

Atrial fibrillation: Advances in management

Regardless of the strategy chosen, the most important aspect of atrial fibrillation management remains the prevention of stroke and systemic embolization.

ABSTRACT: Atrial fibrillation is the most common sustained arrhythmia seen in clinical practice. Key advances over the past decade have helped guide knowledge and the care of patients afflicted by this arrhythmia. A rate-control strategy may be preferable for many of these patients and may reduce unnecessary admissions for reversion to sinus rhythm. There have been significant advances in our ability to restore and maintain sinus rhythm in select patients, notably in the form of atrial fibrillation ablation. Regardless of whether a rate- or rhythm-control strategy is chosen, the most important aspect of atrial fibrillation management remains the prevention of stroke and systemic embolization. Although warfarin remains the standard of care for patients at moderate or high risk of stroke, there are ever-increasing options for treating patients unable to take warfarin, and exciting developments continue to occur.

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice and accounts for the majority of arrhythmia-related emergency room visits and hospital admissions. In fact, the total number of patients hospitalized for AF is more than that for all other arrhythmias combined.¹ In addition to reduced quality of life, functional status, and cardiac performance, patients with AF are at higher risk of overall mortality when compared to non-AF patients.²

AF is estimated to affect nearly 2.5 million Americans and 4.5 million Europeans.³⁻⁴ While the overall prevalence of AF is approximately 1% in the general population, the incidence and prevalence increases significantly with age, affecting 1 in 25 over the age of 60 years and nearly 1 in 10 over the age of 80 years.^{3,5} At age 40, the estimated lifetime risk for developing AF is 26% for men and 23% for women.⁶ When the AF population is examined the vast majority (84%) are over the age of 65, and 32% are over the age of 80.⁵ As a result, attempts have been made to estimate the upcoming burden of AF based on extrapolation from census data. Based on these analyses, the number of patients with AF is likely to increase 2.5-fold over the next 40

years, reflecting the growing proportion of elderly individuals.³ Given this aging population it is clear that AF is poised to become a national public health crisis.

Rate versus rhythm

Two separate strategies are used to manage atrial fibrillation: one involves controlling ventricular rate with atrioventricular nodal blocking agents or atrioventricular nodal ablation (rate control), and the other involves re-establishing and maintaining sinus rhythm with antiarrhythmic medications or atrial fibrillation ablation (rhythm control). Landmark trials published over the past 10 years have clearly established that the strategy of rate control is not inferior to rhythm control with contemporary antiarrhythmic medications. The results of five large prospective randomized tri-

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als have all demonstrated that a rate-control strategy targeting a resting heart rate less than 80 bpm is at least equivalent to a rhythm-control strategy in terms of all-cause mortality (odds ratio [OR] 0.87; 95% confidence interval [CI] 0.74–1.02; $P = .09$) and risk of stroke (OR 0.5; CI 0.14–1.83; $P = .30$).⁷ Similarly, there was no difference in quality of life between rate control and rhythm control in the relatively asymptomatic individuals found in these large trials.⁸⁻¹²

However, until this past year, it was unknown whether patients with established heart failure would benefit from an aggressive rhythm-control strategy. This was because despite the fact that up to 40% of heart failure patients have AF, they were excluded from previous trials evaluating rate control versus rhythm control. While clinical practice was dominated by the assumption of a benefit to rhythm control in this high-risk group, the results of the recent AF-CHF trial have shown this not to be the case.¹³ In this study, 1376 patients with clinical heart failure and an ejection fraction less than 35% were randomly assigned to rate-control and rhythm-control groups. After a mean 37 months of follow-up there were no differences between the two groups in the rates of cardiovascular death (25% for rate control and 27% for rhythm control; hazard ratio [HR] 1.06; CI 0.86–1.3; $P = .59$), all-cause mortality (33% vs 37%), stroke (3% vs 4%), or worsening heart failure (28% vs 31%).¹³ In fact, there was an observed increased risk of hospitalization in the rhythm-control group (64% vs 59% at 1 year; $P = .06$), primarily due to recurrent AF and bradyarrhythmias.

