CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Role of Anticoagulation in Patients with Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia. It is estimated that >200,000 Canadians suffer from this rhythm disturbance and, in 2000, 555 hospitalizations per 100,000 population in Canada were attributed to AF or atrial flutter.[1] The prevalence of AF is dependent on age: >5% of individuals >80 years are affected and approximately 70% of individuals with AF are between the ages of 65 and 85 years. There are no gender differences in incidence or prevalence. This issue of *Cardiology Rounds* discusses AF, focusing on its associated mortality and morbidity, the challenges and limitations of anticoagulation therapy including risk stratification, issues surrounding cardioversion, and new therapies (eg, direct thrombin inhibitors and platelet inhibitors).

Clinical significance

The Framingham Heart Study evaluated over 8000 men and women >40 years old and discovered that the lifetime incidence of AF was 1 in 6, even in the absence of antecedent congestive heart failure or myocardial infarction (MI).[2] Despite the increase in the prevalence of AF with age, many young patients without risk factors may also present with AF and, at times, may in fact be more symptomatic from intermittent, self-limited episodes, than elderly individuals with persistent or permanent AF.

The significant morbidity associated with AF is directly related to the sensation of a rapid and irregular heartbeat and the indirect consequences of AF, including reduced cardiac output and increased left atrial pressure that usually manifest as one or more of the following:

- fatigue
- dyspnea on exertion
- presyncope
- an overwhelming sense of feeling "unwell."

Thromboembolism and, specifically, stroke, is one of the most important clinical consequences of AF. A recent meta-analysis of 6 randomized controlled trials revealed that 5.4% of patients with AF suffered vascular death and 4.6% had a fatal or nonfatal stroke.[3] The Framingham Heart Study examined the impact of AF on stroke incidence in 5070 participants after 34 years of follow-up. The study demonstrated that the percentage of strokes attributable to AF increases with age. The investigators concluded that AF is a major cause of stroke, particularly among elderly patients. Additionally, because patients with AF require ongoing optimization and monitoring of drug therapy, including anticoagulation, even chronic, stable AF has a significant impact on health economics. For age- and diagnosis-matched hospitalized individuals, the presence of AF significantly increases the length of stay and hospitalization cost.[4] Finally, in multiple retrospective patient cohorts, AF has been associated with a 1.5- to 1.9-fold increase in mortality, after accounting for such risk factors as age, hypertension, smoking, diabetes, left ventricular hypertrophy, MI, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack.[3]

A prospective cohort study of 3 years duration compared >13,000 hospitalized Medicare patients with AF and 1 other cardiovascular diagnosis to a matched cohort without AF.[4] It revealed a significantly higher mortality in the study group with AF. Despite this known risk, pharmacologic treatment of AF has never been shown to reduce mortality. The pathophysiology associated with increased mortality is not clearly understood, but may involve thromboembolic complications secondary to stasis-induced thrombus in the left atrial appendage, increased platelet activation, and/or an association

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with other vascular atherosclerotic diseases and subsequent atheroembolism.

Role of anticoagulation

Recommendations for anticoagulation are based on multiple studies that have principally investigated aspirin (ASA) and warfarin in various patient groups with AF. Importantly, several large randomized trials, both independently and when analyzed using a meta-analysis (Figure 1), demonstrate that oral anticoagulation with either warfarin or ASA is superior to placebo for prevention of thromboembolic complications in patients with AF.[5-11,13] Further, warfarin is superior to aspirin in patients who have high risk features (as described above).[11-15] As such, ASA is generally prescribed for patients with AF who do not have such high risk features or in whom the perceived risk of excess bleeding attributable to warfarin therapy outweighs the potential benefit. This evidence demonstrates that there is no effective therapy to target the vascular complications of AF.

Risk stratification – Who to anticoagulate?

