Anticoagulation Interruption in Atrial Fibrillation – a BRIDGE Too Far?

Aug 20, 2015  |  Aaron W. Aday, MD

Managing anticoagulation can be challenging for patients undergoing invasive medical procedures, particularly those with an increased risk of periprocedural hemorrhage. Approximately 250,000 individuals with atrial fibrillation (AF) interrupt anticoagulation annually in preparation for various procedures.\(^1\)

Interruption of long-acting anticoagulants, most notably warfarin, poses various issues as they must be discontinued prior to the procedure to ensure clearance from the body; similarly, it may take several days after resumption to reach therapeutic levels. This exposes the patient to potentially increased risk of systemic thromboembolism. As a result, clinicians often employ a strategy of bridging anticoagulation, whereby patients transition to a short-acting anticoagulant, usually unfractionated heparin (UFH) or low molecular weight heparin (LMWH), in the periprocedural period. The goal of this strategy is to normalize the bleeding risk during the procedure while minimizing the risk of thromboembolism. However, the data supporting this strategy have been sparse, and both clinicians and patients have had limited guidance to determine whether such a strategy is warranted.

Data from a retrospective analysis showed an increased risk of stroke with cessation of anticoagulation; however, this was measured over 60 days rather than the short time period typically required for warfarin clearance and resumption.\(^2\) A systemic review of 31 separate studies found a 0.6% risk of periprocedural arterial thromboembolism, and a 0.3% risk of stroke in patients who discontinued anticoagulation prior to a procedure without bridging anticoagulation.\(^3\) Although these rates were predicted to be higher than normal, this was based on mathematical modeling, and the studies used in the analysis were small in size and varied widely in their methodology. Since then, additional studies have attempted to quantify the risk of both arterial thromboembolism as well as hemorrhage with bridging anticoagulation, as shown in Table 1.
### Table 1: Studies of Bridging Anticoagulation in Patients on Warfarin

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Bridging Agent</th>
<th>Follow-up</th>
<th>Arterial Thromboembolism (N, %)</th>
<th>Major Bleeding (N, %)</th>
<th>Death (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovacs et al. (2004)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>224</td>
<td>Dalteparin</td>
<td>3 months</td>
<td>2 (0.9)</td>
<td>15 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Spyropoulos et al. (2006)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>832</td>
<td>UFH or LMWH</td>
<td>1 month</td>
<td>8 (1)</td>
<td>31 (3.7)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Douketis et al. (2004)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>650</td>
<td>Dalteparin</td>
<td>14 days</td>
<td>4 (0.6)</td>
<td>6 (0.9)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Pengo et al. (2009)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1262</td>
<td>Nadroparin or Enoxaparin</td>
<td>1 month</td>
<td>2 (0.2)</td>
<td>15 (1.2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Overall, these studies showed low event rates of arterial thromboembolism but significantly elevated rates of major bleeding associated with bridging anticoagulation. Similarly, a meta-analysis of observational bridging studies involving 12,278 patients on vitamin K antagonists for AF or mechanical heart valves showed no significant difference in arterial thromboembolism (incidence 0.9% with bridging and 0.6% without bridging) and an increased risk of major bleeding with bridging (odds ratio 3.60; 95% confidence interval [CI], 1.52 to 8.50).<sup>8</sup>

Not surprisingly, the risk of periprocedural major bleeding varies depending on the time interval between cessation of anticoagulation and the procedure. In an analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial, the risk of major bleeding was 3.6% for those withholding warfarin more than 72 hours prior to the procedure but exceeded 15% if anticoagulation was
stopped within 24 hours of the procedure.⁹ The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) trial examined 7,372 patients on oral anticoagulation and a total of 2,803 episodes of anticoagulation interruption.¹⁰ Within this cohort, bridging anticoagulation was associated with a higher rate of bleeding events (5% versus 1.3%, p <0.0001). Additional data have shown that utilizing a LMWH bridge following pacemaker and defibrillator implantation increases the risk of chest wall hematoma.¹¹ In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL) trial, 681 patients undergoing pacemaker or defibrillator implantation were randomized to continue warfarin therapy or transition to bridging anticoagulation with UFH or LMWH.¹² The trial was terminated early due to an increased risk of device pocket hematoma in the bridging anticoagulation versus the warfarin therapy groups (16% vs. 3.5%, respectively). There was no significant difference in thromboembolic events between the two groups.

