Clinical Case

A 68-year-old woman with well-controlled hypertension is having 3 to 4 episodes of paroxysmal atrial fibrillation (AF) each month. Despite a ventricular rate of 80 to 100/min while in AF, she complains of palpitations, chest discomfort, and light-headedness. Oral flecainide failed to improve her symptoms, and she refuses to take amiodarone because of concerns about its potential toxicity. She was started on dabigatran (150 mg twice daily) for stroke prevention; her creatinine clearance was calculated at 92 ml/min. AF ablation has been scheduled, and advice is needed regarding periprocedural dabigatran management.

Introduction

AF, the most common cardiac arrhythmia, is a major cause of stroke. Although many AF patients are asymptomatic or have adequate symptom palliation with rate-controlling medications, some require treatment strategies aimed at maintaining sinus rhythm. In the United States, it is estimated that >150,000 AF patients undergo catheter ablation each year in an attempt to achieve rhythm control. Originally targeted to younger AF patients without structural heart disease, catheter ablation is performed in a broader population now that outcomes have improved. Consequently, the number of ablation procedures performed is expected to increase exponentially over the next decade.

Current guidelines recommend anticoagulant prophylaxis in all but the lowest-risk AF patients. Until recently, vitamin K antagonists, such as warfarin, were the only option for stroke prevention in such patients. This situation changed with the introduction of new oral anticoagulants (NOACs), which target thrombin or factor Xa. With a more predictable anticoagulant response and shorter half-lives than warfarin, NOACs have the potential to streamline periprocedural management in AF patients undergoing ablation. However, data with NOACs in this setting are limited, and at times contradictory, which complicates their integration into routine practice in patients undergoing catheter ablation.

Comparison of the Pharmacological Properties of the NOACs With Those of Warfarin

NOACs have pharmacological properties that distinguish them from warfarin. These are summarized in Table 1.

Need for Anticoagulation in AF Patients Undergoing Catheter Ablation

Stroke is one of the most feared complications of catheter ablation. The stimulus for thromboembolism, the underlying cause of most strokes in AF patients, differs before, during, and after ablation, which may influence the optimal choice of anticoagulant.

Anticoagulation Before AF Ablation

Because catheter manipulation during ablation may dislodge preexisting thrombi, it is important to minimize the risk of left atrial thrombus formation before the procedure. Guidelines recommend at least 4 weeks of therapeutic anticoagulation before ablation in all but the lowest-risk AF patients. With their rapid and predictable anticoagulant effects, therapeutic anticoagulation
Table 1. Comparative Pharmacology of Warfarin and the New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>VKORC1</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>6%</td>
<td>60% to 80%*</td>
<td>60%</td>
</tr>
<tr>
<td>Dosing</td>
<td>o.d.</td>
<td>BID (o.d.)</td>
<td>o.d. (BID)</td>
<td>BID</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>4–5 d</td>
<td>1–2 h</td>
<td>2–3 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>12–17 h</td>
<td>7–11 h</td>
<td>12 h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>None</td>
<td>80%</td>
<td>33%†</td>
<td>25%</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

BID indicates twice-daily; o.d., once-daily; and VKORC1, C1 subunit of the vitamin K epoxide reductase enzyme.

*Bioavailability of rivaroxaban decreases as the dose is increased because of poor drug solubility; with once-daily doses of 20 and 10 mg, the bioavailabilities are 60% and 80%, respectively.

†Only 33% of rivaroxaban is excreted unchanged by the kidneys; an additional 33% is excreted as inactive metabolites.

is more readily achieved with NOACs than with warfarin. In addition, the rapid offset of NOACs has the potential to obviate the need for bridging in most patients.