Irrespective of the type of AF, certain patient-specific risk factors are responsible for an increased risk of stroke in the presence of AF. These risk factors are well-accepted and allow stratification of patients with AF into high, low, and moderate risk categories. Although it is clear that patients at high risk benefit from anticoagulation with antithrombotic medications and those at low risk do not, recommendations for patients at moderate risk are not definitive and are usually left to the physician's discretion.

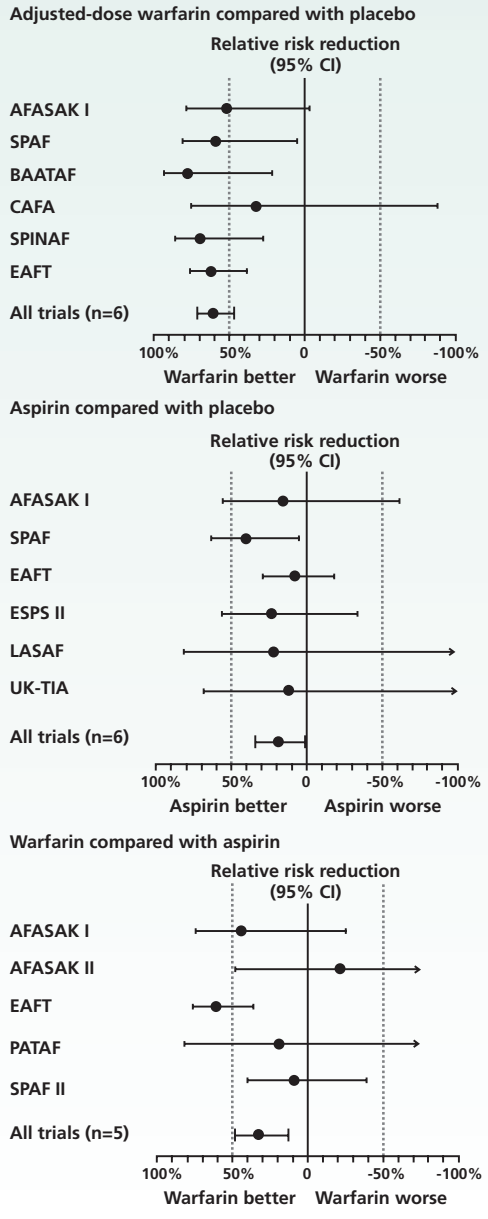
Unfortunately, although a large number of trials have been conducted to assess efficacy of various anticoagulation regimes in patients with AF, many trials had varying definitions of high or low risk.[11,16,17] In general, high risk patients are those with one or more of the following risk factors:

- age >75 years
- presence of hypertension
- left ventricular dysfunction or congestive heart failure
- rheumatic heart disease
- previous thromboembolism.

Additionally, patients >60 years with either diabetes or coronary artery disease are also considered to be high risk. Low risk patients are those <60 years who do not have any of the above high risk factors.[18] A population-based study of the natural history of "lone AF" – defined as no associated cardiopulmonary disease or precipitating illness – suggested the stroke risk in such individuals was very low: 1.3% at 15 years follow-up.[19]

Generally-accepted guidelines, as suggested in a joint publication by the American College of Cardiology, American Heart Association, and the European Society of Cardiology, for anticoagulation of patients with AF are shown in Table 1. Since the publication of these guidelines, further efforts have been made to more precisely define risk attributable to key patient characteristics. The Framingham Study group created a risk profile using point assignment for certain risk predictors in a community-based study of patients with new-onset, non-rheumatic AF to determine 5-year stroke risk.[20] They identified increasing blood pressure and age as incremental risk factors, with the presence of diabetes and previous stroke or transient ischemic attack as 2 other independent factors that influence stroke risk. The incremental risks of age and blood pressure suggest that thromboembolic risk in patients with AF is a continuum, requiring re-evaluation over time. This is shown graphically in Figure 2.