That being said, the failure of the rhythm-control strategy may indicate more about the inadequacies of our current therapies than it does about the strategy itself. It is well known that

contemporary antiarrhythmic therapies can be dishearteningly ineffective at maintaining sinus rhythm in patients with AF, and thus the potential benefit of a rhythm-control strategy may be lessened by the limited efficacy of these drugs as well as their potential proarrhythmic complications. While prospective trials have demonstrated that amiodarone is the most effective antiarrhythmic currently available, only two-thirds of patients are able to maintain sinus rhythm at 12 to 16 months.^{14,15} Unfortunately flecainide, quinidine, sotalol, and propafenone are even less effective, with only one-third to one-half of patients maintaining sinus rhythm at 12 to 16 months.^{14,15}

When the results of the trials for rhythm control versus rate control were re-examined according to whether sinus rhythm was achieved, and not merely by group allocation, subjects who were actually maintained in sinus rhythm had better outcomes.¹⁶ However, the ability to maintain sinus rhythm may itself be a marker of better prognosis. As such, in a given patient, the decision regarding rate control versus rhythm control must be individualized. Whichever strategy is chosen, the clinician can be reassured that the evidence suggests both are equally effective.

Rhythm control with antiarrhythmics

In some circumstances a desire to pursue a rhythm-control strategy may exist based on patient preference or clinical characteristics (first presentation with AF, persistent symptoms despite adequate rate control, inability to attain adequate rate control). It is within this domain that two recent advances have been made.

As mentioned above, amiodarone is currently the drug most effective at maintaining sinus rhythm. Unfortu-

nately, amiodarone is also associated with multiple side effects and toxicities, including hyperthyroidism, hypothyroidism, hepatotoxicity, and pulmonary fibrosis. To this end, a novel class III antiarrhythmic drug that is

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similar to amiodarone in chemical structure but is purported to have a more favorable side effect profile has been developed. Results from EURIDIS and ADONIS show that dronedarone effectively reduces the time to recurrent AF and atrial flutter with an adverse event profile similar to placebo. However, unpublished data from the ongoing DIONYSOS trial suggest that dronedarone may be less effective than amiodarone.¹⁷

While these early studies show dronedarone to be safe, concerns have been raised regarding the utility of this agent in patients with moderate-to-severe congestive heart failure and ventricular dysfunction. In the ANDROMEDA trial, dronedarone was compared to placebo with the goal of decreasing heart-failure-related hospitalization in patients with recently decompensated heart failure.

Unfortunately, an interim safety analysis showed higher mortality in the dronedarone group, prompting the early discontinuation of the trial (8.1% vs 3.8%; HR 2.13; CI 1.07–4.25; $P = .03$). Analyses of the data showed that

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the observed mortality was due to both heart-failure-related mortality (3.2% vs 0.6%), and arrhythmia-related mortality (3.2% vs 1.9%). Follow-up of enrolled patients demonstrated that the mortality curves returned to normal within 6 months of dronedarone discontinuation.¹⁸

These concerns regarding increased risk of death were not observed in the other trials of dronedarone.^{17,19} While ATHENA included patients with class II or III heart failure, ANDROMEDA was the only trial to exclusively include patients with significant systolic dysfunction and decompensated heart failure. In direct contrast to ANDROMEDA, the ATHENA trial demonstrated a significant reduction in cardiovascular mortality (2.7% vs

3.9%) arrhythmia-related mortality (1.1% vs 2.1%) as well as the combined endpoint of cardiovascular hospitalization or mortality (31.9% vs 39.4%) with dronedarone when compared to placebo in patients with chronic AF over a mean follow-up of 21 months (31.9% vs 39.4%; HR 0.76; CI 0.69–0.84; $P < .001$). In fact, in direct contrast to ANDROMEDA findings, dronedarone resulted in a significant cardiovascular and arrhythmia-related mortality benefit (2.7% vs 3.9%; HR 0.71; CI 0.51–0.98; $P = .03$; and 1.1% vs 2.1%; $P = .01$, respectively).¹⁹ The reason for the disparate effects on mortality between the ATHENA and ANDROMEDA trials is unknown. Largely as a result of the ATHENA trial, dronedarone has been approved by the FDA for treating AF in patients with NYHA class I and II heart failure.

Rhythm control with catheter ablation

Owing to the inadequacies of contemporary antiarrhythmic therapy, nonpharmacological restoration of sinus rhythm has gained prominence in the past few years. The most common and effective procedure involves electrical isolation of the triggers for paroxysmal AF, the pulmonary veins, from the vulnerable substrate in the left atrium. This is commonly achieved using electroanatomic mapping to guide circumferential radiofrequency ablation of the left atrial tissue surrounding the pulmonary vein (PV) ostia with or without additional targeting of specific sites of electrical conduction within the PV ostia. This procedure targeting specific sites of electrical conduction within the PV ostia is performed in specialized electrophysiology labs, such as those at St. Paul's Hospital in Vancouver and Royal Jubilee Hospital in Victoria.