**Anticoagulation During AF Ablation**

The risk of stroke increases during AF ablation through mechanisms that invoke all components of Virchow’s triad. These include endothelial injury induced by passage of sheaths and catheters into the left atrium and by application of ablation energy; hypercoagulability triggered by contact of the blood with the foreign surface of the ablation hardware and with thrombogenic debris generated at the ablation interface; and altered blood flow that occurs after conversion of AF to sinus rhythm. These insults induce tissue factor expression, which initiates the extrinsic pathway of coagulation, and DNA, RNA, and inorganic polyphosphates released from activated or damaged cells trigger clotting via the intrinsic pathway (Figure 1). Consequently, the anticoagulant used during the ablation procedure must not only be capable of suppressing clotting that occurs through the extrinsic tissue factor-initiated pathway, but also that initiated via the intrinsic pathways. Multi-targeted anticoagulants appear to do this better than those that target only a single clotting enzyme. For example, heparin is better than fondaparinux at preventing catheter thrombosis in vitro, and warfarin is superior to dabigatran for stroke prevention in patients with mechanical heart valves. However, even the best anticoagulant strategy may not eliminate stroke induced by embolism of necrotic debris generated at the ablation interface. Fortunately, saline-irrigated ablation catheters have reduced the risk of this complication. Contemporary surveys report thromboembolic events, mainly presenting as transient ischemic attacks, in ≈1% of ablation patients.3

**Anticoagulation After AF Ablation**

There is a risk of stroke after ablation, even in patients without preexisting risk factors. This occurs because atrial tissue remains stunned for several weeks after the procedure, with a resultant decrease in contractility. In addition, endothelium injured by ablation energy requires time to heal, so that its natural antithrombotic properties can be restored. For these reasons, guidelines recommend continuing anticoagulation for at least 2 to 3 months after the procedure.4

**Balancing Thromboembolic and Bleeding Risks in Patients Undergoing Catheter Ablation**

The risk of stroke during catheter ablation must be balanced with the risk of bleeding during and after the procedure. Access site bleeding is the most common hemorrhagic complication because multiple vascular sites are accessed with large sheaths during the ablation procedure. Cardiac perforation and subsequent tamponade as a consequence of bleeding into the pericardium is the leading cause of death in patients undergoing ablation.5 Perforation can occur during trans-septal access into the left atrium, or as a result of the application of ablation energy. In an attempt to reduce the risk of tamponade at the time of trans-septal puncture, some centers use intracardiac echocardiography to perform the puncture under direct visualization. The need to strike a balance between the risk of stroke and the risk of serious bleeding has prompted a variety of periprocedural anticoagulation strategies, which span the spectrum from interrupted therapy, with or without bridging, to uninterrupted therapy.
Current Approaches to Periprocedural Warfarin Management

There is considerable experience with warfarin in the AF ablation setting, and periprocedural management has evolved in many centers from an interrupted to an uninterrupted approach (Figure 2 and Table 2). Each is briefly discussed.

Interrupted Strategy

Typically, warfarin is withheld 5 days before ablation. Many centers bridge patients with intravenous heparin or with subcutaneous low-molecular-weight heparin (LMWH). Bridging is often initiated 3 days before the procedure, because it takes at least 2 days for the international normalized ratio to fall below the therapeutic range when warfarin is withheld. To minimize the risk of bleeding during the procedure, intravenous heparin is stopped 4 to 6 hours before ablation, whereas the last dose of subcutaneous LMWH is usually administered 12 hours before ablation.

To mitigate the thromboembolic risk during ablation, intravenous heparin is given immediately before or after transseptal puncture in bolus doses sufficient to achieve an activated clotting time (ACT) of 300 to 400 sec. This ACT target was chosen because it is associated with a lower risk of thromboembolic events than ACT values below these levels. After completion of the procedure, sheaths are removed when the ACT falls to 200 to 250 sec. To shorten the time to sheath removal, some centers give protamine sulfate to rapidly reverse the anticoagulant effect of heparin.

Warfarin is restarted after ablation. In many centers, LMWH bridging is reinstituted several hours after sheath removal and is continued until the international normalized ratio is ≥2, indicating a therapeutic level of anticoagulation with warfarin. The dose of LMWH varies; some centers use full-dose regimens, whereas others use half doses to reduce the risk of bleeding. It is unclear whether preprocedure bridging is necessary in patients at low risk of thromboembolism, and acceptable outcomes have been reported even with low-dose LMWH bridging regimens after the ablation. This is not surprising because based on an annualized risk of stroke of 1.5 to 2.8% in low-risk patients, the attributable risk of stroke with an interrupted strategy is probably in the range of 0.004 to 0.008%.