Figure 1: Oral anticoagulation with warfarin or aspirin is superior to placebo



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AFASAK = Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study
SPAF = Stroke Prevention and Atrial Fibrillation trial
BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA = Canadian Atrial Fibrillation Anticoagulation study
SPINAF = Stroke Prevention in Non-rheumatic Atrial Fibrillation study
EAFT = European Atrial Fibrillation Trial
ESPS II = The Second European Stroke Prevention Study
LASAF = Low-dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study
UK-TIA = UK Transient Ischemic Attack trial
PATAF = Primary Prevention of Atrial Thromboembolism in Non-rheumatic Atrial Fibrillation

Table 1: Risk-based approach to antithrombotic therapy in patients with atrial fibrillation

Patient features	Antithrombotic therapy	Grade of recommendation
Age <60 years, no heart disease (lone AF)	Aspirin (325 mg/day) or no therapy	I
Age <60 years, heart disease but no risk factors*	Aspirin (325 mg/day)	I
Age ≥60 years, no risk factors*	Aspirin (325 mg/day)	I
Age ≥60 years with diabetes mellitus or CAD	Oral anticoagulation (INR 2.0-3.0) Addition of aspirin, 81-162 mg/day is optional	I IIb
Age ≥75 years, especially women	Oral anticoagulation (INR ≈2.0)	I
HF		
LV ejection fraction ≤0.35, thyrotoxicosis, and hypertension	Oral anticoagulation (INR 2.0-3.0)	I
Rheumatic heart disease (mitral stenosis) Prosthetic heart valves Prior thromboembolism Persistent atrial thrombus on TEE	Oral anticoagulation (INR 2.5-3.5 or higher may be appropriate)	I

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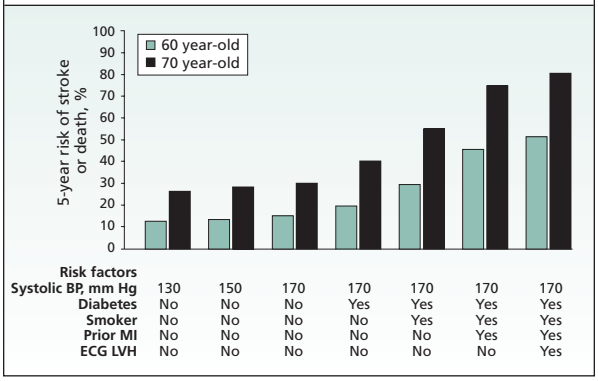
AF indicates atrial fibrillation; HF, heart failure; INR, international normalized ratio; LV, left ventricular; CAD, coronary artery disease; TEE, transesophageal echocardiography.
*Risk factors for thromboembolism include HF, LV ejection fraction <0.35, and history of hypertension.

Figure 2: Impact of selected risk factors on the predicted 5-year risk of stroke or death



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Predicted event rates apply to men and women without valvular disease.
ECG = electrocardiographic left ventricular hypertrophy; MI = myocardial infarction

Rhythm and risk

The annualized risk of ischemic stroke is similar in patients with paroxysmal (self-terminating episodes) versus permanent AF.[21] However, until recently, the general consensus among the medical community was to aggressively treat patients with AF using antiarrhythmic drugs in an attempt to maintain sinus rhythm with the goal of reducing the risk of thromboembolic complications. Recent trials have assessed the impact of rate control versus rhythm control treatment strategies on mortality and thromboembolism in patients with AF. Although no differences in mortality have been discerned, interestingly, pooled data from the AFFIRM,[22] RACE,[23] STAF,[24] and PIAF[25] studies demonstrate a trend toward *increased* cerebrovascular events in patients who were randomized to the rhythm-control strategy. Possible explanations for this trend include the relatively modest efficacy of antiarrhythmic drugs at eliminating all episodes of AF and the likelihood that patients with asymptomatic episodes of AF who are deemed to be "cured" (and hence taken off anticoagulants) continue to have a high risk of embolic events. Thus, at the very least, these studies suggest that aggressive antiarrhythmic drug use is not mandated by improved patient outcomes and those patients perceived to maintain sinus rhythm should likely be maintained on anticoagulants for life.

