

Perioperative atrial fibrillation: A systematic review of evolving therapeutic options in pharmacologic and procedural management

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ABSTRACT

Given the high incidence of atrial fibrillation (AF) in the surgical population and the associated morbidity, physicians managing these complicated patients in the perioperative period need to be aware of the new and emerging trends in its therapy. The cornerstones of AF management have always been rate/rhythm control as well as anticoagulation. Restoration of sinus rhythm remains the fundamental philosophy as it maintains the atrial contribution to cardiac output and improves ventricular function. The recent years have seen a dramatic increase in the number of randomized AF trials that have made significant advances to our understanding of both pharmacologic and procedural management, from the introduction of the new generation of oral anticoagulants (NOAC's) to catheter approaches for AF ablation. This paper will summarize the newest data that will affect the perioperative management of these patients.

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INTRODUCTION

Atrial fibrillation (AF), the most common atrial arrhythmia, ranges from being minimally symptomatic to cause debilitating symptoms. It increases the risk of stroke so that most patients require systemic anticoagulation. Several recent trials significantly expand our understanding of treating AF with a catheter or surgical ablation, preventing stroke with device therapies or anticoagulants, and managing complications of medical and procedural therapies. The impact of these trials will likely affect periprocedural anticoagulation management and intraprocedural management of patients treated for AF.

current guidelines,^[1] (2) provided new data to inform current practice where little data existed, (3) evaluated a new therapy, or (4) compared two or more treatments in a randomized, prospective fashion. The studies selected involve two areas relevant to the practicing anesthesiologist caring for patients in the perioperative or intensive care setting: Anticoagulation management and ablation procedural approach. These studies are discussed in detail below.

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METHODS

A MEDLINE search was performed for studies published or reported in the past 6 months regarding AF treatment. Studies were selected that either (1) challenged

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Stroke prevention and anticoagulation management Antithrombotic therapy in low risk patients

Whether AF is paroxysmal, persistent, or permanent; whether it is rate-controlled or ablated, stroke prevention with antithrombotic therapy is usually required. The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 for 2 points, diabetes mellitus, stroke for 2 points, vascular disease, age 65–74, and sex category with 1 point for females) scoring system has been validated as an estimator of clinical risk of stroke, with each point being roughly equivalent to 1% risk per year. Patients with a score ≥ 2 benefit from anticoagulation, and aspirin is recommended for lower-risk patients without contraindications.^[1]

Lip *et al.* studied a cohort of 39,400 patients in the Danish National Patient Register with nonvalvular AF and a CHA₂DS₂-VASc score of 0 or 1.^[2] Diagnosis codes were used to identify patients with AF, exclude patients with valvular heart disease, calculate the stroke risk with the CHA₂DS₂-VASc score, and determine the outcomes of bleeding, stroke, thromboembolism, and intracranial hemorrhage. Patients with a CHA₂DS₂-VASc score of 0–1 for males and 0–2 for females were divided into groups based on whether oral anticoagulation, aspirin, or no antithrombotic therapy was prescribed within 1 year of AF diagnosis. Based on this treatment, the results were analyzed by intention-to-treat. Mean follow-up was 5.2 years; 23,572 patients were untreated. In patients with no risk factors besides female sex, the annual rate of stroke was 0.47% in untreated patients, compared to 0.71% in patients treated with aspirin and 0.76% in patients treated with warfarin. The annual bleeding rate was 0.97% in untreated patients, 1.29% in patients on aspirin, and 1.42% in patients on warfarin. The patients with 1 risk factor besides female sex had stroke rates of 1.24% if untreated, 1.22% on aspirin, and 1.08% on warfarin; bleeding rates were 1.97% with no treatment, 2.21% on aspirin, and 2.32% on warfarin, by intention-to-treat analysis. Additionally, there was a reduction in death in the patients with 1 risk factor taking warfarin (hazard ratio 0.86). This study provides compelling evidence that aspirin is not effective stroke prevention in AF; it only increases bleeding risk. Anticoagulation for patients with an additional stroke risk factor besides sex is reasonable, weighed against the patient's individual bleeding risk.