As a result of these data, clinicians have been forced to weigh the benefits of thromboembolism reduction with the increased risk of periprocedural bleeding when deciding whether to employ bridging anticoagulation. In order to provide guidance to clinicians, the American College of Chest Physicians recommends bridging anticoagulation in high-risk individuals (CHADS₂ score of 5 or 6), but not in individuals at lower risk.¹ The guidelines recommend warfarin cessation five days prior to the procedure and resumption 12 to 24 hours following the procedure, assuming adequate hemostasis. These guidelines are similar to those of other clinical groups, although the level of evidence supporting these guidelines is categorized as Grade 2C.¹,¹³ Importantly, there are no data from randomized, controlled trials to guide clinicians in their decision making.

Fortunately, data from the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial were recently published to address this gap in our clinical knowledge.¹⁴ In this randomized double-blind trial, 1,884 patients were enrolled and randomized to either bridging therapy or placebo control. All patients were taking warfarin for either AF or atrial flutter. Patients were excluded if they had a history of mechanical heart valve implantation, arterial embolism (stroke, transient ischemic attack, or systolic embolism) within 12 weeks, or major bleeding within six weeks. Those planning to undergo cardiac, intracranial, and intraspinal surgeries were also excluded. Warfarin was discontinued five days prior to the procedure and restarted within 24 hours afterward. Bridging was accomplished
with LMWH (100 IU of dalteparin per kilogram twice daily) and began three days prior to the procedure. It was discontinued 24 hours prior to the procedure and then continued for five to ten days afterward, until a therapeutic international normalized ratio was achieved. Investigators followed patients for 30 days, and the primary outcomes were arterial thromboembolism and major bleeding. Ultimately, 913 patients in the placebo group and 891 in the bridging group completed the study. Arterial thromboembolism occurred in 0.4% of those in the placebo group and 0.3% in the bridging group (95% CI, -0.6 to 0.8, p = 0.73), as shown in Table 2. The mean CHADS2 score of those who developed arterial thromboembolism was 2.6. Major bleeding rates were 1.3% in the placebo group and 3.2% in the bridging group (relative risk 0.41; 95% CI, 0.20 to 0.78, p = 0.005). Minor bleeding was more common in the bridging group than the placebo group (20.9% vs. 12%). There were no significant between-group differences in the rates of death, myocardial infarction, or venous thromboembolism.

Table 2: BRIDGE Trial Efficacy and Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=913) (N, %)</th>
<th>Bridging (N=895) (N, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12.0)</td>
<td>189 (20.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Overall, the outcomes of the BRIDGE trial indicate no benefit from bridging anticoagulation, with respect to arterial thromboembolism."14 Furthermore; bridging anticoagulation nearly tripled the risk of major bleeding in this study. Nonetheless, there are some important limitations to the study. Only 58 total patients with a CHADS\textsubscript{2} score of 5 or 6 were included in the analysis, as such, it may not be possible to generalize these outcomes to all patients requiring anticoagulation interruption. In addition, procedures that place individuals at high risk for both bleeding and arterial thromboembolism, such as cardiac surgery and intracranial surgery, were excluded.

Despite these considerations, the BRIDGE trial represents the first randomized controlled trial to investigate the utility of bridging anticoagulation in patients with AF."14 Based on these data, bridging anticoagulation should not be uniformly adopted for patients undergoing invasive procedures. It is clear that such a strategy exposes individuals to an increased risk of bleeding with no obvious benefit. For now, the appropriate strategy for high-risk individuals (e.g. CHADS\textsubscript{2} score ≥5) has not yet been defined. However, based on the preponderance of data, physicians may consider reserving bridging anticoagulation using LMWH solely for individuals who have suffered a confirmed recent stroke presumed to be cardioembolic in nature. It is conceivable that such patients have an active process that would benefit from minimal interruptions in anticoagulation as part of its therapy. Furthermore, clinical guidelines should be updated to recommend against routine bridging anticoagulation and clearly document the lack of randomized controlled trials supporting bridging anticoagulation in any patient cohort. Hopefully, more studies will be available in the future to help risk stratify a wide range of patients undergoing procedures of varying risk.

References


2. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without
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Keywords: Anticoagulants, Atrial Fibrillation, Atrial Flutter, Cardiac Surgical Procedures, Contusions, Dalteparin, Defibrillators, Double-Blind Method, Embolism, Enoxaparin, Follow-Up Studies, Heart Valves, Hematoma, Hemostasis, Heparin, Heparin, Low-Molecular-Weight, International Normalized Ratio, Ischemic Attack, Transient, Myocardial Infarction, Nadroparin, Pulmonary Embolism, Registries, Retrospective Studies, Risk, Stroke, Thoracic Wall, Thromboembolism, Venous Thromboembolism, Venous Thrombosis, Vitamin K, Warfarin

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