Perioperative anticoagulant management in patients with atrial fibrillation: practical implications of recent clinical trials

Alfonso Tafur1, James D. Douketis2

1 Department of Medicine, Northshore University Health System, Evanston, Illinois, United States; University of Chicago, Chicago, Illinois, United States
2 Department of Medicine, McMaster University, Hamilton, Ontario, Canada

KEY WORDS
anticoagulation, atrial fibrillation, perioperative, procedure, warfarin

ABSTRACT
Defining the safest perioperative anticoagulation management approach for patients who are receiving chronic anticoagulant therapy stroke prevention has been a challenging and long-standing dilemma, especially for patients with atrial fibrillation who constitute the most common patient group receiving long-term anticoagulation. Using a case-based format, we summarize the findings of recent clinical trials which have helped to inform best practices for perioperative anticoagulant management in patients with atrial fibrillation and provide an algorithmic management approach to this problem. We have done so by exploring the evidence to address 3 key questions: Is it necessary to interrupt anticoagulation for a procedure? How to estimate a patient’s risk for perioperative thromboembolism and bleeding? If chronic anticoagulation interruption is required, is bridging anticoagulation with heparin needed?

Introduction
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and with an aging population, its prevalence is expected to reach 2.6 million cases by 2030 in the United States alone.1 Anticoagulation is an important component of stroke prevention in patients with AF, and such patients who require an elective surgery or procedure appear to be at increased risk for perioperative stroke.2 Thus, in a retrospective population-based study, the 30-day post-operative rate of stroke among 69,202 patients with AF was 1.8% as compared with 0.6% among 2.4 million patients without AF.2 Given that approximately 10% of patients with AF need temporary interruption of their anticoagulation every year for an elective surgery or procedure, this emphasizes the clinical importance of determining best practices regarding perioperative anticoagulant management in such patients.3

In patients with AF who require interruption of anticoagulation for an elective surgery or procedure, the use of pre- and postprocedure heparin bridging, typically with a low-molecular-weight heparin (LMWH) has been widely used with the intent of minimizing the time patients are not therapeutically anticoagulated around the time of their surgery or procedure with the intent, in turn, to minimize their risk for arterial thromboembolism.4 However, the question of whether bridging anticoagulation mitigates the risk for arterial thromboembolism, which comprises stroke, transient ischemic attack (TIA), and systemic embolism, has been a topic of long-standing uncertainty.3,5,6 Against this putative benefit of bridging, heparin bridging appears to confer a 3% to 4% risk for major bleeding and 13% to 15% risk for overall bleeding in the perioperative setting, as observed in a meta-analysis of 34 non-randomized, observational studies that assessed 7118 bridged and 5160 nonbridged patients.7 A personalized evaluation of the potential bleeding and thromboembolic risk is required to provide an adequate perioperative anticoagulation plan for these patients. Only recently, high-quality data have become available to define best practices.8 Against this background, we present a case-based approach to the perioperative anticoagulant management of patients with AF who are receiving anticoagulant therapy with warfarin. Overall, there are 3 questions that should be considered when deciding about perioperative management: Is it necessary to interrupt...
anticoagulation for a procedure? How to estimate a patient’s risk for perioperative thromboembolism and bleeding? If chronic anticoagulation interruption is required, is bridging with heparin anticoagulation needed?

**Case vignette 1**  A 73-year-old woman has been recently diagnosed with nonvalvular AF. She has a history of diabetes and hypertension but no prior stroke. She is now on warfarin but her rhythm control has been challenging due to symptomatic bradycardia from β-blocker therapy. She has been diagnosed with sick sinus syndrome and will undergo pacemaker implantation. Does the patient need to stop anticoagulation?

In this case, we recommend not stopping anticoagulation. In some clinical scenarios, it is safe to continue anticoagulation without interruption. Heparin bridging can increase the risk for developing pocket hematoma, in excess of 20% of the cases. Paradoxically, the use of bridging in this scenario may necessitate anticoagulation interruption for a longer period, increased cost of hospitalization, and increasing the window of risk for perioperative stroke. This calls into question whether it is safer to continue anticoagulation instead of bridging patients who need a pacemaker implantation. This was addressed by the BRUISE-CONTROL study, a randomized controlled trial involving 343 patients who continued warfarin anticoagulation and 338 who interrupted warfarin and received bridging with therapeutic-dose LMWH or intravenous heparin, given preoperatively and starting within 24 hours postoperatively. Almost 90% of patients in this study had AF. Clinically significant pocket hematoma occurred in 3.5% of the warfarin continuation group and in 16% of the warfarin interruption and bridging group. Although the rate of pocket hematoma may have been reduced in the bridging group if bridging had been administered in a less aggressive manner (ie, commenced 24–48 hours postprocedure), the magnitude of the effect was considerable (one additional pocket hematoma for every 8 patients bridged), and with no demonstrable effect to mitigate the risk for arterial thromboembolism.