Uninterrupted Therapy

Increasingly, AF ablation is being performed with uninterrupted warfarin. The move to uninterrupted warfarin was prompted by data suggesting that heparin bridging around the time of procedures increases the risk of bleeding. Thus, in a randomized trial comparing interrupted warfarin and heparin bridging with uninterrupted warfarin in patients undergoing pacemaker or cardioverter-defibrillator implantation, the rate of device pocket hematoma formation was 16% and 3.5% with interrupted therapy and uninterrupted warfarin, respectively. Even with uninterrupted warfarin, intravenous heparin is given during the procedure in doses sufficient to achieve the ACT target outlined above, and sheaths are removed when the ACT is near normal.

Rates of thromboembolic and bleeding complications with uninterrupted warfarin have been compared with those observed with interrupted therapy and LMWH bridging. In retrospective cohort studies from high-volume centers that include data on >6000 patients, stroke or transient ischemic attack occurred in 0.9% of 1348 patients in the interrupted cohort and in none of the 2618 patients receiving uninterrupted warfarin, even though the latter group had higher CHADS2 scores and a more persistent pattern of AF. Rates of major bleeding in those receiving interrupted and uninterrupted therapy
Interrupted NOAC
Stop NOAC 5 days or more before procedure and switch to warfarin or bridge with LMWH
Give heparin to achieve an ACT >300 s
Stop heparin and consider protamine; remove sheath when ACT is <150 s; restart NOAC 6–8 h after sheath removal; re-evaluate at 3 mo

Interrupted strategy because it streamlines care.

Extrapolating From Warfarin to NOACs
The strategies used for warfarin have been extrapolated to NOACs and include interrupted, minimally interrupted, or uninterrupted approaches.

Interrupted Strategy
Dabigatran is often stopped for extended periods of time before ablation. In centers that have embraced uninterrupted warfarin, patients are sometimes switched from dabigatran to warfarin at least a month before the procedure; they undergo ablation with uninterrupted warfarin and then are switched back to dabigatran after the procedure. To avoid switching from a short-acting NOAC to long-acting warfarin and back again, other centers withhold dabigatran for 5 days or more before the procedure; the drug is held for a protracted period to ensure complete clearance by the time of ablation. In some cases, LMWH bridging is provided as described above. A similar approach is used with the other NOACs, although there is less concern about a prolonged half-life in patients with renal impairment because, in contrast to dabigatran, rivaroxaban and apixaban are only partially cleared through the kidneys.

Minimally Interrupted or Uninterrupted Therapy
Data from the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial provide some reassurance about the safety of dabigatran in the periprocedural setting. Thus, during a mean follow-up of 2 years, >4500 patients enrolled in the trial underwent >7500 procedures. Despite the lack of an antidote for dabigatran, the rate of major bleeding in patients who underwent procedures within 24 hours of study drug discontinuation was significantly lower in those on dabigatran than in those taking warfarin. Furthermore, a higher proportion of dabigatran-treated patients were able to undergo their surgery or procedure <48 hours after study drug interruption, likely reflecting the shorter half-life of dabigatran relative to warfarin. Although these data are promising, experience with dabigatran in patients undergoing AF ablation is limited, and consensus on optimal periprocedural management has yet to be reached. Nonetheless, there is mounting evidence that a minimally interrupted strategy is effective and safe with dabigatran, and there is some evidence that uninterrupted therapy may be possible with rivaroxaban.