Precise estimates of the effectiveness of catheter-based circumferential

pulmonary vein ablation (CPVA) at maintaining sinus rhythm are hard to delineate because of the heterogenous and evolving nature of contemporary techniques. Despite this limitation, multiple studies have tried to quantify the expected outcomes. In a nonrandomized study of 1171 consecutive patients with symptomatic atrial fibrillation, CPVA was shown to be more effective at maintaining sinus rhythm at 1, 2, and 3 years when compared to medical therapy (84% vs 61% at 1 year; 79% vs 47% at 2 years; and 78% vs 37% at 3 years; all P values $< .001$).²⁰ These findings were confirmed in three small, randomized trials that demonstrated the efficacy of CPVA to maintain sinus rhythm at 1 year to be 87% to 93% versus 23% to 37% with antiarrhythmic therapy.^{21–23} Furthermore, a meta-analysis published last year revealed that the AF recurrence-free survival rates with CPVA were 3.73 times that of antiarrhythmic therapy (CI 2.47–5.63).²⁴ Interestingly, one small study found CPVA to be associated with a significant improvement in mortality (HR 0.46; CI 0.31–0.68; $P < .001$), heart-failure-related and stroke-related morbidity (HR 0.45; CI 0.31–0.64; $P < .001$), as well as quality of life when compared to antiarrhythmic therapy.²⁰

Given the invasive nature of this technique, legitimate safety concerns have been raised. A recent survey of physicians performing CPVA demonstrated that in over 45 000 procedures the incidence of procedure-related mortality was less than 0.1%.²⁵ Likewise, other significant complications are reasonably rare, with the reported rates of at least one major complication occurring in less than 6% of patients undergoing the procedure. The most common serious complications were tamponade (1.2%), transient ischemic attack (0.53%), and stroke (0.23%).²⁶ When CPVA was

compared with antiarrhythmic therapy, fewer adverse events were reported with CPVA.²⁴ Currently, however, catheter-based ablation procedures remain second-line therapy and are only recommended for those who do not respond to antiarrhythmic medications. This is likely to change as the procedure is refined and both safety and efficacy improve.

Stroke and systemic embolization

Patients with permanent, persistent, or paroxysmal AF are all at an increased risk of stroke and systemic embolization (i.e., noncerebrovascular or noncoronary embolization usually resulting in limb or intestinal ischemia). Multiple studies have found the risk of these devastating complications to be 4 to 5 times that observed in the non-AF population.^{27,28}

As a result of these findings, multiple studies have evaluated the efficacy of antiplatelet agents (e.g., ASA) and vitamin K antagonists (e.g., warfarin) in the management of patients with AF. Recent meta-analyses have demonstrated that adjusted-dose warfarin therapy was 64% more efficacious than placebo at preventing stroke and 71% more efficacious at preventing systemic embolization.^{29,30} While antiplatelet agents are significantly better than placebo in stroke prevention (22% reduction), warfarin results in a further 39% reduction in the risk of stroke and a 50% reduction in the risk of systemic embolization when compared to antiplatelet agents alone.^{29,30} This must all be tempered with the knowledge that when compared to placebo, warfarin results in a twofold to threefold increased risk of major bleeding, albeit the absolute rates of these complications are small.^{29,30}

To help guide clinical management, various stroke prediction scores have been developed, the most com-

Table. Recommendations for treatment based on CHADS2 score for stroke risk.

Score	Annual stroke risk %	NNT	Risk category	Recommendation
0	1.9	80	Low	ASA 81–325 mg daily
1	2.8	55	Moderate	Either ASA or warfarin
2	4.0	38	Moderate	Warfarin to target of INR 2–3
3	5.9	26	High	Warfarin to target of INR 2–3
4	8.5	18	High	Warfarin to target of INR 2–3
5	12.5	12	High	Warfarin to target of INR 2–3
6	18.2	8	High	Warfarin to target of INR 2–3

mon being the CHADS2 score, which allows an annual stroke risk to be calculated based on a history of five simple clinical characteristics.³¹ This score ascribes 1 or 2 points to each of the following:

- Congestive heart failure (1 point).
- Hypertension (1 point).
- Age greater than 75 years (1 point)
- Diabetes mellitus (1 point)
- Stroke or transient ischemia attack (2 points)

The sum of these points can then be translated into an annual stroke risk score and used to guide anticoagulation recommendations. The **Table** includes recommendations for warfarin or antiplatelet agents along with the number needed to treat (NNT) to prevent one stroke with adjusted-dose warfarin therapy.³¹ For those with a score of 2 or higher, warfarin anticoagulation to a target INR of 2–3 is recommended in the absence of contraindications. Conversely, a score of 0 is felt to be of low relative risk and ASA (81–325 mg daily) is recommended. For those with intermediate risk or a score of 1 point, ASA is typically recommended; however, warfarin may be used based on physician discretion or patient preference.