Other procedures that can be performed without interruption of warfarin anticoagulation include minor dental procedures such as tooth extractions or endodontic procedures (root canal); cataract surgery, due to its avascular technique; cardiac catheterization (especially if done with a radial artery approach); and minor dermatologic procedures such as skin biopsies or removal of small skin cancers. Overall, there is increasing recognition that certain surgeries and procedures may not require anticoagulant interruption in circumstances where the risk for bleeding is low or in situations whereby if bleeding occurs it can be easily visualized and addressed during the procedure.

**Case vignette 2**  A 67-year-old exsmoker male patient with AF has been on warfarin for 3 years and has a history of hypertension and stable peripheral artery disease but no prior stroke or systemic embolism. He is now scheduled for knee arthroscopy. What is his estimated thromboembolic risk? Should we administer bridging anticoagulation?

There is no ideal clinical prediction score that is specific for cardioembolic stroke prediction in patients with AF. Thus, in a cohort study with 32721 person-years of follow-up and 685 validated thromboembolic events, the CHADS 2 (Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke) score had a relatively poor predictive utility for cardioembolic stroke based on a c-statistic of 0.58. In a meta-analysis of 8 studies, the c-statistic ranged from 0.60–0.80 for CHADS 2, and 0.64–0.79 for CHA 2DS2-VASc (adds female sex, age 65–74 years, and vascular disease). Despite these limitations, the CHADS 2 and CHA 2DS2-VASc scores are widely used as the best estimators of stroke risk among patients with nonvalvular AF and have been adopted, rightly or wrongly, for use in the perioperative setting to estimate stroke risk among patients with AF who require an elective surgery or procedure. However, the predictive utility of the CHADS 2 and CHA 2DS2-VASc scores to predict perioperative stroke has not been validated. Consequently, although these scores may be widely used to estimate perioperative stroke risk and, in turn, determine the need for bridging anticoagulation during anticoagulant interruption, the use of such prediction scores in the perioperative setting is empiric without prospective validation.

Assuming that this patient is at low risk for perioperative arterial thromboembolism, an important management question is whether bridging anticoagulation is needed during warfarin interruption. This question was addressed in the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial. This was a randomized, double-blind, placebo-controlled trial of patients with chronic AF or flutter on warfarin who required an elective surgery or procedure. Patients with a mechanical heart valve or recent (within 3 months) stroke, TIA, or systemic embolism were excluded. Patients were randomly allocated to bridging with dalteparin, 100 units/kg twice daily, or no bridging. The study population had a mean CHADS 2 score of 2.3, with 17% having a history of stroke or TIA, and only 3% having a CHADS 2 score of 5 or 6. The 30-day postprocedure incidence of arterial thromboembolism was not significantly different between no bridging and bridging groups: 0.4% vs 0.3% (mean between-group difference 95% confidence interval [CI], −0.6 to 0.8). The rate of major bleeding, however, was significantly lower in the no-bridging than bridging group: 1.3% vs 3.2% (relative risk, 0.41; 95% CI, 0.20–0.78). In addition, there was no significant difference in the rates of acute myocardial infarction, deep
vein thrombosis, pulmonary embolism, or death in the bridging and no-bridging groups.

Overall, the BRIDGE trial addresses the question of “should we bridge” and supports foregoing bridging anticoagulation in most patients with AF who require perioperative warfarin interruption. However, the findings may not be generalizable to selected patient subgroups with AF, including those considered at high risk for stroke, perhaps characterized as patients with a CHADS2 score exceeding 4 or those with a recent stroke or TIA. For this clinical scenario, we recommend perioperative interruption of warfarin without bridging.

Case vignette 3 A 66-year-old woman with AF on warfarin with hypertension who had a prior stroke 6 months ago has been waiting for over a year for knee arthroplasty and now is scheduled for surgery. She has minimal deficits form her stroke and is completely independent. She has no history of diabetes, peripheral artery disease, or heart failure. What is the estimated thromboembolic risk? What are the risk and benefits of bridging?

