Editorial

Anticoagulation Interruptus
Not Without Risk

Michael D. Ezekowitz, MBChB, DPhil, FRCP

The need to withhold anticoagulation in patients requiring elective surgery poses a particularly important challenge when the risk of thrombosis and thromboembolism is high. In spite of the increasing use of prosthetic heart valves and the increasing prevalence of atrial fibrillation in the aging population, Kovacs et al\(^1\) make the important point in this issue of *Circulation* that there is a paucity of information in the literature to guide the clinician to optimal care. This observation motivated the design of the prospective study they report. Patients’ anticoagulation therapy was discontinued before surgery. There were 3 reporting phases: preoperative, intraoperative, and postoperative.

In the preoperative phase, warfarin was stopped 5 days before the procedure and replaced with dalteparin, a low-molecular-weight heparin administered at a dose of 200 IU/kg on the mornings of the third and second days before the procedure. On the morning of surgery, dalteparin was administered at 100 IU/kg. For patients whose international normalized ratio (INR) was >1.4 on the day before surgery, 1 mg oral vitamin K was prescribed. For those patients requiring vitamin K, INR measurement was repeated the day of surgery, and if >1.4, postponement of surgery was considered. Aspirin was stopped 7 days before the surgery. The major positive finding of the paper is that this regimen worked; there were no bleeding or valve thromboses or thromboembolic complications.

Phases 2 and 3 provide more questions than answers. During surgery, the authors report “bleeding complications,” which were used as a reason for not starting anticoagulation earlier than was “usual practice.” No details were given about the types of bleeds that occurred during the procedures or specifically why these precluded administration of anticoagulation therapy.

In the postprocedural period, the deficiencies of the study design and approach become most manifest. There was a higher than anticipated event rate for both thrombotic events and bleeding events. To draw generalizations from this study is difficult because the authors fail to report the type of prosthetic valves (presumably mechanical), whether these were in the aortic or mitral position, or whether any of these patients had 2 valve prostheses or had coexisting atrial fibrillation. No data are given on ventricular function, a factor that influences risk.

The pivotal question that needs resolution is the manner in which patients should be managed intraoperatively and postoperatively. The fact that this study is prospective and involves consecutive series of patients is a strength; however, there is no comparator, and a single strategy was used in a “catch-all study design” without consideration of the type of surgery involved. The high complication rate is even more significant given that most of the procedures were relatively minor (eg, diagnostic catheterization). No data were provided on revascularization, genitourinary surgery (not defined), and dental procedures that presumably involved extractions. Some patients had major orthopedic surgery. The postoperative management of these patients is complicated by the fact that orthopedic surgery requires venous thrombosis prophylaxis, for which standards have been established. Typically, though, the venous prophylaxis studies exclude patients with atrial fibrillation and heart valves and do not address the question of interrupting anticoagulation.

It is clear that prospective, blinded clinical data are needed for each common procedure for which interruption of anticoagulation is required. Consideration should be given to the likely clinical impact of outcomes—eg, groin hematoma infrequently leads to long-term adverse effects, yet a thrombosed valve or embolic episode could be devastating. Thus, manageable bleeds might be a tolerable price to pay for protection against stroke during and after the procedure. Patients, procedures, and possible outcomes should be risk stratified.

Kovacs and colleagues\(^1\) have timed their article well. A promising new generation of oral anticoagulants is being developed that could be evaluated in an interruption trial. The drug most advanced in clinical trials is ximelagatran.\(^2\) Ximelagatran is a prodrug (active metabolite is melagatran) and acts by direct thrombin inhibition. The advantages of ximelagatran include rapid absorption, low protein binding, and absence of food or drug interaction. More importantly, it is administered in fixed doses without coagulation monitoring. The Stroke Prevention using Oral Thrombin Inhibition in atrial Fibrillation (SPORTIF) III trial has shown that ximelagatran (36 mg twice a day) is as effective as warfarin (INR between 2 and 3) in stroke prevention in atrial fibrillation. No difference is observed in the rate of major bleeds (1.3% versus 1.8%; *P*=NS). One of the most common adverse effects was elevation of liver enzyme levels during the first 6 months of treatment in about 6.5% patients in ximelagatran.

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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In a coagulation interruption study, these parameters would need to be closely monitored. Ximelagatran is excreted by the kidneys, and hence, dose adjustments would be needed in patients with renal impairment. As further data on the use of oral direct thrombin inhibitors emerge, it is likely that such agents will become a viable alternative to heparin (either unfractionated or fractionated) and certainly warfarin and therefore should be tested in an interruption study. Other agents such as dabigatran are being evaluated but are not as far along in development.

Some are interested in the development of nonpharmacological approaches to prevent embolism. One approach is the elimination of the left atrial appendage as a source of embolism. A new percutaneous technique called the percutaneous left atrial appendage transcatheter occlusion (PLAATO) system is less invasive than surgery and could have a role in an interruption trial. Another approach involves transcatheter placement of a mesh stent into the bifurcation of the internal and external carotid artery. The stent acts as a sieve, preventing emboli from entering the internal carotid artery and diverting them to the less crucial external carotid artery. These devices will need further studies and clinical evaluation before they can be tested in a trial. Now is the time to design a trial. Opportunities for stroke and unwanted thrombosis prevention have never been better. In the meantime, it is clear that interrupting anticoagulation is not without danger.

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References


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