Rhythm-determined versus risk-determined anticoagulation

Patients frequently ask whether they can stop anticoagulation if they spontaneously convert back to sinus rhythm. Current recommendations are to continue

uninterrupted anticoagulation based on the patient's stroke risk according to the CHA₂DS₂-VASc score in all patients diagnosed with AF, even if they spontaneously convert to sinus rhythm. Martin *et al.* performed a trial to determine whether or not anticoagulation based on the rhythm the patient was actually in could be performed using already implanted cardiac devices via remote monitoring.^[3] In the intervention group, oral anticoagulation with warfarin or a non-Vitamin K-antagonist oral anticoagulant (NOAC) was initiated immediately once rapid atrial tachyarrhythmias were detected, and discontinued if the patient was free of atrial tachyarrhythmias for >30 days for a CHADS₂ score of 1–2 or >90 days for a CHADS₂ score >2 if they had no history of thromboembolism. The 1357 patients in the intervention group were compared to 1361 patients randomized to usual care and analyzed both by intention-to-treat and per protocol. The primary outcomes of stroke, systemic thromboembolism, and bleeding were not significantly different in either arm after 5430 patient-years of follow-up. Comparing intervention and control groups, annual ischemic stroke rates were 0.7% and 1.6%; thromboembolism rates were 1.0% and 1.6%, and major bleeding rates were 1.6% and 1.2%, respectively. Stroke and thromboembolic events were not temporally related to the development of atrial tachyarrhythmias. This study is a well-done randomized assessment of whether or not patients would benefit from a rhythm-determined anticoagulation strategy. However, the findings of (1) no significant clinical benefit, (2) no reduction in bleeding, and (3) no temporal association between rhythm events and thromboembolic events indicate that anticoagulation should be continued without significant interruption in patients with AF as directed by the CHA₂DS₂-VASc score, regardless of spontaneous conversion to sinus rhythm.

Periprocedural anticoagulation “bridging”

When surgeries are necessary for patients with AF, oral anticoagulation is often suspended so that patients more easily achieve hemostasis. While the anticoagulation effects are normalizing, patients may be maintained on either unfractionated or low-molecular-weight heparin for “bridging.” Steinberg *et al.*, analyzed a registry of patients with AF, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation to assess for outcomes related to temporary interruption of anticoagulation and compare patients who were bridged with unfractionated or low-molecular weight heparin to those who were not bridged.^[4] The registry included 10,132 patients, among whom there were

2803 interruptions of oral anticoagulation. Bridging anticoagulation was used in 665 interruptions, 73% of which were with low-molecular-weight heparin. Bridging anticoagulation was not used in 2138 interruptions. The mean CHA₂DS₂-VASc score was higher in bridged patients (4.25 vs. 4.03), and bridged patients were more likely to have heart failure, prior stroke, and valvular heart disease, particularly mechanical prosthetic valves (9.6% of bridged patients). Major bleeding events were more frequent in bridged patients (3.6% vs. 1.2%, odds ratio 3.84). Thrombotic events were also more common in bridged patients (0.8% vs. 0.6%), with a 0.6% occurrence of stroke in bridged patients compared to a 0.3% occurrence of stroke in patients who were not bridged. This registry provides data that bridging anticoagulation during periprocedural interruptions of oral anticoagulation does not reduce thrombotic complications in most patients with AF, and significantly increases the risk of major bleeding. The registry does not provide sufficient data on patients with mechanical valves, prior thromboembolic disease, and prior strokes, and anticoagulation bridging should probably be used for these patients.

Dabigatran anticoagulation reversal

A major disadvantage of the NOACs has been the lack of reversibility in the event of bleeding. Pollack *et al.*, report clinical experience with a monoclonal antibody fragment idarucizumab for reversing one of the NOACs, dabigatran.^[5] In 51 patients with serious bleeding and 39 patients requiring an urgent procedure, idarucizumab successfully restored normal hemostasis in all patients on dabigatran. All patients had confirmed abnormalities in coagulation studies that were normalized by monoclonal antibody within 4 h. Despite the effective reversal of anticoagulation, there were 18 deaths and 3 thrombotic events in the group of patients with serious bleeding. This study raises hope that soon reversal agents for NOACs will be available. However, it also highlights the fact that serious bleeding still can be fatal, despite reversal of anticoagulation.