Assuming that this patient is at high risk for perioperative arterial thromboembolism, based on the history of a recent stroke, the results of the BRIDGE trial should be interpreted with caution for such patients who were underrepresented in this trial. For this patient, we would recommend perioperative LMWH bridging. Recurrent ischemic stroke, especially if cardioembolic, carries a high rate of in-hospital mortality during its acute phase, which is as high as 27%. The odds of postoperative stroke are 2-times more likely among patients with a prior history of stroke (odds ratio [OR], 2.3; 95% CI, 2.2–2.5). While there is paucity of good quality evidence to either support or discourage bridging patients such as this example, one must also be mindful of the potential bleeding risk with LMWH bridging. Consistent with the bridging protocol used in the BRIDGE trial, the last preoperative dose of LMWH should be half the daily dose and administered 24 hours before surgery. Thus, if a patient is receiving bridging with enoxaparin, 1 mg/kg twice daily, the last dose of enoxaparin is given on the morning of the day before surgery with no evening dose given. Post-operative anticoagulation reinitiation should be contingent on clinical evaluation of hemostasis and should allow flexibility to patient- and surgery-specific circumstances, as was done in the BRIDGE trial. Thus, LMWH bridging can be resumed approximately 24 hours (the next morning) after a low bleeding risk surgery or procedure. On the other hand, as in our case, the resumption of bridging should be delayed for 48 to 72 hours after a high-bleeding-risk surgery or procedure. Overall, the BRIDGE trial also helps inform best practices on “how to bridge” patients, among those patients in whom perioperative LMWH bridging is administered.

Case vignette 4 A 65-year-old former smoker male patient with AF is chronically anticoagulated with warfarin and has been found to have renal cell cancer. The patient has normal renal function, no prior history of major bleeding complications, normal hemoglobin and platelet levels, and good anticoagulation control. He is scheduled for a partial nephrectomy. What is the likelihood of serious perioperative bleeding?

In a study involving 2182 patients who formed an inception cohort for the evaluation of perioperative anticoagulation, predictors of bleeding risk were evaluated. Most of the patients of this cohort were anticoagulated due to venous thromboembolism and 30% due to AF. The 90-day rate of bleeding was 6% for those who received heparin bridging and half of them were major bleeding events. In this cohort, mitral mechanical heart valve (hazard ratio [HR], 2.4; 95% CI, 1.1 to 4.9), moderate-to-high bleeding risk procedure (HR, 1.9; 95% CI, 1.0–3.6), active cancer (HR, 1.9; 95% CI, 1.0–3.5), platelet count <150 000/l (HR, 2.3; 95% CI, 1.1–4.6), and a history of bleeding (HR, 2.1; 95% CI, 1.1–4.1) were independent predictors of major bleeding. The authors proposed the “Bleed MAP Score” to estimate perioperative bleeding risk, assigning 1 point for the following risk factors: prior bleeding (Bleed), mechanical mitral heart valve (M), active cancer (A), and low platelets (P). For bridged patients and more than 2 risk factors, the rate of major bleeding was 12.12% (95% CI, 3.4–28.2) compared with lower rates for those with 0 points (95% CI, 0.2–1.7), or 1 to 2 points (95% CI, 2.2–4.7). To date, however, this score has not been prospectively validated. The HAS-BLED score has also been evaluated in the specific setting of perioperative bleeding. In a prospective multicenter registry of anticoagulated patients, results of 1000 procedures were evaluated. Patients with a HAS-BLED score of more than 2 were substantially more likely to bleed (HR, 11.8; 95% CI, 5.6–24.9). While many of the risk factors for bleeding are fixed, the bridging process in itself is a modifiable risk factor for bleeding. In a post hoc analysis of patients in the RELY trial, which compared dabigatran (110 mg or 150 mg twice daily) with warfarin for stroke prevention among patients with nonvalvular AF, those who required anticoagulation interruption were studied. Among warfarin-treated patients, those who received heparin bridging had an over 3-times higher risk for major bleeding than those who were not bridged (6.8% vs 1.6%; HR, 4.62; 95% CI, 2.45–8.72).

Our patient in this vignette has a higher bleeding risk due to an underlying cancer. Pertinent to this, in a perioperative anticoagulation management inception cohort, in which 493 (of 2282) patients had cancer, the 3-month incidence of major bleeding was higher among patients with malignancy (3.4% vs 1.7%); this difference in major bleeding was heightened among those patients with cancer who were bridged (5% vs 1%). Paradoxically, this high bleeding risk needs to be balanced with higher risk of postoperative venous thromboembolism among patients having...
In the interim, the Dresden NOAC Registry may shed some light to the method. Thus, of 2179 included patients, 7% underwent an elective surgery procedure, with most patients receiving rivaroxaban for stroke prevention related to AF. Most procedures were minor and 187 patients (22%) did not require DOAC interruption. Among those who continued the DOAC, there were no major bleeding events and 7 clinically relevant nonmajor bleeds (3.7%). This suggests there is a population of patients undergoing low bleeding risk procedures in whom DOACs can safely be continued. An exception may be radio frequency ablation for AF. In a multicenter registry, patients taking uninterrupted rivaroxaban (n = 321) during radiofrequency AV node ablation were age- and sex-matched with patients on continued warfarin anticoagulation (n = 321). There were no differences in the rate of major bleeding (1.6% vs 1.9%) or minor bleeding (5.0% vs 5.9%). In a similar study with 200 patients on apixaban compared with 200 patients on warfarin who underwent radiofrequency ablation without treatment discontinuation, the postprocedure bleeding rate was not different. We shall not extrapolate data from different DOACs for perioperative anticoagulant management. This is stressed on a multicentric prospective registry of anticoagulation patients who needed radio frequency ablation. Among the 145 patients on dabigatran who held their dose the morning of the procedure, there were 3 thromboembolic complications (2.1%). In contrast, the rate of major bleeding was significantly higher also for dabigatran (6% vs 1%; $P = 0.02$) compared with patients who continued warfarin (n = 145).