An early observational study that included 290 patients undergoing AF ablation in 8 high-volume centers reported a higher rate of bleeding and thrombotic complications in patients on dabigatran than in those given uninterrupted warfarin, but this was a relatively small observational study with inherent susceptibility to bias. Furthermore, dabigatran was restarted 3 hours after sheath removal, which may have contributed to the higher bleeding rate. Recent studies have yielded more encouraging results. For example, in a study that randomized 90 patients undergoing AF ablation to dabigatran, which was stopped 24 hours before the procedure, or to warfarin, the rate of access site bleeding was reduced by >50% in those assigned to dabigatran. In another single-center cohort study that included 763 consecutive patients undergoing AF ablation, 191 patients were receiving dabigatran. The drug was held for 24 hours before the procedure, and was restarted 4 hours

Table 2. Anticoagulation Management Strategies Before, During, and After Ablation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Before Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted warfarin</td>
<td>Stop warfarin 5 days prior to procedure and bridge with LMWH; stop LMWH 12 h before ablation</td>
</tr>
<tr>
<td></td>
<td>Give heparin to achieve an ACT &gt;300 s</td>
</tr>
<tr>
<td></td>
<td>Stop heparin and consider protamine; remove sheath when ACT is &lt;250 s</td>
</tr>
<tr>
<td></td>
<td>restart warfarin and bridge with LMWH until INR is therapeutic; re-evaluate at 3 mo</td>
</tr>
<tr>
<td>Uninterrupted warfarin</td>
<td>Continue warfarin</td>
</tr>
<tr>
<td></td>
<td>Give heparin to achieve an ACT &gt;300 s</td>
</tr>
<tr>
<td></td>
<td>Stop heparin and consider protamine; remove sheath when ACT is &lt;250 s</td>
</tr>
<tr>
<td></td>
<td>continue warfarin and re-evaluate at 3 mo</td>
</tr>
<tr>
<td>Interrupted NOAC</td>
<td>Stop NOAC 5 days or more before procedure and switch to warfarin or bridge with LMWH</td>
</tr>
<tr>
<td></td>
<td>Give heparin to achieve an ACT &gt;300 s</td>
</tr>
<tr>
<td></td>
<td>Stop heparin and consider protamine; remove sheath when ACT is &lt;150 s</td>
</tr>
<tr>
<td></td>
<td>restart NOAC 6–8 h after sheath removal; re-evaluate at 3 mo</td>
</tr>
<tr>
<td>Minimally interrupted or uninterrupted NOAC</td>
<td>Stop NOAC 12–24 h before procedure</td>
</tr>
<tr>
<td></td>
<td>Give heparin to achieve an ACT &gt;300 s</td>
</tr>
<tr>
<td></td>
<td>Stop heparin and consider protamine; remove sheath when ACT is &lt;250 s</td>
</tr>
<tr>
<td></td>
<td>resume NOAC 6–8 h after sheath removal; re-evaluate at 3 mo</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; and NOAC, new oral anticoagulant.
after sheath removal. Compared with uninterrupted warfarin, there was no increase in bleeding or vascular complications with dabigatran. Another single-center cohort study enrolled 999 consecutive patients undergoing ablation; 376 patients were taking dabigatran (150 mg twice-daily), whereas the remainder were on warfarin and had a therapeutic international normalized ratio. Only 1 or 2 doses of dabigatran were held before the ablation, and the drug was restarted at the end of the procedure; this strategy was compared with uninterrupted warfarin. Using propensity score matching to generate a cohort of 344 patients in each group with balanced baseline data, major hemorrhage before the procedure occurred in 1.1% and 1.6% of patients in the dabigatran and warfarin groups, respectively, and in 1.2% and 1.5% of patients after the procedure. A single thromboembolic event occurred in both groups. Finally, in a study that included 720 consecutive patients undergoing AF ablation in 3 high-volume centers, 298 received periprocedural dabigatran, 153 underwent the procedure with uninterrupted warfarin, and 269 had interrupted warfarin with LMWH bridging. Dabigatran was held 12 hours before ablation and was restarted in the evening after the procedure. Rates of stroke or transient ischemic attack in the 3 groups were 0.6, 1.3, and 1.7%, respectively. Only in the interrupted warfarin group was red cell transfusion or an intervention required to manage bleeding in 1.1% and 1.5% of patients, respectively. Based on the results of these studies, which are summarized in Table 3, the risks of thromboembolic and bleeding complications with minimally interrupted dabigatran appear to be similar to those with uninterrupted warfarin; a conclusion supported by a recent meta-analysis.