Anticoagulation-associated intracerebral hemorrhage

There is no more dreaded complication of chronic anticoagulation than intracerebral hemorrhage. What is particularly perplexing is the management of patients with intracerebral hemorrhage who have a strong indication for anticoagulation. Kuramatsu *et al.*, studied 1322 patients across Germany with anticoagulation-associated intracerebral hemorrhage, identified patients where the hematoma enlarged, and then attempted to find risk factors leading to

enlargement.^[6] The primary modifiable variables that affected hematoma enlargement included the degree that anticoagulation was reversed, the time from symptoms for that reversal to take place and the systolic blood pressure. Receiver operating characteristic analysis demonstrated that the optimal international normalized ratio (INR) to reverse anticoagulation to was 1.3, and should be reversed within 4 h of symptom onset. A systolic blood pressure >160 mmHg significantly increased the risk of hematoma enlargement. In 172 patients, oral anticoagulation was restarted after a mean of 31 days. Patients, where anticoagulation was not restarted, had a 3-fold higher risk of subsequent ischemic cerebrovascular and cardiovascular complications compared to those who restarted anticoagulation (15.2% vs. 5.0%), and hemorrhagic complications were not significantly different (6.6% vs. 8.1%). Additionally, mortality was significantly less in the group that restarted anticoagulation, but this group was younger and had a less neurologic disability compared to the group that did not restart anticoagulation. This study will impact the clinical decisions that must be made in patients presenting with intracerebral hemorrhage from oral anticoagulation therapy. It places a priority on anticoagulation reversal and blood pressure management and gives targets for the clinician to achieve. The resumption of anticoagulation after a potentially devastating intracerebral hemorrhage will remain a difficult decision, but this study indicates that anticoagulation likely can be safely resumed after a few weeks.

Left atrial appendage exclusion

One exciting option for patients with devastating bleeds is a nonpharmacologic treatment, the newly-approved Watchman device (Boston Scientific, Marlborough, MA, USA). While other devices have been developed, the Watchman is the only such device approved in the United States. This device is a nitinol framework that is delivered percutaneously via trans-septal puncture to the left atrial appendage under echocardiographic and fluoroscopic guidance. After full endothelialization in a few months, antithrombotic therapy is no longer required for stroke prevention. Reddy *et al.* studied 707 patients randomized in a 2:1 unblinded fashion to Watchman device or anticoagulation with warfarin.^[7] Follow-up has continued in this study now for 4 years. The mean CHADS₂ score was 2.2–2.3, and baseline characteristics, including duration of AF, were not different between the groups. In the warfarin group, the mean time in therapeutic range was 70%, indicating good adherence to therapy. The Watchman device was

successfully implanted in 88%. The adverse effects from the Watchman device implantation were primarily periprocedural: 4.8% risk of serious pericardial effusion, 1.1% risk of periprocedural ischemic stroke, and 0.6% risk of device embolization. The cumulative risk of ischemic stroke was 1.5/100 patient-years with the Watchman device and 2.2/100 patient-years with warfarin. The cumulative risk of hemorrhagic stroke with the Watchman device was 0.2/100 patient-years and 1.1/100 patient-years with warfarin. Cardiovascular and cerebrovascular mortality was significantly lower in the Watchman group, 3.7% versus 9%. The combined primary efficacy endpoint not only met criteria for noninferiority, but also superiority.

The Watchman device is currently approved for patients who can be anticoagulated but also have “an appropriate reason” for seeking nonpharmacologic stroke prevention. This and future devices will hopefully further reduce cerebrovascular complications from AF.

Ablation techniques

Many ablation techniques have been developed for AF. Recent studies have attempted to compare approaches. In this section, the ablation approaches will be briefly described, along with the studies of their efficacy.

