Anticoagulation, Novel Agents, and Procedures:

Can We “Pardon the Interruption”?

Running title: Garcia et al.; Anticoagulation interruption

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When a patient with atrial fibrillation (AF) interrupts oral anticoagulation to undergo an invasive procedure, the clinician must answer two questions: for how long should the anticoagulant be stopped before the procedure, and should a “bridging” strategy be used with a shorter-acting agent? These questions are extremely important to the clinician who wants neither to use too much anticoagulation around procedures and cause unnecessary bleeding nor use too little and result in stroke. Based on decades of use of warfarin, the provider is left to choose an approach based on a subjective sense of the likely risks and benefits based on patient and procedural factors (Table 1). These decisions must be based on surprisingly little reliable evidence\textsuperscript{1,2}.

Because warfarin achieves its anticoagulant effect (reported as the international normalized ratio or INR) by causing the synthesis of dysfunctional clotting factors and the half-lives of some of these endogenous factors are quite long, warfarin needs to be discontinued 4 to 5 days before an intervention to restore adequate coagulation. For much of this time (and for several days after the warfarin is resumed), the patient with AF may be left with sub-optimal protection against stroke. In an effort to reduce this perceived risk, clinicians have traditionally administered unfractionated or low molecular weight heparin during the pre- and post-procedure days on which the INR is low, at least for high-risk patients.

Although the practice of administering “bridge therapy” with a rapid-onset, short-lived anticoagulant has a sound rationale, there is little reliable evidence that bridging benefits patients with AF. On one hand, a retrospective analysis of a large population-based linked administrative database suggests that, compared to patients without AF, patients in AF have a 2-fold increase in post-operative stroke\textsuperscript{3}. However, observational studies indicate that many (if not most) AF patients who simply interrupt warfarin for < 7 days (without bridging) have a very low risk of stroke\textsuperscript{4,5}. Even if one presumes that peri-procedural anticoagulant (bridge) therapy can reduce
this already low risk of stroke after warfarin interruption, the net clinical benefit is unclear because the extent to which bridging therapy increases major bleeding is not known. One prospective cohort study of 224 consecutive patients who received LMWH as peri-procedural anticoagulation, reported a major bleeding rate of 6.7% (95% CI 4.1 to 10.8)\(^6\), raising questions about whether in some scenarios bridging may do more harm than good. Ongoing studies, including the BRIDGE (http://clinicaltrials.gov/ct2/show/NCT00786474) and Canadian PERI-OP2 (http://clinicaltrials.gov/ct2/show/NCT00432796) trials, will provide important information regarding the risk and benefit of bridging for warfarin-treated patients.

But we are entering a new era of anticoagulation for AF with two approved\(^7,8\) and two pending\(^9,10\) novel oral anticoagulants, each of which have a half-life of about 12 hours in patients with normal renal function. These new oral agents, in theory, could be stopped just before and re-started soon after an invasive procedure. The ability to resume these medicines after hemostasis and rapidly re-establish effective anticoagulation without an overlapping parenteral agent is potentially a major advantage, both clinically and logistically. For urgent procedures, there has been considerable concern raised for the new agents regarding the lack of an antidote and the absence of a standard approach to measuring the anticoagulant effect.

Regarding these issues, Healy and colleagues provide important new information in this issue of Circulation\(^11\). They describe treatment and outcomes of over 4,500 hundred AF patients who temporarily stopped their oral anticoagulant therapy for a procedure at least once during the RE-LY trial. This is a major contribution since it comprises not only one of the largest descriptions of peri-procedural warfarin interruption, but also comparative information regarding dabigatran. Discontinuation prior to the procedure averaged 2 days in the dabigatran and 5 days in the warfarin groups. A minority of patients received “bridging” in the warfarin group, and
relatively few received vitamin K or fresh frozen plasma. What can we learn from this report?