For those with a contraindication for warfarin but a high risk of stroke, recent evidence suggests combination

therapy with ASA (75–100 mg daily) and clopidogrel (75 mg daily) may be more beneficial than ASA alone.³² In the ACTIVE A trial, 7552 patients who were at high risk for stroke but were not candidates for warfarin therapy were randomly assigned to receive ASA (75–100 mg daily) and clopidogrel (75 mg daily) or ASA alone. Combination therapy effectively reduced the incidence of the primary composite endpoint of stroke, MI, systemic embolus, or vascular death (6.8% vs 7.6% per year; relative risk [RR] 0.89; CI 0.81–0.98; $P = .01$). However, the significant reduction in the incidence of stroke (2.4% vs 3.3% per year; RR 0.72; CI 0.62–0.83; $P < .001$) was almost balanced by a significant increase in the risk of major hemorrhage (2.0% vs 1.3% per year; RR 1.57; CI 1.29–1.92; $P < .001$). While warfarin remains the standard of care, in those patients at high risk for stroke who are unable to take warfarin, combination therapy with ASA and clopidogrel becomes a viable alternative to ASA alone.

Effective warfarin therapy carries with it the unfortunate combination of a narrow therapeutic window and an unpredictable pharmacological profile, which contributes to the twofold to threefold increased risk of major bleeding observed with warfarin

therapy when compared to placebo.^{29,30} While the absolute rates of these complications remain small, attempts have been made to develop novel oral agents with a predictable pharmacological profile, which may minimize the risk of bleeding while negating the need for frequent INR monitoring. Of the potential targets in the coagulation cascade, recent efforts have centred on the development of direct thrombin inhibitors and oral factor Xa inhibitors, of which there are at least six in various stages of development. Dabigatran, the only oral direct thrombin inhibitor in late-stage development, has been shown to be safe and effective in the prevention and treatment of venous thromboembolism.³³ In fact, the recently published RE-LY trial demonstrated that dabigatran (110 mg twice daily) was noninferior to warfarin in the prevention of stroke and systemic embolism (1.53% vs 1.69% per year for dabigatran and warfarin, respectively; $P < .001$ for noninferiority) but was associated with a lower rate of major hemorrhage (2.71% vs 3.36% per year for dabigatran and warfarin, respectively; $P = .003$). In contrast, dabigatran (150 mg twice daily) was associated with lower rates of stroke and systemic embolism (1.11% vs 1.69% per year; $P < .001$ for superiority) but was associated with similar rates of major hemorrhage when compared to warfarin therapy (3.11% vs 3.36% per year for dabigatran and warfarin, respectively; $P = .31$).³⁴

Interestingly, technical advances may eventually eliminate the need for oral anticoagulation therapy. Short-term data from the PROTECT-AF study of a novel percutaneous left atrial appendage closure device suggest that this device is noninferior to warfarin in terms of cardiovascular death, stroke, or systemic embolism.³⁵ The investigators enrolled 707 patients

with nonvalvular AF and randomly assigned them to two groups—one was treated with the percutaneous left atrial appendage closure device followed by discontinuation of warfarin 45 days later, and the other group was treated with continued warfarin therapy alone. After a mean follow-up of 16 months there was no significant difference in the primary composite outcome of cardiovascular death, stroke, or systemic embolism between the device group and the control group (3.4 events per 100 patient-years vs 5.0 events per 100 patient-years; $P < .05$ for noninferiority). The overall rate of stroke was noninferior between groups (3.4 events per 100 patient-years vs 3.6 events per 100 patient-years). However, there were significantly fewer hemorrhagic strokes in the device group (1 vs 6; $P < .05$ for superiority).

Conclusions

With the changing demographics of the Canadian population, BC physicians will most certainly encounter atrial fibrillation more and more frequently. A rate-control strategy may be preferable for many of these patients and may reduce unnecessary admissions for reversion to sinus rhythm. Nonetheless, there have been significant advances in our ability to restore and maintain sinus rhythm in select patients, notably in the form of atrial fibrillation ablation. Regardless of whether a rate- or rhythm-control strategy is chosen, the most important aspect of atrial fibrillation management remains the prevention of stroke and systemic embolization. Although warfarin remains the standard of care for patients at moderate or high risk of stroke, there are ever-increasing options for treating patients unable to take warfarin, and exciting developments continue to occur.

Competing interests

None declared.

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