Paroxysmal atrial fibrillation: Radiofrequency ablation versus cryoablation for pulmonary vein isolation

Paroxysmal AF is predominantly mediated by premature beats and tachycardia arising from the pulmonary veins. The primary approaches to isolate, or make an electrical barrier between the pulmonary vein and the left atrial myocardium, are with radiofrequency energy to cauterize the tissue, or with cryoenergy to freeze the tissue to form a scar that will not conduct the action potential. Radiofrequency ablation is delivered point-by-point, one lesion at a time until a circular lesion surrounds each pulmonary vein. Cryoenergy is delivered via a balloon that is inflated within each pulmonary vein ostium, checked for completeness of occlusion by contrast injection within the pulmonary vein, and then cooled to less than -50°C for approximately 3 min per application. Both approaches require transeptal puncture for left atrial access. Both approaches require general anesthesia and controlled ventilation along with complete patient immobility.

Luik *et al.* are comparing cryoablation to radiofrequency ablation for pulmonary vein isolation (PVI) to treat paroxysmal AF in the Freeze study.^[8] Patients were randomized 1:1 to each arm and efficacy and

safety endpoints were compared. The results are unpublished at this time, but 12-month follow-up data on 315 patients were presented at the 2015 Heart Rhythm Society meeting, showing noninferiority between the two approaches. With a single procedure, 64–65% of patients were free of AF at 6 months, and with an additional procedure for patients who had recurrence, the rate of freedom from AF at 12 months improved to 72–74% without antiarrhythmics. Cryoablation has a 5.8% risk of phrenic nerve injury, which in most cases is asymptomatic and improves with time. Additionally, likely because of the larger sheath required, cryoablation has a higher risk of vascular complications (5% vs. 3% in radiofrequency ablation, a difference not statistically significant). Both of these complications have significant anesthetic implications. There appears to be no statistically significant difference in other complication rates, including pericardial effusion, tamponade, atriopharyngeal fistula, and pulmonary vein stenosis. While cryoablation cases tend to be shorter and require less fluoroscopic time, the mean total radiation dose is actually higher than in radiofrequency ablation cases.

Paroxysmal atrial fibrillation: Visually-guided laser balloon catheter ablation

Another balloon-based ablation technology has been developed, in this case, utilizing an endoscopic system through a transparent balloon to allow direct visualization of the pulmonary vein ostium. The ablation is then performed with laser energy. This system has not yet been approved for use in the United States. Dukkupati *et al.* report their investigational experience with this method of ablation.^[9] While acute isolation occurred in 97% of veins attempted, only 61% of patients had freedom from AF after 12 months. The 3.5% occurrence of pericardial tamponade and 6% risk of temporary phrenic nerve palsy are similar to other methods. There is the possibility that with increased operator experience with this system that the procedural outcomes would improve.

Paroxysmal and persistent atrial fibrillation: Anatomic versus electrogram-guided ablation strategy

There is considerable debate regarding whether AF ablation should be anatomically guided (for example, ablating circumferentially around each pulmonary vein) or electrically guided (ablating sources or triggers of fibrillation). Atenza *et al.*, compared patients with paroxysmal or persistent AF randomized to PVI only or high-frequency source ablation.^[10] High-frequency atrial electrograms were identified with a computer-based

algorithm. Of 232 patients randomized, 49% had paroxysmal, and 51% had persistent AF. The difference in success between the two approaches was not significant. The percent of patients free from AF or atrial tachycardia at 6 months was 69% in paroxysmal AF patients receiving PVI only; 65% in patients receiving high-frequency source ablation only. In patients with persistent AF, 56–59% of patients were free of recurrent AF after a single procedure, with no significant difference between groups. There were fewer procedural complications in patients with high-frequency source ablation compared to PVI, likely related to the smaller ablation lesions required for high-frequency source ablation. While the noninferiority threshold was not reached for single procedures, after redo procedures were allowed, high-frequency source ablation was non inferior to PVI.

