Anticoagulation, Novel Agents, and Procedures
Can We Pardon the Interruption?

David A. Garcia, MD; Christopher B. Granger, MD, FACC, FAHA

When a patient with atrial fibrillation (AF) interrupts oral anticoagulation to undergo an invasive procedure, the clinician must answer 2 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 to 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). These decisions must be based on surprisingly little reliable evidence.1,2

Because warfarin achieves its anticoagulant effect (reported as the international normalized ratio) by causing the synthesis of dysfunctional clotting factors and because the half-lives of some of these endogenous factors are quite long, warfarin needs to be discontinued 4 to 5 days before an intervention if adequate coagulation is to be restored. For much of this time (and for several days after the warfarin is resumed), the patient with AF may be left with suboptimal 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 postprocedure days on which the international normalized ratio 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 with patients without AF, patients in AF have a 2-fold increase in postoperative major bleeding is not known. One prospective cohort study of 224 consecutive patients who received LMWH as periprocedural anticoagulation reported a major bleeding rate of 6.7% (95% confidence interval, 4.1–10.8),9 raising questions about whether in some scenarios bridging may do more harm than good. Ongoing studies, including the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE; http://clinicaltrials.gov/ct2/show/NCT00786474) and Canadian Perioperative 2 (Periop2; 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 2 approved7,8 and 2 pending9,10 novel oral anticoagulants, each of which has a half-life of ~12 hours in patients with normal renal function. These new oral agents, in theory, could be stopped just before and restarted soon after an invasive procedure. The ability to resume these medicines after hemostasis and rapidly reestablish 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, Healey and colleagues11 provide important new information in this issue of Circulation. They describe treatment and outcomes of >4500 AF patients who temporarily stopped their oral anticoagulant therapy for a procedure at least once during the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. This is a major contribution, because it comprises not only one of the largest descriptions of periprocedural warfarin interruption but also comparative information regarding dabigatran. Discontinuation before 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 2 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, which corroborates previously published observational data that the risk of briefly interrupting anticoagulation is low. Of 4591 unique procedure-related interruptions that occurred during...
RE-LY, only 21 (0.5%) patients experienced the primary efficacy end point (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 16% of the patients allocated to dabigatran received periprocedural anticoagulation with a parenteral agent. The risk of postoperative bleeding was 4% to 5% and was similar with warfarin versus dabigatran. Thus, using the interruption approach in RE-LY, there were 8× more major bleeding events than strokes in the periprocedure 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 >1 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 because of 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 postprocedure 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 compared with dabigatran for urgent surgery should serve as a reassurance to those who are concerned both about the lack of a standard way to measure anticoagulant effect of dabigatran and about the absence of a specific antidote for dabigatran. Although 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 Healey leave several questions unanswered. Although 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 U.S. 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.

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.

References

Table. Factors Influencing Whether or Not to Provide Peri-Procedural Bridging Therapy

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<tr>
<th>Factors Favoring Bridging</th>
<th>Factors Favoring No Bridging</th>
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<tr>
<td>Higher risk of stroke or systemic embolism</td>
<td>Lower risk of stroke or systemic embolism</td>
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<td>Low bleeding risk of patient</td>
<td>High bleeding risk of patient</td>
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<td>Low bleeding risk of procedure</td>
<td>High bleeding risk of procedure</td>
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<td>Longer time off of oral anticoagulant (or without therapeutic effect)</td>
<td>Cost and complexity</td>
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