Although there is less information about the efficacy and safety of other NOACs in patients undergoing ablation, data are emerging. Thus, in a multicenter prospective study, uninterrupted rivaroxaban was compared with uninterrupted warfarin in 157 patients undergoing AF ablation. There were no strokes, but 1 patient in each group suffered a periprocedural transient ischemic attack; major bleeding occurred in 1.9% of patients in the rivaroxaban group and in 2.5% of those given warfarin, a difference that was not statistically significant. In another single-center retrospective study, 170 patients underwent ablation on uninterrupted rivaroxaban. There were no reported thromboembolic complications or major bleeds. In a prospective registry of patients undergoing AF ablation in 8 centers, 321 underwent the procedure with uninterrupted rivaroxaban and 321 had uninterrupted warfarin. Rates of embolic complications were 0.3% in both groups and rates of major bleeding were 1.6% and 1.9%, respectively. Based on these limited data, it may be possible to perform AF ablation with uninterrupted rivaroxaban, but confirmation is needed.

**Conclusions and Future Directions**

Balancing the risks of stroke and bleeding remains a challenge in patients undergoing AF ablation. For years, interrupted warfarin with LMWH bridging was the anticoagulation strategy of choice based on the assumptions that (1) performing the procedure on warfarin would increase the risk of bleeding, and (2) bridging with LMWH, a short-acting anticoagulant, before and after the procedure would reduce the risk of periprocedural stroke without increasing the risk of bleeding. Results of randomized clinical trials suggest that both of these assumptions are wrong. Thus, uninterrupted warfarin appears to be more effective and safer than interrupted therapy with LMWH or heparin bridging. It is likely that switching patients back and forth from long-acting anticoagulants like warfarin to short-acting agents like heparin or LMWH not only leaves patients unprotected from thromboembolic events for periods of time, but also increases the risk of bleeding because the two anticoagulants are often overlapped.

Can the findings with warfarin be translated to the NOACs? Although the results of the studies to date suggest that the answer is yes, there are