**Summary and future research** In this review, we aimed to summarize the results of recent clinical trials involving perioperative anticoagulant management of patients with AF. In FIGURE 1, we presented an algorithmic approach to the risk stratification pertinent for perioperative anticoagulant management. This algorithm is meant to be a suggested guideline, and individualized patient management may differ depending on patient-specific circumstances. Moreover, there are additional risk factors for arterial or venous thromboembolism, such as the type of surgery, which is not captured by this algorithm but should be addressed during individual patient management. The key changes to practice relate to the findings from the BRUISE-CONTROL and BRIDGE trials. Additional research is needed to determine best perioperative anticoagulant practices in selected patients with AF who are receiving warfarin and have a CHADS$_2$S, score exceeding 4 or a recent stroke, and among patients with AF who are receiving a DOAC.

---

**FIGURE 1** Algorithmic approach to perioperative anticoagulant management of the anticoagulated patient with nonvalvular atrial fibrillation

- **Does the patient need to stop anticoagulation?**
  - **Yes:** Proceed without interruption
  - **No:** May continue anticoagulation: pacemaker placement, dental extraction, cataract surgery, joint aspiration, dermatologic biopsy, venography, radio frequency ablation

- **Is the risk of stroke high?**
  - **No:** Stop warfarin 5 days before the procedure; no heparin bridging
  - **Yes:** Reasonable to consider preoperative bridging
    - Assess bleeding risk
    - Last preoperative dose of low-molecular-weight heparin is 24 hours before the intervention and $\frac{1}{2}$ of the daily dose

- **Provide postoperative venous thromboembolism prophylaxis in all patients**

---

**Perioperative management of patients on direct oral anticoagulants** Less is known about the perioperative management of patients with AF who are receiving a direct oral anticoagulant (DOAC), which comprises dabigatran, apixaban, rivaroxaban, and edoxaban. Most guidance statements suggest stopping DOACs 1 day before a low bleeding risk surgery/procedure and 2 to 4 days before a high bleeding risk surgery/procedure. The ongoing Perioperative Anticoagulant Use for Surgery Evaluation Study (PAUSE) (NCT02228798) aims to define how to safely manage patients who require perioperative interruption of DOACs.
REFERENCES


Okołooperacyjne leczenie przeciwkrzepliwe u chorych z migotaniem przedsionków – praktyczne implikacje przeprowadzonych ostatnio badań klinicznych

Alfonso Tafur¹, James D. Douketis²

¹ Department of Medicine, Northshore University Health System, Evanston, Illinois; University of Chicago, Chicago, Illinois, Stany Zjednoczone
² Department of Medicine, McMaster University, Hamilton, Ontario, Kanada

SŁOWA KLUCZOWE
antykoagulacja, migotanie przedsionków, okołooperacyjne, warfaryna, zabieg

STRESZCZENIE
Okraczenie najbezpieczniejszego podejścia do okołooperacyjnej antykoagulacji u chorych, którzy otrzymują przewlekłe leki przeciwkrzepliwe w ramach prewencji udaru mózgu ciągle stanowi wyzwanie, szczególnie w odniesieniu do chorych z migotaniem przedsionków, którzy są grupą najczęściej przyjmującą długo-terminowo leki przeciwkrzepliwe. W poniższym opracowaniu podsumowano na podstawie przypadków klinicznych wyniki ostatnich badań klinicznych, które pomogły w określeniu zasad najlepszej praktyki dotyczącej okołooperacyjnej strategii przeciwkrzepliwej u chorych z migotaniem przedsionków oraz pozwoliły na opracowanie algorytmu postępowania w takich sytuacjach. Przeszedziono dane naukowe dotyczące 3 kluczowych pytań: czy konieczne jest przerwanie antykoagulacji z powodu zabiegu operacyjnego? Jak oszacować okołooperacyjne ryzyko zakrzepowo-zatorowe i ryzyko krwawienia u danego chorego? Jeśli wymagane jest przerwanie przewlekłej antykoagulacji, to czy potrzebne jest pomostowe leczenie przeciwkrzepliwe heparyną?