Cardioversion for AF

The primary purpose of this issue of *Cardiology Rounds* is to discuss long-term anticoagulation issues surrounding AF; however, mention should be made of a clinical circumstance that is commonly faced in such patients, namely, elective cardioversion. It is generally accepted that stroke risk is higher around the time of cardioversion because of atrial stunning and transient electromechanical dissociation that potentially leads to stasis and thrombus formation, regardless of whether cardioversion is performed chemically or electrically.[26-30] Generally, it is accepted that patients who do not meet the requirements for long-term anticoagulation and who require cardioversion within 48 hours of AF onset, do not require anticoagulation pre- or post-cardioversion. The theoretical reason for this is that thrombus formation likely requires >48 hours of AF to develop and that the stunning after cardioversion of <48 hours of AF is minimal. Unfortunately, however, no controlled clinical trials have evaluated the safety of this approach. Certainly, for patients who have had AF for >48 hours, the standard approach is therapeutic anticoagulation for at least 3-4 weeks prior to, and after, cardioversion. The requirement for the prolonged post-procedure anticoagulation is based on studies that show 98% of thromboembolic events occur up to 10 days after cardioversion.[31]

An alternative treatment strategy for anticoagulation therapy around the time of cardioversion was studied in the ACUTE trial.[32] Patients with AF for >48 hours were randomized to either conventional therapy (as outlined above) or transesophageal echocardiography (TEE)-guided therapy. Both groups were started on anticoagulation at randomization, with the TEE group placed initially on intravenous heparin. If, at TEE, there was no thrombus present, cardioversion (either electrical or pharmacologic) was performed with the patient on heparin, followed by 4 weeks of warfarin. The study was underpowered, but the results revealed no statistically significant differences in the rate of systemic embolization between the 2 treatment arms (0.8% TEE-guided, 0.5% conventional, $p = 0.50$) and a decreased number of hemorrhages in the TEE-treatment group.

Interestingly, there were more deaths at follow-up in the TEE group (2.4% versus 1%); however, this did not reach statistical significance. Despite these limitations and results, the authors concluded that the TEE-guided approach is a safe and effective alternative. Overall, this approach should likely only

be used in the patient who cannot be anticoagulated prior to cardioversion for technical, medical, or other reasons. The remainder of patients presenting with AF of >48 hours duration or unknown duration should simply be anticoagulated for 3-4 weeks prior to, and after, cardioversion.

Limitations of warfarin use

Clearly, warfarin is the most effective, currently available therapy to prevent thromboembolic complications in at-risk individuals with AF. However, perhaps more so than with other medical therapies, there are significant risks, contraindications, and difficulties associated with warfarin administration that limit its use clinically.

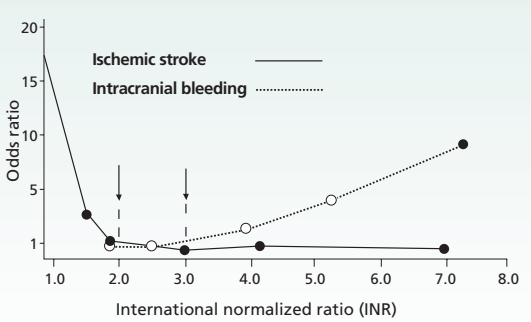
The most important risk is excess bleeding. Studies have shown that the relative risk of developing major bleeding with oral anticoagulation is between 1.5- and 2-fold the relative risk observed with antiplatelet agents.[33] This risk of bleeding is further complicated by warfarin's narrow therapeutic window. For AF, thromboembolic risk is only significantly reduced when the international normalized ratio (INR) in the individual patient on warfarin is maintained within the range of 2.0 to 3.0. Below 2.0, warfarin therapy becomes less effective and the risk of thromboembolism is increased. Above 3.0, the risk of bleeding complications increases, including the potentially fatal complication of intracranial hemorrhage or massive gastrointestinal bleeding. This therapeutic challenge is illustrated graphically in Figure 3.

