromboembolic events to suboptimal anticoagulation in this period despite their use of preprocedural and postprocedural LMWH. This study emphasizes the need for more aggressive anticoagulation after ablation. It is clear that a suboptimal dose of LMWH does not prevent thromboembolic events and that a full dose causes an unacceptable rate of hematomas. In agreement with Oral et al, even with the lower dose of LMWH, we found a higher risk of bleeding.

At our center, it is our practice at this time to start warfarin treatment at least 2 months before ablation. The procedure is then performed without the need for a transeosophageal echocardiogram if therapeutic INR levels are maintained for 3 weeks before the procedure. We aim for an INR between 2 and 3.5. We try to avoid the ablation procedure in patients without achieving therapeutic INRs.
with an INR >4. We have not changed our heparinization protocol because it is not known whether less heparin is in fact needed in patients fully anticoagulated with warfarin. It is not known whether therapeutic INRs are equivalent to full heparinization in this setting, because this has not been evaluated. We have not experienced any significant excess bleeding in our patients.

If tamponade were to occur, heparin should be stopped and reversed. Fresh-frozen plasma and possibly vitamin K to reverse warfarin should be given. This is in conjunction with emergent pericardiocentesis and fluid/blood resuscitation and use of pressors as needed. If continued significant drainage or reaccumulation of effusion occurs, as seen on surface 2D echocardiography or intracardiac echocardiography, despite these measures, then emergent open surgical exploration should be considered.

Study Limitations
This was an observational study. It is possible that the operators, knowing that a patient was on full anticoagulation, were more careful in gaining access; however, this does not negate our findings. The present study was a sequential and not a randomized experience. Other possible iterations of bridging were not assessed, such as continuous intravenous heparin until therapeutic INRs are achieved. This, however, would have required a significant increase in length of stay and overutilization of healthcare resources.

Clinical Implications
Continuation of oral anticoagulation to maintain therapeutic INRs is safe in patients undergoing AF ablation. Such a strategy may be used as an alternative to bridging strategies that use enoxaparin or heparin in the periprocedural period.

Disclosures
None.

References

CLINICAL PERSPECTIVE
Management of anticoagulation before and after atrial fibrillation ablation is necessary to prevent thromboembolism while avoiding bleeding complications. The best approach is not known. Most centers discontinue warfarin and use subcutaneous enoxaparin or intravenous heparin to “bridge” anticoagulation before and after ablation. The discontinuation of warfarin may increase the risk of thromboembolism. Administration of enoxaparin or heparin may increase the risk of bleeding, especially early after ablation. We assessed whether it is feasible to maintain anticoagulation with warfarin throughout the periprocedural period without preprocedural or postprocedural enoxaparin by comparing 3 different anticoagulation strategies implemented sequentially in 355 consecutive patients undergoing ablation for persistent atrial fibrillation. In groups 1 and 2, coumadin was stopped 3 days before ablation; enoxaparin 1 mg/kg twice daily (group 1) or 0.5 mg/kg twice daily (group 2) was used while warfarin therapy was restarted after ablation. In group 3, warfarin was continued throughout, with the international normalized ratio maintained between 2 and 3.5. During the ablation procedure, all groups received anticoagulation with heparin. Ischemic strokes occurred in 1 of 105 patients in group 1, 2 of 100 patients in group 2, and none of the 150 patients in group 3. Bleeding complications were not increased in group 3. Maintenance of anticoagulation with warfarin throughout the periprocedural period without administration of enoxaparin is an acceptable alternative to bridging strategies that use enoxaparin periprocedurally.