First, procedures were very common, with one quarter patients having surgery or an invasive procedure over the two years of the trial. This underscores the clinical importance of this issue. The second important finding was the very low risk of thromboembolic periprocedural events in the trial that corroborates previously published observational data that the risk of briefly interrupting anticoagulation is low. Out of 4,591 unique procedure-related interruptions that occurred during RE-LY, only 21 (0.5%) patients experienced the primary efficacy endpoint (stroke or systemic embolism) during the 7 days before to 30 days after their procedure. Bridging for the warfarin group in this open-label trial was to be used (or not used) according to local norms. The third important finding is that only 28.5% of the patients allocated to warfarin and approximately 16% of the patients allocated to dabigatran received peri-procedural anticoagulation with a parenteral agent. The risk of post-operative bleeding was 4 to 5% and was similar with warfarin versus dabigatran. Thus, using the interruption approach in RE-LY, there were 8 times more major bleeding events than strokes in the peri-procedure period, for both warfarin and dabigatran. Even assuming that one could shift this ratio with more or less complete anticoagulation around the time of procedure, the optimal balance is not known. More bleeding may paradoxically contribute to more subsequent thrombotic events through poorly defined mechanisms that include the discontinuation of antithrombotic therapy. The fact that major (defined as lasting greater than one hour) procedures had higher rates of bleeding than minor ones underscores the opportunity to incorporate procedural bleeding risk into the decision about duration of discontinuation and use of bridging. Surprisingly, bleeding rates were at least as high in patients who avoided dabigatran for at least 72 hours before their intervention compared with shorter interruptions, likely due to confounding such that physicians stopped
anticoagulation longer for higher risk patients. This underscores the importance of patient- and procedure-specific risk factors for bleeding that are important irrespective of the anticoagulation strategy. This should prompt extra care (including cautious post-procedure resumption of anticoagulation) to reduce hemorrhage in those patients at highest risk.

Urgent surgery was associated with much higher rates of bleeding than elective procedures, as expected. But the fact that bleeding was similar (in fact numerically higher) with warfarin than dabigatran for urgent surgery should serve as a reassurance to those who are concerned about the lack of a standard way to measure anticoagulant effect and of a specific antidote with dabigatran. While such tools would be desirable, the lack of them should not be a factor that would make one favor use of warfarin, based on these outcome data.

The analyses by Healy leave several questions unanswered. While the efficacy and safety around procedures were similar with dabigatran versus warfarin, there were too few thrombotic events to determine whether or not there is a modest difference. This study does not provide the basis for specific guidance as to the ideal duration of dabigatran interruption to minimize both ischemic events and bleeding for various patients and procedures. We lack important information to guide management around urgent procedures, including how often vitamin K was used for the warfarin patients and other factor replacement for the dabigatran patients. The change to the protocol recommendation about when dabigatran should be interrupted made in the last 8 months of the study “based on an improved understanding of the anticoagulant effect of dabigatran” adds to our uncertainty. That notwithstanding, the guidance in the package insert approved by the US Food and Drug Administration provides sensible recommendations for interruption of dabigatran based on renal function: “If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min)
before invasive or surgical procedures because of the increased risk of bleeding.”

In conclusion, the data from these analyses of the RE-LY trial indicate that for patients with AF, stroke and systemic embolism are very uncommon after brief elective interruptions of anticoagulation, either with dabigatran or with warfarin. Although the anticoagulant interruptions were briefer in the dabigatran-treated patients, the rate of dabigatran-associated major bleeding did not differ from the rate observed in the patients treated with warfarin, even in the setting of urgent surgery. Taken together, these observations support the welcome hypothesis that novel shorter-acting oral anticoagulants will simplify the process of interrupting therapy for elective invasive procedures.

Conflicts of Interest Disclosures: Dr. Garcia discloses that, in the past 3 years, he has received modest compensation for occasional service as an advisor to BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Dr. Granger discloses that, in the past 3 years, he has received compensation for research grants as well as from consulting/honaria from BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. Full disclosure available on https://www.dcri.org/about-us/conflict-of-interest.

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*Circulation.* 2012; 126: XX-XXX.

Table 1. Factors influencing whether or not to provide peri-procedural bridging therapy.

<table>
<thead>
<tr>
<th>Factors favoring bridging</th>
<th>Factors favoring no bridging</th>
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<tbody>
<tr>
<td>Higher risk of stroke or systemic embolism</td>
<td>Lower risk of stroke or systemic embolism</td>
</tr>
<tr>
<td>Low bleeding risk of patient</td>
<td>High bleeding risk of patient</td>
</tr>
<tr>
<td>Low bleeding risk of procedure</td>
<td>High bleeding risk of procedure</td>
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<tr>
<td>Longer time off of oral anticoagulant (or without therapeutic effect)</td>
<td>Cost and complexity</td>
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