Maintaining the INR between 2.0 and 3.0 is a clinical challenge; however, it is critical to patient outcome. Hylek et al studied 596 patients with AF admitted to hospital with a diagnosis of ischemic stroke.[34] Patients were stratified by the type of anticoagulation and further stratified within the warfarin group into those with an admission INR of less or greater than 2.0. Patients with a subtherapeutic (<2.0) admission INR had a significantly worse outcome, compared to those who were therapeutic at presentation and similar to those patients who were only taking ASA. This suggests that coumadin therapy is critical not only for thromboembolism prevention, but also to maintain positive outcomes when thromboembolism occurs.

Contraindications to warfarin also limit its use in certain patients, including those with prior intracranial hemorrhage, poorly controlled hypertension, current alcohol abuse, concomitant use of non-steroidal anti-inflammatory drugs, recent gastrointestinal/genitourinary bleed, unexplained anemia, and a predisposition to trauma. In a large, contemporary cohort of ambulatory patients with AF, Go and colleagues found that 17.5% have contraindications to warfarin therapy.[35]

Another challenge with warfarin administration is the presence of multiple diet and drug interactions that can alter the INR achieved with a given dose. Dietary interactions are primarily based on the intake of foods containing high amounts of vitamin K that may increase warfarin requirements or reduce INR values. There are sufficient data to suggest that patients taking warfarin should maintain a diet that is consistent in vitamin K content from one day to the next and that meet dietary recommendations of 65-80 micrograms per day.[36] Foods particularly high in vitamin K content include asparagus, broccoli, brussel sprouts, cabbage, collards, and spinach. Drug interactions are generally related to altered clearance of coumadin and may either increase or reduce the need for coumadin. Antibiotics may actually reduce the need for coumadin by depleting bacterial flora that are essential for vitamin K synthesis. Overall, patients who are anticoagulated with warfarin should be monitored more frequently than usual when new medications are started.

Figure 3: Maintaining the INR between 2.0 and 3.0 is a challenge. Above 3.0, the risk of bleeding increases



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Although the risk of bleeding with warfarin is real, close surveillance of INR values, patient education, and avoidance of warfarin in patients with documented contraindications should strike a fine balance between risk and benefit. However, in the "real world," recommendations for warfarin use in patients with AF are not easily followed. In Go's study (mentioned above), 11,082 patients with AF had ≥1 risk factors for thromboembolism and no known contraindications to warfarin therapy. Prescription rates for warfarin use in this cohort only ranged from 35% to 61%, with the lowest rate of use in the population of patients aged >85 years – arguably the population that would have the greatest potential benefit from warfarin use.[35] In addition, of the patients that are anticoagulated, a minority (44%) are anticoagulated within the target range at any one time, with 38% below target and 18% above target.[37] Thus, although clinical trials suggest that warfarin use with a target INR of 2 to 3 is associated with a significant reduction in thromboembolism, practical limitations of warfarin use significantly impair the clinician's ability to effectively limit thromboembolic complications in this patient population.

New treatments

Direct thrombin inhibitors

Studies are now focusing on new therapies that can match or possibly exceed the efficacy of warfarin, without its limitations. An interesting class of medications

currently under investigation is the direct thrombin inhibitors. Traditionally, these medications were only available intravenously or by subcutaneous injection; however, more recently, oral preparations have been tested. This class has several potential advantages including predictable pharmacokinetics, fixed dosing, no coagulation monitoring, a wider therapeutic window, and minimal drug and diet interactions.

The most notable drug in this class of medications is ximelagatran. Although this drug has been studied in many different medical conditions requiring anticoagulation – including prophylaxis and treatment of deep venous thrombosis – the group responsible for testing it to treat AF is the Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) investigator group. After initial trials demonstrated safety and tolerability, efficacy was first tested in a large group of patients with AF in an open-label fashion in SPORTIF III.[38] Subsequently, SPORTIF V, a large randomized, double-blind study of fixed-dose ximelagatran (36 mg BID) was compared to adjusted dose warfarin in patients with non-valvular AF and risk factors for stroke.[39] While the SPORTIF III study was conducted in 23 nations worldwide, SPORTIF V was conducted only in North America. SPORTIF V was designed as a non-inferiority study. During the trial, the adjusted dose warfarin study group was well-controlled and an INR goal of 2.0-3.0 was achieved 83% of the time. As mentioned earlier, this type of control significantly exceeds the type of anticoagulation control that is possible in the community.