Persistent atrial fibrillation: Catheter ablation approaches

Additional atrial ablation lines or other attempts at modifying the atrial substrate are often performed in patients with persistent AF. Verma *et al.*, randomized patients with persistent AF in a 1:4:4 fashion to PVI alone, PVI with complex fractionated atrial electrogram ablation or PVI with empiric mitral valve isthmus line and roof line.^[11] There were no significant differences in freedom from atrial arrhythmias or complications in either group, but a trend toward fewer atrial arrhythmias in the PVI only group. When the ablation with linear lines group was compared pairwise with the PVI only group, there were significantly fewer recurrences of AF in the PVI only group. The smaller number of patients randomized to pulmonary isolation alone may have underpowered this study, but these findings are worth confirming since they run counter to current practice.

Persistent atrial fibrillation: Surgical ablation approaches

Procedural treatment for AF began in the operating room with the development of the Cox-Maze procedure, where sources of AF were isolated by atriotomy scars (“cut and sew”). Gillinov *et al.*, recently investigated different methods of surgical ablation of AF in 260 patients undergoing mitral valve surgery who had persistent AF.^[12] Patients were randomized 1:1 to surgical ablation or no ablation, and then the patients undergoing surgical ablation were randomized to a biatrial maze procedure or PVI alone with conduction block confirmed intraoperatively. There was a significant difference in freedom from AF, which was 29.4% in the control group and 63.2% in the ablation group. Freedom from AF was not significantly greater in the group undergoing biatrial maze procedure (66%) compared to those undergoing PVI only (61%). There was no significant difference in

mortality, antiarrhythmic use, or stroke rate in either group. Implantation of a permanent pacemaker was significantly higher in the ablation group at 21%, in contrast to 8% in the control group.

There are many valid ways to ablate AF, with different catheter types, different lesion sets, and different ablation strategies all being investigated. While the noninferiority of each approach has been demonstrated, no superior approach has been proven. In fact, recent trials raise the question of whether there is any additional benefit for creating lesions beyond PVI during initial procedures. The trials discussed above are a significant step toward understanding the individual benefits of each approach. The goal of further research remains to improve efficacy, reduce complications and fluoroscopy, and procedure times.

Clinical implications for perioperative management and summary

Treatment of AF requires a multi-disciplinary approach. Recent trials advance our understanding beyond the most recent guideline statements. The findings above may be challenged by other trials, but for now, we have evidence to conclude:

- Aspirin does not significantly reduce stroke in low risk patients with AF; it only increases bleeding risk;
- Anticoagulation based on stroke risk assessed by the CHA₂DS₂-VASc score should be continued indefinitely, despite spontaneous conversion to sinus rhythm;
- “Bridging” anticoagulation when oral anticoagulation is interrupted is unnecessary except in patients with prior thromboembolic disease and mechanical valves;
- Effective reversal agents for NOACs are on the verge of becoming available;
- Evidence now informs the management of anticoagulation-associated intracerebral hemorrhage, with the following therapeutic targets:
 - Reversal of anticoagulation (INR \leq 1.3) within 4 h of symptom onset;
 - Reduction of systolic blood pressure to <160 mmHg;
 - Restarting oral anticoagulation after about 1 month, which does not increase the risk of repeat hemorrhage and reduces the risk of ischemic stroke significantly;
- Patients with an appropriate reason to discontinue anticoagulation can be considered for the newly-approved Watchman left atrial appendage closure device;

- Efficacy of radiofrequency ablation and cryoablation are about equal; cryoablation has a higher rate of temporary phrenic nerve palsy and vascular access complications;
- Efficacy of a visually-guided laser balloon is similar to other methods, despite little experience in this technique;
- While there are fewer complications with high-frequency source ablation, it has less effectiveness as a single procedure than PVI alone;
- In both catheter ablation and surgical treatment of persistent AF, there appears to be little additional benefit for additional ablation lesions, whether linear or targeted at complex fractionated atrial electrograms;
- Surgical treatment of AF during mitral valve surgery significantly reduces the risk of recurrent AF but increases the risk of requiring a permanent pacemaker.

With the advances in stroke prevention, anticoagulation management, and ablation techniques seen in the past few months, optimizing AF treatment for individual patients is becoming increasingly possible.

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Conflicts of interest

There are no conflicts of interest.

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