---

**Table 3. Summary of Key Studies Comparing Dabigatran With Warfarin in Patients Undergoing Ablation**

<table>
<thead>
<tr>
<th>Study Type (Reference)</th>
<th>n</th>
<th>Dabigatran Regimen</th>
<th>Warfarin Regimen</th>
<th>Bleeding Rates</th>
<th>Thrombo-embolism Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter cohort (11)</td>
<td>290</td>
<td>Held morning of procedure; restarted 4 h after procedure</td>
<td>Continuous</td>
<td>6% and 1% with dabigatran and warfarin, respectively (P=0.019)</td>
<td>2.1% and 0% with dabigatran and warfarin, respectively (P=0.25)</td>
</tr>
<tr>
<td>Single-center randomized (12)</td>
<td>90</td>
<td>Held 2 doses before procedure; restarted when hemostasis achieved</td>
<td>Continuous</td>
<td>20% and 44% with dabigatran and warfarin, respectively (P=0.013)</td>
<td>0% and 2.2% with dabigatran and warfarin, respectively (P=NS)</td>
</tr>
<tr>
<td>Single-center cohort (13)</td>
<td>763</td>
<td>Held 2 doses before procedure; restarted 4 h after procedure</td>
<td>Continuous</td>
<td>4.7% and 4.3% with dabigatran and warfarin, respectively (P=0.8)</td>
<td>0% with dabigatran and warfarin (P=NS)</td>
</tr>
<tr>
<td>Single-center cohort (14)</td>
<td>999</td>
<td>Held 1 or 2 doses before procedure; restarted at procedure end</td>
<td>Continuous</td>
<td>1.2% and 1.5% with dabigatran and warfarin, respectively (P=0.74)</td>
<td>0.3% with dabigatran and warfarin (P=NS)</td>
</tr>
<tr>
<td>Multicenter cohort (15)</td>
<td>720</td>
<td>Held 1 dose before procedure; restarted evening after procedure</td>
<td>Continuous or interrupted</td>
<td>0%, 0.6%, and 5.6% with dabigatran, continuous warfarin, and bridging, respectively (P=0.0001)</td>
<td>0.6%, 1.3%, and 0.7% with dabigatran, continuous warfarin, and bridging respectively (P=0.76)</td>
</tr>
</tbody>
</table>
questions that still need to be addressed. For example, although a minimal NOAC interruption strategy appears to be effective and safe in patients undergoing AF ablation, is the same true with an uninterrupted strategy? The answer to this question depends on whether the risk of bleeding with NOACs during the procedure is different from that with warfarin. NOACs are associated with less intracranial bleeding than warfarin; is the same true for intracardiac bleeding because like the brain, the heart also is rich in tissue factor? Even if the risk of bleeding during ablation is similar or lower than that with warfarin, what do we do if tamponade occurs? The anticoagulant effects of warfarin can rapidly be reversed with a combination of vitamin K and prothrombin complex concentrate. In contrast, there are no specific antidotes for the NOACs. Although prothrombin complex concentrate reverses the anticoagulant effect of rivaroxaban,20 we do not know whether it attenuates bleeding. The disconnect between reversal of the anticoagulant activity of NOACs and control of bleeding is highlighted by the observation that prothrombin complex concentrate administration does not influence the prolonged activated partial thromboplastin time in dabigatran-treated rabbits, yet it attenuates injury-induced bleeding in a dose-dependent fashion.21 Antidotes for the NOACs are in development. These include a neutralizing monoclonal antibody fragment against dabigatran and a recombinant variant of factor Xa that serves as a decoy for oral factor Xa inhibitors, such as rivaroxaban and apixaban. Until such antidotes are available, a minimal interruption strategy is likely the safest approach for periprocedural NOAC management in patients undergoing AF ablation.

Case Resolution
With a creatinine clearance >80 mL/min, the half-life of dabigatran in the described patient is ≈13 hours. Based on the results of studies performed to date, it would be reasonable to recommend withholding 3 doses of dabigatran so that the drug is stopped 24 hours before the procedure and is held on the morning of the procedure. During the procedure, heparin will be given as described above. The patient can be advised to resume dabigatran therapy in the evening after the procedure provided that at least 4 to 8 hours have elapsed since sheath removal. Bridging with LMWH is unnecessary before the procedure because of the low risk of stroke in the short period that dabigatran therapy is withheld, and is not required after the procedure because of the rapid onset of action of dabigatran. This strategy is being prospectively evaluated in a large cohort study that is being conducted in Canada. In this study, dabigatran is withheld for 24 hours before ablation in patients with a creatinine clearance >50 mL/min and for 48 hours in those with a creatinine clearance of 30 to 50 mL/min and resumption of dabigatran is delayed for 8 hours after sheath removal. In addition to cohort studies like this, registries and randomized trials are needed to define the optimal periprocedural management of dabigatran and other NOACs in patients undergoing AF ablation.

Acknowledgments
Dr Weitz holds the Canada Research Chair (Tier 1) in Thrombosis and the J.F. Mustard/Heart and Stroke Foundation Chair in Cardiovascular Research.

Sources of Funding
This work was supported in part by funding from Canadian Institutes for Health Research and the Heart and Stroke Foundation.

Disclosures
Dr Weitz has served as a consultant and has received honoraria from Boehringer-Ingelheim, Bayer, Janssen Pharmaceuticals, Bristol Myers Squibb, and Pfizer. Dr Healey has received research funding from Boehringer-Ingelheim, Bristol Myers Squibb, and Pfizer. Dr Skanes has received honoraria from Boehringer-Ingelheim, Bayer, and Pfizer; research funding from Boehringer Ingelheim; and is on the Physician Advisory Board for Biosense Webster. Dr Verma has received research funding from Boehringer-Ingelheim and Bayer, and honoraria from Bayer.

References