The primary endpoint of both studies was ischemic stroke. Ximelagatran was shown to be non-inferior to warfarin in both studies and after analysis of pooled data. Although there were no significant differences in the rates of intracerebral hemorrhage (0.06% in both groups) or major bleeding episodes (2.4% with ximelagatran versus 3.1% with warfarin, p=0.16), there were significantly fewer minor bleeding episodes in the ximelagatran group (37% versus 47%, p<0.0001). Importantly, when assessing the utility of anticoagulants, it is useful to examine a more clinical endpoint (eg, the combination of ischemic stroke, major bleeding, and death). When this analysis was performed, there was no significant difference in total events within the SPORTIF V data (5.8% ximelagatran versus 6.3% warfarin); however, the pooled analysis suggests a significant event reduction for ximelagatran compared to warfarin (5.2% versus 6.2%, p=0.038).

Despite these promising outcomes, one adverse event (liver enzyme elevation to >3 times control values in about 6% of patients) led the American Food and Drug Administration (FDA) not to approve ximelagatran. In general, liver enzymes return to baseline levels on drug discontinuation and most of the elevation occurs in the first 4-6 months, suggesting that close initial supervision can determine which patients are at risk. However, within the study, there was at least one death, presumed secondary to liver toxicity and, therefore, the FDA recommended that further study was necessary before ximelagatran received a labeled indication for use.

Platelet inhibition

Given the results of early, large, randomized studies that clearly demonstrate the superiority of warfarin over aspirin for thromboembolism prevention in patients with AF, most attention for innovative therapies has focused on altering coagulation pathways. However, it is plausible that much of the excess mortality in this group of patients is secondary to vascular events that may be more efficiently targeted with antiplatelet agents instead of antithrombotic agents. This argument may be strengthened by the knowledge that the currently available and approved antithrombotic agent, warfarin, has significant limitations (as mentioned above). As a result, attention has been focused on the platelet inhibitor, clopidogrel. Its superiority to aspirin has already been demonstrated in vascular patients in the large CAPRIE[40] study that demonstrated a significant reduction in the combined endpoint of stroke, MI, and vascular death. In addition, the CURE trial[41] demonstrated the safety and efficacy of ASA and clopidogrel combined therapy in reducing stroke, MI, or vascular death in acute coronary syndromes.

With these results in mind, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) study is randomizing patients with AF who are deemed to be at high risk for vascular events (including ischemic stroke) to 1 of 2 treatment arms. ACTIVE W randomizes patients to either oral anticoagulation with warfarin or a combination of clopidogrel plus aspirin, whereas ACTIVE A randomizes warfarin-ineligible patients to aspirin plus placebo versus aspirin plus clopidogrel. The study is enrolling approximately 15,000 patients worldwide, with a mean follow-up of 3 years, and the much-anticipated results are expected to be available by 2007. The ACTIVE trial will provide further insight into the effectiveness and risk associated with aggressive antiplatelet therapy.

Conclusion

Atrial fibrillation is a common arrhythmia with significant morbidity and mortality. These risks persist despite "adequate" rhythm treatment. Antiplatelet and anticoagulation treatments have proven efficacy in the reduction of thromboembolism. Risk stratification must be performed for each patient to determine their risk and benefit, to individualize therapy. Currently, warfarin is the most effective drug for stroke prevention, although the significant limitations associated with its use result in suboptimal anticoagulation in a majority of patients. New anticoagulant strategies show promise and are being investigated in several clinical trials. A safe, easily-administered, and effective therapeutic anticoagulation strategy remains a significant challenge for patients with atrial fibrillation.

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